Evidence Report/Technology Assessment

Number 223

Omega-3 Fatty Acids and Cardiovascular Disease: An Updated Systematic Review

Agency for Healthcare Research and Quality

Effective Health Care Program

Evidence Report/Technology Assessment
Number 223

Omega-3 Fatty Acids and Cardiovascular Disease: An Updated Systematic Review

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
5600 Fishers Lane
Rockville, MD 20857
www.ahrq.gov

Contract No. 290-2012-00012-I

Prepared by:
Brown Evidence-based Practice Center
Providence, RI

Investigators:
Ethan M. Balk, M.D., M.P.H.
Gaelen P. Adam, M.L.I.S.
Valerie Langberg, Sc.M.
Christopher Halladay, B.A., Sc.M.
Mei Chung, M.P.H., Ph.D.
Lin Lin, M.A., Sc.M.
Sarah Robertson, B.S.
Agustin Yip, M.D.
Dale Steele, M.D.
Bryant T. Smith, M.P.H., C.P.H.
Joseph Lau, M.D.
Alice H. Lichtenstein, D.Sc.
Thomas A. Trikalinos, M.D., Ph.D.

AHRQ Publication No. 16-E002-EF
August 2016

This report is based on research conducted by the Brown Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2015-00002-I). The report is sponsored by the National Institutes of Health Office of Dietary Supplements (NIH/ODS). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ or NIH/ODS. Therefore, no statement in this report should be construed as an official position of AHRQ, NIH/ODS, or the U.S. Department of Health and Human Services.

None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

AHRQ or U.S. Department of Health and Human Services endorsement of any derivative products that may be developed from this report, such as clinical practice guidelines, other quality enhancement tools, or reimbursement or coverage policies, may not be stated or implied.

This report may periodically be assessed for the currency of conclusions. If an assessment is done, the resulting surveillance report describing the methodology and findings will be found on the Effective Health Care Program Web site at www.effectivehealthcare.ahrq.gov. Search on the title of the report.

Persons using assistive technology may not be able to fully access information in this report. For assistance contact EffectiveHealthCare@ahrq.hhs.gov.

Suggested citation: Balk EM, Adam GP, Langberg V, Halladay C, Chung M, Lin L, Robertson S, Yip A, Steele D, Smith BT, Lau J, Lichtenstein AH, Trikalinos TA. Omega-3 Fatty Acids and Cardiovascular Disease: An Updated Systematic Review. Evidence Report/Technology Assessment No. 223. (Prepared by the Brown Evidence-based Practice Center under Contract No. 290-2012-00012-I.) AHRQ Publication No. 16-E002-EF. Rockville, MD: Agency for Healthcare Research and Quality; August 2016.
www.effectivehealthcare.ahrq.gov/reports/final.cfm. DOI: https://doi.org/10.23970/
AHRQEPCERTA223.

Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

If you have comments on this systematic review, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

Andrew Bindman, M.D.
Director
Agency for Healthcare Research and Quality

Arlene S. Bierman, M.D., M.S.
Director
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Stephanie Chang, M.D., M.P.H.
Director
Evidence-based Practice Center Program
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Aysegul Gozu, M.D., M.P.H.
Task Order Officer
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

The list of Technical Experts who provided input to this report follows:

Philip Calder, Ph.D., R.Nutr.
University of Southampton
Southampton, United Kingdom

William R. Harlan, M.D.*
Associate Director for Disease Prevention (Ret)
National Institutes of Health
Chevy Chase, MD

Van S. Hubbard, M.D., Ph.D.
Current:
Rear Admiral, U.S. Public Health Service (Ret)
At time of review:
National Institutes of Health
Director
Division of Nutrition Research Coordination
Associate Director for Nutritional Sciences
National Institute of Diabetes and Digestive and Kidney Diseases
Washington, DC

Charlotte Pratt, Ph.D., R.D.
National Institutes of Health
National Heart, Lung and Blood Institute
Washington, DC

Lu Wang, M.D., Ph.D.*
Harvard Medical School
Brigham and Women's Hospital
Boston, MA

* Provided input on Draft Report.

Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

The list of Peer Reviewers follows:

Ingeborg A. Brouwer, Ph.D., M.Sc.
Vrije Universiteit Amsterdam
Amsterdam, The Netherlands

David A. Lathrop, Ph.D.
National Institutes of Health
National Heart, Lung and Blood Institute
Washington, DC

JoAnn E. Manson, M.D., M.P.H., Dr.P.H.
Harvard Medical School
Harvard T.H. Chan School of Public Health
Brigham and Women's Hospital
Boston, MA

Hildegard Przyrembel, M.D., Ph.D.
Bundesinstitut für Risikobewertung (Federal Institute for Risk Assessment)
Berlin, Germany

Omega-3 Fatty Acids and Cardiovascular Disease: An Updated Systematic Review

Structured Abstract

Background. The effect and association of omega−3 fatty acids (n-3 FA) intake and biomarker levels with cardiovascular (CV) clinical and intermediate outcomes remains controversial. We update prior Evidence Reports of n-3 FA and clinical and intermediate CV disease (CVD) outcomes.

Objectives. Evaluate the effect of n-3 FA on clinical and selected intermediate CV outcomes and the association of n-3 FA intake and biomarkers with CV outcomes. The n-3 FA under review include eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), docosapentaenoic acid (DPA), stearidonic acid (SDA), and alphalinolenic acid (ALA).

Data sources. MEDLINE®, Embase®, the Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and CAB Abstracts from 2000 or 2002 to June 8, 2015, and eligible studies from the original reports and relevant existing systematic reviews.

Review methods. We included randomized controlled trials (RCTs) of any n-3 FA intake compared to no, lower, or other n-3 FA intake with an outcome of interest conducted in healthy adults, those at risk for CVD, or those with CVD. We also included prospective observational studies of the association between baseline n-3 FA intake or biomarker level and followup outcomes. We required 1 year or more of followup for clinical outcomes and 4 weeks for intermediate outcomes (blood pressure [BP] and lipids).

Results. From 11,440 citations (from electronic literature searches and existing systematic reviews), 829 abstracts met basic eligibility criteria; 61 RCTs and 37 longitudinal observational studies (in 147 articles) were included. Most RCTs and observational studies had few risk-of-bias concerns.

Total n-3 FA: There is low strength of evidence (SoE) of no association between total n-3 FA intake and stroke death or myocardial infarction. There is insufficient evidence for other outcomes.

Marine oils, total: There is moderate to high SoE that higher marine oil intake lowers triglycerides (Tg), raises high density lipoprotein cholesterol (HDL-c), and lowers the ratio of total cholesterol to HDL-c but raises low density lipoprotein cholesterol (LDL-c); also that higher marine oil intake does not affect major adverse CV events, all-cause death, sudden cardiac death, coronary revascularization, atrial fibrillation, or BP. There is low SoE of associations between higher marine oil intake and decreased risk of CVD death, coronary heart disease (CHD), myocardial infarction, ischemic stroke, and congestive heart failure (CHF). There is low SoE of no association with CHD death, total stroke, hemorrhagic stroke, or angina pectoris. There is insufficient evidence for other outcomes.

Marine oil FA individually: There is low SoE of no associations between EPA or DHA intake (separately) and CHD, and between EPA or DPA and atrial fibrillation. There is low SoE of no association between EPA biomarkers and atrial fibrillation, but moderate SoE of no effect of purified DHA supplementation on BP or LDL-c. There is insufficient evidence for other specific marine oil FA and outcomes.

ALA: There is moderate SoE of no effect of ALA intake on BP, LDL-c, HDL-c, or Tg. There is low SoE of no association between ALA intake or biomarker level and CHD, CHD death, atrial fibrillation, and CHF. There is insufficient evidence for other outcomes.

Other n-3 FA analyses: There is insufficient evidence comparing n-3 FA with each other or for SDA.

Subgroup analyses: Nineteen of 22 studies found no interaction of sex on any effect of n-3 FA. Likewise, 19 of 20 studies found no differential effect by statin co-use. Within 16 studies evaluating diabetes subgroups, 2 found statistically significant beneficial effects of n-3 FA in those with diabetes but not in those without diabetes, but no test of interaction was reported.

Conclusions. The 61 RCTs mostly compared marine oil supplements with placebo on CVD outcomes in populations at risk for CVD or with CVD, while the 37 observational studies mostly examined associations between various individual n-3 FA and long-term CVD events in generally healthy populations. Compared with the prior report on n-3 FA and CVD, there is more robust RCT evidence on ALA and on clinical CV outcomes; also, by design there are newly added data on associations between n-3 FA biomarkers and CV outcomes. However, conclusions regarding the effect of n-3 FA intake on CV outcomes or associations with outcomes remain substantially unchanged. Marine oils statistically significantly raise HDL-c and LDL-c by similar amounts (≤2 mg/dL), while lowering Tg in a dose-dependent manner, particularly in individuals with elevated Tg; they have no significant effect on BP. ALA has no significant effect on intermediate outcomes. Limited data were available from RCTs on the effect of n-3 FA on clinical CVD outcomes. Observational studies suggest that higher marine oil intake (including from dietary fish) is associated with lower risk of several CVD outcomes. No clear differences in effects or associations were evident based on population, demographic features, or cointerventions. Future RCTs would be needed to establish adequate evidence of the effect of n-3 FA on CVD outcomes or to clarify differential effects in different groups of people. However, future trials are unlikely to alter conclusions about the effects of n-3 FA supplementation on intermediate cardiovascular outcomes (BP, LDL-c, HDL-c, or Tg).

Contents

Tables

Figures

Appendixes

Executive Summary

Introduction

Since the first ecological study published in the late 1970s noted a relatively low cardiovascular (CV) mortality in a Greenland Eskimo population with high fish consumption,[1] there have been hundreds of observational studies and clinical trials conducted to evaluate the effect of omega-3 fatty acids (n-3 FA) on CV disease (CVD) and its risk factors and intermediate markers. The n-3 FA (including alphalinolenic acid [ALA], stearidonic acid [SDA], eicosapentaenoic acid [EPA], docosapentaenoic acid [DPA], and docosahexaenoic acid [DHA]) are a group of long-chain and very-long-chain polyunsaturated fatty acids (PUFA) that are substrates for the synthesis of eicosanoids and are important components of cell membranes that impact fluidity. Major dietary sources of ALA include soybean and canola oils, some nuts, and flaxseed. The major dietary sources of EPA and DHA are fish, other marine life, and marine-derived supplements. There is no naturally occurring source of SDA that, per serving, provides amounts of n-3 FA approaching levels (of EPA and DHA) present in oily fish. Naturally occurring sources of SDA—hemp and echium seed oils—are not consumed by the general population.

Since the publication of the original Agency for Healthcare Research and Quality (AHRQ) n-3 FA systematic reviews in 2004[2, 3] the topic of n-3 FA and CVD has remained controversial. This topic has been evaluated by several expert panels considering whether recommendations or reference values for intakes of EPA and DHA were warranted, either through naturally occurring sources of n-3 FA (e.g., fish consumption) and/or through the use of dietary supplements and fortified foods.[4-7] In 2002, the Institute of Medicine (IOM) considered the evidence inadequate to establish an estimated average requirement for n-3 FA.[5] For healthy adults, the adequate intake values for ALA are 1.1 g/d for females and 1.6 g/d for males.[5] After evaluating evidence linking the very-long-chain n-3 FA—EPA and DHA—to coronary heart disease (CHD, also known as coronary artery disease) and stroke, the IOM panel suggested that n-3 FA may provide beneficial health effects with respect to CHD and stroke; the acceptable macronutrient distribution range (a range of intakes that is associated with reduced risk of chronic diseases while providing adequate intakes of essential nutrients) for ALA was set at 0.6 to 1.2 percent of energy (roughly equivalent to 1 to 3 g/d), where 10 percent of this range can be consumed as EPA and/or DHA.[5] For comparison, the mean intake of ALA in the United States has been estimated at 0.6 percent of energy intake (standard deviation 1.0%),[8] equivalent to approximately 1.4 g/d. This intake level is fairly consistent across developed countries (0.3-1.0% of energy). However, estimated EPA and DHA intake in the United States are only 0.05 g/d and 0.08 g/d, respectively.[8] In contrast, mean intake in South Korea is 0.4 g/d of EPA and DHA, combined. Three other expert reports evaluated the potential health benefits of fish and seafood consumption.[4, 6, 7] Based primarily on the availability of observational study data, these panels consistently suggested that regular consumption of fish and seafood is associated with lower risk of CHD and cardiac death. These recommendations were based primarily on assumptions of benefits from EPA and DHA and their content in fish and seafood. However, determination of n-3 FA intake is problematic, both for population recommendations and in regards to research. In practice, all nutrients are quantified using a nutrient database, e.g., the U.S. Department of Agriculture National Nutrient Database for Standard Reference (http://ndb.nal.usda.gov/). The quantity of a nutrient is then estimated by the standard amount of nutrients in foods that are indexed in the nutrient database multiplied by the amount and frequency of the food consumption. However, n-3 FA in foods are not well estimated in the nutrient database and questionnaires commonly do not ask about cooking oils or dressings and may not ask about supplements (so that n-3 FA intake is estimated only from fish consumption); therefore quantification of n-3 FA intake from food frequency questionnaires is poor. Furthermore, some questionnaires do not include portion size, so further estimation or extrapolation of intake is required.

There have been secular trends in the prevention and treatment of CVD over the past several decades, particularly since the 2004 AHRQ reports on n-3 FA and CVD. These trends may have had an important impact on the potential effect or association between n-3 FA intake and CVD outcomes. Important among these trends are the lower rates of cardiac and cerebrovascular disease, concomitant with higher rates of treatment and control of dyslipidemia and hypertension. For at least the past 20 years American adults are increasingly likely to be treated with statins, antihypertensives, and low-dose aspirin. All of these pharmacologic interventions act on metabolic and biochemical pathways that n-3 FA also impact and this confounding may impact the purported CV benefits of n-3 FA, including lipid metabolism, blood pressure (BP) and vascular homeostasis, and inflammatory and coagulation pathways. These treatment trends may have contributed to the lower population-level CV benefit of higher n-3 FA intake because the underlying risk of CVD is now lower, hence, diminishing the potential impact of n-3 FA intake. Furthermore, diagnostic criteria for CVD events (e.g., myocardial infarction [MI]) and CV risk factors (e.g., metabolic syndrome) have been refined over time which may make older studies less applicable in terms of their outcomes and populations.

There are ongoing concerns in the scientific community regarding systematic biases and random errors in the determination of intakes of n-3 FA from dietary and supplement sources, using currently available assessment tools. Nutrient biomarkers can provide an objective measure of dietary status.[9] However, the correspondence between intake and biomarker concentration not only reflects recent intake but also subsequent metabolism. Current biomarkers used to estimate n-3 FA intake include ALA, EPA, DHA, and, less frequently, SDA and DPA, measured in adipose tissue, erythrocytes, plasma, or plasma phospholipids.[9-11] Adipose tissue FA are thought to reflect long-term intake, erythrocyte FA are thought to reflect intake over the previous 120 days, and plasma FA are thought to reflect more recent intake.[10]

Scope of the Review

The National Institutes of Health's Office of Dietary Supplements (ODS) has a long history of commissioning AHRQ-based systematic reviews and research methodology reports for nutrition-related topics (http://ods.od.nih.gov/Research/Evidence-Based_Review_Program.aspx). The purpose of the current ODS-sponsored systematic review is twofold: 1) to update earlier reviews of the state-of-the science on the topic of the effects of n-3 FA on CVD[3] and selected CVD risk factors and intermediate markers of CVD,[2] and 2) to collect additional information that will enhance the usefulness of this report for policy and clinical applications. This review updates the outcomes reported in the previous review and expands the scope to include additional CVD outcomes (peripheral vascular disease, congestive heart failure (CHF), and arrhythmias); it updates BP and plasma lipid outcomes and adds incident hypertension; it adds associations between biomarkers of n-3 FA intake and outcomes. The primary target audience for this report is clinical and nutrition researchers and policymakers, including ODS and panels revising dietary intake recommendations.

Key Questions

The Key Questions address issues of efficacy (i.e., causal relationships from trials), as well as associations (i.e., prospective observational cohort study associations of n-3 FA intake and/or biomarkers with long-term outcomes; or biomarker associations reported in randomized controlled trials [RCTs]). Compared with the Key Questions from the 2004 reports, the current Key Questions expand the scope of the review to include additional CV outcomes (BP, CHF, and arrhythmias), focus on the intermediate outcomes plasma lipids and BP, add the intermediate outcome hypertension, and include associations between biomarkers of intake and outcomes.

1. What is the efficacy or association of n-3 FA (EPA, DHA, EPA+DHA, DPA, SDA, ALA, or total n-3 FA) exposures in reducing CVD outcomes (incident CVD events, including all-cause death, CVD death, nonfatal CVD events, new diagnosis of CVD, peripheral vascular disease, CHF, major arrhythmias, and hypertension diagnosis) and specific CVD risk factors (BP, key plasma lipids)?
    - What is the efficacy or association of n-3 FA in preventing CVD outcomes in people
        - Without known CVD (primary prevention)
        - At high risk for CVD (primary prevention), and
        - With known CVD (secondary prevention)?
    - What is the relative efficacy of different n-3 FA on CVD outcomes and risk factors?
    - Can the CVD outcomes be ordered by strength of intervention effect of n-3 FA?

2. n-3 FA variables and modifiers:
    - How does the efficacy or association of n-3 FA in preventing CVD outcomes and with CVD risk factors differ in subpopulations, including men, premenopausal women, postmenopausal women, and different age or race/ethnicity groups?
    - What are the effects of potential confounders or interacting factors—such as plasma lipids, body mass index, BP, diabetes, kidney disease, other nutrients or supplements, and drugs (e.g., statins, aspirin, diabetes drugs, hormone replacement therapy)?
    - What is the efficacy or association of different ratios of n-3 FA components in dietary supplements or biomarkers on CVD outcomes and risk factors?
    - How does the efficacy or association of n-3 FA on CVD outcomes and risk factors differ by ratios of different n-3 FA—DHA, EPA, and ALA, or other n-3 FA?

- How does the efficacy or association of n-3 FA on CVD outcomes and risk factors differ by source (e.g., fish and seafood, common plant oils (e.g., soybean, canola), fish oil supplements, fungal-algal supplements, flaxseed oil supplements)?
- How does the ratio of n-6 FA to n-3 FA intakes or biomarker concentrations affect the efficacy or association of n-3 FA on CVD outcomes and risk factors?
- Is there a threshold or dose-response relationship between n-3 FA exposures and CVD outcomes and risk factors? Does the study type affect these relationships?
- How does the duration of intervention or exposure influence the effect of n-3 FA on CVD outcomes and risk factors?
- What is the effect of baseline n-3 FA status (intake or biomarkers) on the efficacy of n-3 FA intake or supplementation on CVD outcomes and risk factors?

3. Adverse events:
   - What adverse effects are related to n-3 FA intake (in studies of CVD outcomes and risk factors)?
   - What adverse events are reported specifically among people with CVD or diabetes (in studies of CVD outcomes and risk factors)?

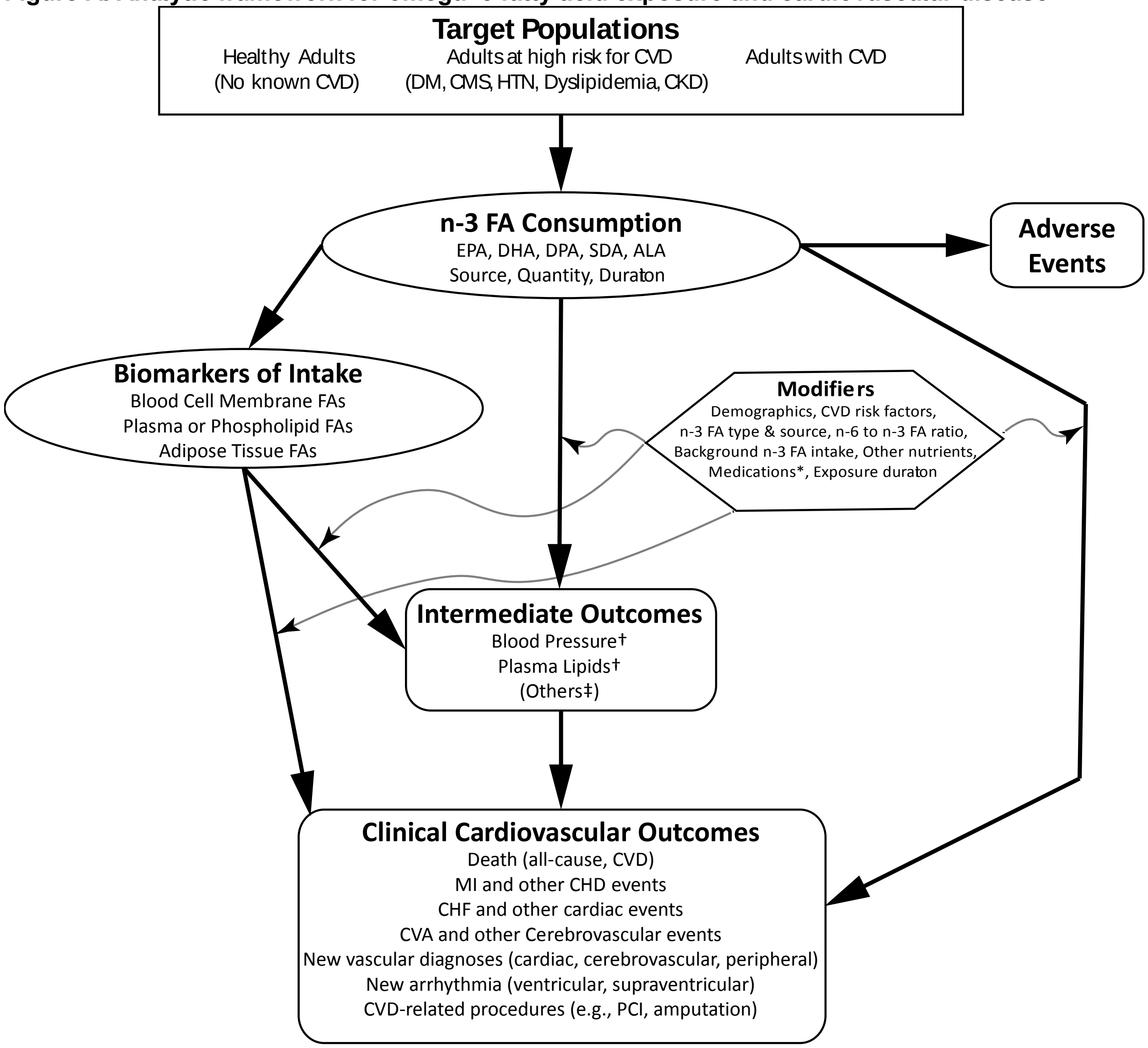
Analytic Framework

To guide the assessment of studies that examine the association between n-3 FA intake and CV outcomes, the analytic framework maps the specific linkages associating the populations of interest, exposures, modifying factors, and outcomes of interest (Figure A). The framework graphically presents the key components of well-formulated study questions:

1. Who are the participants (i.e., what is the population and setting of interest, including the diseases or conditions of interest)?
2. What are the interventions?
3. What are the outcomes of interest (intermediate and health outcomes)?
4. What study designs are of value?

Specifically, this analytic framework depicts the chain of logic that evidence must support to link the intervention (exposure to n-3 FA) to improved health outcomes.

Figure A. Analytic framework for omega−3 fatty acid exposure and cardiovascular disease



Legends: This framework concerns the effect of n-3 FA exposure (as a supplement or from food sources) on CVD and CV risk factors. Populations of interest are noted in the top rectangle, exposure in the oval, outcomes in the rounded rectangles, and effect modifiers in the hexagon.

* Specifically, CV medications, statins, antihypertensives, diabetes medications, hormone replacement regimens.
† Systolic blood pressure, diastolic blood pressure, mean arterial pressure, high density lipoprotein cholesterol (HDL-c), low density lipoprotein cholesterol (LDL-c), total/HDL-c ratio, LDL-c/HDL-c ratio, triglycerides.
‡ Many other intermediate outcomes are likely in the causal pathway between n-3 FA intake and CV outcome, but only blood pressure and plasma lipids were included in the review.

Abbreviations: ALA = alphalinolenic acid, CHD = coronary heart disease, CHF = congestive heart failure, CKD = nondialysis-dependent chronic kidney disease, CMS = cardiometabolic syndrome, CVA = cerebrovascular accident (stroke), CVD = cardiovascular disease, DHA = docosahexaenoic acid, DM = diabetes mellitus, DPA = docosapentaenoic acid, EPA = eicosapentaenoic acid, FA = fatty acid, HTN = hypertension, MI = myocardial infarction, n-3 = omega−3, n-6 = omega−6, PCI = percutaneous coronary intervention, SDA = stearidonic acid.

Methods

The present review evaluates the effects of, and the associations between, n-3 FA (EPA, DPA, ALA and n-3 FA biomarkers) and CVD outcomes. The Brown Evidence-based Practice Center (EPC) conducted the review based on a systematic review of the published scientific literature using established methodologies as outlined in the AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews (Methods Guide).[12]

The review was conducted in parallel with a systematic review of n-3 FA and child and maternal health, conducted by another EPC. Several aspects of the review were coordinated, including eligibility criteria and search strategies regarding interventions and exposures structure of the reviews, as well as assessments of the studies' risk of bias, strength of the bodies of evidence, and extraction of study characteristics needed to assess causality.

We convened a Technical Expert Panel (TEP) to help refine the research questions and protocol, including the Key Questions, analytic framework, study eligibility criteria, literature search, and analysis plans.

Literature Search

Search Strategy

We conducted literature searches of studies in MEDLINE®, both the Cochrane Central Trials Registry® and Cochrane Database of Systematic Reviews®, Embase®, and CAB Abstracts® from 2002 to 8 June 2015 (to overlap with the last search run for the 2004 reviews). We searched publications back to 2000 for the newly added outcomes and for biomarkers of n-3 FA intake. We also rescreened and included all studies from the original reviews that met current eligibility criteria. Titles and abstracts were independently double-screened to identify articles relevant to each Key Question. We also reviewed reference lists of related systematic reviews for other potentially eligible studies.

Inclusion and Exclusion Criteria

For all Key Questions, the eligibility criteria are:

Populations

- Healthy adults (≥18 years) without CVD or with low to intermediate risk for CVD
- Adults at high risk for CVD (e.g., with diabetes, cardiometabolic syndrome, hypertension, dyslipidemia, nondialysis chronic kidney disease)
- Adults with clinical CVD (e.g., history of myocardial infarction [MI], angina, stroke, arrhythmia)
- Exclude populations chosen for having a non-CVD or nondiabetes-related disease (e.g., cancer, gastrointestinal disease, rheumatic disease, dialysis)

Interventions/Exposures

- n-3 FA supplements
- n-3 FA supplemented foods (e.g., eggs)
- n-3 FA content in diet
- Biomarkers of n-3 FA intake

- n-3 FA content of food or supplements must have been explicitly quantified (by any method). Therefore, studies, such as those of fish diet where only servings per week were defined or Mediterranean diet studies without quantified n-3 FA, were excluded. The n-3 FA quantification could be of total n-3 FA, of a specific n-3 FA (e.g., ALA, purified DHA) or of combined long-chain n-3 FA (EPA, DHA, and DPA, regardless of source; hereafter referred to as marine oils).
- Exclude mixed interventions of n-3 FA and other dietary or supplement differences (e.g., n-3 FA and vitamin E versus placebo; n-3 FA as part of a low-fat diet versus usual diet). However, factorial design (and other) studies that compared (for example) n-3 FA versus control, with or without another intervention (e.g., statins) were included.
- Exclude n-3 FA dose ≥6 g/d
- Exclude weight-loss interventions

Comparators

- Placebo or no n-3 FA intervention
- Different n-3 FA source intervention
- Different n-3 FA concentration intervention
- Different n-3 FA dietary exposure (e.g., comparison of quantiles)
- Different n-3 FA biomarker levels (e.g., comparison of quantiles)

Outcomes

- All-cause death
- Cardiovascular (CV), cerebrovascular, and peripheral vascular events:
    - Fatal vascular events (e.g., due to MI, stroke)
    - Total incident vascular events (e.g., MI, stroke, transient ischemic attack, unstable angina, major adverse CV events [MACE]; total events include fatal and nonfatal events; total stroke includes ischemic and hemorrhagic stroke)
    - Coronary heart disease (CHD, also known as coronary artery disease), new diagnosis
    - Congestive heart failure (CHF), new diagnosis
    - Cerebrovascular disease, new diagnosis
    - Peripheral vascular disease, new diagnosis
    - Ventricular arrhythmia, new diagnosis, including sudden cardiac death [SCD]
    - Supraventricular arrhythmia (including atrial fibrillation [AFib]), new diagnosis
    - Major vascular interventions/procedures (e.g., revascularization, thrombolysis, lower extremity amputation, defibrillator placement)
- Major CVD risk factors (intermediate outcomes):
    - Blood pressure (BP) (new-onset hypertension, systolic, diastolic, and mean arterial pressure [MAP])
    - Key plasma lipids (i.e., high density lipoprotein cholesterol [HDL-c], low density lipoprotein cholesterol [LDL-c], total/HDL-c ratio, LDL-c/HDL-c ratio, triglycerides [Tg])
- Adverse events (e.g., bleeding, major gastrointestinal disturbance), only from intervention studies of supplements

Timing

- Clinical outcomes, including new-onset hypertension (all study designs): ≥1 year followup (and intervention duration, as applicable)
- Intermediate outcomes (BP and plasma lipids) (all study designs): ≥1 month followup
- Adverse events (all study designs): no minimum followup

Setting

- Community-dwelling (noninstitutionalized) individuals

Study Design

- RCTs (all outcomes)
- Randomized cross-over studies (BP and plasma lipids, adverse events)
- Prospective nonrandomized comparative studies (clinical outcomes, adverse events)
- Prospective cohort (single group) studies, where groups were compared based on n-3 FA intake or intake biomarker values (clinical outcomes). Observational studies must have reported multivariate analyses.
- <u>Exclude:</u> Retrospective or case control studies or cross-sectional studies (but include prospective nested case control studies). Studies must have had measures of intake prior to outcome.

- Minimum sample sizes

  Due to the very large number of potentially eligible studies (more than 400), we applied arbitrary thresholds based on sample size, followup duration, and whether subgroup or interaction analyses were reported. These were designed to give preference to larger studies with longer followup duration or that reported interaction analyses of interest.
    - RCTs
        - We aimed for a minimum of about 25 RCTs for each of the BP and plasma lipid outcomes. We preferentially included RCTs that reported relevant subgroup, interaction, or factorial analyses.
            - For RCTs with BP or lipid outcomes with subgroup, interaction, or factorial analyses, we included parallel design RCTs with a minimum of 30 participants per arm, factorial RCTs with a minimum of 30 participants per n-3 FA intervention, and crossover trials with a minimum of 20 participants.
            - For RCTs with lipid outcomes without subgroup analyses, we included parallel design RCTs with a minimum of 200 participants per arm, factorial RCTs with a minimum of 200 participants per n-3 FA intervention, and crossover trials with a minimum of 100 participants.
            - For RCTs with BP outcomes without subgroup analyses, if followup was ≥6 months, we included all RCTs; if followup was <6 months (≥1 month), we included parallel design RCTs with a minimum of 80 participants per arm, factorial RCTs with a minimum of 80 participants per n-3 FA intervention, and crossover trials with a minimum of 40 participants.
            - For RCTs with CVD event outcomes, we included all RCTs with at least 10 participants per arm.

- Longitudinal observational studies
    - We aimed for a minimum of about 10 observational studies for each broad clinical outcome (see bullets below) and also for dietary marine oils, dietary ALA, marine oil biomarkers, and ALA biomarkers.
        - For cardiac event outcomes, we included observational studies with at least 10,000 participants.
        - For death outcomes, we included observational studies with at least 10,000 participants.
        - For stroke event outcomes, we included observational studies with at least 3000 participants.
        - For arrhythmia event outcomes, we included observational studies with at least 2000 participants.
        - For CHF event outcomes, we included observational studies with at least 700 participants.
        - For peripheral vascular disease event, incident hypertension, MACE, and revascularization outcomes, we included observational studies with at least 500 participants.
        - We screened smaller sample size observational studies (starting with the largest studies) to include additional studies of ALA biomarkers, regardless of the outcomes analyzed.
- In all instances, if a study met eligibility criteria for any outcome, we extracted all outcomes of interest from that study; therefore, there are multiple instances of studies being included for an outcome even though the study might not have met study size criteria for that specific outcome.

- English language publications
- Peer reviewed publications

Quality (Risk of Bias) Assessment of Individual Studies

We assessed the methodological quality of each study based on predefined criteria. For RCTs, we used the Cochrane risk of bias tool[13] and for observational studies we used relevant questions from the Newcastle Ottawa Scale.[14] Additionally, we included nutrition study specific risk of bias questions (e.g., related to uncertainty of dietary assessment measurements).[15-17]

Data Synthesis

Statistical analyses were conducted in Stata version 13.1 (StataCorp, College Station, Texas). We conducted random effects model meta-analyses of comparative studies (i.e., RCTs) if, for each set of studies with the same outcome and intervention and comparator pair, there were at least six studies. We meta-analyzed multivariate observational cohorts when at least four cohorts analyzed the same n-3 FA, measure, and outcome.

Strength of the Body of Evidence

We graded the strength of the body of evidence per the AHRQ Methods Guide on assessing the strength of evidence for each outcome.[18] The strength-of-evidence dimensional ratings are summarized in Evidence Profile tables that detail our reasoning behind the overall strength of evidence rating.

Peer Review and Public Commentary

A draft version of this report was reviewed by a panel of expert reviewers and the general public. The reviewers were either directly invited by the EPC or offered comments through a public review process. Revisions of the draft were made, where appropriate, based on their comments. The draft and final reports were also reviewed by the Task Order Officer and an Associate Editor from another EPC. However, the findings and conclusions are those of the authors, who are responsible for the contents of the report.

Results

The literature searches yielded 11,440 citations. Reference lists from existing systematic reviews yielded 203 additional citations (which mostly represented articles published before 2002). Of these, 829 abstracts met basic eligibility criteria. As described in the Methods chapter of the full report (under *Study Selection*), using an evidence map process, we selected 463 articles for full text review, of which 147 articles met eligibility criteria, representing 61 RCTs (in 82 articles) and 37 longitudinal observational studies (in 65 articles).

Across RCTs, the studies generally had few risk of bias concerns. Among the 61 RCTs, 23 (38%) had no high risk of bias / study quality limitations; an additional 26 RCTs (43%) had one risk of bias limitation and 6 (10%) had two risk of bias limitations. None of the remaining 6 RCTs (10%) had more than four study limitations (of 10 explicitly assessed potential limitations). The most common risk of bias limitation was a lack of intention-to-treat analyses; 12 RCTs (20%) clearly did not conduct intention-to-treat analyses (one of these conducted an intention-to-treat analysis for the outcome death, but not for lipid outcomes); 12 additional RCTs (20%) were unclear whether intention-to-treat analyses were conducted. Ten RCTs (16%) did not blind study participants (and 4 additional, 7%, were unclear whether they blinded participants), often because the intervention was dietary and could not be blinded. However, only 7 RCTs (11%) clearly did not blind outcome assessors (nine additional RCTs, 14%, were unclear regarding outcome assessor blinding). Attrition bias, primarily due to dropout rates greater than 20 percent, was present in 9 RCTs (15%). Other potential biases were less common.

Across the observational studies, there were fairly few risk of bias concerns. Nine of 37 studies (24%) had no high risk of bias concerns; 20 (54%) had only a single high risk of bias concern (of 7 explicitly assessed potential limitations) and 6 (16%) had two risk of bias concerns. The 2 remaining studies (5%) had three risk of bias concerns. No study was deemed to have high risk of selection bias (regarding whether the outcome was present at baseline) and all adequately adjusted for confounders. The majority of studies used a dietary assessment tool that did not include dietary supplements (18 of 29 applicable studies; 62%); an additional 4 studies (14%) were unclear whether dietary supplements were used. Sixteen studies (43%) did not adequately reported baseline nutrient exposures. Bias due to lack of outcome assessor blinding was infrequent (3 studies [8%]; 4 studies [11%] were unclear), as was attrition bias (1 study [3%]; 4 studies [11%] were unclear). All observational studies reported multivariate analyses (this was an eligibility criterion).

The trials of clinical outcomes were almost all conducted in populations at increased risk of CVD, largely related to dyslipidemia, or with CVD. The trials that reported intermediate outcomes (BP and lipoproteins), were conducted in generally healthy, at-risk, and CVD populations. The observational studies, in contrast, were almost all conducted in general (unrestricted by CVD or risk factors) or healthy populations. One observational study evaluated BP; none evaluated lipids.

In this Executive Summary, we present the results by n-3 FA, first summarizing the strength of evidence across studies, then separately summarizing the clinical CV event outcomes from RCTs, the intermediate CV outcomes from RCTs, the observational study associations with n-3 FA intake, and the observational study associations with n-3 FA biomarkers. We also include the findings regarding adverse events and a summary directly addressing each Key Question. For the interested reader, the main report primarily summarizes the study results first by outcome, then by n-3 FA, then by study design. A listing of effects or associations of n-3 FA and outcomes by the strength of evidence supporting the findings is included at the start of the Discussion section.

Summary by n-3 FA

The trials of clinical outcomes were almost all conducted in populations at increased risk of CVD, largely related to dyslipidemia, or with CVD. The trials that reported intermediate outcomes (BP and lipoproteins), were conducted in generally healthy, at-risk, and CVD populations. The observational studies, in contrast, were almost all conducted in general (unrestricted by CVD or risk factors) or healthy populations. One observational study evaluated BP; none evaluated lipids.

Total n-3 FA (ALA+EPA+DHA)

Overall, there is insufficient evidence regarding the effect of or association between total n-3 FA (combined ALA and marine oils) and clinical or intermediate outcomes. There is low strength of evidence of no association between total n-3 FA intake and stroke death, and total (fatal and nonfatal) MI (each association based on longitudinal observational studies of dietary intake). For both outcomes, the strength of evidence was rated low because of a lack of confirmatory RCT data.

Clinical Event Outcomes, RCTs

No RCTs reported clinical event outcomes for comparisons of total n-3 FA versus placebo.

Intermediate Outcomes, RCTs

Two RCTs that evaluated BP compared combined ALA and marine oil (ALA 1.2 g/d [canola oil] or 2 g [“plant oil”] and 3.6 or 0.4 g EPA+DHA) versus placebo reported on intermediate outcomes. Neither trial found significant effects on BP, LDL-c, HDL-c, Tg, or Total:HDL-c ratio.

Observational Studies, Intake

Seven studies evaluated total n-3 FA intake. For each outcome there was no consistent (and replicated) significant association between total n-3 FA intake and risk reduction. One of three studies found a significant association between higher total n-3 FA intake and *higher* risk of MACE. In contrast, one of three studies found an association of higher intake with reduced risk of CVD death; one of two studies found a significant association of higher intake with reduced risk of MI death; one study each found significant associations of higher intake with lower risk of death from ischemic stroke or CHF. The other studies found no significant associations. No studies found significant associations with all-cause death (1 study), CHD death (2 studies), total (ischemic and hemorrhagic) stroke death (3 studies), total MI (1 study), total stroke (fatal and nonfatal) (1 study), SCD (1 study), or incident hypertension (1 study).

One study found no significant difference in association of total n-3 FA with total CVD death between men and women. Another study found no significant differences in association by different baseline Total:HDL-c ratios between total n-3 FA intake and risk of MI death, total stroke death, or ischemic stroke death.

Observational Studies, Biomarkers

Three studies evaluated biomarkers for total n-3 FA (combined; plasma, blood, or erythrocyte). One study evaluated numerous outcomes and found significant associations between higher biomarker level and reduced risk of most outcomes (CVD death, CHD death, all-cause death, CHD, ischemic stroke, SCD, AFib, and CHF), but not stroke death, total stroke, or hemorrhagic stroke. In contrast, a second study found no significant association with CHD. The third study found no significant association overall with incident hypertension, but did find a significant association in between higher total n-3 FA biomarker levels and lower risk of hypertension in younger women (<55 years old) but not in older women.

Marine Oil, Total: EPA+DHA±DPA

Overall, there is low, moderate, or high strength of evidence of no effect (or association) of marine oils and most clinical CVD outcomes and BP, and high strength of evidence of significant effects of higher marine oil intake on lipoproteins and Tg. There is insufficient evidence for many outcomes of interest. Specifically, there is high strength of evidence of that marine oils statistically significantly lower Tg—possibly with greater effects with higher doses and in people with higher baseline Tg—and statistically significantly raise HDL-c and LDL-c by similar amounts. There is also high strength of evidence that marine oil significantly lowers Total:HDL-c ratio and low strength of evidence that marine oil significantly lowers risk of ischemic stroke (for which no RCTs confirmed the observational study finding). There is a high strength of evidence of no effect of marine oil on risk of MACE, all-cause death, SCD, revascularization, and BP, moderate strength of evidence of no effect of marine oil on risk of AFib, and low strength of evidence of no effect of marine oil on risk of CVD death, CHD death, total CHD, MI, CHF, total stroke, and hemorrhagic stroke. Strength of evidence was rated as low for CHD and hemorrhagic stroke due to a lack of confirmatory RCT data; and for CVD death, CHF, and total stroke because RCTs and observational studies yielded conflicting conclusions (RCTs found no effect, observational studies found statistically significant associations). Strength of evidence was rated low for CHD death primarily because RCTs and observational studies both yielded imprecise estimates suggesting no effect/association. For MI, the strength of evidence was rated low primarily because the summary effect size estimate was relatively strong (HR = 0.88), but the 95% CI only minimally crossed the significance threshold (95% CI 0.77 to 1.02); this scenario yielded low confidence that the conclusion would remain stable with future RCTs and subsequent greater statistical power. This issue was also pertinent for CVD death where summary HR = 0.92 (95% CI 0.82 to 1.02).There is insufficient evidence for other outcomes.

Four RCTs explicitly evaluated (purified) EPA and/or DHA ethyl esters; all other trials explicitly or implicitly evaluated marine oil preparations. No study directly compared formulations. The effects on clinical and intermediate outcomes found among the ethyl ester trials were all statistically or qualitatively similar to the effects found in other studies.

Clinical Event Outcomes, RCTs

Regarding clinical event outcomes, 19 trials in populations at increased risk for CVD (3 RCTs) and CVD populations (17 RCTs) mostly found no significant effects of marine oil (EPA+DHA±DPA) versus placebo on specific clinical event outcomes. Across RCTs, EPA+DHA doses ranged from 0.34 to 6 g/d (median 0.866 g/d). Followup ranged from 1 to over 10 years (median 3.9 years).

Two of 17 trials found significantly lower risk of all-cause death with EPA+DHA (both 0.866 g/d; HR = 0.79 and 0.91), however, the meta-analyzed HR was nonsignificant at 0.97 (95% CI 0.92 to 1.03) with no differences across trials by marine oil dose, followup time, or population (CVD, at risk, healthy). Four trials also found no within-study subgroup differences in effect on death for multiple subgroup comparisons.

Ten RCTs reported on MACE, only two of which found significant reductions in outcome with 0.866 g/d EPA+DHA at 3.9 year followup and with 1.8 g/d EPA at 5 year followup (in an at-risk population, but not in a parallel CVD population). Meta-analysis of MACE found a no effect (HR=0.96; 95% CI 0.91 to 1.02) with no significant differences across studies by marine oil dose (range 0.4−2 g/d), followup time (range 1−5 y), or population category. Within-study subgroup analyses found a significant effect in women but not men in one trial, but no significant difference in effect between sexes in a second trial, and no differences between multiple subgroups in three trials.

None of the 11 trials that reported on total MI found a significant effect. Meta-analysis, however, found a nonsignificant effect size (HR=0.88; 95% CI 0.77 to 1.02), with no significant differences across studies by marine oil dose, followup time, or population category. In one trial, no significant difference in effect was found based on cointervention with B vitamins.

Two of seven RCTs found significant effects of 0.866 g/d marine oil (EPA+DHA) on risk of CVD death in populations of people with existing CVD. Meta-analysis found a nonsignificant effect size (HR=0.92; 95% CI 0.82 to 1.02), with no significant differences across studies by marine oil dose, followup time, or population.

Nine RCTs all found no significant effect of EPA+DHA with SCD; by meta-analysis (with the EPA trial), summary HR=1.04 (95% CI 0.92 to 1.17). Seven RCTs also found no significant effect of marine oils with total stroke; by meta-analysis, summary HR=0.98 (95% CI 0.88 to 1.09).

Six RCTs evaluated angina pectoris, three stable angina, one hospitalization for angina, and three unstable angina. One trial found that 1.8 g/d of purified EPA ethyl ester had an additive effect on statin to reduce unstable angina incidence after 5 years in people with dyslipidemia; however the five trials in people with existing CVD found no significant effects of 0.84 to 6 g/d marine oils. The six RCTs evaluating CHF had a similar pattern. The one trial of 0.85 g/d marine oil in people with multiple risk factors for CHF found a significant risk reduction in CHF hospitalization with n-3 FA supplementation, but the five studies in people with existing CVD found no significant effects of 0.84 to 6 g/d marine oils.

All EPA+DHA RCTs that evaluated revascularization (6 trials), CHD death (4 trials), total stroke death (3 trials), AFib (3 trials), and CHF death (1 trial) found no significant effect of marine oils. One trial found an effect in participants with diabetes that was not seen in those without diabetes, but no test of interaction was reported. Two trials compared effect of marine oils on AFib in multiple subgroups, finding no significant differences.

Four EPA+DHA RCTs found inconsistent effects on cardiac death, with effect sizes ranging from 0.45 to 1.45. One trial found a statistically significant *reduction* in cardiac death with 0.866 g/d EPA+DHA at 3.5 years (RR=0.65; 95% CI 0.51 to 0.82); one trial found a statistically significant *increase* in cardiac death with a fish diet with EPA+DHA supplements (0.855 g/d EPA+DHA; HR=1.45; 95% CI 1.05 to 1.99), but no significant effect on cardiac death among people only given advice to increase fish intake (by 0.45 g/d EPA+DHA) or in two other trials of 0.96 and 2.6 g/d EPA+DHA. The trial that found increased risk with combined fish diet and EPA+DHA supplementation found no significant difference in effect between multiple sets of subgroups based on drug cointervention.

Intermediate Outcomes, RCTs

Twenty-nine RCTs that compared EPA+DHA to placebo evaluated systolic BP, of which 28 also reported on diastolic BP. Ten RCTs were in healthy populations, 13 in those at risk for CVD, and six in those with CVD. All trials found no significant difference in BP across EPA+DHA doses of 0.30 to 6 g/d and followup durations of 1 month to 6 years. By meta-analysis, no significant effects on systolic (summary net difference = 0.10 mmHg; 95% CI −0.20 to 0.40) or diastolic (summary net difference = −0.19 mmHg; 95% CI −0.43 to 0.05) BP were found. Four of the trials also found no effect on MAP. By meta-regression, no differences in effect across studies were found by marine oil dose, followup duration or population. Three trials directly compared different EPA+DHA doses and found no differences in effect (1.7 vs. 0.8 g/d; 1.8 vs. 0.9 or 0.45 g/d; 3.4 vs. 1.7 g/d). One trial found no difference in effect between people with normal BP or prehypertension.

Numerous included RCTs compared the effect of marine oils and placebo (or equivalent) on blood lipids. Thirty-nine RCTs evaluated LDL-c and 34 evaluated HDL-c. Marine oil doses ranged from 0.3 to 6 g/d (median 2.4 g/d) and study followup times ranged from 1 month to 6 years (median 3 months). Meta-analysis of the effect of marine oils on LDL-c found a statistically significant, but small effect *increasing* LDL-c (1.98 mg/dL; 95% CI 0.38 to 3.58). Marine oils increased HDL-c also by a statistically significant, but small effect (0.92 mg/dL; 95% CI 0.18 to 1.66). For both lipoprotein fractions, no significant differences in effect across studies were found by marine oil dose, followup duration or population. Seven studies found no significant differences in effect within study by EPA+DHA dose. For HDL-c, three trials found no significant difference in effect between people using statins or not; one or two trials, each, found no significant differences between subgroups based on sex or age. One trial found a larger HDL-c effect in a subgroup also randomized to an exercise regimen; one of two trials found a larger HDL-c effect in people with impaired glucose tolerance compared to those with normoglycemia. Eight trials mostly found no significant effects of marine oil (0.4−5 g/d for 1 month to 3 years) on Total:HDL-c ratio, but with a statistically significant summary effect of −0.17 (95% CI −0.26 to −0.09). One trial of 2.8 g/d EPA+DHA found no significant effect on LDL:HDL-c ratio; another trial found no significant difference in change in ratio between 3.4 and 1.7 g/d EPA+DHA.

Forty-one included RCTs mostly found significant effects of marine oils (0.3−6 g/d; median 2.4 g/d for 1 month to 6 years; median 3 months) on Tg levels. Meta-analysis found a summary net change of −24 mg/dL (95% CI −31 to−18), with no significant difference in effect based on population or followup time across studies. By metaregression, each increase in mean baseline Tg concentration by 1 mg/dL was associated with a greater net decrease in Tg concentration of −0.15 mg/dL (95% CI −0.22 to−0.08; P<0.0001); each increase of EPA+DHA dose by 1 g/d was also associated with a greater net decrease in Tg concentration of −5.9 mg/dL (95% CI −9.9 to−2.0; P=0.003). No clear inflection point was found at any dose. Five of six trials found no significant difference in Tg change by EPA+DHA dose, but across trials all doses of 3.4 and 4 g/d lowered Tg concentration by at least 30 mg/dL more than lower doses (1−2 g/d), while all pairwise comparisons of lower doses (1.7−3 g/d) to even lower doses (0.7−2.25 g/d) found much smaller differences between doses (−17 to 6 mg/dL). Two trials both found significantly larger Tg concentration lowering effects of EPA (3.6 or 3.3 g/d) than DHA (3.8 or 3.7 g/d). No significant differences were found based on statin use (4 trials), vitamin C use (1 trial), concurrent high or low linoleic acid diet (1 trial), concurrent general dietary advice (1 trial), or age (1 trial). One trial found a significantly larger effect on Tg among people also taking a multivitamin. One trial found a larger effect of higher dose EPA+DHA (1.8 g/d) in men than women, but no significant difference between sexes at 0.8 g/d. One trial found no significant difference in effect between people with impaired glucose tolerance and those with noninsulin dependent diabetes, but among those with diabetes, a larger effect was found in those with baseline HDL-c ≤35 mg/dL compared to higher levels.

Observational Studies, Intake

Twenty-one observational studies evaluated associations between total EPA+DHA±DPA intake (regardless of source) and numerous clinical outcomes. Only eight (38%) of these found significant associations with any clinical outcome.

By meta-analysis, overall there is a statistically significant association between marine oil intake and CVD death across a median dose range of 0.066 to 1.58 g/d (effect size per g/d = 0.88; 95% CI 0.82 to 0.95). Meta-analyses with the addition of a spline knot point at different dose thresholds (from 0.1 to 1.2 g/d) consistently found a stronger association (of higher dose being associated with lower risk) at *lower* doses than at higher doses (ES below knot less than 1; ES above knot closer to 1). This implies the possibility of a ceiling effect (where intake above a certain level adds no further benefit). However, at no dose threshold was there a statistically significant difference between the ES below the dose threshold (knot) and above the threshold. The best fit curve was found with a knot at 0.3 g/d. The lowest P value between lower-dose and higher-dose ES estimates was found at 0.2 g/d (P=0.26).

By meta-analysis, overall there no significant association between marine oil intake and CHD death across a median dose range of 0.04 to 2.1 g/d (effect size per g/d = 1.09; 95% CI 0.76 to 1.57). Meta-analyses with the addition of a spline knot point at different dose thresholds (from 0.1 to 1.2 g/d) found stronger associations (of higher dose being associated with lower risk) at lower doses than at higher doses (ES below knot less than 1; ES above knot closer to 1) for knots below 0.7 g/d, but stronger associations at higher doses above 0.7 g/d. However, the differences in effect size between lower and higher doses were always highly nonsignificant, implying no difference in association. The best fit curve was found with a knot at 0.5 g/d. The lowest P value between lower-dose and higher-dose ES estimates was found at the lowest tested threshold, 0.1 g/d (P=0.46).

By meta-analysis, overall there no significant association between marine oil intake and all-cause death across a median dose range of 0.066 to 1.58 g/d (effect size per g/d = 0.62; 95% CI 0.31 to 1.25). However, meta-analyses with the addition of a spline knot point at different dose thresholds (from 0.1 to 1.2 g/d) consistently found stronger associations (of higher dose being associated with lower risk) at *lower* doses than at higher doses (ES below knot less than 1; ES above knot closer to 1). This implies the possibility of a ceiling effect (where intake above a certain level adds no further benefit). For thresholds ≤0.4 g/d the associations are statistically significant at lower doses, but not statistically significant at higher doses. The difference between low- and high-dose associations is statistically significantly different at a threshold of 0.2 g/d (P=0.047). The best fit curve was found with a knot at 0.3 g/d. This analysis may suggest that marine oil intake above about 0.2 to 0.4 g/d may not further strengthen any association between higher marine oil intake and lower rate of all-cause death.

By meta-analysis, overall there no significant association between marine oil intake and CHD across a median dose range of 0.038 to 3.47 g/d (effect size per g/d = 0.94; 95% CI 0.81 to 1.10). Meta-analyses with the addition of a spline knot point at different dose thresholds (from 0.1 to 1.4 g/d) consistently found a stronger association (of higher dose being associated with lower risk) at *lower* doses than at higher doses (ES below knot less than 1, ES above know about 1). At all knot points the differences were nonsignificant. This weakly suggests the possibility of a ceiling effect (where intake above a certain level adds no further benefit). The best fit curve was found with a knot at 0.4 g/d. The P values for differences between lower- and higher-dose knots were between 0.12 and 0.14 at all knots ≥0.3 g/d.

By meta-analysis, overall there is a statistically significant association between marine oil intake and total stroke across a median dosage range of 0.025 to 0.6 g/d (effect size per g/d = 0.68; 95% CI 0.53 to 0.87). Meta-analyses with the addition of a spline knot point at different dose thresholds (from 0.1 to 0.5 g/d) consistently found a much stronger association (of higher dose being associated with lower risk) at *lower* doses than at higher doses (ES below know less than 1; ES above know greater than 1); although, the difference in effect sizes above and below the knots were never statistically significant This implies a possible ceiling effect ceiling effect (where intake above a certain level adds no further benefit). However, given that the differences between lower and higher dose ES remained large across the range of testable dose thresholds, the actual ceiling dose threshold may be above the analyzable range (i.e., >0.5 g/d). The best fit curve was found with the lowest knot at 0.1 g/d. The P values for differences between lower- and higher-dose effect sizes ranged from 0.14 to 0.20.

By meta-analysis, overall there is a statistically significant association between higher marine oil intake and *lower* risk of ischemic stroke across a median dosage range of 0.025 to 0.6 g/d (effect size per g/d = 0.51; 95% CI 0.29 to 0.89). Meta-analyses with the addition of a spline knot point at different dose thresholds (from 0.1 to 0.5 g/d) consistently found a much stronger association (of higher dose being associated with lower risk) at *lower* doses than at higher doses (ES below knot less than 1; ES above knot near or greater than 1). All effect sizes below the knots were statistically significant and all above the knots were nonsignificant. The differences between lower- and higher-dose effect sizes were all statistically significant (P=0.03-0.049). This implies a ceiling effect (where intake above a certain level adds no further benefit). However, it is unclear what the threshold may be, as it may be greater than the highest threshold tested (0.4 g/d). The best fit curve was found with a knot at either 0.3 or 0.4 g/d. The difference between lower-dose and higher-dose ES estimates was statistically significant with a knot at 0.1 g/d.

By meta-analysis, overall there is no significant association between marine oil intake and hemorrhagic stroke across a median dosage range of 0.025 to 0.6 g/d (effect size per g/d = 0.61; 95% CI 0.34 to 1.11). Meta-analyses with the addition of a spline knot point at different dose thresholds (from 0.1 to 0.5 g/d) consistently found similar associations above and below the knots. At no threshold was the difference in effect sizes statistically significant. The best fit curve was found with a knot at 0.1 g/d. The lowest P value between lower-dose and higher-dose ES estimates was found at 0.5 g/d (P=0.78).

By meta-analysis, overall there is a just-significant association between higher marine oil intake and decreased risk of CHF across a median dosage range of 0.014 to 0.71 g/d (effect size per g/d = 0.76; 95% CI 0.58 to 1.00). Meta-analyses with the addition of a spline knot point at different dose thresholds (from 0.1 to 0.5 g/d) consistently found a stronger association (of higher dose being associated with lower risk) at *lower* doses than at higher doses (ES below knot less than 1; ES above knot closer to 1). This implies the possibility of a ceiling effect (where intake above a certain level adds no further benefit). However, given that the differences between lower and higher dose ES remained large across the range of testable dose thresholds, the actual ceiling dose threshold may be above the analyzable range (i.e., >0.5 g/d). At thresholds of 0.1 and 0.2 g/d, the difference in effect size at lower and higher doses were statistically significant (P values 0.04 and 0.03, respectively). But the most significant difference was found at the highest threshold tested, 0.5 g/d (P=0.02). The best fit curve was found with the lowest knot tested, 0.1 g/d.

A minority of studies found significant associations of decreased risk of other outcomes with increasing intake of EPA+DHA±DPA: MACE (1 of 2 studies), all-cause death (1 of 3 studies), CVD death (1 of 4 studies), CHD death (3 of 7 studies), MI (1 of 2 studies), incident CHF (1 of 5 studies), and AFib (1 of 3 studies). No studies found significant associations with cardiac death (1 study), total stroke death (1 study), ischemic stroke death (1 study), coronary revascularization (1 study), ventricular arrhythmia (1 study), SCD (2 studies), and incident hypertension (1 study). One study each analyzed MI death and ischemic stroke death and found a significant association.

Observational Studies, Biomarkers

Five studies evaluated combined EPA+DHA±DPA biomarkers, including adipose tissue, cholesteryl ester, erythrocyte, phospholipid, and plasma n-3 FA levels. Of the outcomes evaluated, none was analyzed by more than two studies. One study each found no significant association between various biomarker levels and MI, hemorrhagic stroke, total stroke (with a P value of 0.07), or cardiac death. One study found a significant association between higher phospholipid EPA+DHA+DPA and incident CHD. Another found a significant association between higher adipose EPA+DHA+DPA and acute coronary syndrome in men, but not in women. Two studies each evaluated CHF, ischemic stroke, and MACE. For each outcome only one of the studies found significant associations with EPA+DHA±DPA biomarker levels. In one of the studies of CHF, phospholipid EPA+DHA+DPA level was associated with the outcome in women only but cholesteryl ester EPA+DHA+DPA levels were not associated in either sex.

EPA

For the most part, there is insufficient evidence regarding the effect of or association with EPA (specifically) and CVD clinical and intermediate outcomes. There is low strength of evidence of no association between EPA intake and CHD and between EPA biomarkers and AFib; no RCTs evaluated these outcomes.

Clinical Event Outcomes, RCTs

Regarding clinical event outcomes, one trial in an at risk population (dyslipidemia), found that after 5 years, compared with placebo, people taking purified EPA 1.8 g/d had significantly lower risk of MACE and angina, but no significant difference in all-cause death, CHD death, coronary revascularization, SCD, or MI (also in the subgroup of people with prior CVD). Subgroup analysis for CHD death found no clear difference between those who also had CVD versus those without CVD.

Intermediate Outcomes, RCTs

Two RCTs evaluated BP or lipid outcomes. One trial of purified EPA 3.8 g/d versus placebo found no significant effect of EPA supplementation on systolic BP, diastolic BP, or MAP. This trial and another of EPA 3.3 g/d found no significant effect of EPA supplementation on LDL-c or HDL-c. Both trials, however, found significant net reductions in Tg concentration (−42 and −23 mg/dL). The trial of EPA 3.8 g/d also found a significant reduction in Total:HDL-c ratio (−0.2).

Observational Studies, Intake

Eight studies evaluated associations between estimated total EPA intake and clinical outcomes. No outcome was evaluated by more than two studies. One study each found no significant association between EPA intake and acute coronary syndrome, ischemic stroke, or total stroke death. One study found a significant association between higher EPA intake and lower ischemic stroke death in healthy adults (in quantiles with median EPA intake >0.07 g/d in men and >0.06 g/d in women), but no association with hemorrhagic stroke death. One study found a significant association between higher EPA intake and lower risk of all-cause death (>0.01 g/d) in healthy adults; another study found a significant association with lower risk of MACE in healthy adults (>0.09 g/d). Two studies, each, found no significant associations between EPA intake and incident CHD (although P=0.06 in one) or CHD death. For both incident hypertension and CVD death, one of two studies found significant associations between higher EPA (0.02 g/d for hypertension and 0.01 g/d for CVD death) intake and lower risk of hypertension and CVD death; the other studies found no such associations.

Observational Studies, Biomarkers

Ten studies evaluated associations between various EPA biomarkers and clinical outcomes. Three studies of healthy adults evaluated incident CHD. Two of these studies found that increased plasma or phospholipid EPA levels were associated with reduced risk of CHD; the third study found no significant association between blood EPA levels and CHD risk. Three studies (two in healthy adults, one in people with hypercholesterolemia) evaluated MACE; the study of people with hypercholesterolemia found an association of reduced MACE risk with higher plasma EPA, as did one study of phospholipid EPA in healthy adults. The third study found no significant association between erythrocyte EPA and MACE in healthy adults. Three studies, two in healthy adults and one in adults with a history of MI, evaluated CHF; in one study of healthy adults, higher plasma EPA was associated with reduced CHF risk, but the other study of healthy adults found no association with phospholipid or cholesteryl ester EPA and CHF risk. The study in people with a history of MI also found an association between higher blood EPA level and lower CHF risk. In this latter study, significant interactions were found for sex (no association was seen in women, in contrast with a significant association in men), statin use (those on statins had no association, in contrast with those not on statins), and baseline HDL-c level (those with higher HDL-c, ≥40 mg/dL, had no association, in contrast with those with lower HDL-c, <40 mg/dL). No interactions were found for age, use of angiotensin receptor blocker drugs, use of beta blocker drugs, diabetes, dyslipidemia, baseline LDL-c, hypertension, glomerular filtration function, or hypertriglyceridemia.

One of three studies found a significant association between higher EPA biomarkers (plasma EPA) and lower risk of death in healthy adults, but a second study of plasma EPA in healthy adults found no such association; nor did a study of blood EPA in people with a history of MI. One of two studies of plasma EPA in healthy adults found a significant association of higher plasma EPA with lower risk of CVD death. Two studies found no significant association between EPA biomarkers and ischemic stroke. One study found a significant association between erythrocyte EPA and incident hypertension. One study each found no associations between EPA biomarker levels and acute coronary syndrome, AFib, SCD, MI, hemorrhagic stroke, total stroke, cardiac death, CHD death, or total stroke death.

DHA

For the most part, there is insufficient evidence regarding the effect of or association with DHA and CVD clinical and intermediate outcomes. There is moderate strength of evidence of no effect of purified DHA supplementation on BP or LDL-c and low strength of evidence of no association between DHA intake and incident CHD (from observational studies only).

Clinical Event Outcomes, RCTs

No trial that reported clinical event outcomes evaluated DHA alone.

Intermediate Outcomes, RCTs

Two trials compared purified DHA (3.6 and 2 g/d) to placebo and found no significant effects on systolic or diastolic BP. One of the trials also found no significant effect on MAP. Three trials of DHA (3.7, 3.6, or 2 g/d) also found no significant effect compared to placebo on LDL-c or HDL-c. Two trials (3.7 and 3.6 g/d) reported on Tg concentration changes and both found significant net reductions compared to placebo with DHA supplementation (−27 and −29 mg/dL). The trial of DHA 3.6 g/d also found a significant reduction in Total:HDL-c ratio (−0.3) compared to placebo.

Observational Studies, Intake

Eight studies evaluated the association between estimated total DHA intake (specifically) and risk of clinical outcomes. No outcome was reported in more than two studies. Two studies found significant associations between higher DHA intake and lower risk of incident hypertension in healthy young adults (18−30 years old in one study; 39−54 year old women in a subgroup of one study), but not in an older subgroup (55−89 years old in one study). In the study of young adults, a significant association was found in quartiles with DHA intake >0.06 g/d compared to quartiles with lower intake. One of two studies of healthy adults found an association of lower CVD death with DHA intake >0.15 g/d. Two studies each found no association with CHD death or incident CHD (in populations with a broad range of ages, from 20−69 to 45−84 years old). One study each found significant associations of higher DHA intake with increased incidence of MACE (>0.15 g/d DHA), ischemic stroke death (>0.15 g/d), and all-cause death (>0.02 g/d). In one study each, no associations were found with acute coronary syndrome, ischemic stroke, hemorrhagic stroke death, or total stroke death.

Observational Studies, Biomarkers

Eleven studies evaluated various DHA biomarkers and their associations with clinical outcomes. Overall, a high proportion of observational studies found statistically significant associations between higher DHA biomarker levels and decreased risk of outcomes. Four studies evaluated MACE (with various definitions); two found significant associations between higher DHA biomarker levels (phospholipid and adipose DHA) and lower risk of MACE in healthy adults. The other two studies found no association, one in hypercholesterolemic adults on statins (plasma DHA) and one in healthy adults (erythrocyte DHA). Two of three studies in healthy adults found significant associations between higher plasma or phospholipid DHA and lower CHD risk; the third study, also in healthy adults, found no association with blood DHA. Three studies evaluated CHF. One found associations between higher cholesteryl ester and phospholipid DHA and lower risk of incident CHF in healthy women, but not healthy men (whether the associations were significantly different between women and men was not reported). One study found that overall, there was no significant association of CHF with blood DHA in adults with a history of MI, but that there were significant associations in subgroups of people, such that significant association between higher blood DHA and lower risk of CHF were found in a population with a history of MI not taking a statin (P interaction with statin use = 0.003), ≥65 years old (P interaction = 0.051), with LDL-c ≥100 mg/dL (P interaction = 0.068), and with HDL-c ≤40 mg/dL (P interaction = 0.096). Three studies also evaluated all-cause death, two of which found significantly lower risk of death with higher plasma DHA (healthy adults) and blood DHA (in people with a history of MI who were not taking statins); another study of healthy adults found no association with plasma DHA.

Two studies found nonsignificant associations between higher cholesteryl ester DHA (P=0.07), phospholipid DHA (P=0.08), and plasma DHA (P=0.052) and lower risk of ischemic stroke in healthy adults. One study of healthy adults found an association between higher plasma DHA and lower risk of CVD death (both studies evaluated plasma DHA). One study each found significant associations between higher DHA biomarker levels and lower incidence of AFib, SCD, and CHD death (all plasma DHA in healthy adults). One study found a significant association between higher adipose DHA and lower risk of acute coronary syndrome in healthy men, but not healthy women. Another study found a significant association between higher erythrocyte DHA and lower risk of incident hypertension in healthy women aged 39 to 54 years, but not in women older than 54 years. One study found no significant associations between plasma DHA and both total stroke and total stroke death in healthy adults. One study, each, found no significant associations with MI, hemorrhagic stroke, or cardiac death.

DPA

Overall, there is insufficient evidence regarding effect of or association between DPA (specifically) and CVD clinical and intermediate outcomes. There is low strength of evidence of no association between DPA biomarker levels and risk of AFib (from observational studies only).

RCTs

No eligible RCTs compared purified DPA formulations versus placebo.

Observational Studies, Intake

Two observational studies evaluated estimated total DPA intake (specifically). One study found no significant association between DPA intake and acute coronary syndrome in either healthy men or women. The other found significant associations between higher DPA intake and both incident CHD and MACE in healthy adults, in both instances with a significant association in the quartile with DPA intake >0.04 g/d.

Observational Studies, Biomarkers

Seven studies evaluated the association of various DPA biomarkers with clinical outcomes, all in healthy adults. No outcome was evaluated by more than three studies. One study in adults age ≥65 years evaluated several clinical outcomes. It found significant associations between higher plasma DPA and lower risks of all-cause and CVD death, nonsignificant associations with incident CHF (P=0.057) and total stroke death (P=0.056), but no significant associations with AFib, SCD, hemorrhagic, ischemic, or total stroke, or CHD death. For both CHD and MACE, one study found a significant association between higher blood DPA and lower incident CHD, but two studies found no association with plasma or phospholipid DPA. Similarly, one study found a significant association between higher adipose tissue DPA and lower MACE risk, but two found no association with phospholipid or erythrocyte DPA. One study evaluated acute coronary syndrome and found a significantly lower risk in men with higher adipose tissue DPA, but no significant association in women. One study evaluated incident hypertension and found a significant association of higher erythrocyte DPA and lower hypertension risk in younger women (39−54 years old), but not older women (55−89 years old). One study found no significant association with cardiac death.

SDA

Overall, there is insufficient evidence regarding effect of or association between SDA (specifically) and CVD clinical and intermediate outcomes.

RCTs

A single study compared 1.2 g/d SDA to placebo in patients at risk for CVD and found no significant differences in change in systolic or diastolic BP, or LDL-c, HDL-c, or Tg at 6 weeks.

Observational Studies

A single eligible observational study in healthy men evaluated baseline erythrocyte SDA and clinical outcomes. Erythrocyte SDA was not significantly associated with either MACE or cardiac death.

Marine Oil FA Comparisons

There is insufficient evidence regarding comparisons of specific marine oil FA (e.g., EPA vs. DHA).

Clinical Event Outcomes, RCTs

No trial that reported clinical event outcomes compared marine oil FA.

Intermediate Outcomes, RCTs

Two trials that compared marine oil FA (EPA 3.8 g/d vs. DHA 3.6 g/d; EPA+DHA 3.4 and 1.7 g/d vs. EPA 1.8 g/d) found no significant differences in effect on BP, LDL-c, HDL-c, Tg, or Total:HDL-c ratio.

One trial compared 2.0 g/d SDA and 1.9 g/d EPA+DHA+DPA in healthy people. At 2 month followup, no significant differences in change in systolic or diastolic BP, or LDL-c, HDL-c, Tg, Total:HDL-c, or LDL:HDL-c ratios were found.

ALA

There is moderate strength of evidence of no significant effect of ALA intake on BP, LDL-c, HDL-c, or Tg. There is low strength of evidence of no association between ALA intake or biomarker level and CHD or CHD death, AFib, and CHF, each based primarily on observational studies; there was only a single or no RCTs evaluating these outcomes. There is insufficient evidence regarding other outcomes.

Clinical Event Outcomes, RCTs

Two RCTs that evaluated ALA supplementation versus placebo reported clinical event outcomes, one in participants with CVD and one in healthy participants. All analyses were nonsignificant, for all-cause death (2 trials) and from one trial each, MACE, CVD death, cardiac death, CHD death, CHF death, total MI, incident angina, total stroke, ventricular arrhythmia, and SCD. Within-study subgroup analyses revealed no significant differences in effect for various subgroups for MACE (1 trial) or with or without diabetes for CHD death (1 trial).

Intermediate Outcomes, RCTs

Five ALA RCTs evaluated BP, with doses ranging from 1.4 to 5.9 g/d for 1 to 3.4 years. All found no significant effect on systolic or diastolic BP, mostly with wide confidence intervals. One of the trials found no significant difference in effect of ALA on BP between a subgroup with hypertension and the study population as a whole. Another trial found no significant difference in effect between 1.4 and 5.9 g/d ALA. No trial reported on MAP.

Five trials reported no significant effects of ALA on LDL-c, HDL-c, Tg, or Total:HDL-c ratio (3 trials). No differences in effect were found in the one trial that compared 1.4 and 5.9 g/d ALA. No trial reported on LDL:HDL-c ratio.

Observational Studies, Intake

Thirteen observational studies evaluated ALA intake. One of these was a pooling of 11 prior studies (the pooled studies were not included in duplicate for the outcomes evaluated by the pooling study). The large majority of analyses found no significant associations; only two studies found any significant associations between higher ALA intake and clinical outcomes.

By meta-analysis, overall there is no statistically significant association between ALA intake and CHD death across a median dose range of 0.59 to 2.5 g/d (effect size per g/d = 0.94; 95% CI 0.85 to 1.03). Meta-analyses with the addition of a spline knot point at different dose thresholds (from 0.6 to 1.2 g/d) consistently found a stronger association (of higher dose being associated with lower risk) at *higher* doses than at lower doses (ES above knot < ES below knot); although the differences were generally small and all were nonsignificant. The best fit curve was found with a knot at 0.9 g/d. The lowest P value between lower-dose and higher-dose ES estimates was found at 1.2 g/d (P=0.44), the highest dose threshold that could be tested.

By meta-analysis, overall there is no association between ALA intake and CHD across a median dosage range of 0.2 to 2.5 g/d (effect size per g/d = 0.97; 95% CI 0.92 to 1.03). Meta-analyses with the addition of a spline knot point at different dose thresholds (from 0.5 to 1.4 g/d) consistently found marginally smaller ES at lower doses than at higher doses. At no dose threshold was there a statistically significant difference between the ES below the dose threshold (knot) and above the threshold. The best fit curve was found with a knot at 0.7 g/d, the threshold that also had the lowest P value (P=0.34).

Two studies both found significant associations between higher ALA intake and reduced all-cause death (>2.2 g/d in healthy adults; also in healthy men but insufficient data were reported regarding a dose threshold). One of two studies found a significant association between higher ALA intake (>0.6 g/d) and lower risk of SCD in healthy women but not in a subset of women with CVD; the second study found no significant association in healthy adults. One of two studies found a significant association between higher ALA intake (unclear threshold) and lower risk of CVD death in younger men (35−57 years old), but another study found no association in older men (≥65 years old). For all other analyzed clinical outcomes, no significant associations were found with ALA intake, including CHF (4 studies), CVD (3 studies), MACE (2 studies), hemorrhagic and ischemic stroke (2 studies each), AFib (1 study), and hypertension (1 study).

Observational Studies, Biomarkers

Eight studies evaluated various ALA biomarkers. Almost all analyses found no significant associations between ALA biomarkers and clinical outcomes. No outcome was evaluated by more than three studies. For CHF, one study found a significant association between higher plasma ALA and CHF in healthy men, but two other studies found no significant associations in healthy adults across levels of plasma, cholesteryl ester, or phospholipid ALA. One of two studies found a significant association between higher plasma ALA and lower risk of CVD death, but the other study found no significant association with plasma ALA in healthy adults. No significant associations were found for ischemic stroke (3 studies), incident CHD, hemorrhagic and total stroke (2 studies each), MACE (2 studies), all-cause death (2 studies), or AFib, SCD, incident hypertension, cardiac death, or CHD death (1 study each).

Marine Oil Versus ALA

There is insufficient evidence of direct comparisons between marine oil and ALA intake on CVD outcomes. Across studies, the indirect comparison between marine oil and ALA is unclear, largely because there are insufficient studies that evaluated ALA. However, for Tg and HDL-c, where there is high strength of evidence of significant effects of higher dose of marine oil improving Tg and HDL-c, there is moderate strength of evidence of no effect of ALA intake on these intermediate outcomes.

Clinical Event Outcomes, RCTs

No trial that reported clinical event outcomes directly compared marine oils and ALA.

Intermediate Outcomes, RCTs

One trial that compared two doses of EPA+DHA (1.7 and 0.8 g/d) with ALA 4.5 g/d found no differences in systolic or diastolic BP at 4 months. Across trials, there was no evidence that intake of any type of n-3 FA had an effect on BP; no difference in effect was apparent between marine oil and ALA trials.

Two trials that compared EPA+DHA (0.8 and 1.7 g/d in one trial, 0.4 g/d in the other) to ALA (4.5 g/d [rapeseed oil margarine] and 2 g/d ["plant oil" margarine], respectively) for 6 months and 3.4 years found no differences between intake of n-3 FA and LDL-c, HDL-c, or Tg levels. Neither trial reported on lipid ratios. No evident differences were found across trials between marine oils and ALA for their (nonsignificant) effects on LDL-c and HDL-c. In contrast with the two trials that directly compared EPA+DHA and ALA, 32 marine oil (versus placebo) trials fairly consistently found significant effect on Tg reduction in contrast with the four ALA (versus placebo) trials, which mostly had imprecise estimates of effects on Tg.

Subgroup Analyses Summary

Overall, 24 RCTs and 9 observational studies reported on subgroup (or factorial) analyses. For most outcomes, there is insufficient evidence regarding differential effects (or associations) in different subgroups of study participants evaluated within studies. Metaregression results across studies are summarized in the summary by n-3 FA, above. (In brief, only for the effect of marine oil on Tg was there an indication across studies of interactions by dose and baseline Tg, with larger effects with higher dose and higher baseline Tg.) Among outcomes with sufficient RCT data to allow meta-analysis, no discernable difference in effect was found across trials based on publication year.

Twenty-two subgroup analyses by sex were reported (10 with ALA, 11 with marine oil, 1 with total n-3 FA). One of three RCTs of marine oil on MACE found a greater beneficial effect of n-3 FA in women (HR [supplement vs. placebo] =0.82 in women vs. 1.04 in men; P interaction = 0.04). One of three observational studies of CHF found a stronger association with between higher blood EPA and lower risk of CHF in men than women (HR [lower intake vs. higher intake] = 5.82 in men vs. 0.69 in women; P interaction = 0.008), but no interaction with blood DHA. One RCT found a stronger effect on lowering Tg of supplementation with higher-dose marine oil (1.8 g/d) in men than in women (difference not reported; P interaction = 0.038), but this interaction was not found with lower-dose marine oil (0.7 g/d). All 19 other analyses were not statistically significant (or no statistical difference was reported).

Twenty subgroup analyses by statin use were reported (1 with ALA, 19 with marine oil). All but one study found difference in effect or association based on statin use. One study found a stronger association between higher blood DHA and, separately, higher blood EPA, and lower risk of CHF in those not using statins; DHA: HR [lower intake vs. higher intake] = 6.65 (without statins) vs. 0.74 (with statins), P interaction = 0.003; EPA: HR [lower intake vs. higher intake] = 6.40 (without statins) vs. 1.45 (with statins), P interaction = 0.048. A relatively small number of RCTs of lipoproteins (LDL-c and HDL-c) and Tg analyzed interactions between n-3 FA and statins and found no interaction between statin use and the effect of marine oil supplementation on lipids (LDL-c 5 RCTs, Tg 4 RCTs, HDL-c 3 RCTs). No studies explicitly compared the interaction of n-3 FA intake (or biomarker level) with aspirin intake on outcomes.

Sixteen subgroup analyses comparing those with and without diabetes were reported (6 with ALA, 10 with marine oil). Two RCT analyses reported only that a statistically significant effect of n-3 FA was found among participants with diabetes but no significant effect was found those without diabetes (marine oil and CHD death, ALA and ventricular arrhythmia). All other analyses reported no difference in effect or association based on diabetes status.

Adverse Events

Of 61 RCTs included in this systematic review, only 4 RCTs of EPA/DHA ethyl ester, 19 RCTs of marine oils (EPA+DHA), 1 RCT of ALA, and 1 RCT comparing total n-3 FA, marine oil, ALA, and placebo reported information on adverse events that may or may not be associated with the interventions. There were no serious adverse events that were considered related to the study interventions in these 25 RCTs. Four of the 20 marine oil RCTs and one of the two ALA trials reported no adverse events. Most of the reported adverse events were mild and transient, such as gastrointestinal discomforts, nausea, skin abnormalities, eczema, pain, allergic reactions, fishy taste, headache, and infection. The most common adverse events related to n-3 FA supplements (that occurred more frequently among those taking supplements) were mild gastrointestinal effects such as belching (0.4-58% [marine oil] vs. 1.7-4% [placebo]; 2 studies), nausea (3.6-8.9% vs. 1.0-5.6%, 2 studies), diarrhea (5.1-8.9% vs. 2.0%, 1 study), or fishy taste (5.3-67% vs. 0-3%, 2 studies), or combined gastrointestinal symptoms (e.g., nausea, diarrhea, or epigastric discomfort) (marine oil: 1.5.0-6% vs. 0.8-4.5%, 7 studies; total n-3 FA: 1.3% vs. 0.8%, 1 study; ALA: 0.8% vs. 0.8%). Only one study explicitly reported on bleeding (hemorrhages such as cerebral and fundal bleedings, epistaxis, and subcutaneous bleeding), finding a higher rate with EPA ethyl ester and statin (1.1%) versus statin alone (0.6%, $P<0.0001$). This study was one of only two trials that reported statistically significantly more adverse events with marine oils than placebo. No study reported statistically significant higher rates of serious or severe adverse events between study arms, and no serious or severe adverse event was attributed to n-3 FA. Six of the marine oil trials explicit stated that most or all adverse events were mild. Three studies reported on the rate of adverse events leading to discontinuation, none of which were reported as statistically significantly different between groups (1.4-17% vs. 0.9-26%).

Summary by Key Question

Key Question 1

What is the efficacy or association of n-3 FA (EPA, DHA, EPA+DHA, DPA, SDA, ALA, or total n-3 FA) exposures in reducing CVD outcomes (incident CVD events, including all-cause death, CVD death, nonfatal CVD events, new diagnosis of CVD, peripheral vascular disease, CHF, major arrhythmias, and hypertension diagnosis) and specific CVD risk factors (BP, key plasma lipids)?

- Total n-3 FA
  - Overall, there is insufficient evidence regarding the effect of or association between total n-3 FA (combined ALA and marine oils) and clinical or intermediate outcomes. There is low strength of evidence of no association between total n-3 FA intake and stroke death, and total (fatal and nonfatal) MI (each association based on longitudinal observational studies of dietary intake).
  - For each outcome there was no consistent (and replicated) significant association between total n-3 FA intake and risk reduction.
- Marine oils
  - There is high strength of evidence of that marine oils statistically significantly lower Tg—possibly with greater effects with higher doses and in people with higher baseline Tg—and statistically significantly raise HDL-c and LDL-c by similar amounts. There is also high strength of evidence that marine oil significantly lowers Total:HDL-c ratio.

  - There is low strength of evidence that marine oil significantly lowers risk of ischemic stroke.
  - There is a high strength of evidence of no effect of marine oil on risk of MACE, all-cause death, SCD, revascularization, and BP; moderate strength of evidence of no effect of marine oil on risk of AFib; and low strength of evidence of no effect of marine oil on risk of CVD death, CHD death, total CHD, MI, angina pectoris, CHF, total stroke, and hemorrhagic stroke. There is insufficient evidence for other outcomes.
- Marine oil, EPA
  - There is insufficient evidence regarding the effect of or association with EPA (specifically) and most CVD clinical and intermediate outcomes. There is low strength of evidence of no association between EPA intake and CHD and between EPA biomarkers and AFib.
- Marine oil, DHA
  - For the most part, there is insufficient evidence regarding the effect of or association with DHA and CVD clinical and intermediate outcomes. There is moderate strength of evidence of no effect of purified DHA supplementation on BP or LDL-c and low strength of evidence of no association between DHA intake and incident CHD (from observational studies).
- Marine oil, DPA
  - Overall, there is insufficient evidence regarding effect of or association between DPA (specifically) and most CVD clinical and intermediate outcomes. There is low strength of evidence of no association between DPA biomarker levels and risk of AFib.
- SDA
  - Overall, there is insufficient evidence regarding effect of or association between SDA (specifically) and CVD clinical and intermediate outcomes.
- ALA
  - There is moderate strength of evidence of no significant effect of ALA intake on BP, LDL-c, HDL-c, or Tg. There is low strength of evidence of no association between ALA intake or biomarker level and CHD or CHD death, AFib, and CHF, each based on observational studies. There is insufficient evidence regarding other outcomes.

Key Question 1, Subquestions

1.1.1. What is the efficacy or association of n-3 FA in preventing CVD outcomes in people without known CVD (primary prevention)?

- There was insufficient evidence for cardiac death, CHF death, ischemic stroke death, hemorrhagic stroke death, revascularization, acute coronary syndrome, angina pectoris, ventricular arrhythmia, incident hypertension, TC/HDL-c ratio, and LDL-c/HDL-c ratio.
- There was insufficient RCT evidence and inconsistent observational evidence for CHD death, MI death, all-cause death, total MI, and SCD.
- There was insufficient RCT evidence but observational evidence of no association for MACE, CVD death, total stroke death, incident CHD, total stroke, ischemic stroke, hemorrhagic stroke, AFib, and CHF.

- There was strong RCT evidence for no effect for BP (systolic and diastolic), MAP (only 3 trials), LDL-c, and HDL-c.
- There was strong RCT evidence for a significant protective effect for Tg.

1.1.2. What is the efficacy or association of n-3 FA in preventing CVD outcomes in people at high risk for CVD (primary prevention)?

- There was insufficient evidence for CVD death, cardiac death, CHD death, MI death, CHF death, total stroke death, ischemic stroke death, hemorrhagic stroke death, incident CHD, revascularization, acute coronary syndrome, angina pectoris, total stroke, ischemic stroke, hemorrhagic stroke, SCD, AFib, ventricular arrhythmia, CHF, incident hypertension and MAP.
- There was inconsistent RCT evidence for total MI.
- There was strong RCT evidence for no effect for MACE, all-cause death, BP (systolic and diastolic), LDL-c, HDL-c, TC/HDL-c ratio, and LDL-c/HDL-c ratio.
- There was strong RCT evidence for a significant protective effect for Tg.

1.1.3. What is the efficacy or association of n-3 FA in preventing CVD outcomes in people with known CVD (secondary prevention)?

- There was insufficient evidence for MI death, CHF death, total stroke death, ischemic stroke death, hemorrhagic stroke death, CHD, acute coronary syndrome, angina pectoris, ischemic stroke, hemorrhagic stroke, ventricular arrhythmia, incident hypertension, MAP, TC/HDL-c ratio, and LDL-c/HDL-c ratio.
- There was inconsistent RCT evidence for CVD death and cardiac death. There was RCT evidence of no effect for MACE, CHD death, all-cause death, total MI, revascularization, total stroke, SCD, AFib, and CHF.
- There was strong RCT evidence of no effect for BP (systolic and diastolic) and LDL-c.
- There was strong RCT evidence of a protective effect for HDL-c and Tg.

1.2. What is the relative efficacy of different n-3 FA on CVD outcomes and risk factors?

- There is low strength of evidence of no difference between EPA+DHA and its individual components.
- There is low strength of evidence of greater efficacy of marine oils over ALA.

1.3. Can the CVD outcomes be ordered by strength of intervention effect of n-3 FA ?

- Based on the summary effect sizes of meta-analyzed RCTs, marine oils had no significant effect on CVD outcomes. The order of effect sizes of CVD outcomes with sufficient data to allow meta-analysis, was MI (ES=0.88), CVD death (ES=0.92), MACE (ES=0.96), all-cause death (ES=0.97), total stroke (ES=0.98), and SCD (ES=1.04).

Key Question 2

n-3 FA variables and modifiers

2.1. How does the efficacy or association of n-3 FA in preventing CVD outcomes and with CVD risk factors differ in subpopulations, including men, premenopausal women, postmenopausal women, and different age or race/ethnicity groups?

- There was insufficient evidence to assess the efficacy or association of n-3 FA in preventing CVD outcomes and with CVD risk factors in subgroups based on race/ethnicity and whether women were pre- or postmenopausal.
- 5 studies (mostly observational) found no significant differences in association based on age, with cutoffs for subgroups ranging between 60 and 70 years of age.
- Two studies found no interaction with age as a continuous variable. One trial found a significant difference in favor of women, two observational studies found a significant difference in favor of men, and 9 studies (mix of RCT and observational) found no difference between men and women.

2.2 What are the effects of potential confounders or interacting factors—such as plasma lipids, body mass index, BP, diabetes, kidney disease, other nutrients or supplements, and drugs (e.g., statins, aspirin, diabetes drugs, hormone replacement therapy)?

- There was insufficient evidence to assess the following potential confounders or interacting factors: beta-blocker use, baseline HDL-c, glargine use, nitrate use, digoxin use, diuretic use, eGFR, ACEi use, anticoagulant use, total cholesterol levels, or use of fish oil supplements.
- There was inconsistent evidence for the following potential confounders or interacting factors: Tg levels, statin use, b-vitamin use, and baseline LDL-c.
- There was evidence of no interactions with body mass index, hypertension status, diabetes status, and baseline TC/HDL-c ratio.

2.3 What is the efficacy or association of different ratios of n-3 FA components in dietary supplements or biomarkers on CVD outcomes and risk factors?

- No study directly compared efficacy or association of different ratios of n-3 FA components on outcomes. Across studies, there were insufficient data to make these assessments.

2.4 How does the efficacy or association of n-3 FA on CVD outcomes and risk factors differ by ratios of different n-3 FA—DHA, EPA, and ALA, or other n-3 FA?

- No study directly compared efficacy or association of different ratios of n-3 FA components on outcomes. Across studies, there were insufficient data to make these assessments.

2.5 How does the efficacy or association of n-3 FA on CVD outcomes and risk factors differ by source (e.g., fish and vs. seafood, common plant oils (e.g., soybean vs,, canola), fish oil supplements, fungal-algal supplements, flaxseed oil supplements)?

- No study directly compared efficacy or association of different sources of n-3 FA on outcomes. Across studies, there were insufficient data to make these assessments.

2.6 How does the ratio of n-6 FA to n-3 FA intakes or biomarker concentrations affect the efficacy or association of n-3 FA on CVD outcomes and risk factors?

- No trial or observational studies evaluated n-6 FA to n-3 FA intake concentrations and no differences across studies by this ratio was evident.

2.7 Is there a threshold or dose-response relationship between n-3 FA exposures and CVD outcomes and risk factors? Does the study type affect these relationships?

- Among trials, for all clinical CVD outcomes there is insufficient evidence regarding a dose-response relationship within or between trials.
- For BP, LDL-c, and HDL-c, trials do not find significant differences in effect by marine oil dose either within or between trials.
- Trials comparing marine oil doses mostly found no significant difference between higher and lower dose marine oils. However, a possible pattern could be discerned such that higher doses of 3.4 or 4 g/d reduced Tg by at least 30 mg/dL more than lower doses of 1 to 2 g/d. Higher doses ≤3 g/d (1.7−3 g/d) yielded much smaller relative differences in Tg change compared to lower doses (0.7−2.25 g/d). By metaregression, each increase of EPA+DHA dose by 1 g/d was associated with a greater net change Tg of −5.9 mg/dL (95% CI −9.9 to−2.0; P=0.003); no inflection point was found above which the association plateaued.
- Metaregressions of observational studies yielded the following conclusions:
    - For all-cause death, there may be a ceiling effect at about 0.2 g/d, such that increasing marine oil intake up to this level may be associated with lower all-cause death, but increasing intake above this level may not be associated with further decreased risk.
    - For total stroke, ischemic stroke, and CHF, at lower ranges of intake there were statistically significant associations between higher marine oil intake level and lower risk of outcome, in contrast to associations found at higher ranges of intake. However, the associations at lower and higher doses were not statistically significant from each other. For ischemic stroke, associations between higher doses and risk of stroke were stronger and statistically significant across lower doses than at higher doses (with thresholds between lower and higher doses from 0.1 and 0.4 g/d) and the differences in associations between lower and higher doses were statistically significant. Any dose inflection point that may exist is likely to be beyond the range of testable thresholds (i.e., >0.4 g/d). Similarly, for CHF significant associations were found at lower doses, in contrast to at higher doses, with thresholds ranging from 0.1 to 0.5 g/d, and the differences were statistically significant at most thresholds. Any dose inflection point that may exist is likely to be beyond the range of testable thresholds (i.e., >0.5 g/d).
    - For CVD death, CHD death, total CHD, and hemorrhagic stroke, there were no apparent differences in association between marine oil intake dose and outcome at lower or higher dose ranges.
    - For CHD death and CHD, there were no apparent differences in association between ALA intake dose and outcome at lower or higher dose ranges.

2.8 How does the duration of intervention or exposure influence the effect of n-3 FA on CVD outcomes and risk factors?

- None of the meta-regressions found a significant interaction for follow-up time. No difference in effect was found within studies at different durations of intervention. Observational studies did not evaluate differences in duration of exposure.

2.9 What is the effect of baseline n-3 FA status (intake or biomarkers) on the efficacy of n-3 FA intake or supplementation on CVD outcomes and risk factors?

- No study found a significant difference in subgroups based on baseline fish or n-3 FA intake.

Key Question 3

Adverse events

3.1 What adverse effects are related to n-3 FA intake (in studies of CVD outcomes and risk factors)?

- No serious or severe adverse events were related to n-3 FA intake (supplementation). Most reported adverse events were mild and gastrointestinal in nature; however, only 2 of 25 trials reported statistically significant differences in adverse events between n-3 FA supplements and placebo.

3.2 What adverse events are reported specifically among people with CVD or diabetes (in studies of CVD outcomes and risk factors)?

- Among 10 trials of patients with CVD (9 with marine oil, 1 with total n-3 FA, 2 with ALA), either no adverse events or no significant difference between n-3 FA and placebo were reported.
- A single study reported adverse events from a trial of people with diabetes, finding no significant differences in serious or nonserious adverse events between marine oil and placebo.

Discussion

Overall Summary of Key Findings

In this systematic review we identified 61 eligible RCTs (in 82 publications) and 37 eligible prospective longitudinal studies (in 65 publications) for inclusion, based on prespecified eligibility criteria. Most of the RCTs evaluated the effects of marine oil supplements (EPA+DHA) compared with placebo on clinical CVD outcomes in populations at risk for CVD or with CVD, while most of the observational studies examined the associations between intake of various individual n-3 FA, alone and in combination with each other, in relation to long-term CVD events in generally healthy populations. The RCTs of intermediate CVD outcomes (BP and lipids) were conducted in all three populations of interest (generally healthy, at risk for CVD—primarily due to dyslipidemia, or with CVD). However, none of the observational studies evaluated BP or lipids.

The main findings of the studies, regarding effect or association of higher n-3 FA intake or biomarker level and outcomes are summarized in the following tables. Table A includes analyses of n-3 FA and outcome pairs for which there is evidence to support an effect or association of higher n-3 FA intake and risk of a CVD outcome or on a CV risk factor. These include high strength of evidence that higher marine oil intake statistically significantly raises HDL-c, lowers Tg concentration and Total:HDL-c ratio, but also raises LDL-c. There is low strength of evidence that higher marine oil intake is associated with lower risk of ischemic stroke.

Table B includes analyses of n-3 FA and outcome pairs for which there is evidence supporting no effect or association of n-3 FA intake (or biomarker level) and outcomes. These include high strength of evidence for no effect of or association between marine oil intake and MACE, all-cause mortality, SCD, coronary revascularization, or BP; moderate strength of evidence of no association between marine oil intake and AFib, and between DHA intake and BP or LDL-c, and between ALA and BP, LDL-c, HDL-c, or Tg; and low strength of evidence of no association between total n-3 FA intake and stroke death or MI; between marine oil intake and CVD death, CHD death, total CHD, MI, angina pectoris, CHF, total stroke or hemorrhagic stroke; between EPA intake and CHD; between EPA biomarkers and AFib; between DHA intake and CHD; between DPA biomarkers and AFib; and between ALA intake and CHD, CHD death, AFib, or CHF. Analyses of n-3 FA and outcome pairs not included in the table provided insufficient evidence.

In brief, 61 RCTs and 37 longitudinal observational studies were included. Most RCTs and observational studies had few risk of bias concerns.

- **Total n-3 FA** (EPA+DHA+ALA):
    - There is low strength of evidence of no association between total n-3 FA intake and stroke death or MI.
    - There is insufficient evidence for other outcomes.
- **Marine oils, total** (primarily EPA+DHA):
    - There is high strength of evidence that higher marine oil intake lowers Tg, raises HDL-c, lowers Total:HDL-c ratio, but raises LDL-c; also moderate or high strength of evidence that higher marine oil intake does not affect MACE, all-cause death, SCD, coronary revascularization, AFib, or BP.
    - There is low strength of evidence of associations between higher marine oil intake and decreased risk of ischemic stroke. There is low strength of evidence of no association with CVD death, CHD death, total CHD, MI, angina pectoris, CHF, total stroke, or hemorrhagic stroke.
    - There is insufficient evidence for other outcomes.
- **Marine oil FA (EPA, DHA, DPA)**, individually:
    - There is moderate strength of evidence of no effect of purified DHA supplementation (intake) and altering BP or LDL-c.
    - There is low strength of evidence of no associations between EPA or DHA intake (separately) and CHD, and between EPA or DPA biomarkers and AFib.
    - There is insufficient evidence for other specific marine oil FA (EPA, DHA, DPA, or SDA) and outcomes.
- **ALA**:
    - There is moderate strength of evidence of no effect of ALA intake on BP, LDL-c, HDL-c, or Tg.
    - There is low strength of evidence of no association between ALA intake or biomarker level and CHD, CHD death, AFib, and CHF.
    - There is insufficient evidence for other outcomes.

- **Other n-3 FA analyses**:
    - There is insufficient evidence comparing n-3 FA to each other.
- **Subgroup analyses**:
    - 19 of 22 studies found no interaction of sex on any effect of n-3 FA.
    - 19 of 20 studies found no differential effect by statin co-use.
    - Within 16 studies evaluating diabetes subgroups, 2 found statistically significant beneficial effects of n-3 FA in those with diabetes, but not in those without diabetes, but no test of interaction was reported.

The 61 RCTs mostly compared marine oil supplements to placebo on CVD outcomes in populations at risk for CVD or with CVD, while the 37 observational studies mostly examined associations between various individual n-3 FA and long-term CVD events in generally healthy populations. Compared to the prior report on n-3 FA and CVD, there is more robust RCT evidence on ALA and on clinical CV outcomes; also, by design there are newly added data on associations between n-3 FA biomarkers and CV outcomes. However, conclusions regarding the effect of n-3 FA intake on CV outcomes or associations with outcomes remain substantially unchanged. Future RCTs would be needed to establish adequate evidence of the effect of n-3 FA on CVD outcomes or to clarify differential effects in different groups of people.

Studies within each category of analysis (by study design and by n-3 FA) were diverse, due to differences in outcomes evaluated, definitions of specific outcomes, as well as the n-3 FA intervention doses or compositions (for RCTs) or the dietary/biomarker n-3 FA exposure assessments and quantifications (for observational studies). Overall we found a lack of conclusive or consistent findings for CVD events within RCTs, mostly due to sparse data and underpowered trials as indicated by wide confidence intervals. The majority of the individual RCTs did not find statistically significant effects of marine oil supplements (EPA+DHA, various doses) on CVD outcomes. Pooled meta-analyses suggest that people with CVD or at risk for CVD who received marine oil supplements may have a small risk reduction in CVD death (pooled HR 0.92; 95% CI 0.82 to 1.02) compared with those who received placebo. Across outcomes, the effects of marine oil supplements were often larger in earlier RCTs than in more recent RCTs. These data may be confounded by shifts over time in concomitant therapy to reduce CVD risk (e.g., statins, aspirin), decreasing smoking rates, and overall declining rates of CVD events. No meta-regression across studies found significant changes in effect sizes by publication year; however, it is likely that all such meta-regressions of clinical outcomes were underpowered due to relatively small numbers of trials.

Observational studies were mixed regarding the associations between n-3 FA intake or biomarkers and risk of MACE (where each study used its own combination of specific CVD outcomes). The strength of associations between higher levels of n-3 FA and lower risk of CVD outcomes, when found, were often larger than those in RCTs. While all observational studies adjusted associations for potentially confounding variables, the specific variables included in models varied greatly across observational studies. Furthermore, all observational studies compared higher intake levels of n-3 FA with lowest intake level, which included people who may have other nutrition deficiencies that may affect chronic disease risks but often cannot be "controlled for" in the analyses (resulting in residual, uncontrolled confounding).

Table A. Main findings of high, moderate, or low strength of evidence of significant effects or associations between omega-3 fatty acids and outcomes

There is **high** strength of evidence for the following effects or associations of *higher* n-3 FA intake or biomarker levels and *lower* cardiovascular disease (CVD) risks or events:

- Marine oil* supplementation (or increased intake) and an increase in HDL-c
  - RCTs (of mostly supplements)
  - Summary net change in HDL-c: 0.9 mg/dL (95% CI 0.2, 1.6)
- Marine oil* supplementation (or increased intake) and a decrease in Tg
  - RCTs (of mostly supplements)
  - Summary net change in Tg: −24 mg/dL (95% CI −31, −18)
- Marine oil* supplementation (or increased intake) and a decrease in total cholesterol to HDL-c ratio
  - RCTs (of mostly supplements)
  - Summary net change in Total:HDL-c ratio: −0.17 (95% CI −0.26, −0.09)

There is **high** strength of evidence for the following effects or associations of *higher* n-3 FA intake or biomarker levels and *higher* CVD risk:

- Marine oil* supplementation (or increased intake) and an increase in LDL-c
  - RCTs (of mostly supplements)
  - Summary net change in LDL-c: 2.0 mg/dL (95% CI 0.4, 3.6)

There is **low** strength of evidence for the following effects or associations of *higher* n-3 FA intake and *lower* CVD risks or events:

- Marine oil* higher dietary intake and a lower risk of ischemic stroke
  - Observational studies (of total dietary intake), significant by metaregression: 0.51 (95% CI 0.29, 0.89) per g/d

*Statements about "marine oil" are based on all evidence of analyses of EPA+DHA+DPA, EPA+DHA, EPA, DHA, and DPA as supplements (e.g., fish oil) or as components of dietary intake (e.g., from fatty fish).

Abbreviations: CHD = coronary heart disease (also known as coronary artery disease), CHF = congestive heart failure, CI = confidence interval, CVD = cardiovascular disease, DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, EPA = eicosapentaenoic acid, HDL-c = high density lipoprotein cholesterol, HR = hazard ratio, LDL-c = low density lipoprotein cholesterol, n-3 FA = omega-3 fatty acids, RCT = randomized controlled trial, Tg = triglycerides.

Table B. Main findings of high, moderate, or low strength of evidence of no significant effects or associations between omega-3 fatty acids and outcomes

There is **high** strength of evidence of *no effect or association* of n-3 FA intake or biomarker level and the following outcomes:

- Marine oil* supplementation (or increased dietary intake) and risk of major adverse cardiovascular event (MACE)
  - RCTs (of mostly supplements); observational studies (of total dietary intake) also found no significant associations
  - Summary effect size (RCTs): 0.96 (95% CI 0.91, 1.02)
- Marine oil* supplementation (or increased dietary intake) and all-cause death
  - RCTs (of mostly supplements) supported by observational studies (of total dietary intake)
  - Summary effect size (RCTs): 0.97 (95% CI 0.92, 1.03)
  - Observational studies (of total dietary intake): 0.62 (95% CI 0.31, 1.25) per g/d
- Marine oil* supplementation (or increased dietary intake) and sudden cardiac death (SCD)
  - RCTs (of mostly supplements) supported by an observational study (of total dietary intake)
  - Summary effect size (RCTs): 1.04 (95% CI 0.92, 1.17)
- Marine oil* supplementation (or increased dietary intake) and coronary revascularization
  - RCTs (of mostly supplements) supported by an observational study (of total dietary intake)
- Marine oil* supplementation (or increased dietary intake) and systolic or diastolic blood pressure
  - RCTs (of mostly supplements)
  - Summary net change in systolic blood pressure: 0.1 mg/dL (95% CI −0.2, 0.4)
  - Summary net change in diastolic blood pressure: −0.2 mg/dL (95% CI −0.4, 0.5)

There is **moderate** strength of evidence of *no effect or association* of n-3 FA intake or biomarker level and the following outcomes:

- Marine oil* supplementation (or increased dietary intake) and atrial fibrillation
  - RCTs (of mostly supplements); observational studies of intake were inconsistent
- Purified DHA supplementation and systolic or diastolic blood pressure
  - RCTs (of supplements only)
- Purified DHA supplementation and LDL-c
  - RCTs (of supplements only)
- ALA supplementation (or increased dietary intake) and systolic or diastolic blood pressure
  - RCTs (of mostly supplements)
- ALA supplementation (or increased dietary intake) intake and LDL-c, HDL-c, and Tg
  - RCTs (of mostly supplements)

Table B. Main findings of high, moderate, or low strength of evidence of no significant effects or associations between omega-3 fatty acids and outcomes (continued)

There is **low** strength of evidence of *no effect or association* of n-3 FA intake or biomarker level and the following outcomes:

- Total n-3 FA higher dietary intake and stroke death
    - Observational studies (of total dietary intake and biomarkers)
- Total n-3 FA higher dietary intake and myocardial infarction
    - Observational studies (of total dietary intake)
- Marine oil* supplementation (or increased dietary intake) and cadiovascular disease (CVD) death
    - Summary effect size (RCTs): 0.92 (95% CI 0.82, 1.02)†
    - Observational studies (of total dietary intake): 0.88 (95% CI 0.82, 0.95) per g/d
- Marine oil* supplementation (or increased dietary intake) and coronary heart disease (CHD) death
    - RCTs (of mostly supplements) imprecise
    - Observational studies (of total dietary intake): 1.09 (95% CI 0.76, 1.57) per g/d
- Marine oil* higher dietary intake and coronary heart disease (CHD)
    - Observational studies (of total dietary intake), supported by a single study of n-3 FA biomarkers
    - Observational studies (of total dietary intake): 0.94 (95% CI 0.81, 1.10) per g/d
- Marine oil* supplementation (or increased dietary intake) and myocardial infarction
    - Summary effect size (RCTs): 0.88 (95% CI 0.77, 1.02)†
- Marine oil* supplementation and angina pectoris
    - RCTs (of supplements) with heterogeneous outcomes (definitions of angina pectoris)
- Marine oil* supplementation (or increased dietary intake) and congestive heart failure (CHF)
    - RCTs (of mostly supplements) imprecise and could not be meta-analyzed, all nonsignificant
    - Observational studies (of total dietary intake) significant by metaregression: 0.76 (95% CI 0.58, 1.00) per g/d ($P<0.05$)
- Marine oil* supplementation (or increased dietary intake) and total stroke (fatal and nonfatal ischemic and hemorrhagic stroke)
    - Summary effect size (RCTs): 0.97 (95% CI 0.83, 1.13)
    - Observational studies (of total dietary intake): 0.68 (95% CI 0.53, 0.87) per g/d
- Marine oil* higher dietary intake and hemorrhagic stroke
    - Observational studies (of total dietary intake): 0.61 (95% CI 0.34, 1.11) per g/d
- EPA higher dietary intake and CHD
    - Observational studies (of total dietary intake)
- EPA higher biomarker levels and atrial fibrillation
    - Observational studies (of biomarkers)
- DHA higher dietary intake and CHD
    - Observational studies (of total dietary intake and biomarkers)
- DPA higher biomarker levels and atrial fibrillation
    - Observational studies (of biomarkers)
- ALA higher dietary intake and CHD death and, separately, total CHD
    - Observational studies (of total dietary intake); CHD death finding supported by one RCT (of supplementation) and one observational study of biomarkers
    - Observational studies (of total dietary intake): CHD death 0.94 (95% CI 0.85, 1.03) per g/d
    - Observational studies (of total dietary intake): CHD 0.97 (95% CI 0.92, 1.03) per g/d
- ALA higher dietary intake and atrial fibrillation
    - Observational studies (of total dietary intake and biomarkers)
- ALA supplementation (or increased dietary intake) and CHF
    - Observational studies (of total dietary intake and biomarkers), supported by one RCT (of supplementation)

* Statements about "marine oil" are based on all evidence of analyses of EPA+DHA+DPA, EPA+DHA, EPA, DHA, and DPA as supplements (e.g., fish oil) or as components of dietary intake (e.g., from fatty fish).
† There is low confidence that this summary estimate would remain suggestive of no effect with the addition of future trial data (and greater statistical power).

Abbreviations: ALA = alphalinolenic acid, CHD = coronary heart disease, CHF = congestive heart failure, DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, EPA = eicosapentaenoic acid, HDL-c = high density lipoprotein cholesterol, LDL-c = low density lipoprotein cholesterol, MACE = major adverse cardiovascular event (including cardiac and stroke events and death; variously defined by studies), n-3 FA = omega-3 fatty acids, RCT = randomized controlled trial, SCD = sudden cardiac death, Tg = triglycerides.

The overall findings for the effects of marine oil supplements on intermediate CVD outcomes remain largely unchanged since the original report. In this update, there were no significant effects found in 22 RCTs that compared marine oils (0.3−6 g/d) on systolic or diastolic BP compared with placebo. Thirty-nine RCTs evaluated LDL-c and HDL-c. Meta-analyses of the effect of marine oils on HDL-c and LDL-c found small, but statistically significant amounts (summary net change HDL-c = 0.9 mg/dL [95% CI 0.2 to 1.7]; LDL-c = 2.0 mg/dL [95% CI 0.4 to 3.6]). The clinical significance of these small increases in both HDL-c and LDL-c on CVD outcomes, particularly in combination, is unclear. For both lipid outcomes, no differences in effect across studies were found by marine oil dose, followup duration or population. The strongest effect of marine oils (0.3−6 g/d) was found among the 41 RCTs of Tg. Meta-analysis found a summary net change of −24 mg/dL (95% CI −31 to −18), with no significant difference in effect based on population or followup time across studies. However, across trials, the effect was dose-dependent and also dependent on the studies' mean baseline Tg values. By metaregression, each increase of EPA+DHA dose by 1 g/d was also associated with a greater net change Tg of −5.9 mg/dL (95% CI −9.9 to −2.0) and each increase in mean baseline Tg level by 1 mg/dL was associated with a greater net change Tg of −0.15 mg/dL (95% CI −0.22 to −0.08). However, the few trials that directly compared marine oil doses did not consistently find consistently find a dose effect; although, marine oil doses ≥3 g/d all resulted in larger reductions in Tg compared to lower doses, in contrast to doses <3 g/d which had smaller reductions in Tg compared to even lower doses. There were no observational studies evaluating these intermediate CVD outcomes.

In the original report, there was only one RCT of ALA (linseed oil) versus control oil (sunflower seed oil), conducted in the 1960s, that evaluated clinical event outcomes. In this update we identified only one additional RCT of ALA (plant source not reported) versus placebo (oleic acid) in participants with a history of MI that reported clinical outcomes. Given the sparseness of trials of the effect on clinical CVD outcomes of higher ALA intake and the differences between the two trials, no conclusion can be drawn regarding effect of ALA on CVD outcomes. For intermediate outcomes, five ALA RCTs (with doses ranging from 1.4 to 5.9 g/d) evaluated BP outcomes, and four of the five RCTs also evaluated LDL-c, HDL-c, Tg, or Total:HDL-c ratio (2 trials) outcomes. All found no significant differences in these outcomes between ALA and placebo. Thirteen observational studies evaluated ALA intake. The large majority of analyses found no significant associations; only two studies found any significant associations between higher ALA intake and clinical outcomes (reduced all-cause death, SCD, and CHD death risks).

The potential intake threshold-effects of n-3 FA on CVD events could not be determined from the RCTs because there were limited number of RCTs for many outcomes and most RCTs did not find significant effects. Using data from observational studies, the linear dose-response and potential threshold effects of n-3 FA on several CVD events were tested by meta-analytical techniques. There was a significant association between higher EPA and DHA intake and lower risk of ischemic stroke across a median dosage range of 0.025 to 0.6 g/d (effect size per g/d = 0.51; 95% CI 0.29 to 0.89), but no dose-response relationships found between EPA and DHA intake and both CHD and hemorrhagic stroke. The interpretations of the threshold-effects (in observational studies) were limited because differences in associations at lower doses (statistically significant associations between higher intake and lower risk) and associations at higher doses (no significant associations between intake and outcome) were generally similar regardless of the cut point chosen between lower and higher dose analyses.

No differences in effects or associations were found between different populations (healthy or general population, at increased risk for CVD—largely due to dyslipidemia, or with CVD). However, this conclusion is weak given that few studies compared populations, few RCTs were conducted in healthy populations and few observational studies were conducted in at risk or CVD populations.

Limitations

Overall, both RCTs and observational studies (i.e., longitudinal observational and nested case-control studies) included in this systematic review generally had few risk of bias concerns. For clinical CVD outcomes, all but one of the RCTs was conducted in either high risk individuals or people with existing CVD. In contrast, most observational studies examining the associations between dietary n-3 FA intake or biomarkers of n-3 FA intake and clinical outcomes were conducted in generally healthy populations. Few trials compared n-3 FA dose, formulation, or source. No trial compared different n-3 to n-6 FA ratios of supplements or intake. None of the observational studies attempted to determine a threshold effect of any associations between n-3 FA and the outcome of interest.

There are numerous differences between RCTs and observational studies, making the comparisons across the two study designs difficult to make. Of note, the doses of marine oil supplements (EPA+DHA) in RCTs were often much higher than the highest intake reported for observational studies. Furthermore, not all observational studies explicitly included n-3 FA supplements in their assessment of intake and very few of the RCTs attempted to account for background fish or n-3 FA intake as an effect modifier.

While this report represents a complete systematic review, it does not encompass all trials or longitudinal observational studies that report on CVD and intermediate outcomes. Particularly, if one includes small studies (trials with <30 participants per study group or observational studies with <100 participants, several hundred more studies could potentially have met eligibility criteria. Due to time and resource limitations, we restricted the review to the approximately 100 studies that are most likely to have adequately addressed the primary research questions of interest.

Future Research Recommendations

Future RCTs should fully characterize both the preparations of n-3 FA interventions and placebos used for the intervention in terms of the FA composition and molecular form of the FA (e.g., ethyl esters, Tg), as well as indicating their sources. The placebo foods and oils should have the same caloric density and to the extent possible similar food or oil types as the source of n-3 FA. The composition of the background diet should also be reported, as should FA composition, macronutrient content and whether the participants were weight-stable. Researchers are encouraged to use standard, common CVD outcomes to allow comparison across studies. Assessment of n-3 FA status and intake should be evaluated at study entry and post-intervention in all study participants using to better understand potential changes in n-3 FA intake in populations with different background diets (e.g., whether the effect of supplementation differs in people with high- or low-fish diets). If trials include participants with a broad range of n-3 FA status or intake (e.g., with both high- and low-fish diets), subgroup analyses should be conducted to evaluate possible differential effects based on n-3 these variables. The effects (or lack thereof) of marine oils (EPA+DHA) on BP, LDL-c, HDL-c, and Tg are well established so additional

RCTs on these intermediate outcomes alone are unlikely to add any new knowledge, and therefore are not recommended.

There is an ongoing need to improve self-reported dietary assessment methods and food databases for all nutrients including n-3 FA. As national dietary patterns shift and new processed foods are introduced into the marketplace, food composition tables used to analyze food frequency questionnaire data need to be updated to ensure accurate estimation of n-3 FA (and other nutrient) intake. Similar to trial registries, a data repository for raw observational study data would greatly improve the transparency of data analyses (potentially reduce both reporting and publication biases) and the appropriateness and methodology of meta-analytical techniques for pooling observational studies. An individual participant-level meta-analysis of observational studies of marine oils could address limitations of the study-level meta-analyses that are currently feasible.

Conclusions

Results from the RCTs of clinical event outcomes are applicable only to at-risk-of-CVD and CVD populations because there is insufficient trial evidence of the effect of n-3 FA on clinical CVD outcomes in healthy populations. Results from the RCTs of intermediate outcomes; however, are applicable to all populations (healthy, at risk, and with CVD) since the trials included a range of people from the different populations. In contrast, results from observational studies (which did not evaluate intermediate outcomes) are applicable only to generally healthy populations. We graded the strength of the body of evidence for each intervention/exposure and comparison of intervention, and for each outcome by assessing the number of studies, their study designs, the study limitations (i.e., risk of bias and overall methodological quality), the directness of the evidence to the Key Questions, the consistency of study results, the precision of any estimates of effect, the likelihood of reporting bias, and the overall findings across studies. We concluded that there is insufficient evidence regarding the effect of or association between total n-3 FA (ALA + marine oils [EPA+DHA±DPA]) and clinical or intermediate outcomes. There is low strength of evidence of no association between total n-3 FA intake and stroke death, and total MI (each association based on longitudinal observational studies). For marine oil (EPA+DHA±DPA), there is insufficient evidence for most outcomes of interest but there is low to high strength of evidence of a beneficial effect of higher marine oil intake for selected CVD and intermediate outcomes. Specifically, there is high strength of evidence that marine oils clinically and statistically significantly lower Tg—possibly with greater effects with higher doses and in people with higher baseline Tg. There is also high strength of evidence that marine oils statistically, but arguably not clinically, significantly raise both HDL-c and LDL-c. There is also high strength of evidence that marine oil significantly lowers Total:HDL-c ratio. There is low strength of evidence that marine oil supplementation lowers risk of ischemic stroke. There is a high strength of evidence of no effect of marine oil on risk of MACE, all-cause death, sudden cardiac death, coronary revascularization, and blood pressure; moderate strength of evidence of no effect of marine oil on risk of atrial fibrillation; and low strength of evidence of no associations of marine oil intake and cardiovascular death, CHD death, CHD, myocardial infarction, angina pectoris, CHF, total stroke, or hemorrhagic stroke.

For individual n-3 FA, there is insufficient evidence regarding the effect of or association with EPA, DHA, DPA, SDA, or ALA (specifically) and most CVD clinical outcomes. For EPA, there is low strength of evidence of no association between EPA intake and CHD and between EPA biomarkers and AFib. For DHA, there is moderate strength of evidence of no effect of purified DHA supplementation on BP or LDL-c and low strength of evidence of no association between DHA intake and incident CHD (from observational studies). For DPA, there is low strength of evidence of an association between higher DPA biomarker levels and lower risk of AFib. For ALA, there is moderate strength of evidence of no significant effect of ALA intake on BP, LDL-c, HDL-c, or Tg. There is low strength of evidence of no association between ALA intake or biomarker level and CHD or CHD death, AFib, or CHF, based on observational studies.

There is insufficient evidence of direct comparisons between marine oil and ALA intake on CVD outcomes. Across studies, the indirect comparison between marine oil and ALA is unclear, largely because there is insufficient evidence regarding the effect or association of ALA with clinical CVD outcomes. However, where there is high strength of evidence of significant effects of marine oil on improving Tg and HDL-c, there is moderate strength of evidence of no effect of ALA intake on these intermediate outcomes. No RCTs examined the additive effects of n-3 FA versus the effects of individual n-3 FA.

References

1. Bang HO, Dyerberg J, Hjoorne N. The composition of food consumed by Greenland Eskimos. Acta medica Scandinavica. 1976;200(1-2):69-73. PMID: 961471.

2. Balk E, Chung M, Lichtenstein A, et al. Effects of omega-3 fatty acids on cardiovascular risk factors and intermediate markers of cardiovascular disease. Evid Rep Technol Assess (Summ). 2004 Mar(93):1-6. PMID: 15133887.

3. Wang C, Chung M, Lichtenstein A, et al. Effects of omega-3 fatty acids on cardiovascular disease. Evid Rep Technol Assess (Summ). 2004 Mar(94):1-8. PMID: 15133888.

4. Report of the Joint FAO/WHO Expert Consultation on the Risks and Benefits of Fish Consumption. Food and Agriculture Organization of the United Nations; Geneva: World Health Organization Rome; 2011.

5. Institute of Medicine, Panel on Micronutrients. Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein and Amino Acids. Panel on Macronutrients Panel on the Definition of Dietary Fiber, Subcommittee on Upper Reference Levels of Nutrients, Subcommittee on Interpretation and Uses of Dietary Reference Intakes, and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board: National Academies Press; 2005.

6. McGuire S. US Department of Agriculture and US Department of Health and Human Services, Dietary Guidelines for Americans, 2010. Washington, DC: US Government Printing Office, January 2011. Adv Nutr. 2011;2(3):293-4.

7. Institute of Medicine. Seafood Choices: Balancing Benefits and Risks. Nesheim MC, Yaktine AL, editors. Washington, DC: The National Academies Press; 2007.

8. Harika RK, Eilander A, Alssema M, et al. Intake of fatty acids in general populations worldwide does not meet dietary recommendations to prevent coronary heart disease: a systematic review of data from 40 countries. Ann Nutr Metab. 2013;63(3):229-38. PMID: 24192557.

9. Hodson L, Skeaff CM, Fielding BA. Fatty acid composition of adipose tissue and blood in humans and its use as a biomarker of dietary intake. Prog Lipid Res. 2008 Sep;47(5):348-80. PMID: 18435934.

10. Serra-Majem L, Nissensohn M, Overby NC, et al. Dietary methods and biomarkers of omega 3 fatty acids: a systematic review. Br J Nutr. 2012 Jun;107 Suppl 2:S64-76. PMID: 22591904.

11. Fekete K, Marosvolgyi T, Jakobik V, et al. Methods of assessment of n-3 long-chain polyunsaturated fatty acid status in humans: a systematic review. Am J Clin Nutr. 2009 Jun;89(6):2070S-84S. PMID: 19420097.

12. Methods guide for effectiveness and comparative effectiveness reviews: Agency for Healthcare Research and Quality; 2011.

13. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ (Clinical research ed). 2011;343:d5928. PMID: 22008217.

14. Wells GA SB, O’Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. [9/25/2014]; Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp, .

15. Chung M, Balk EM, Brendel M, et al. Vitamin D and calcium: a systematic review of health outcomes. Evidence report/technology assessment. 2009 Aug(183):1-420. PMID: 20629479.

16. Chung M, Balk EM, Ip S, et al. Reporting of systematic reviews of micronutrients and health: a critical appraisal. Am J Clin Nutr. 2009 Apr;89(4):1099-113. PMID: 19244363.

17. Lichtenstein AH, Yetley EA, Lau J. Application of systematic review methodology to the field of nutrition. J. Nutr. 2008 Dec;138(12):2297-306. PMID: 19022948.

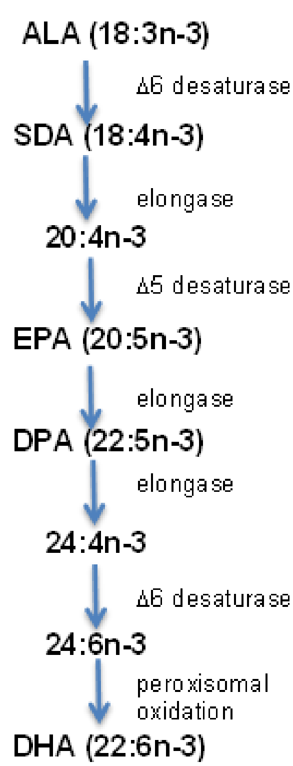
18. Berkman ND, Lohr KN, Ansari MT, et al. Grading the strength of a body of evidence when assessing health care interventions: an EPC update. J Clin Epidemiol. 2014 Dec 20. PMID: 25721570.

Introduction

Background

Since the first ecological study published in the late 1970s noted a relatively low cardiovascular (CV) mortality in a Greenland Eskimo population with high fish consumption,[1] there have been hundreds of observational studies and clinical trials conducted to evaluate the effect of omega−3 fatty acids (n-3 FA) on CV disease (CVD) and its risk factors and intermediate markers. The n-3 FA (including alphalinolenic acid [ALA], stearidonic acid [SDA], eicosapentaenoic acid [EPA], docosapentaenoic acid [DPA], and docosahexaenoic acid [DHA]) are a group of long-chain and very-long-chain polyunsaturated fatty acids (PUFA) that are substrates for the synthesis of eicosanoids and are important components of cell membranes that impact fluidity. Eicosanoids (including prostaglandins, thromboxanes, and leukotrienes) have wide ranges of physiologic effects and play a key role in inflammation regulation. The metabolic pathway of n-3 FA is shown in Figure 1. ALA is the shortest n-3 FA from which all other n-3 FA, if not ingested preformed, are metabolically derived. ALA is an essential nutrient; it cannot be made by the human body and must come from the diet. SDA can be formed from ALA via Δ6 desaturase, the rate-limiting enzyme in the pathway. If SDA enters the metabolic pathway preformed , between 15 and 30 percent can be elongated and saturated to EPA. EPA can be converted to DPA and vice versa. However, the elongation and desaturation of ALA to EPA and DHA is inefficient. Based on stable-isotope tracer studies the estimated conversion rates are broad, ranging from 0.2 to 5 percent.[2] Major dietary sources of ALA include soybean and canola oils, some nuts, and flaxseed. The major dietary sources of EPA and DHA are fish, other marine life, and marine-derived supplements. There is no naturally occurring source of SDA that, per serving, provides amounts of n-3 FA approaching levels (of EPA and DHA) present in oily fish. Naturally occurring sources of SDA—hemp and echium seed oils—are not consumed by the general population. In the future, though, SDA may be present in genetically modified soybeans.

Figure 1. Metabolic pathway of omega-3 fatty acids



Abbreviations: ALA = alphalinolenic acid, SDA = stearidonic acid, EPA = eicosapentaenoic acid, DPA = docosapentaenoic acid, DHA = docosahexaenoic acid, n-3 = omega-3 fatty acids

Since the publication of the original Agency for Healthcare and Research Quality (AHRQ) n-3 FA systematic reviews in 2004[3, 4] the topic of n-3 FA and CVD has remained controversial and dynamic. This topic has been evaluated by several expert panels that were considering whether recommendations or reference values for intakes of EPA and DHA were warranted, either through naturally occurring sources of n-3 FA (e.g., fish consumption) and/or through the use of dietary supplements and fortified foods.[5-8]

In 2002, the Institute of Medicine (IOM) considered the evidence inadequate to establish an estimated average requirement for n-3 FA.[6] Thus the IOM established only adequate intake values for ALA, based on current population ALA intake and an apparent absence of deficiency symptoms. For healthy adults, the adequate intake values for ALA are 1.1 g/d for females and 1.6 g/d for males.[6] After evaluating evidence linking the very-long-chain n-3 FA—EPA and DHA—to coronary heart disease (CHD, also known as coronary artery disease) and stroke, the IOM panel suggested that n-3 FA may provide beneficial health effects with respect to CHD and stroke ; the acceptable macronutrient distribution range (a range of intakes that is associated with reduced risk of chronic diseases while providing adequate intakes of essential nutrients) for ALA was set at 0.6 to 1.2 percent of energy (roughly equivalent to 1 to 3 g/d), where 10 percent of this range can be consumed as EPA and/or DHA.[6] For comparison, the mean intake of ALA in the United States has been estimated at 0.6 percent of energy intake (standard deviation 1.0%),[9] equivalent to approximately 1.4 g/d. This intake level, is fairly consistent across developed countries (0.3-1.0% of energy). However, estimated EPA and DHA intake in the United States are only 0.05 g/d and 0.08 g/d, respectively. In contrast, mean intake in South Korea is 0.4 g/d of EPA and DHA, combined.[9]

SDA and DPA have only infrequently been analyzed in regards to their association with CVD. Three other expert reports evaluated the potential health benefits of fish/seafood consumption.[5, 7, 8] Based primarily on the availability of observational study data, these panels consistently suggested that regular consumption of fish and seafood is associated with lower risk of CHD and cardiac death. These recommendations were based primarily on assumptions of benefits from EPA and DHA and their content in fish and seafood.

However, determination of n-3 FA intake is problematic, both for population recommendations and in regards to research. In practice, all nutrients are quantified using a nutrient database, e.g., the U.S. Department of Agriculture National Nutrient Database for Standard Reference (http://ndb.nal.usda.gov/). The quantity of a nutrient is then estimated by the standard amount of nutrients in foods that are indexed in the nutrient database multiplied by the amount and frequency of the food consumption. However, n-3 FA in foods are not well estimated in the nutrient database and questionnaires commonly do not ask about cooking oils or dressings and may not ask about supplements (so that n-3 FA intake is estimated only from fish consumption); therefore quantification of n-3 FA intake from food frequency questionnaires is poor. Furthermore, some questionnaire do not include portion size, so further estimation or extrapolation of intake is required.

There have been secular trends in the prevention and treatment of CVD over the past several decades, particularly since the 2004 AHRQ reports on n-3 FA and CVD. These trends may have had an important impact on the potential effect or association between n-3 FA intake and CVD outcomes. Important among these trends are the lower rates of cardiac and cerebrovascular disease, concomitant with higher rates of treatment and control of dyslipidemia and hypertension. For at least the past 20 years American adults are increasingly likely to be treated with statins, antihypertensives, and low-dose aspirin. All of these pharmacologic interventions act on metabolic and biochemical pathways that n-3 FA also impact and this confounding may impact the purported CV benefits of n-3 FA, including lipid metabolism, blood pressure (BP) and vascular homeostasis, and inflammatory and coagulation pathways. These treatment trends may have contributed to the lower population-level CV benefit of higher n-3 FA intake because the underlying risk of CVD is now lower, hence, diminishing the potential impact of n-3 FA intake. Furthermore, diagnostic criteria for CVD events (e.g., myocardial infarction) and CV risk factors (e.g., metabolic syndrome) have been refined over time which may make older studies less applicable in terms of their outcomes and populations.

Scope and Key Questions

Scope of the Review

The National Institutes of Health's Office of Dietary Supplements (ODS) has a long history of commissioning AHRQ-based systematic reviews and research methodology reports for nutrition-related topics (http://ods.od.nih.gov/Research/Evidence-Based_Review_Program.aspx). n-3 FA and their potential relationship to a broad range of health outcomes formed the basis for nine of these systematic reviews published between 2004 and 2006 and also served as examples for several methodological reports.[10-23]

There are ongoing concerns in the scientific community regarding systematic biases and random errors in the determination of intakes of n-3 FA from dietary and supplement sources using currently available assessment tools. The limitations of the current methods have been discussed elsewhere.[24-26] To date, no alternate methods are available. Until "error-free" or "bias-free" methodologies are developed, it is crucial to evaluate the available data with these methodological quality and limitations in mind. Nutrient biomarkers can provide an objective measure of dietary status.[27] However, the correspondence between intake and biomarker concentration not only reflects recent intake but subsequent metabolism (e.g., elongation, desaturation, metabolism to bioactive compounds). Current biomarkers used to estimate n-3 FA intake include ALA, EPA, DHA, and, less frequently, SDA and DPA, measured in adipose tissue, erythrocytes, plasma, or plasma phospholipids.[27-29] Adipose tissue FA are thought to reflect long-term intake, erythrocyte FA are thought to reflect the previous 120 day intake, and plasma FA are thought to reflect more immediate intake.[28]

Several recent systematic reviews of randomized controlled trials (RCTs) in individuals with diagnosed CVD or at high risk of CVD have suggested mixed results as to whether there are benefits of very-long-chain PUFA (EPA and DHA) for reducing the risk of adverse CV outcomes.[21, 30-36] Reasons for the apparent inconsistent scientific conclusions among several of the expert panels and the more recent systematic reviews are varied but may relate, in part, to whether the n-3 FA exposures were from fish (or other marine) or plant sources, or from dietary supplements. The expert reviews also vary as to whether they relied primarily on observational studies or RCTs.[21, 30-36] Studies of different designs each have their own strengths and weakness that may result in differences in conclusions. For example, observational studies based on self-reported dietary assessments (e.g., food frequency questionnaires) may inaccurately estimate n-3 FA intake; RCTs of specific fish or other n-3 FA-rich food may impose an artificial dietary pattern that might not be applicable to the general population; RCTs of supplements might not fully account for differences in background n-3 FA intake; studies using either study design may have subtle differences in eligibility criteria, e.g., length of followup duration, or inclusion of ALA, EPA and DHA or only EPA and DHA, that significantly impacted the final conclusions. Since there are limitations to different study designs and ways of assessing associations, it is of interest to systematically compare results across different study types (e.g., interventional vs. prospective cohort studies) and different ways of evaluating exposures, and to account for differences in background n-3 FA intake. Also of interest is a systematic evaluation of possible reasons for inconsistencies between observational and RCT findings,[37] in particular a tabulation of causality-related study features.

The purpose of the current systematic review is twofold: 1) to update earlier reviews of the state-of-the science on the topic of the effects of n-3 FA on CVD,[4] and selected CVD risk factors and intermediate markers of CVD,[3] and 2) to use this new review to collect additional information that would enhance the usefulness of this report for policy and clinical applications. The primary target audience for this report is clinical and nutrition researchers and policymakers, including ODS and panels revising dietary intake recommendations. The 2004 reviews screened about 7,500 abstracts and retrieved and screened 768 full text articles for potentially relevant human data. For CVD outcomes, 11 RCTs and one prospective cohort study reported outcomes in individuals with diagnosed CVD, and 22 prospective cohort studies and one RCT reported data on the general population. The report on intermediate CVD outcomes included the 25 largest RCTs with lipid outcomes, an existing systematic review of BP,[38] and six RCTs of BP in people with diabetes (who had been excluded from the existing systematic review). This review updates the previous review for the outcomes included and also expands the scope to include additional CVD outcomes (peripheral vascular disease, congestive heart failure (CHF), and arrhythmias); it updates BP and plasma lipid outcomes from, and adds incident hypertension to, the 2004 review of CVD risk factors and intermediate markers of CVD[3]; it adds associations between biomarkers of n-3 FA intake and outcomes.

Key Questions

The Key Questions address both issues of efficacy (i.e., causal relationships from trials) as well as associations (i.e., prospective observational cohort study associations of n-3 FA intake and/or biomarkers with long-term outcomes; biomarker associations reported in RCTs). Compared with the Key Questions from the 2004 reports, the current Key Questions expand the scope of the review to include additional CV outcomes (BP, CHF, and arrhythmias), focus on the intermediate outcomes plasma lipids and BP, adds the intermediate outcome hypertension, and include associations between biomarkers of intake and outcomes.

1. What is the efficacy or association of n-3 FA (EPA, DHA, EPA+DHA, DPA, SDA, ALA, or total n-3 FA) exposures in reducing CVD outcomes (incident CVD events including all-cause death, CVD death, nonfatal CVD events, new diagnosis of CVD, peripheral vascular disease, CHF, major arrhythmias, and hypertension diagnosis) and specific CVD risk factors (BP, key plasma lipids)?
    - What is the efficacy or association of n-3 FA in preventing CVD outcomes in people
        - Without known CVD (primary prevention)
        - At high risk for CVD (primary prevention), and
        - With known CVD (secondary prevention)?
    - What is the relative efficacy of different n-3 FA on CVD outcomes and risk factors?

- Can the CVD outcomes be ordered by strength of intervention effect of n-3 FA?

2. n-3 FA variables and modifiers:
   - How does the efficacy or association of n-3 FA in preventing CVD outcomes and with CVD risk factors differ in subpopulations, including men, premenopausal women, postmenopausal women, and different age or race/ethnicity groups?
   - What are the effects of potential confounders or interacting factors—such as plasma lipids, body mass index, BP, diabetes, kidney disease, other nutrients or supplements, and drugs (e.g., statins, aspirin, diabetes drugs, hormone replacement therapy)?
   - What is the efficacy or association of different ratios of n-3 FA components in dietary supplements or biomarkers, on CVD outcomes and risk factors?
   - How does the efficacy or association of n-3 FA on CVD outcomes and risk factors differ by ratios of different n-3 FA—DHA, EPA, and ALA, or other n-3 FA?
   - How does the efficacy or association of n-3 FA on CVD outcomes and risk factors differ by source (e.g., fish and seafood, common plant oils (e.g., soybean, canola), fish oil supplements, fungal-algal supplements, flaxseed oil supplements)?
   - How does the ratio of n-6 FA to n-3 FA intakes or biomarker concentrations affect the efficacy or association of n-3 FA on CVD outcomes and risk factors?
   - Is there a threshold or dose-response relationship between n-3 FA exposures and CVD outcomes and risk factors? Does the study type affect these relationships?
   - How does the duration of intervention or exposure influence the effect of n-3 FA on CVD outcomes and risk factors?
   - What is the effect of baseline n-3 FA status (intake or biomarkers) on the efficacy of n-3 FA intake or supplementation on CVD outcomes and risk factors?

3. Adverse events:
   - What adverse effects are related to n-3 FA intake or biomarker concentrations (in studies of CVD outcomes and risk factors)?
   - What adverse events are reported specifically among people with CVD or diabetes (in studies of CVD outcomes and risk factors)?

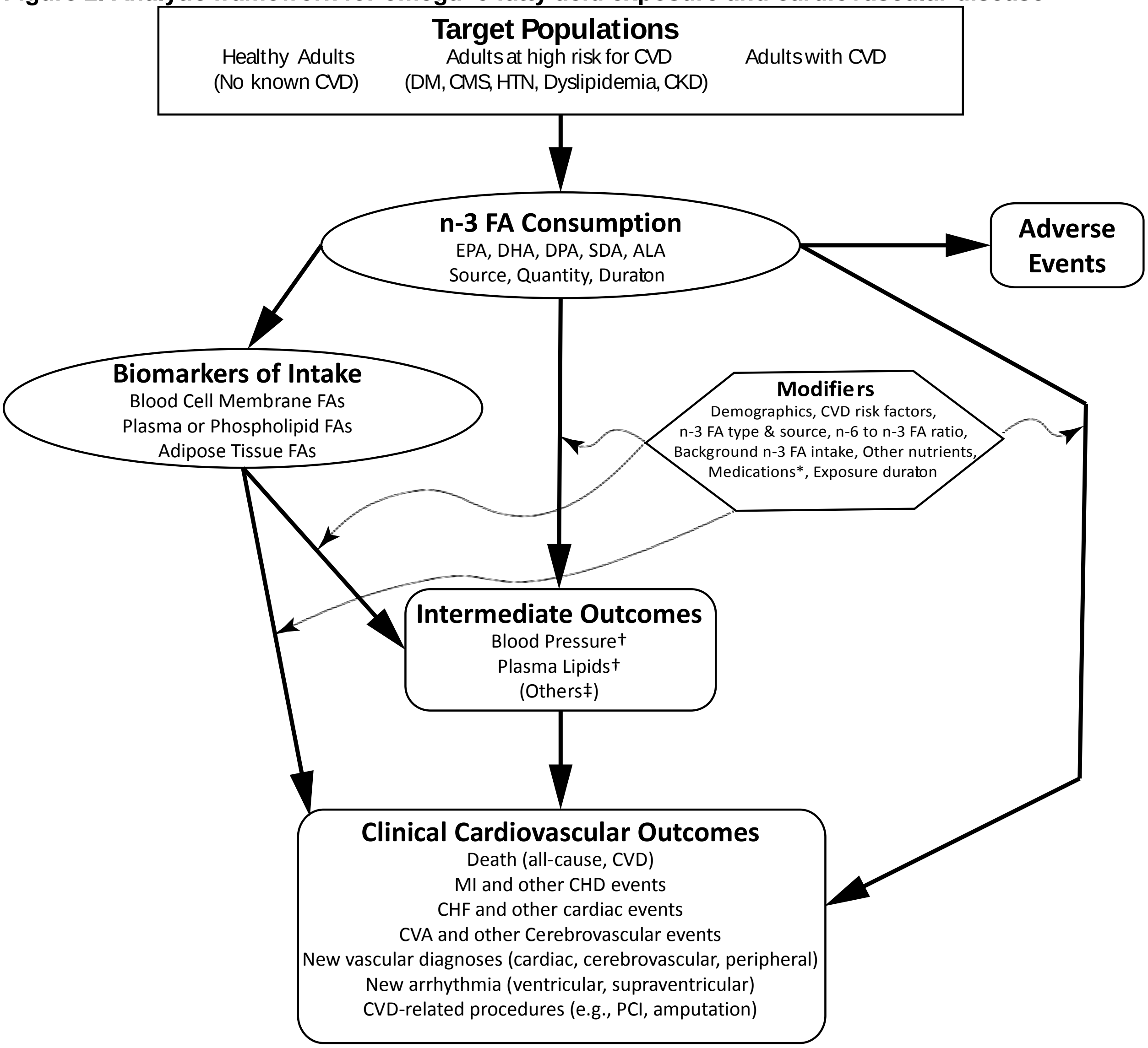
Analytic Framework

To guide the assessment of studies that examine the association between n-3 FA intake and CV outcomes, the analytic framework maps the specific linkages associating the populations of interest, the exposures, modifying factors, and outcomes of interest (Figure 2). The framework graphically presents the key components of well-formulated study questions:

1. Who are the participants (i.e., what is the population and setting of interest, including the diseases or conditions of interest)?
2. What are the interventions?
3. What are the outcomes of interest (intermediate and health outcomes)?
4. What study designs are of value?

Specifically, this analytic framework depicts the chain of logic that evidence must support to link the intervention (exposure to n-3 FA) to improved health outcomes.

Figure 2. Analytic framework for omega−3 fatty acid exposure and cardiovascular disease



This framework concerns the effect of n-3 FA exposure (as a supplement or from food sources) on CVD and CVD risk factors. Populations of interest are noted in the top rectangle, exposure in the oval, outcomes in the rounded rectangles, and effect modifiers in the hexagon.

* Specifically, cardiovascular medications, statins, antihypertensives, diabetes medications, hormone replacement regimens.
† Systolic blood pressure, diastolic blood pressure, mean arterial pressure, high density lipoprotein cholesterol (HDL-c), low density lipoprotein cholesterol (LDL-c), total/HDL-c ratio, LDL-c/HDL-c ratio, triglycerides.
‡ Many other intermediate outcomes are likely in the causal pathway between n-3 FA intake and cardiovascular outcome, but only blood pressure and plasma lipids were included in the review.

Abbreviations: ALA = alphalinolenic acid, CHD = coronary heart disease, CHF = congestive heart failure, CKD = nondialysis-dependent chronic kidney disease, CMS = cardiometabolic syndrome, CVA = cerebrovascular accident (stroke), CVD = cardiovascular disease, DHA = docosahexaenoic acid, DM = diabetes mellitus, DPA = docosapentaenoic acid, EPA = eicosapentaenoic acid, FA = fatty acid, HDL-c = high density lipoprotein cholesterol, HTN = hypertension, LDL-c = low density lipoprotein cholesterol, MI = myocardial infarction, n-3 = omega−3, n-6 = omega−6, PCI = percutaneous coronary intervention, SDA = stearidonic acid.

Methods

The present review evaluates the effects of, and the associations between, omega-3 fatty acids (n-3 FA)—including alphalinolenic acid (ALA), stearidonic acid (SDA), eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), and docosahexaenoic acid (DHA) and n-3 FA biomarkers— and cardiovascular disease (CVD) outcomes. The Brown Evidence-based Practice Center (EPC) conducted the review based on a systematic review of the published scientific literature using established methodologies as outlined in the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[39]

The review was conducted in parallel with a systematic review of n-3 FA and child and maternal health, conducted by another Evidence-based Practice Center (EPC). Several aspects of the review were coordinated, including eligibility criteria and search strategies regarding interventions and exposures structure of the reviews, and assessments of the studies' risk of bias, strength of the bodies of evidence, and extraction of study characteristics needed to assess causality.

Topic Refinement and Review Protocol

We convened a Technical Expert Panel (TEP) to help refine the research questions and protocol. The TEP included five experts in nutrition, n-3 FA research specifically, CVD epidemiology, and cardiology. Also included in the discussions with the TEP were the Director of and a Senior Scientist at the Office of Dietary Supplements (ODS), and the AHRQ Task Order Officer. We discussed the Key Questions, analytic framework, study eligibility criteria, literature search, and analysis plans.

In regards to the populations of interest, we explicitly expanded the definition of the at risk for CVD population to include adults with cardiometabolic syndrome (and related conditions) and nondialysis dependent chronic kidney disease. Regarding the interventions of interest, we discussed the changes from the original AHRQ reports on n-3 FA, specifically that we included only studies that quantify n-3 FA content of the intervention, and that we added n-3 FA biomarkers as an exposure of interest. We also clarified that we excluded weight loss interventions that included n-3 FA as part of the intervention. Weight-loss studies, by definition need to create energy deficits; interventions generally aim to reduce total energy intake and/or increasing energy expenditure. Energy deficits trigger metabolic changes including altering lipid metabolism. Since CVD outcomes were the main outcome of interest, weight loss is a major confounder that may be in the causal pathway between exposures of interest (i.e., n-3 FA) and CVD outcomes. Regarding outcomes of interest, we refined the list of "major lipids" of interest to include only low density lipoprotein cholesterol (LDL-c), high density lipoprotein cholesterol (HDL-c), triglycerides (Tg), LDL-c to HDL-c ratio, and total cholesterol to HDL-c ratio. Compared to the original n-3 FA and CVD outcome report, we added peripheral vascular disease, arrhythmia events, congestive heart failure (CHF), and incident hypertension. We discussed a number of potential modifiers of interest to be searched for, including demographic features, weight, blood pressure (BP), source and type of n-3 FA, exposure duration, C reactive protein level, and specific co-interventions (i.e., statins, vitamin E).

It was agreed to maintain a minimum duration of followup of 1 month for intermediate outcomes (lipids and BP) and 1 year for all clinical outcomes. We agreed to include only randomized controlled trials (RCT) of specific comparisons of interventions and large, prospective, longitudinal observational studies of exposure (either baseline dietary intake or biomarker level). We also agreed to include the RCTs that are largest or report subgroup or factorial analyses, and the largest observational studies to constrain the total number of included studies to approximately 75 to 100. The search strategy was refined based on suggestions from the TEP. The TEP agreed that the primary literature search would be conducted for the period from 2002 to the present to capture studies published since the original EPC report, with older studies to come from existing systematic reviews including the original EPC report. For new topics (e.g., biomarkers, peripheral vascular disease), the TEP agreed that searches back to 2000 would be sufficient to capture relevant analyses.

In addition, in separate discussions with the Office of Dietary Supplements (ODS) representative and our Task Order Officer (TOO) we considered how and whether to assess the concept of causality, particularly for the observational studies. After discussion of the Bradford Hill criteria and related issues regarding causality,[40] we agreed upon the creation of an appendix table (Appendix G) that provides the study-level data for items that may be pertinent for users of this report to assess causality.

Furthermore, we had joint discussions with the Southern California EPC—which conducted a parallel report of n-3 FA and maternal and child health—and our TOO and the ODS representative to coordinate our protocols and processes. The protocol was entered into the PROSPERO register (registry number CRD42014015602).

Literature Search

We conducted literature searches of studies in MEDLINE®, both the Cochrane Central Trials Registry® and Cochrane Database of Systematic Reviews®, Embase®, and CAB Abstracts® from 2002 to 8 June 2015 (to overlap with the last search run for the 2004 reviews). We searched earlier publications back to 2000 for the newly added outcomes (peripheral vascular disease, CHF, arrhythmias, hypertension) and for biomarkers of n-3 FA intake. We also rescreened and included all studies from the original reviews that met current eligibility criteria. We revised the search strategy used in the original reviews to capture new terms for n-3 FA, biomarkers, and additional outcomes. In electronic searches, we combined terms for n-3 FA (and biomarkers), CVD and risk factors (BP, plasma lipids, hypertension), limited to humans, English language, and relevant research designs. Titles and abstracts were screened to identify articles relevant to each Key Questions. We also reviewed reference lists of related systematic reviews for other potentially eligible studies. We invited TEP members to provide additional citations. In addition, a call for potentially relevant articles was posted on the Federal Register (in lieu of Scientific Information Packets), but yielded no additional studies. Appendix A displays the current complete search strategy.

Study Eligibility Criteria

The current eligibility criteria are mostly similar to the criteria used in the original 2004 review. The populations remain the same. The interventions and exposures have been expanded to include n-3 FA biomarkers. The list of CVD outcomes of interest has been expanded. Similar study designs were included.

For all Key Questions, the eligibility criteria are:

Populations

- Healthy adults (≥18 years) without CVD or with low to intermediate risk for CVD

- Adults at high risk for CVD (e.g., with diabetes, cardiometabolic syndrome, hypertension, dyslipidemia, nondialysis dependent chronic kidney disease)
- Adults with clinical CVD (e.g., history of myocardial infarction [MI], angina, stroke, arrhythmia)
- Exclude populations chosen for having a non-CVD or nondiabetes-related disease (e.g., cancer, gastrointestinal disease, rheumatic disease, dialysis)

Interventions/Exposures

- n-3 FA supplements
- n-3 FA supplemented foods (e.g., eggs)
- n-3 FA content in diet
- Biomarkers of n-3 FA intake

- n-3 FA content of food or supplements must have been explicitly quantified (by any method). Therefore, studies such as those of fish diet where only servings per week were defined or Mediterranean diet studies without n-3 FA quantified were excluded. The n-3 FA quantification could be of total n-3 FA, of a specific n-3 FA (e.g., ALA) or of combined EPA+DHA ("marine oil").
- Exclude mixed interventions of n-3 FA and other dietary or supplement differences (e.g., n-3 FA and vitamin E versus placebo; n-3 FA as part of a low fat diet versus usual diet). However, factorial design (and other) studies that compared (for example) n-3 FA versus control, with or without another intervention (e.g., statins) were included.
- Exclude n-3 FA dose ≥6 g/d, per the original review's protocol based on the assessment that n-3 FA intake above this amount is impractical and has little relevance on health care recommendations.
- Exclude weight loss interventions

Comparators

- Placebo or no n-3 FA intervention
- Different n-3 FA source intervention
- Different n-3 FA concentration intervention
- Different n-3 FA dietary exposure (e.g., comparison of quantiles)
- Different n-3 FA biomarker levels (e.g., comparison of quantiles)

Outcomes

- All-cause death
- Cardiovascular (CV), cerebrovascular, and peripheral vascular events:
    - Fatal vascular events (e.g., due to MI, stroke)
    - Total incident vascular events (e.g., MI, stroke, transient ischemic attack, unstable angina, major adverse CV events [MACE]; total events include fatal and nonfatal events; total stroke includes ischemic and hemorrhagic stroke)
    - Coronary heart disease (also known as coronary artery disease), new diagnosis
    - CHF, new diagnosis
    - Cerebrovascular disease, new diagnosis
    - Peripheral vascular disease, new diagnosis

- Ventricular arrhythmia, new diagnosis, including sudden cardiac death
  - Supraventricular arrhythmia (including atrial fibrillation), new diagnosis
  - Major vascular interventions/procedures (e.g., revascularization, thrombolysis, lower extremity amputation, defibrillator placement)
- Major CVD risk factors (intermediate outcomes):
  - BP (new-onset hypertension, systolic, diastolic, and mean arterial pressure)
  - Key plasma lipids (i.e., HDL-c, LDL-c, total/HDL-c ratio, LDL-c/HDL-c ratio, Tg)
- Adverse events (e.g., bleeding, major gastrointestinal disturbance), only from intervention studies of supplements

Timing

- Clinical outcomes, including new-onset hypertension (all study designs): ≥1 year followup (and intervention duration, as applicable)
- Intermediate outcomes (BP and plasma lipids) (all study designs): ≥1 month followup
- Adverse events (all study designs): no minimum followup

Setting

- Community-dwelling (noninstitutionalized) individuals

Study Design

- RCTs (all outcomes)
- Randomized cross-over studies (BP and plasma lipids, adverse events), minimum washout period to be determined
- Prospective nonrandomized comparative studies (clinical outcomes, adverse events)
- Prospective cohort (single group) studies, where groups were compared based on n-3 FA intake or intake biomarker values (clinical outcomes) . Observational studies must have reported multivariate analyses.
- Exclude: Retrospective or case control studies or cross-sectional studies (but include prospective nested case control studies). Studies must have had measures of intake prior to outcome.

- Minimum sample sizes
  Due to the very large number of potentially eligible studies (more than 400), we applied arbitrary thresholds based on sample size, followup duration, and whether subgroup or interaction analyses were reported. These were designed to give preference to larger studies with longer followup duration or that reported interaction analyses of interest.
  - RCTs
    - We aimed for a minimum of about 25 RCTs for each of the BP and plasma lipid outcomes. We preferentially included RCTs that reported relevant subgroup, interaction, or factorial analyses.
      - For RCTs with BP or lipid outcomes with subgroup, interaction, or factorial analyses, we included parallel design RCTs with a minimum of 30 participants per arm, factorial RCTs with a minimum of 30 participants per n-3 FA intervention, and crossover trials with a minimum of 20 participants.

        - For RCTs with lipid outcomes without subgroup analyses, we included parallel design RCTs with a minimum of 200 participants per arm, factorial RCTs with a minimum of 200 participants per n-3 FA intervention, and crossover trials with a minimum of 100 participants.
        - For RCTs with BP outcomes without subgroup analyses, if followup was ≥6 months, we included all RCTs; if followup was <6 months (≥1 month), we included parallel design RCTs with a minimum of 80 participants per arm, factorial RCTs with a minimum of 80 participants per n-3 FA intervention, and crossover trials with a minimum of 40 participants.
        - For RCTs with CVD event outcomes, we included all RCTs with at least 10 participants per arm.
    - Longitudinal observational studies
        - We aimed for a minimum of about 10 observational studies for each broad clinical outcome (see bullets below) and also for dietary marine oils, dietary ALA, marine oil biomarkers, and ALA biomarkers.
            - For cardiac event outcomes, we included observational studies with at least 10,000 participants.
            - For death outcomes, we included observational studies with at least 10,000 participants.
            - For stroke event outcomes, we included observational studies with at least 3000 participants.
            - For arrhythmia event outcomes, we included observational studies with at least 2000 participants.
            - For CHF event outcomes, we included observational studies with at least 700 participants.
            - For peripheral vascular disease event, incident hypertension, MACE, and revascularization outcomes, we included observational studies with at least 500 participants.
            - We screened smaller sample size observational studies (starting with the largest studies) to include additional studies of ALA biomarkers, regardless of the outcomes analyzed.

    - In all instances, if a study met eligibility criteria for any outcome, we extracted all outcomes of interest from that study; therefore, there are multiple instances of studies being included for an outcome even though the study might not have met study size criteria for that specific outcome.

- English language publications
- Peer reviewed publications

Study Selection

All citations found by literature searches or through other sources were independently screened by two researchers. Upon the start of citation screening, we implemented a training session where all researchers screen the same articles and conflicts were discussed. We iteratively continue training until we have reached agreement regarding the nuances of the eligibility criteria for screening. During double-screening, we resolved conflicts as a group. All screening of literature citations was done in the open-source, online software Abstrackr (http://abstrackr.cebm.brown.edu/).

All potentially eligible abstracts (regardless of source) were entered into an "evidence map". From each abstract, a single researcher extracted data on the study sample size (total), study design, study duration, the population category (healthy, at risk, CVD), the specific n-3 FA analyzed, whether biomarkers were reported, whether subgroup or factorial analyses were reported, and the outcomes mentioned in the abstract.

Based on the study descriptions in the evidence map, we selected the largest studies and those with subgroup or factorial analyses for full text review, with the goals of including a minimum of about 25 RCTs for each of the BP and plasma lipid outcomes, all RCTs with clinical outcomes, and a minimum of about 10 observational studies for each broad clinical outcome and also for dietary marine oils, dietary ALA, marine oil biomarkers, and ALA biomarkers.

Data Extraction

Each study was extracted by one methodologist. The extraction was reviewed and confirmed by at least one other experienced methodologist. Disagreements were resolved by discussion among the team, with the team leader, or between extractors. Data were extracted into customized forms in Systematic Review Data Repository (SRDR) online system (http://srdr.ahrq.gov) and Excel spreadsheets, each designed to capture all elements relevant to the Key Questions. Upon completion of the review, the Excel spreadsheets (of observational study results data) were uploaded into SRDR and the database has made accessible to the general public (with capacity to read, download, and comment on data) (at http://srdr.ahrq.gov/). The basic elements and design of these forms include elements that address population characteristics; descriptions of the interventions, exposures, or biomarker status (and comparators) analyzed; outcome definitions; enrolled and analyzed sample sizes; study design features; results; and risk of bias assessment. The form was developed off the forms used for the original review. We also included questions pertinent to issues related to causality. We tested the forms on several studies and revised them as necessary before full data extraction.

Quality (Risk of Bias) Assessment of Individual Studies

We assessed the methodological quality of each study based on predefined criteria. For RCTs, we used the Cochrane risk of bias tool,[41] which asks about risk of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other potential biases. For observational studies, we used relevant questions from the Newcastle Ottawa Scale.[42] Additionally we included nutrition study specific risk of bias questions (e.g., related to uncertainty of dietary assessment measurements.[13, 15, 43] Any quality issues pertinent to specific outcomes within a study were noted and applied to those outcomes. Any quality issues pertinent to specific outcomes within a study were noted and considered when determining the overall strength of evidence for conclusions related to those outcomes.

Data Synthesis

All included studies were summarized in narrative form and in summary tables that tabulate the important features of the study populations, design, intervention, outcomes, and results. Other study data are in Appendix tables.

We analyzed different study designs separately and compared and contrasted populations, exposures, and results across study designs. We examined any differences in findings between observational and intervention studies, and evaluated the risk of bias factors as possible explanations for any heterogeneity.

Statistical analyses were conducted in Stata version 13.1 (StataCorp, College Station, Texas). We conducted random effects model meta-analyses of comparative studies (i.e., RCTs) if, for each set of studies with the same outcome and intervention and comparator pair, there were at least six studies. We used the restricted maximum likelihood method (with the metareg command) to calculate the overall and population-specific (healthy, at risk, CVD) effect sizes. For trials that compared multiple n-3 FA doses to placebo, we included only the comparison of the highest dose of n-3 FA versus placebo in meta-analysis. Likewise, for trials that compared both purified EPA and DHA to placebo, we arbitrarily included only the EPA versus placebo comparison.

We summarized included observational studies both qualitatively and quantitatively. We looked at hazard ratios (HR) and their respective confidence intervals of categorical outcomes of interest for each quantile of n-3 FA exposure (intake or biomarker level) within a study versus its reference quantile. The HRs were plotted at the median dose within a quantile's dose range (see below). Separate graphs were drawn for each combination of specific n-3 FA, measure type (e.g., intake, phospholipid level, percent FA), and outcome. We combined analyses of EPA+DHA and EPA+DHA+DPA. Within each graph, we plotted each reported cohort (i.e., from a given study, we plotted the analysis of the total cohort if that was reported, or we plotted both subgroup analyses—usually men and women—if only those were reported). We use unique symbols across graphs for all adults, men, women, and other subgroups.

When a study did not report the median doses for specific dose quantiles, we estimated them using the following rules. If the study provided the minimum and maximum dose within a quantile, we used the midpoint as the median dose. For the lowest and highest quantiles, if only one end of the range was reported (e.g., lowest quintile was <0.5 g/d), we estimated the median dose to be 20% less (or more) than that quantile's upper (or lower) range.[44] For studies that did not report the number of participants or person-years per quantile, we equally divided the total for the whole cohort to estimate the numbers per quantile.

We meta-analyzed multivariate observational cohorts when at least four cohorts analyzed the same n-3 FA, measure, and outcome. For each study cohort to be meta-analyzed, we used the STATA glst command to retrieve a set of coefficients and covariance matrices from generalized least squares trend estimation of splines with one knot each (exposure dose where the curve slope is allowed to change) across a range of knot points. Separately for ALA intake and EPA+DHA±DPA intake (the n-3 FA measured that had sufficient data for meta-analysis), we determined the range of knots for spline models by ordering the median values of all quantiles of all ALA or all EPA+DHA±DPA intake analyses being meta-analyzed (across outcomes) and selected a range from approximately the 5th lowest to 5th highest median values. Knot points were rounded to the nearest 0.1 g/d and stepped up in 0.1 g/d units to the highest knot point. We used the STATA glst command (generalized least squares) to estimate the splines for each cohort being meta-analyzed, across the range of knots. For a particular cohort, if a knot fell outside the cohort's n-3 FA dose range, we generated a linear model without a knot. We then used the STATA mvmeta command to meta-analyze these spline models (at each knot). We captured the Akaike information criterion (AIC) for each meta-analyzed spline (at each knot). We tabulated all meta-analyzed spline models for each set of studies (within a range of knots that pertain to each set of studies). In the figures of the association of n-3 FA exposure versus risk of outcome, we included the meta-analysis spline with the best fit (the lowest AIC value).

Summary of Causality-Related Study Features

We compiled a pair of appendix tables (Appendix G) with data related to possible causality criteria. The list of items in this table was compiled based on discussions between the EPCs and ODS after discussion of the Bradford Hill criteria[37] and other issues related to determining causality. The table includes a listing of included studies with their population category (healthy, at high CVD risk, with CVD), CVD risk type (e.g., diabetes, hypertension, chronic kidney disease, dyslipidemia), demographics (age, sex, race), CVD history, CVD risk factors (BP, plasma lipids, weight), baseline n-3 FA intake, n-3 FA source, n-3 FA type, how n-3 FA intake measured, study design (e.g., RCT, prospective or retrospective longitudinal cohort, or other design), exposure duration, followup duration, outcomes reported, whether outcomes were reported to be primary outcomes (vs. secondary), effect sizes, difference in n-3 FA intake (between low and high intake groups), and a dose-corrected effect size. The determination of primary outcomes was based on an explicit statement of the primary outcomes, the outcome used in reported power calculations, or if implied by focus of the original article. In addition, if the study was found in a registry and its primary outcome in this database differed from the stated primary outcome in the article, this information was included. The dose-corrected effect size is the effect size divided by the daily dose of tested n-3 FA.

Strength of the Body of Evidence

We graded the strength of the body of evidence as per the AHRQ Methods Guide on assessing the strength of evidence for each outcome.[45] Following the standard AHRQ approach, for each intervention and comparison of intervention, and for each outcome, we assessed the number of studies, their study designs, the study limitations (i.e., risk of bias and overall methodological quality), the directness of the evidence to the Key Questions, the consistency of study results, the precision of any estimates of effect, the likelihood of reporting bias, and the overall findings across studies. Based on these assessments, we assigned the strength of evidence rating as being either high, moderate, or low, or there being insufficient evidence to estimate an effect.

We assigned "High" strength of evidence only if there were sufficient, consistent, precise RCTs without limitations and any association studies yielded similar conclusions. Without such RCT evidence, the highest possible strength of evidence was "Moderate".

For outcomes with ≤2 RCTs providing evidence, the highest possible strength of evidence was "Low" under the presumption that observational studies (that analyzed the association between a one-time estimate of n-3 FA status and clinical outcomes ≥1 year in the future) cannot alone provide good evidence of an effect of n-3 FA intake. For outcomes with ≤2 RCTs, ≤2 observational studies of intake, and ≤2 observational studies of biomarkers, the strength of evidence grade was "Insufficient." Where RCTs and observational studies yielded different conclusions about significance of effect/association, we assigned a low strength of evidence of the conclusion of the RCTs. For example, if RCTs found no significant effect, but observational studies found a significant association, we concluded low strength of evidence of no effect. If we were unable to conclude a finding of an association or effect, or no association or effect, (generally because of imprecision or inconsistency across studies), we determined that the evidence was “Insufficient” since it is not meaningful to state that there is a low strength of evidence of an unclear effect/association.

The strength-of-evidence dimensional rating are summarized in Evidence Profile tables detailing our reasoning for arriving at the overall strength of evidence rating. Study characteristics related to causality are tabulated in Appendixes G.1 and G.2.

Applicability

We assessed the applicability within and across studies with reference to whether people in the studies were in the three populations of interest (healthy, at risk, and with CVD), and as pertains to n-3 FA source, type, and dose/exposure.

Peer Review and Public Commentary

A draft version of this report was reviewed by a panel of expert reviewers and the general public. The reviewers were either directly invited by the EPC or offered comments through a public review process. Revisions of the draft were made, where appropriate, based on their comments. The draft and final reports were also reviewed by the Task Order Officer and an Associate Editor from another EPC. However, the findings and conclusions are those of the authors, who are responsible for the contents of the report.

Results

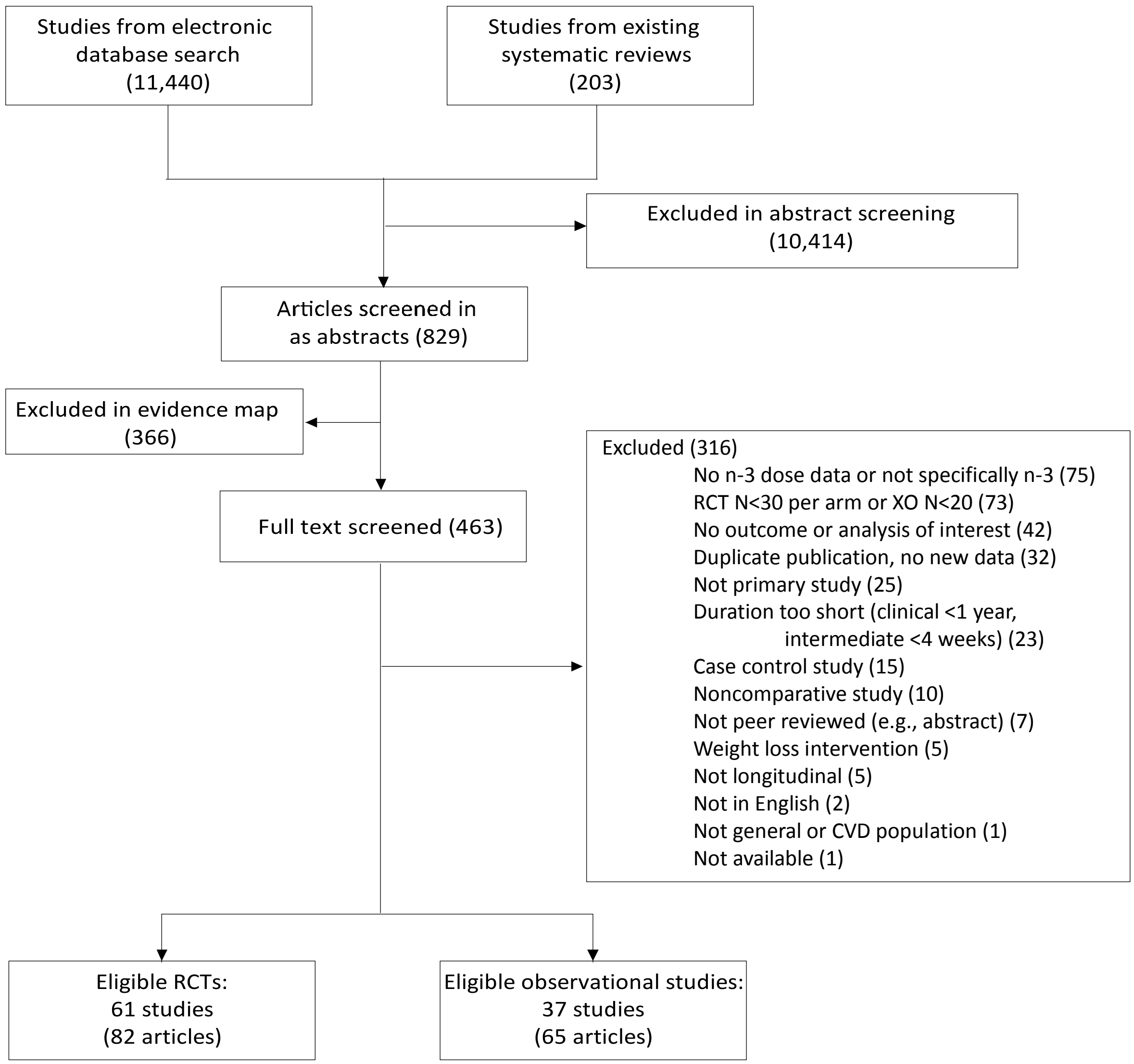
The Results chapter is organized as follows. The chapter starts with an overall description of the included studies and their risk of bias assessment. The bulk of the chapter is organized by outcome, with a description first of the randomized controlled trials (RCT) and their subgroup analyses, followed by the observational studies and their subgroup analyses. Within each description of studies, we follow the basic pattern of first describing the evidence regarding total omega-3 fatty acids (n-3 FA) combined, then alphalinolenic acid (ALA), the individual long-chain n-3 FA (eicosapentaenoic acid [EPA], docosahexaenoic acid [DHA], docosapentaenoic acid [DPA], and stearidonic acid [SDA]), and then combined long-chain n-3 FA (EPA+DHA±DPA). Within the description of the observational studies, we first present the results of associations with n-3 FA intake followed by n-3 FA biomarkers.

Appendix A presents the literature search strategies. Appendix B lists the articles that were reviewed in full text that were excluded, with their rejection reasons. Appendix C presents the study-level risk of bias assessments of all studies. Appendix D presents study-level baseline data. Appendix E presents study-level design features. Appendix F presents the study-level results data for the observational studies. Appendix G presents the "causality tables" described in the Methods section.

Summary of Studies

The literature searches yielded 11,440 citations (Figure 3). Reference lists from existing systematic reviews yielded 203 additional citations (which mostly represented articles published before 2002). Of these, 829 abstracts met basic eligibility criteria. As described in the Methods chapter (under *Study selection*), using an evidence map process, we selected 463 articles for full text review, of which 147 articles met eligibility criteria, representing 61 RCTs (in 82 articles) and 37 longitudinal observational studies (in 65 articles).[46-192]

Figure 3. Literature flow



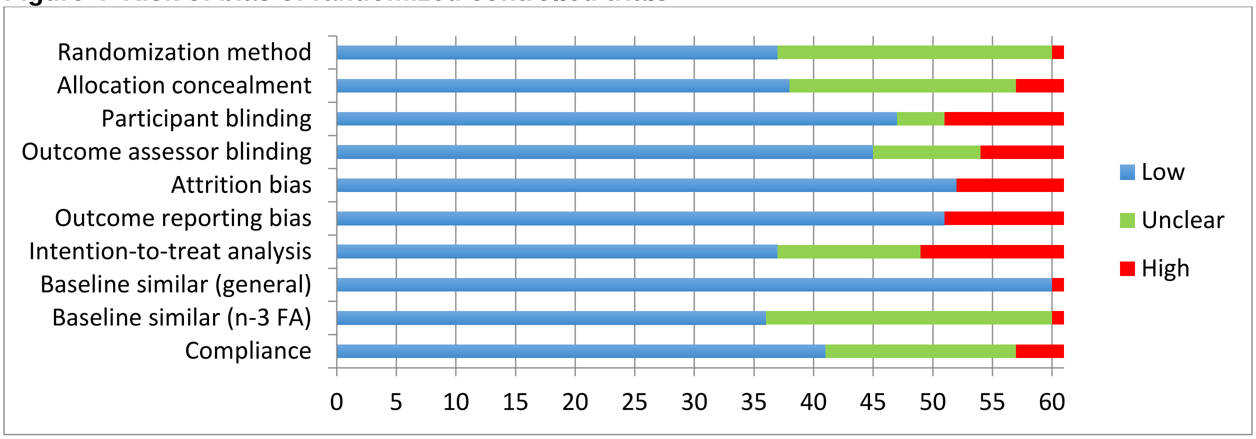
Abbreviations: CVD = cardiovascular disease, n-3 = omega-3 fatty acids, RCT = randomized controlled trial.

Study Risk of Bias

Across RCTs, the studies generally had few risk of bias concerns (Figure 4, Appendix C). Among the 61 RCTs, 23 (38%) had no high risk of bias / study quality limitations; an additional 26 RCTs (43%) had one risk of bias limitation and 6 (10%) had two risk of bias limitations. None of the remaining 6 RCTs (10%) had more than four study limitations (of 10 explicitly assessed potential limitations). The most common risk of bias limitation was a lack of intention-to-treat analyses; 12 RCTs (20%) clearly did not conduct intention-to-treat analyses (one of these conducted an intention-to-treat analysis for the outcome death, but not for lipid outcomes); 12

additional RCTs (20%) were unclear whether intention-to-treat analyses were conducted. Ten RCTs (16%) did not blind study participants (and 4 additional, 7%, were unclear whether they blinded participants), often because the intervention was dietary and could not be blinded. However, only 7 RCTs (11%) clearly did not blind outcome assessors (nine additional RCTs, 14%, were unclear regarding outcome assessor blinding). Attrition bias, primarily due to dropout rates greater than 20 percent, was present in 9 RCTs (15%). Other potential biases were less common.

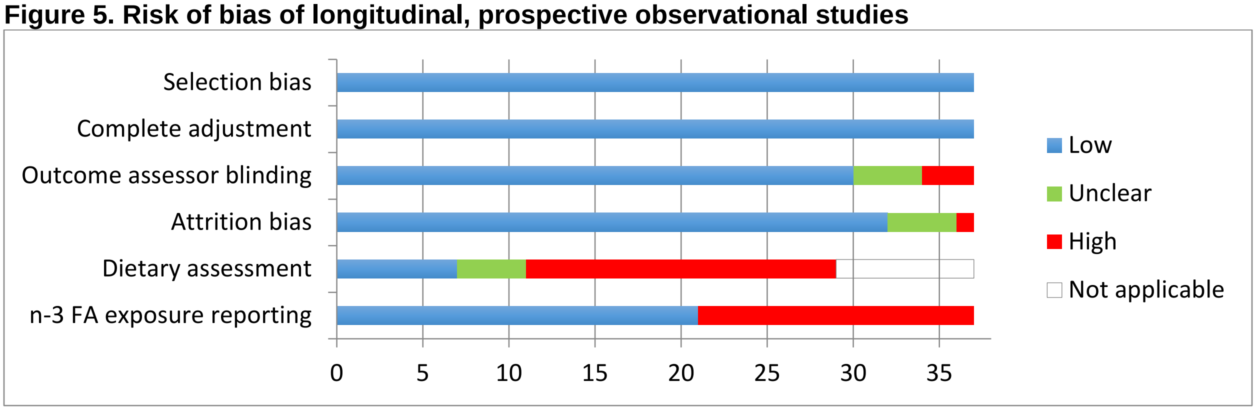
Figure 4. Risk of bias of randomized controlled trials



Risk of bias, by specific question, of the 61 included randomized controlled trials. See Appendix C for details.

Across the observational studies, there were fairly few risk of bias concerns (Figure 5). Nine of 37 studies (24%) had no high risk of bias concerns; 20 (54%) had only a single high risk of bias concern (of 7 explicitly assessed potential limitations) and 6 (16%) had two risk of bias concerns. The 2 remaining studies (5%) had three risk of bias concerns. No study was deemed to have high risk of selection bias (regarding whether the outcome was present at baseline) and all adequately adjusted for confounders. The majority of studies used a dietary assessment tool that did not include dietary supplements (18 of 29 applicable studies; 62%); an additional 4 studies (14%) were unclear whether dietary supplements were used. Sixteen studies (43%) did not adequately reported baseline nutrient exposures. Bias due to lack of outcome assessor blinding was infrequent (3 studies [8%]; 4 studies [11%] were unclear), as was attrition bias (1 study [3%]; 4 studies [11%] were unclear). All observational studies reported multivariate analyses (this was an eligibility criterion).

Figure 5. Risk of bias of longitudinal, prospective observational studies



Risk of bias, by specific question, of the 37 included longitudinal observational studies. For dietary assessment, studies rated high risk of bias if only diet (not supplements) were included in the food frequency questionnaire; studies that evaluate only biomarkers were not evaluated for risk of bias for dietary assessment (not applicable). See Appendix C for details.

Abbreviations: n-3 FA = omega-3 fatty acids.

Tables 1 and 2 enumerate studies by n-3 FA, strength of evidence, and overall effect or association by outcome (clinical and intermediate separately). The table highlights the lack of sufficient evidence for most clinical cardiovascular disease (CVD) outcomes (empty cells and unshaded cells with black font). Only for marine oil (EPA+DHA) is there sufficient evidence for beneficial effect (or association) of higher n-3 FA intake. The body of evidence provides no sufficient evidence of a significant effect (or association) of ALA on CVD outcomes or examined risk factors.

Table 1. Enumeration of studies by clinical outcome and n-3 FA

Outcome	Total n-3 FA			Marine Oil			EPA			DHA			DPA			SDA			ALA			MvA
	R	OI	OB	R	OI	OB	R	OI	OB	R	OI	OB	R	OI	OB	R	OI	OB	R	OI	OB	R
Total (including intermediate outcomes)	2	8	3	55	21	8	1	8	9	1	8	10		2	6			1	6	12	7	3
ACS		1			1	1		1	1		1	1			1							
Angina				L:6			1												1			
AFib			1	M:3	3				L:3			1			L:3					L:3	3	
Card Death				5	1	1			1			1			1			1			1	
CVD Death		4	1	L:7	6			2	1		2	1			1				1	3	2	
CHF			1	L:6	5	2			3			3			1				L:1	4	3	
CHF Death		1		1																		
CHD			2		7	1		L:2	3		L:2	3			3					L:6		
CHD Death		2	1	L:4	7		1	2	1		2	1			1				L:1	4	1	
Death, All-Cause		1	1	H:17	3		1		3			3			1				1		2	
HTN		2			1																	
MACE		3		H:10	3	2	1	1	3		1	4			3			1	1	2		
MI		L:3		L:11	1		1		1		1								1			
MI Death		2			1																	
Revasc				H:6	1		1															
CVA Dth, Hem					1			1			1											
CVA Dth, Isch		2			1			1			1											
CVA Dth, Tot		L:4	1	2	1		1	1	1		1	1			1							
CVA, Hem			1	L:2	5	1	1		1			1			1					2	2	
CVA, Isch			1	↓*L:2*	*5*	*2*	1	1	2		1	2			1					2	3	
CVA, Tot		1	1	L:7	4	2			1			1			1				1	3	2	
SCD		1	1	H:9	1		1		1													
Vent Arrh				1															1			

Table summarizing the number of studies that report on each evaluation of a type of omega−3 fatty acid (n-3 FA) and outcome, by study design. High (H), moderate (M), and low (L) strength of evidence for each n-3 FA-outcome pair are indicated by the respective letters (and bold font). Bold upright (nonitalic) script indicates evidence of no effect or association; bold italic text indicates evidence of a reduced risk of the outcome with higher n-3 FA intake (also indicated by a down arrow). n-3 FA-outcome pairs with regular font had insufficient evidence. Blank cells indicate no studies of the given design type reported on the n-3 FA-outcome pair.

Abbreviations: ACS = acute coronary syndrome, AFib = atrial fibrillation, ALA = alphalinolenic acid, Card = cardiac, CHD = coronary heart disease, CHF = congestive heart failure, CVA = cerebrovascular accident (stroke), CVA Dth = stroke death, CVA, Hem = hemorrhagic stroke, CVA, Isch = ischemic stroke, CVA, Tot = total stroke, CVD = cardiovascular disease, DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, EPA = eicosapentaenoic acid, HTN = incident hypertension, MACE = major adverse cardiac event, MI = myocardial infarction, MvA = direct comparison of marine oil and ALA (in randomized controlled trials), n-3 FA = omega−3 fatty acids, OB = observational studies of n-3 FA biomarkers, OI = observational studies of n-3 FA intake, R = randomized controlled trials, Revasc = revascularization, SCD = sudden cardiac death, Vent Arrh = ventricular arrhythmia.

Table 2. Enumeration of studies by intermediate outcome and n-3 FA

Outcome	Total n-3 FA			Marine Oil			EPA			DHA			DPA			SDA			ALA			MvA
	R	OI	OB	R	OI	OB	R	OI	OB	R	OI	OB	R	OI	OB	R	OI	OB	R	OI	OB	R
Total (including clinical outcomes)	2	8	3	55	21	8	1	8	9	1	8	10		2	6	2		1	6	12	7	3
SBP	2			H:29			2		1	M:3		1			1				M:4			2
DBP	2			H:28			2		1	M:3		1			1				M:4			2
MAP				3			2															
LDL-c	2			↑***H:39***			2			**M:**3						2			**M:**5			2
HDL-c	2			↓***H:34***			2			3						2			**M:**5			2
Tg	2			↓***H:41***			2			2						2			**M:**5			2
Total:HDL-c	2			↓***H:8***			1									1			3			
LDL:HDL-c				3												1			1			

Table summarizing the number of studies that report on each evaluation of a type of omega−3 fatty acid (n-3 FA) and outcome, by study design. High (H), moderate (M), and low (L) strength of evidence for each n-3 FA-outcome pair are indicated by the respective letters (and bold font). Bold upright (nonitalic) script indicates evidence of no effect or association; bold italic text indicates evidence of a reduced (↓) or increased (↑) cardiovascular risk associated with the outcome with higher n-3 FA intake (as indicated by the direction of the arrow). n-3 FA-outcome pairs with regular font had insufficient evidence. Blank cells indicate no studies of the given design type reported on the n-3 FA-outcome pair.

Abbreviations: ALA = alphalinolenic acid, DBP = diastolic blood pressure, DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, EPA = eicosapentaenoic acid, HDL-c = high density lipoprotein cholesterol, LDL:HDL-c = LDL-c to HDL-c ratio, LDL-c = low density lipoprotein cholesterol, MAP = mean arterial pressure, MvA = direct comparison of marine oil and ALA (in randomized controlled trials), n-3 FA = omega−3 fatty acids, OB = observational studies of n-3 FA biomarkers, OI = observational studies of n-3 FA intake, R = randomized controlled trials, SBP = systolic blood pressure, Tg = triglycerides, Total:HDL-c = total cholesterol to HDL-c ratio.

Major Adverse Cardiovascular Events

Randomized Controlled Trials

Ten RCTs reported the composite outcome major adverse cardiac event (MACE) (Table 3).[67, 90, 96, 115, 119, 121, 123, 146, 157, 160] Of these, three studies were conducted in a total of 31,713 people at risk of CVD including dyslipidemia,[90, 115] or a combination of various risk factors.[160] Eight studies were conducted in a total of 35,095 people with CVD, defined as a history of CVD,[123] a history of myocardial infarction (MI),[67, 119, 121] acute MI,[90] previous coronary heart disease (CHD),[90] peripheral artery disease at any time,[90] persistent atrial fibrillation (AFib),[157] heart failure,[96] or, in one study, either a history of CVD or of diabetes.[146] None of the RCTs were conducted in a generally healthy population. One study analyzed MACE as a primary outcome (Roncaglioni 2013); however, the trial changed the primary outcome at 1 year from CVD death due to a low event rate.[160]

MACE was defined differently for each study, but was generally a composite of all-cause death,[96, 121, 157] cardiovascular (CV) death,[123, 146, 160] cardiac death,[67, 90] fatal and nonfatal MI,[67, 90, 115, 119, 123, 146] cardiac arrest,[115, 119] unstable angina,[67, 90] hospitalization for CV reasons,[96, 157, 160] stroke,[115, 119, 121, 123, 146] coronary artery bypass grafting,[90, 115] and/or other CV procedures.[67, 90, 115, 121]

Marine Oil Versus Placebo

Meta-analysis of the 10 RCTs of marine oil versus placebo yielded a nonsignificant summary effect size for risk of MACE: hazard ratio (HR) = 0.96 (95% confidence interval [CI] 0.91 to 1.02) (Figure 6).[67, 90, 96, 115, 119, 121, 123, 146, 160, 166]

At-Risk-for-CVD Population

Among people at risk of CVD, one trial compared EPA ethyl ester (combined with statin) with control (statin alone) in 18,645 participants with dyslipidemia (19.5% with CHD)[90] and two studies compared marine oil (EPA+DHA) to placebo (olive oil or corn oil) in a total of 13,068 participants with dyslipidemia or multiple CVD risk factors.[115, 160] In the study of EPA ethyl ester, the dose of EPA was 1.8 g/d; in the other two studies the doses of EPA+DHA were 0.85 and 2.02 g/d with EPA to DHA ratio either 0.9 or 1.5. Compliance was monitored and the adherence level was greater than 90 percent in one study,[115] but not reported in the other two studies. The duration of followup ranged from 3 to 5 years.

In one RCT, EPA supplementation (1.8 g/d) had a significant additive effect (to statin therapy) on reducing the risk of MACE (including sudden cardiac death [SCD], fatal and nonfatal MI, and nonfatal unstable angina pectoris, angioplasty, stenting, or coronary artery bypass grafting) compared with statin alone after 5 years of followup, both when including the 19.5 percent of patients with CHD (HR 0.81; 95% CI 0.69 to 0.95) and when considering the subpopulation with dyslipidemia only (HR 0.81; 95% CI 0.66 to 1.00).[90] The other two trials found that EPA+DHA supplementation (0.85 and 2.02 g/d) did not significantly reduce the risk of MACE (heterogeneous definitions) compared with placebo (HR 0.98, 95% CI 0.88 to 1.08; HR 0.89, 95% CI 0.55 to 1.44)

Subgroup meta-analysis yielded a summary HR of 0.90 (95% CI 0.77 to 1.05) for people at risk for CVD.

CVD Population

Among people with CVD, eight RCTs (seven parallel design, one a 2-by‒2 factorial RCT) evaluated MACE. Six simple RCTs compared marine oil (EPA+DHA) to placebo (olive oil in two studies and sources not reported in the other two studies) in a total of 22,259 participants with diabetes and history of CVD, all CVD, heart failure or previous persistent AFib.[96, 123, 146, 157] The 2-by‒2 factorial RCT compared the effects of a margarine supplemented with EPA+DHA alone (0.4 g/d), a combination of both EPA+DHA and ALA margarines, and ALA alone (2 g/d) with placebo margarine (oleic acid) in 4837 participants with a history of MI.[119] (The 2-by‒2 factorial trial reported only analyses of EPA+DHA vs. placebo and ALA vs. placebo.) One trial compared 1.8 g/d EPA ethyl ester plus statin with statin alone in two populations: 3,664 with previous CHD and 223 with peripheral artery disease at any time.[90]

Among the seven trials that compared marine oil (EPA+DHA) to placebo, the doses of EPA+DHA used ranged from 0.4 to 3.5 g/d, and the EPA to DHA ratio ranged from 0.5 to 2. Reported in five studies, the compliance ranged from 70 to 90 percent. The duration of followup ranged from 1 to >6 years. Six of the seven trials found that EPA+DHA supplementation did not significantly reduce the risk of MACE (heterogeneous definitions) compared with placebo (HR or odds ratio [OR] ranging from 0.88 to 1.21).[67, 119, 121, 123, 146, 157] The seventh trial found that EPA+DHA ethyl ester supplementation significantly reduced the risk of MACE (defined as death from any cause or admission to the hospital for CV reasons) compared with placebo in 6975 participants with heart failure (HR 0.92, 95% CI 0.85 to 0.99).[96] In the trial that compared EPA plus statin with statin alone, the analysis of patients with previous CHD found no significant additive effect of EPA supplementation on the risk of MACE (HR 0.82; 95% CI 0.63 to 1.06), while the analysis of patients with peripheral artery disease at any time did find a significant additive effect (HR 0.44; 95% CI 0.19 to 0.97).[90]

Subgroup meta-analysis yielded a summary HR of 0.98 (95% CI 0.92 to 1.05) for people with CVD.

ALA Versus Placebo

CVD Population

In the 2-by‒2 factorial RCT, the groups that received ALA margarines had no significant difference in the risk of MACE compared with placebo margarines (HR 0.92; 95% CI 0.73 to 1.11).[119]

RCT Subgroup Analyses

Three RCTs reported subgroup analysis for MACE (Table 4). In one trial, EPA+DHA (vs. placebo) lowered the risk of MACE in women (HR=0.82) in contrast with the effect in men (HR 1.04) and the difference between women and men was statistically significant (P interaction 0.04).[160] The second trial found no difference in effect of EPA versus placebo between men and women (HR 0.76 vs 0.87, P-interaction 0.43).[90] This study analyzed several other subgroups, but found no significant differences in effect between any subgroups. These included age ≥61 versus <61 years, body mass index ≥24 versus <24 kg/m^2, triglycerides (Tg) ≥270 versus <270 mg/dL, Tg ≥150 versus <150 mg/dL, high density lipoprotein cholesterol (HDL-c) ≥58 versus <58 mg/dL, low density lipoprotein cholesterol (LDL-c) ≥181 versus <181 mg/dL, history of CHD versus no CHD, smoker versus nonsmoker, diabetes versus no diabetes, and hypertension versus no hypertension.[90] The third trial reported an incomplete and unclear analysis of many subgroup analyses for both EPA+DHA versus placebo and ALA versus placebo. No interaction analyses were reported, but near-significant effects (P<0.10) of ALA on MACE reduction were seen for those <70 years old (HR 0.83, P=0.08) as opposed to older subjects (HR 1.00, P=0.98) and for women (HR 0.73, P=0.07) as opposed to men (HR 0.96, P=0.60). No significant effects of ALA were found in all subgroups based on time since MI, baseline fish intake, baseline EPA+DHA intake, and history of diabetes. No significant effects of EPA+DHA were found in all subgroups analyzed.

Meta-regression of the marine oil trials found no significant interaction between n-3 FA dose (P=0.15), followup time (P=0.49), or between at risk and CVD populations (P=0.63)

Observational Studies

Seven studies evaluated variously defined MACE (or total CVD events), composite outcomes that combined cardiac, coronary, and cerebrovascular events (Appendix F, Major adverse cardiac events section; Figure 7). Each study used its own combination of diagnoses. The studies included generally healthy adults or, in one instance, "at risk" adults with hypercholesterolemia on low dose statins.[50, 101, 122, 126, 137, 155, 171, 183] Followup durations ranged from 4 to about 20 years.

n-3 FA Intake

Five studies evaluated n-3 FA intake (Danish National Birth Cohort, Health Professional Follow-up Study, Malmo Diet and Cancer, MESA, Physician's Health Study).[50, 101, 137, 155, 171, 183]

Three studies analyzed intake of total n-3 FA combined (Figure 7, plot # 17 & 18). The Physician's Health Study (in healthy men)[50, 155] and the Malmo Diet and Cancer study (in healthy adults)[183] both found no association with MACE at 4 and 14 years of followup. In contrast the Danish National Birth Cohort (in healthy women who were pregnant at the time of enrollment) found significantly *increased* risks of cerebrovascular, ischemic heart disease, or hypertensive disease hospitalization after 12 years on those with higher n-3 FA intake (Figure 7, plot #18).[137] However, no clear intake threshold was found.

The Malmo Diet and Cancer and MESA studies found no association between ALA intake and MACE at 10 and 14 years of followup (Figure 7, plots #1 & 2).[171, 183]

MESA found an overall significant association between both EPA, DHA, and DPA intake (separately) and combined ischemic coronary events, cardiac arrest, stroke, and CVD death in healthy adults after 10 years of followup (Figure 7, plots #4, 8, 14).[171] For DHA intake, the association was near-significant (P<0.10) for the uppermost quartile with a median dose of 0.15 g/d, for DPA 0.02 g/d, and for EPA 0.04 g/d.

Three studies evaluated combined EPA+DHA or EPA+DHA+DPA intake (Figure 7, plots # 11 & 12). The Health Professionals Follow-up Study (evaluating EPA+DHA)[101] and Malmo Diet and Cancer study (evaluating EPA+DHA+DPA)[183] found no significant association at 14 and 18 years of followup. MESA found an overall statistically-significant lower risk of combined ischemic coronary events, cardiac arrest, stroke, and CVD death in healthy adults after 10 years of followup with higher intake of EPA+DHA+DPA.[171] The association was near-significant for the highest quartile with a median intake dose of about 0.3 g/d (P<0.10).

n-3 FA Biomarkers

Five studies evaluated n-3 FA biomarkers (JELIS, Physician's Health Study, Scottish Heart Health Extended Cohort Study, MESA, Hisayama).[50, 122, 126, 155, 168, 171]

The Physician's Health Study and MESA found no associations between erythrocyte or phospholipid ALA levels and MACE (Figure 7, plot # 3, erythrocyte n-3 FA associations not plotted because they were not analyzed by quantile).[50, 155, 171]

Four studies evaluated EPA biomarkers, two of which found statistically significant associations with MACE (Figure 7, plots #10 & 16). The Physician's Health Study found no significant association between erythrocyte EPA and MACE in healthy men.[50, 155] Hisayama found no significant association between plasma EPA and MACE in healthy patients.[168] MESA, in contrast, found a significant association between higher phospholipid EPA and lower MACE (Figure 7, plot #15).[171] In a population of people with dyslipidemia on low-dose statins, JELIS also found a significant association between higher plasma EPA and lower risk of MACE (Figure 7, plot #10).[122]

Five studies evaluated DHA biomarkers, with heterogeneous findings (Figure 7, plots #6 and 7; other biomarkers not plotted due to insufficient reported data or not quantile analysis). Hisayama, JELIS and the Physician's Health Study found no significant associations with plasma or erythrocyte DHA.[50, 122, 155, 168] The Scottish Heart Health Extended Cohort Study, though, found that higher adipose tissue DHA levels were associated with reduced risk of MACE at about 20 years of followup,[126] and the MESA study also found reduced risk of MACE associated with higher phospholipid DHA levels at 10 years of followup.[171]

Three studies evaluated DPA biomarkers, one of which found a significant association (Figure 7, plot #9; other biomarkers not plotted due to insufficient reported data or not quantile analysis). The Scottish Heart Health Extended Cohort Study found that higher adipose tissue DPA levels were associated with lower risk of MACE at about 20 years of followup.[126] In contrast, the Physician's Health Study and MESA found no significant associations with erythrocyte or phospholipid DPA.[50, 155, 171]

The Physician's Health Study also found no significant association between erythrocyte SDA and MACE.[50, 155]

Two studies evaluated combined EPA+DHA biomarkers (Figure 7, plot #13). The Physician's Health Study found no association with erythrocyte EPA+DHA,[50, 155] but MESA found that higher phospholipid EPA+DHA levels were associated with lower risk of MACE at 10 years of followup.[171]

Observational Study Subgroup Analyses

Only MESA reported subgroup analyses.[171] In comparisons of n-3 FA biomarker associations with MACE by race, the study found no significant differences in associations for EPA, DHA, and EPA+DHA+DPA levels, but whites (HR=0.41) and Chinese (HR=0.30) had significantly stronger associations than African Americans (HR=1.51) and Hispanics (HR=1.33; P interaction = 0.01).

Table 3. Major adverse cardiovascular events (composite outcome): RCTs

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int n/N,%	Ctrl n/N,%	Effect Size	Reported P value
Marine oil vs Placebo											
Yokoyama 2007 17398308* Japan	At risk (dyslipidemia; 19.5% with CHD)	EPA+Statin	1.8 g/d (Ethyl ester)	Statin	0	5 y	Local physicians monitored but compliance level was not reported	262/9326, 2.8%	324/9319, 3.5%	HR 0.81 (0.69, 0.95)	0.011
	At risk	EPA+Statin	1.8 g/d (Ethyl ester)	Statin	0	5 y	Local physicians monitored but compliance level was not reported	104/7503 1.4%	127/7478 1.7%	HR 0.81 (0.66, 1.00)	0.048
Einvik 2010 20389249† Scandinavia	At risk	EPA+DHA+ diet intervention	2.02 g/d (Marine oil) [E:D 1.4]	Placebo+diet intervention	0 (Corn oil)	3 y	>90% of the tablets were taken based on pharmacy records, and verified by biomarkers	32/282, 11%	36/281, 13%	HR 0.89 (0.55, 1.44)	0.624
Roncaglioni 2013 23656645‡ Italy	At risk	EPA+DHA	0.85 g/d (Marine oil) [E:D 0.9−1.5]	Placebo	0 (Olive oil)	5 y	Monitored by self-report but compliance level was not reported	733/6239, 12%	745/6266, 12%	HR 0.98 (0.88, 1.08)	0.64
Bosch 2012 22686415§ Canada	CVD (or diabetes)	EPA+DHA	0.84 g/d (Marine oil) [E:D 1.24]	Placebo	0 (Olive oil)	6+ y	FFQ at baseline, 2 years, and end of study (adherence was 88% at the end of study)	1034/6281, 16.5%	1017/6255, 5.1%	HR 1.01 (0.93, 1.10)	0.81

Table 3. Major adverse cardiovascular events (composite outcome): RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int n/N,%	Ctrl n/N,%	Effect Size	Reported P value
Galan 2010 21115589¶ France	CVD	EPA+DHA	0.6 g/d (Marine oil) [E:D 2]	Placebo	0 (nd)	4.7 y	Patient reported (86% reported they took ≥80% of allocated treatment)	81/1253, 7%	76/1248, 6%	HR 1.08 (0.79, 1.47)	0.64
Macchia 2013# 23265344	CVD	EPA+DHA	0.850-0.882 g/d (Marine oil) [E:D 0.5]	Placebo	0 (Olive oil)	1 y	nd	16/289, 6%	20/297, 7%	HR 0.86 (0.44, 1.66)	
Rauch 2010 21060071 Germany	CVD	EPA+DHA	0.46 g EPA, 0.38 g DHA (Marine oil) [E:D=1.2]	Placebo	0 (Olive oil)	1 y	Pill counts at 3 months and 12 months (≥70% of study period)	182/1752, 10.4%	149/1701, 8.8%	OR 1.21 (0.96, 1.52)	0.10
Tavazzi 2008 18757090** Italy	CVD	EPA+DHA	0.850−0.882 g/d (Ethyl esters) [E:D 0.83]	Placebo	0 (nd)	3.9 y	Exam question (~30% not taking n-3 FA or placebo by the end of study)	1981/3494, 57%	2053/3481, 57%	HR 0.92 (0.85, 0.999)	0.009
Kromhout 2010 20929341†† Netherlands	CVD	EPA+DHA (±ALA)	0.4 g/d EPA+DHA and 2 g/d ALA (Marine; Plant oil) [E:D 3:2]	Placebo (±ALA)	0; 2 g/d ALA (Placebo margarine = oleic acid; Plant oil)	3.4 y	90% of the patients adhered fully to the protocol; verified by biomarkers	336/2424, 14.0%	335/2433, 13.8%	HR 1.01 (0.87, 1.17)	0.93
Nilsen 2001 2001 11451717 Norway	CVD	EPA+DHA	EPA-DHA 3.4−3.528 g/d (Marine oil) [E:D=0.5]	Placebo	0 (Corn oil)	median 2.4 y	nd	52/150, 34.7%	49/150, 32.7%	OR 1.09 (0.68, 1.77)	

continued

Table 3. Major adverse cardiovascular events (composite outcome): RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int n/N,%	Ctrl n/N,%	Effect Size	Reported P value
Yokoyama 2007 17398308* Japan	CVD (previous CHD)	EPA+Statin	1.8 g/d (Ethyl ester)	Statin	0	5 y	Local physicians monitored but compliance level was not reported	158/1823 8.7%	197/1841 10.7%	HR 0.82 (0.63, 1.06)	0.132
	CVD (PAD at any time)	EPA+Statin	1.8 g/d (Ethyl ester)	Statin	0	5 y	Local physicians monitored but compliance level was not reported	9/117 7.7%	18/106 17%	HR 0.44 (0.19, 0.97)	0.041
ALA vs. Placebo											
Kromhout 2010 20929341†† Netherlands	CVD	ALA (±EPA+DHA)	0.4 g/d EPA+DHA and 2 g/d ALA (Marine; Plant oil) [E:D 3:2]	Placebo (±EPA+DHA)	0; 0.4 g/d EPA-DHA (placebo = oleic acid; Marine oil) [E:D 3:2]	3.4 y	90% of the patients adhered fully to the protocol; verified by biomarkers	319/2409 , 13.2%	352/2428, 14.5%	HR 0.91 (0.78, 1.05)	0.20

* Sudden cardiac death, fatal and nonfatal myocardial infarction, and other nonfatal events including unstable angina pectoris, angioplasty, stenting, or coronary artery bypass grafting

† Fatal or nonfatal sudden cardiac arrest, myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, cerebral stroke, surgery on abdominal aortic aneurysm, or peripheral revascularization procedures

‡ Death from cardiovascular causes or hospital admission from cardiovascular causes

§ Myocardial infarction, stroke, or death from cardiovascular causes

¶ Nonfatal myocardial infarction, ischemic stroke, or death from cardiovascular disease (including fatal myocardial infarction, stroke, sudden death, aortic dissection, cardiac failure, or other fatal event defined by the medical committee as having a cardiovascular cause)

First occurrence of either all-cause mortality, nonfatal stroke, nonfatal acute myocardial infarction, systemic embolism, heart failure development, or severe bleeding

** Death from any cause or admission to the hospital for cardiovascular reasons

†† Fatal CVD, nonfatal myocardial infarction, nonfatal cardiac arrest, and nonfatal stroke

Abbreviations: ALA = alphalinolenic acid, CHD = coronary heart disease, Ctrl = control, CVD = cardiovascular disease, DHA = docosahexaenoic acid, E:D = EPA to DHA ratio, EPA = eicosapentaenoic acid, F/up = followup, FFQ = food frequency questionnaire, HR = hazard ratio, Int = intervention, n/N = number with outcome/number analyzed, n3 FA = omega-3 fatty acids, n6:3 = omega-6 to omega-3 fatty acid ratio, OR = odds ratio, RCT = randomized controlled trial.

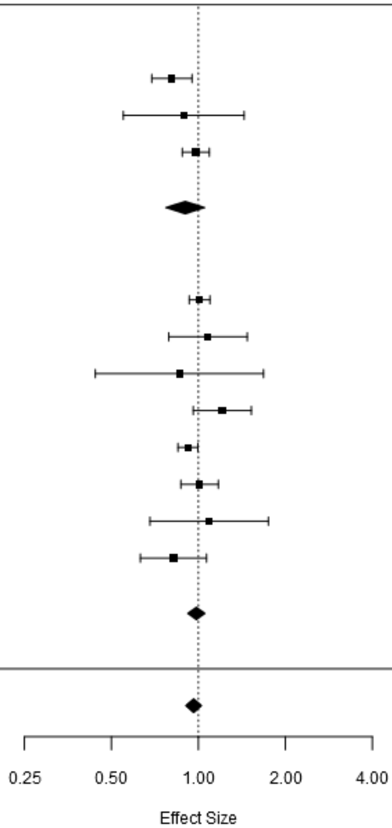
Table 4. Major adverse cardiovascular events (composite outcome): Subgroup analyses, randomized trials

Study	Population	Subgroups	n-3 FA	Comparator	N Total	P difference	Difference	Favors
Roncaglioni 2013 23656645 Italy	At risk	Men vs. women	EPA+DHA	Placebo	12505	0.04	HR 1.04 vs. 0.82	Women
Yokoyama 2007 17398308 Japan	At risk	Men vs. women	EPA	Placebo	18645	0.43		
		Age ≥61 vs. <61 y	EPA	Placebo	18645	0.57		
		Body mass index ≥24 vs. <24 kg/m^2	EPA	Placebo	18645	0.88		
		Tg ≥270 vs. <270 mg/dL	EPA	Placebo	18645	0.46		
		Tg ≥150 vs. <150 mg/dL	EPA	Placebo	18645	0.75		
		HDL-c ≥58 vs. <58 mg/dL	EPA	Placebo	18645	0.26		
		LDL-c ≥181 vs. <181 mg/dL	EPA	Placebo	18645	0.83		
		CHD vs. no CHD	EPA	Placebo	18645	0.95		
		Smoker vs. nonsmoker	EPA	Placebo	18645	0.89		
		Diabetes vs. no diabetes	EPA	Placebo	18645	0.62		
		HTN vs no HTN	EPA	Placebo	18645	0.57		
		PAD vs no PAD at baseline	EPA	Placebo	18645	0.16		
Kromhout 2010 20929341 Netherlands	CVD	≥70 vs. <70 y	EPA+DHA	Placebo or ALA	4837	NS both subgroups		
		Men vs. women	EPA+DHA	Placebo or ALA	4837	NS both subgroups		
		Time since MI ≥3.7 vs. <3.7 y	EPA+DHA	Placebo or ALA	4837	NS both subgroups		
		Baseline fish intake ≥5 vs. <5 g/d	EPA+DHA	Placebo or ALA	4837	NS both subgroups		
		Baseline EPA+DHA intake ≥50 vs. <50 mg/d	EPA+DHA	Placebo or ALA	4837	NS both subgroups		
		Diabetes vs. no diabetes	EPA+DHA	Placebo or ALA	4837	NS both subgroups		
		Statin vs. no statin	EPA+DHA	Placebo	4153	NS both subgroups		
	CVD	≥70 vs. <70 y	ALA	Placebo or EPA+DHA	4837	NS older P=0.08 younger	HR 1.00 vs. 0.83	<70 y (possibly)
		Men vs. women	ALA	Placebo or EPA+DHA	4837	NS men P=0.07 women	HR 0.96 vs. 0.73	Women (possibly)
		Time since MI ≥3.7 vs. <3.7 y	ALA	Placebo or EPA+DHA	4837	NS both subgroups		
		Baseline fish intake ≥5 vs. <5 g/d	ALA	Placebo or EPA+DHA	4837	NS both subgroups		
		Baseline EPA+DHA intake ≥50 vs. <50 mg/d	ALA	Placebo or EPA+DHA	4837	NS both subgroups		
		Diabetes vs. no diabetes	ALA	Placebo or EPA+DHA	4837	NS both subgroups		
		Statin vs. no statin	ALA	Placebo	4153	NS both subgroups		
	CVD	Statin vs. no statin	EPA+DHA+ALA	Placebo	4153	NS statin, 0.051 no statin	HR 1.02 vs. 0.46	No statin (possibly)

Abbreviations: ALA = alphalinolenic acid, CHD = coronary heart disease, CVD = cardiovascular disease, DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid, HDL-c = high density lipoprotein cholesterol, HR = hazard ratio, HTN = hypertension, LDL-c = low density lipoprotein cholesterol, MI = myocardial infarction, n-3 FA = omega-3 fatty acids, NS = not significant, PAD = peripheral artery disease, Tg = triglycerides.

Figure 6. Major adverse cardiovascular events: Randomized trials of marine oils

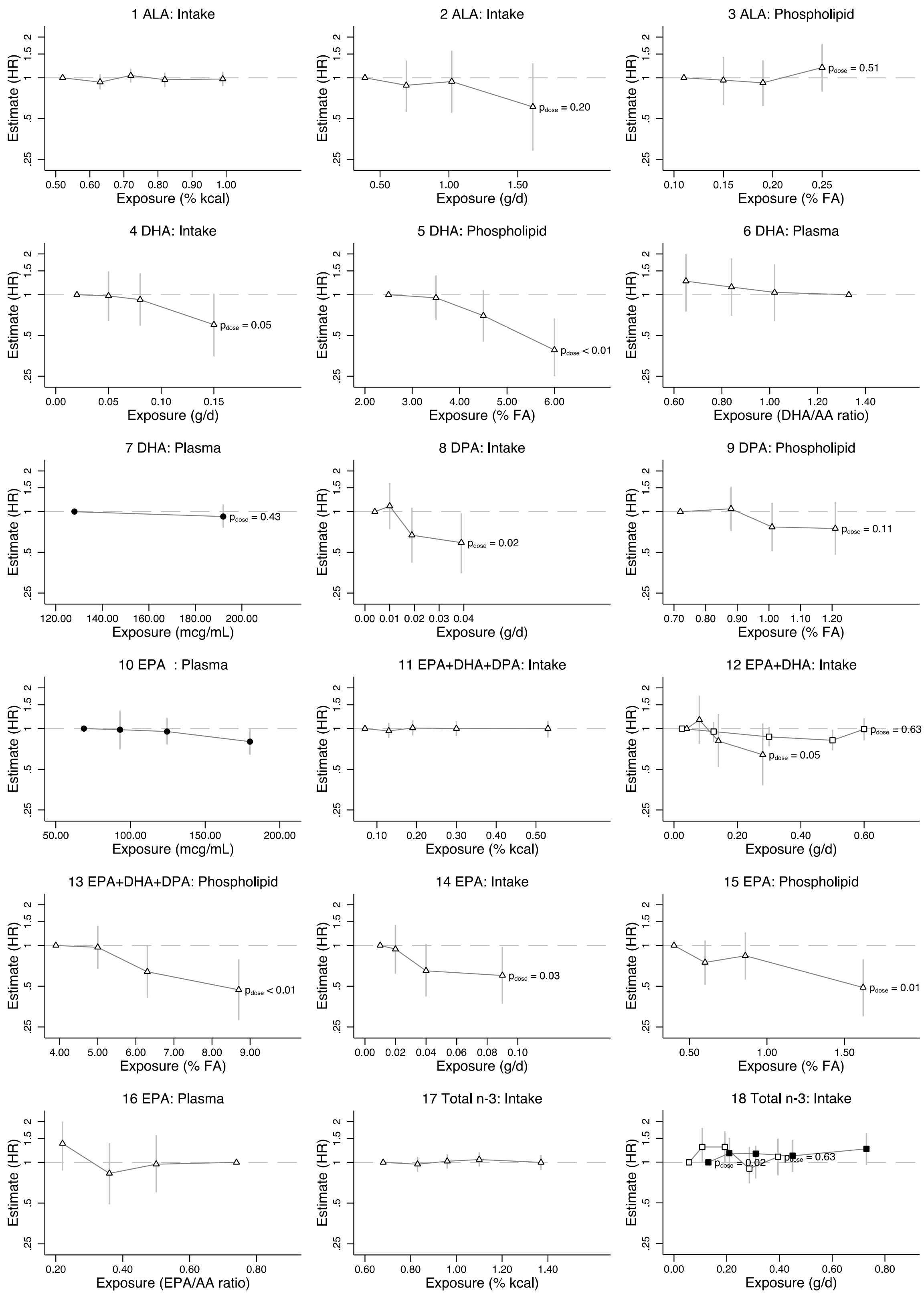
Study PMID	n-3 FA	g/day	Years	n-3 FA n/N	Placebo n/N	Effect Size [95% CI]
At risk population						
Yokoyama 2007 17398308	EPA	1.8	5	262/9326	324/9319	0.81 [0.69, 0.95]
Einvik 2010 20389249	EPA+DHA	2.02	3	32/282	36/281	0.89 [0.55, 1.44]
Roncaglioni 2013 23656645	EPA+DHA	0.85	5	733/6239	745/6266	0.98 [0.88, 1.08]
Summary, at risk						*0.90 [0.77 , 1.05]*
CVD population						
Bosch 2012 22686415	EPA+DHA	0.84	6	1034/6281	1017/6255	1.01 [0.93, 1.10]
Galan 2010 21115589	EPA+DHA	0.6	4.7	81/1253	76/1248	1.08 [0.79, 1.47]
Macchia 2013 23265344	EPA+DHA	0.87	1	16/289	20/297	0.86 [0.44, 1.66]
Rauch 2010 21060071	EPA+DHA	0.46	1	182/1752	149/1701	1.21 [0.96, 1.52]
Tavazzi 2008 18757090	EPA+DHA	0.87	3.9	1981/3494	2053/3481	0.92 [0.85, 0.999]
Kromhout 2010 20929341	EPA+DHA*	0.4	3.5	336/2424	335/2433	1.01 [0.87, 1.17]
Nilsen 2001 11451717	EPA+DHA	3.46	2.4	52/150	49/150	1.09 [0.68, 1.77]
Yokoyama 2007 17398308	EPA	1.8	5	158/1823	197/1841	0.82 [0.63, 1.06]
Summary, CVD						*0.98 [0.92 , 1.05]*
Summary [I-squared=30.248, Phet=0.188]						**0.96 [0.91 , 1.02]**



Random effects model meta-analysis of n-3 FA versus placebo (or no n-3 FA), with subgroup analyses by population. In all meta-analyses, only studies that reported sufficient results data are included.

Abbreviations: CI = confidence interval, CVD = cardiovascular disease, DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid, FA = fatty acid(s), n/N = number with outcome/number analyzed, n-3 FA = omega-3 fatty acids, Phet = P value of chi-squared test of heterogeneity across studies, PMID = PubMed Identification number.

Figure 7. n-3 FA associations with major adverse cardiovascular events: Observational studies



Study (or cohort) level associations between n-3 FA exposure and hazard ratio (HR) for the outcome. Studies that reported associations by continuous exposure (e.g., per g/d intake or per standard deviation) could not be graphed and are omitted. P values are the study-reported P value for the trend across quantiles. Where 95% confidence intervals (vertical lines) are missing, these were not reported in the studies.
White triangles = healthy adults, black circles = adults with dyslipidemia (at risk), white squares = healthy males, black squares = healthy females.

Abbreviations: AA = arachidonic acid, ALA = alphalinolenic acid, DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, EPA = eicosapentaenoic acid, HR = hazard ratio, n-3 FA= omega-3 fatty acids.

CVD Death (Including Stroke)

Randomized Controlled Trials

Seven RCTs reported total CVD death (Table 5).[67, 70, 96, 115, 119, 146, 160] Of these, two were conducted in a total of 13,068 people at risk of CVD defined as dyslipidemia or at least four CVD risk factors,[115, 160] and the other five in a total of 36,002 people with CVD including diabetes, history of CVD, MI or heart failure.[67, 70, 96, 119, 146] None of the trials analyzed CVD death as a primary outcome, but Roncaglioni 2013 reported that it was the *a priori* primary outcome; the primary outcome was changed to MACE at 1 year due to a low event rate for CVD death).[160]

Marine Oil Versus Placebo

Meta-analysis of the seven RCTs of marine oil versus placebo yielded a nonsignificant summary effect size for risk of CVD death: HR=0.92 (95% CI 0.82 to 1.02) (Figure 8).[67, 70, 96, 115, 119, 146, 160]

At-Risk-for-CVD Population

Among people at risk of CVD, two studies compared marine oil (EPA+DHA) to placebo (either olive oil or corn oil) in a total of 13,068 participants.[115, 160] The doses of EPA and DHA were less than 0.85 and 2.02 g/d, and the EPA to DHA ratio ranged from 0.9 to 1.5. Compliance was high (>90%) in one study[115] and not reported (although monitored by self-report) in another study.[160] The durations of followup were 3 and 5 years. Both studies found that EPA+DHA supplementation did not significantly reduce CVD death compared with placebo (HR 1.03, 95% 0.82 to 1.30; OR 0.62, 95% CI 0.24 to 1.64).

Subgroup meta-analysis yielded a summary HR of 0.99 (95% CI 0.77 to 1.28) for people at risk for CVD.

CVD Population

Among people with CVD, five trials compared marine oil (EPA+DHA) to placebo (olive oil in one study, corn oil in another, and source was not reported in one study),[67, 96, 146] to no intervention,[70] and in a factorial study with ALA,[119] in a total of 36,002 participants. The dose of EPA+DHA ranged from 0.84 to 3.5 g/d, and the EPA to DHA ratio ranged from 0.5 to 1.24. Compliance ranged from about 70 to 88 percent. The mean duration of followup ranged from 2.4 to more than 6 years. Two of the five studies found that EPA+DHA supplementation significantly reduced the CVD death compared with no intervention or placebo in 11,334 participants with MI (RR 0.70, 95% CI 0.56 to 0.86)[70] and in 6975 participants with heart failure (adjusted HR 0.91, 95% CI 0.81 to 0.99).[96] Two studies did not find a difference in the risk of CVD death between EPA+DHA and placebo in 12,536 participants with diabetes or history of

CVD (HR 0.98, 95% CI 0.87 to 1.10).[146] and in 300 participants with acute MI (HR 1.37, 95% CI: 0.63 to 3.01).[67] The fifth study was the 2-by–2 factorial RCT described under *Major Adverse CVD Events* that compared EPA+DHA, EPA+DHA and ALA, ALA, and oleic acid margarines in 4837 participants with MI.[119] . During a mean of 3.4 years of followup, EPA+DHA containing margarines had no significant effect on CVD death compared with the ALA alone or placebo margarines (HR 0.98; 95% CI 0.72 to 1.33).

Subgroup meta-analysis yielded a summary HR of 0.90 (95% CI 0.79 to 1.03) for people with CVD.

ALA Versus Placebo

CVD Population

In the 2-by–2 factorial RCT, the groups that received ALA margarines had no significant difference in the risk of MACE compared with placebo margarines (HR 0.94; 95% CI 0.69 to 1.27).[119]

RCT Subgroup Analyses

Three RCTs reported subgroup analysis for CVD death (Table 6). The same 2-by–2 factorial RCT analyzed subgroups based on history of diabetes.[119] For patients with diabetes, EPA+DHA had a nonsignificant reduction in CVD death risk (HR=0.60, P=0.08) in contrast to those without diabetes (HR=1.21, P=0.32); no test for interaction was reported. The effect of ALA on CVD death was similarly nonsignificant in both patients with diabetes (HR=0.87, P=0.63) and those without diabetes (HR=0.97, P=0.87).

Bosch 2012 analyzed subgroups based on glargine use, age over 65, prior CVD events, heart rate over 69 beats per minute, statin use, beta blocker use, tertiles of n-3 FA intake, and triglyceride tertiles, none of which found significant interactions or significant effects of EPA+DHA on CVD death.

Meta-regression of the marine oil trials found no significant interaction between n-3 FA dose (P=0.59), followup time (P=0.33), or between at risk and CVD populations (P=0.75)

Observational Studies

Eight studies evaluated the association between n-3 FA intake or biomarkers and total CVD death in healthy adults from 4 to 31 years of followup (median 11 years) (Appendix F Death from cardiovascular disease section; Figure 9).[47, 50, 72, 95, 98, 159, 162, 175, 186] The studies had heterogeneous findings regarding associations between higher n-3 FA intake or biomarker levels and lower risk of CVD death.

n-3 FA Intake

Eight studies evaluated n-3 FA intake (JACC, MRFIT, NIPPON DATA80, Physician's Health Study, Shanghai Women's and Men's Health Studies, Singapore Chinese Healthy Study, Takayama, VITAL).[47, 50, 72, 98, 155, 162, 170, 175, 176]

Four studies evaluated total n-3 FA intake (JACC, NIPPON DATA80, Physician's Health Study, Singapore Chinese Health Study) (Figure 9, plots #31 & 32).[50, 98, 155, 170, 175, 176] JACC found a significant association between higher total n-3 FA intake (combined) and lower CVD death risk in healthy adults after about 13 years of followup, with a significant association occurring in quantile with median of 2 g/d or higher.[98] JACC and NIPPON DATA80, however, found no significant associations at 4 and 24 years of followup.[98, 175] The Singapore Chinese Health Study found no significant association between higher total n-3 FA intake and lower CVD death risk in CVD adults, but found a significant association in healthy adults (P=0.006).[170]

Three studies evaluated ALA intake with conflicting results (Figure 9, plots #19 & 20). MRFIT found a significant association between higher ALA intake (measured as percent Kcal) and lower CVD risk at about 10 years (particularly in quartiles with median intake greater than about 0.7% Kcal); when ALA intake was measured as g/d, the association was similar, but nonsignificant (P=0.10). The Cardiovascular Health Study found no association at 12 years of followup.[47] The Singapore Chinese Health Study found no significant association between higher ALA intake and lower CVD death risk in CVD adults, but found a significant association in healthy adults (P<0.001).[170]

Two studies evaluated EPA intake, also with conflicting results (Figure 9, plots #28 & 29). NIPPON DATA80 found no association at 24 years of followup,[175] but the Shanghai Women's and Men's Health Studies found a significant association between higher EPA intake and lower risk of CVD death among men (at about 6 years of followup) and women (at about 12 years), combined (with significant associations in all quintiles with median intake of about 0.01 g/d or higher).[162]

The same two studies evaluated DHA intake (Figure 9, plots #22 & 23). NIPPON DATA found no significant association between higher DHA intake and lower CVD death risk (P=0.099).[175] The Shanghai Women's and Men's Health Studies found a significant association between higher EPA intake and lower risk of CVD death, as with EPA.[162] Significant or near-significant (P<0.10) associations were seen in quantiles with median doses of about 1.25 percent Kcal or about 0.02 g/d, or higher.

Six studies evaluated EPA+DHA intake (3 studies; NIPPON DATA80, Shanghai Women's and Men's Health Studies, Singapore Chinese Health Study, Takayama, VITAL)[72, 162, 170, 175, 176] or EPA+DHA+DPA intake (MRFIT) (Figure 9, plots #26 & 27).[47] The Shanghai Women's and Men's Health Studies and MRFIT found significant associations between higher marine oil intake and lower CVD death risk.[47, 162] The Singapore Chinese Health Study found no significant association between higher marine oil intake and lower CVD death risk in CVD adults, but found a significant association in healthy adults (P=0.002).[170] VITAL found no significant associations between higher marine oil intake and lower CVD death risk in both healthy and CVD adults.[176] In MRFIT, the association was statistically significant when marine oil intake (either g/d or % Kcal) was analyzed as a continuous variable in a linear model and near-significant (P<0.10) when analyzed across quintiles.[47] Both NIPPON DATA80 and Takayama found no significant associations overall.[72, 175] For percent Kcal analyses, near-significant associations were found in quantiles with median intake of about 0.30 percent Kcal or higher. In two of the g/d analyses, near-significant associations were found in quantiles with median marine oil intake of about 0.7 g/d.

By meta-analysis (Table 7), overall there is a statistically significant association between marine oil intake and CVD death across a median dose range of 0.066 to 1.58 g/d (effect size per g/d = 0.88; 95% CI 0.82 to 0.95). Meta-analyses with the addition of a spline knot point at different dose thresholds (from 0.1 to 1.2 g/d) consistently found a stronger association (of higher dose being associated with lower risk) at *lower* doses than at higher doses (ES below knot less than 1; ES above knot closer to 1). This implies the possibility of a ceiling effect (where intake above a certain level adds no further benefit). However, at no dose threshold was there a statistically significant difference between the ES below the dose threshold (knot) and above the threshold. The best fit curve was found with a knot at 0.3 g/d. The lowest P value between lower-dose and higher-dose ES estimates was found at 0.2 g/d (P=0.26).

n-3 FA Biomarkers

The Cardiovascular Health Study and ULSAM evaluated n-3 FA plasma levels.[95, 148]

The Cardiovascular Health Study found a significant association between higher total n-3 FA plasma levels and lower risk of CVD death (Figure 9, plot #33).[148]

Both the Cardiovascular Health Study and ULSAM found no association between plasma ALA levels and CVD death risk (Figure 9, plot # 21).[95, 148]

For both plasma EPA and DHA levels (separately), the Cardiovascular Health Study found significant associations between higher plasma levels and lower risk of CVD death at 16 years of followup.[148] In contrast, ULSAM found no significant association at about 31 years of followup (Figure 9, plots #24 & 30).[95]

The Cardiovascular Health Study also found a significant association between higher plasma DPA levels and lower risk of CVD death (Figure 9, plot #25).

Observational Study Subgroup Analyses

Only the Cardiovascular Health Study reported subgroup analyses.[148] In their analysis of ALA intake, they reported no significant difference (without details) in association between participants with high, low, or no fish consumption and between men and women.

Table 5. CVD death (including stroke): RCTs

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int n/N,%	Ctrl n/N,%	Effect Size	Reported P value
Marine oil vs. Placebo											
Kromhout 2010 20929341 Netherlands	CVD	EPA+DHA (±ALA)	0.4 g/d EPA+DHA and 2 g/d ALA (Marine; Plant oil) [E:D 3:2]	Placebo (±ALA)	0; 2 g/d ALA (Placebo margarine = oleic acid; Plant oil)	3.4 y	90% of the patients adhered fully to the protocol; verified by biomarkers	80/2424, 3.3%	82/2433, 3.4%	HR 0.98 (0.72, 1.33)	0.89
Roncaglioni 2013 23656645 Italy	At risk	EPA+DHA	≤0.85 g (Marine oil) [E:D 0.9−1.5]	Placebo	0 (Olive oil)	5 y	Monitored by self-report but compliance level was not reported	142/6239, 2.3%	137/6266, 2.2%	HR 1.03 (0.82, 1.30)	0.8
Einvik 2010 20389249 Norway	At risk	EPA+DHA+ diet intervention	2.02 g/d (Marine oil) [E:D 1.4]	Placebo+ diet intervention	0 (Corn oil))	3 y	>90% of the tablets were taken based on pharmacy records, and verified by biomarkers	7/282, 2%	11/281, 4%	OR 0.62 (0.24, 1.64)[c]	nd
Bosch 2012 22686415 Canada	CVD	EPA+DHA	0.84 g/d (Marine oil) [E:D 1.24]	Placebo	0 (Olive oil)	6+ y	FFQ at baseline, 2 years, and end of study (adherence was 88% at the end of study)	574/6281, 9.1%	581/6255, 9.3%	HR 0.98 (0.87,1.10)	0.72
Marchioli 2002 11997274 Italy	CVD	EPA+DHA	0.850- 0.882 g/d (Marine oil) [E:D 0.5]	No intervention	nd	3.5 y	Followup (adherence was 72.5% at the end of study)	310/5666, 5.5%	370/5668, 6.5%	RR 0.70 (0.56, 0.86)	<0.001

Table 5. CVD death (including stroke): RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int n/N,%	Ctrl n/N,%	Effect Size	Reported P value
Nilsen 2001 2001 11451717 Norway	CVD	EPA+DHA	EPA-DHA 3.4−3.528 g/d (Marine oil) [E:D=0.5]	Placebo	0 (Corn oil)	median 2.4 y	nd	16/150, 11%	12/150, 8%	1.37 (0.63, 3.01)	
Tavazzi 2008 18757090 Italy	CVD	EPA+DHA	0.850−0.882 g/d (Ethyl esters) [E:D 0.83]	Placebo	0 (nd)	3.9 y	Exam question (~30% not taking n-3 FA or placebo by the end of study)	712/3494, 20.4%	765/3481, 22.0%	Adjusted HR 0.90 (0.81, 0.99)[b]	0.045
ALA vs. Placebo											
Kromhout 2010 20929341 Netherlands	CVD	ALA (±EPA+DHA)	0.4 g/d EPA+DHA and 2 g/d ALA (Marine; Plant oil) [E:D 3:2]	Placebo (±EPA+DHA)	0; 0.4 g/d EPA-DHA (placebo = oleic acid; Marine oil) [E:D 3:2]	3.4 y	90% of the patients adhered fully to the protocol; verified by biomarkers	78/2409, 3.2%	84/2428, 3.5%	HR 0.94 (0.69, 1.27)	0.67

Abbreviations: ALA = alphalinolenic acid, Ctrl = control, CVD = cardiovascular disease, DHA = docosahexaenoic acid, E:D = EPA to DHA ratio, EPA = eicosapentaenoic acid, F/up = followup, FFQ = food frequency questionnaire, HR = hazard ratio, Int = intervention, n/N = number with outcome/number analyzed, n6:3 = omega-6 to omega-3 fatty acid ratio, n-3 FA = omega-3 fatty acids, ND = no data, OR = odds ratio, PMID = PubMed Identification number, RCT = randomized controlled trial, RR = relative risk.

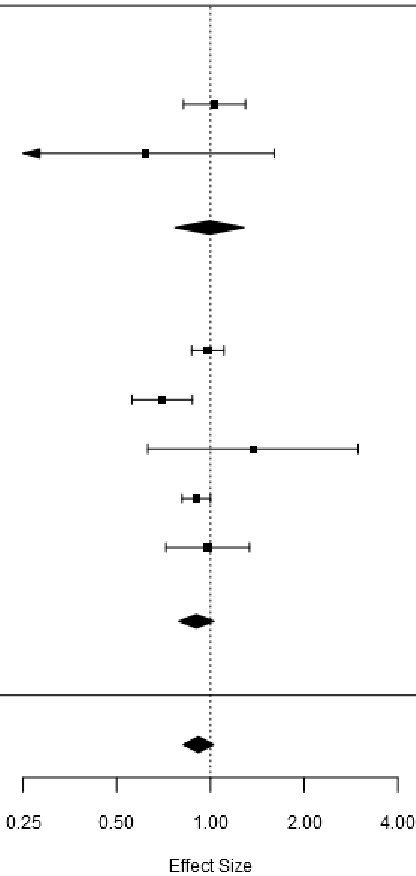
Table 6. CVD death (including stroke): Subgroup analyses, randomized trials

Study Year PMID Region	Population	Subgroups	n-3 FA	Comparator	N Total	P difference	Difference	Favors
Bosch 2012 22686415 Canada	CVD	Glargine vs no glargine	EPA+DHA	Placebo	12536	0.66		
	CVD	Age >= 65 vs < 65	EPA+DHA	Placebo	12536	0.72		
	CVD	Prior CVD event vs. no prior CVD event	EPA+DHA	Placebo	12536	0.70		
	CVD	High heart rate (>=69 beats/min) vs low HR (<69 beats/min	EPA+DHA	Placebo	12536	0.77		
	CVD	Statin vs no statin	EPA+DHA	Placebo	12536	0.72		
	CVD	Beta blocker use vs. no beta blocker use	EPA+DHA	Placebo	12536	0.79		
	CVD	n-3 FA intake in tertiles (lowest to highest)	EPA+DHA	Placebo	12536	0.18		
	CVD	Tg in tertiles (lowest to highest)	EPA+DHA	Placebo	12536	0.48		
Kromhout 2010 20929341 Netherlands	CVD	Diabetes vs. no diabetes	EPA+DHA	Placebo or ALA	4837	0.08 diabetes, 0.32 no diabetes	0.60 vs. 1.21	Diabetes (possibly)
	CVD	Diabetes vs. no diabetes	ALA	Placebo or EPA+DHA	4837	NS both subgroups		

Abbreviations: ALA = alphalinolenic acid, CVD = cardiovascular disease, DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid, HR = hazard ratio, n-3 FA = omega-3 fatty acids, NS = not significant, PMID = PubMed Identification number, Tg = triglycerides.

Figure 8. CVD death: Randomized trials of marine oils

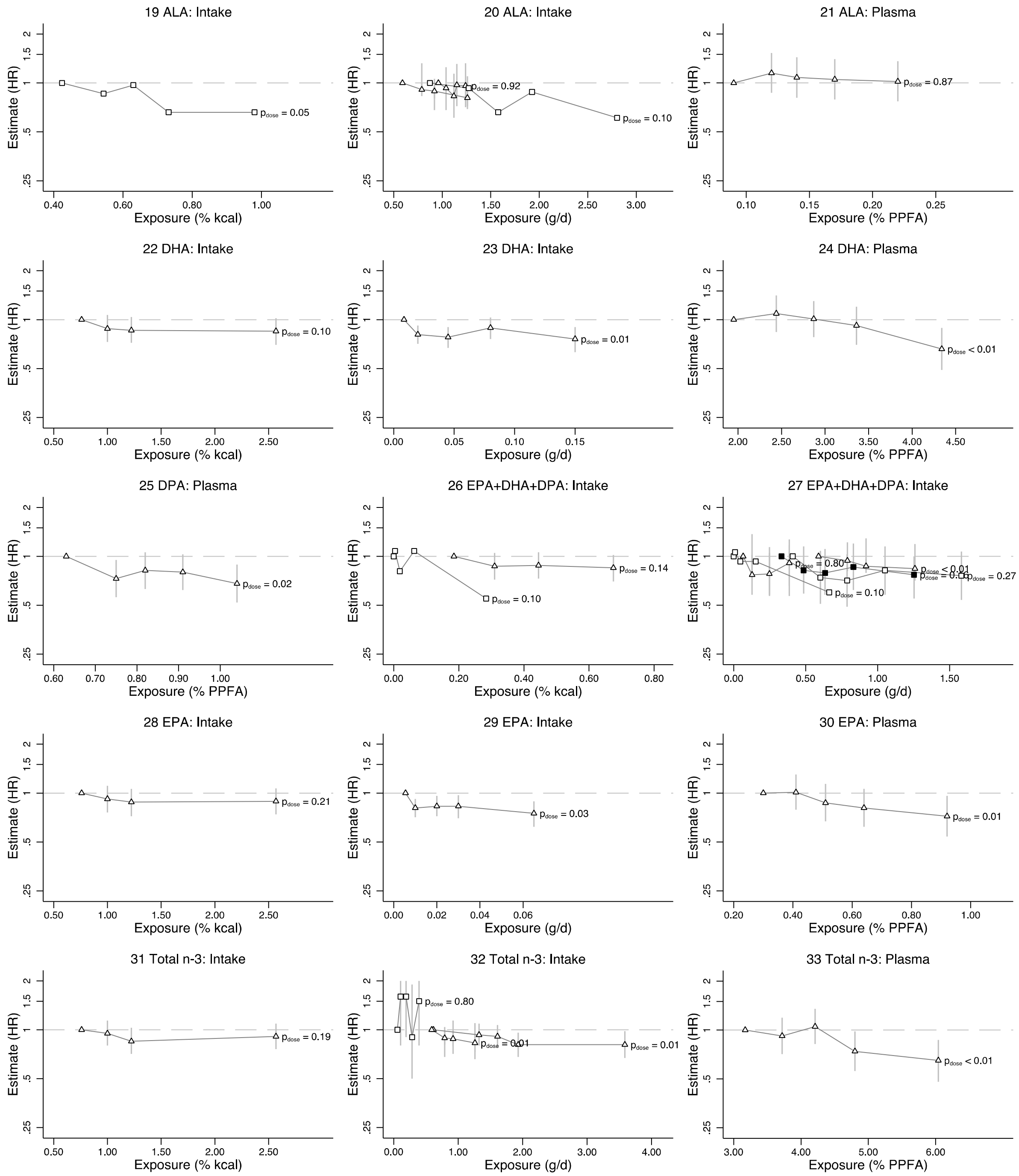
Study PMID	n-3 FA	g/day	Years	n-3 FA n/N	Placebo n/N	Effect Size [95% CI]
At risk population						
Roncaglioni 2013 23656645	EPA+DHA	0.85	5	142/6239	137/6266	1.03 [0.82, 1.30]
Einvik 2010 20389249	EPA+DHA	2.02	3	7/282	11/281	0.62 [0.24, 1.64]
Summary, at risk						*0.99 [0.77 , 1.28]*
CVD population						
Bosch 2012 22686415	EPA+DHA	0.84	6	574/6281	581/6255	0.98 [0.87, 1.10]
Marchioli 2002 11997274	EPA+DHA	0.87	3.5	310/5666	370/5668	0.70 [0.56, 0.86]
Nilsen 2001 11451717	EPA+DHA	3.46	2.4	16/150	12/150	1.37 [0.63, 3.01]
Tavazzi 2008 18757090	EPA+DHA	0.87	3.9	712/3494	765/3481	0.90 [0.81, 0.99]
Kromhout 2010 20929341	EPA+DHA*	0.4	3.4	80/2424	82/2433	0.98 [0.72, 1.33]
Summary, CVD						*0.90 [0.79 , 1.03]*
Summary [I-squared=42.665, Phet=0.134]						**0.92 [0.82 , 1.02]**



Random effects model meta-analysis of n-3 FA versus placebo (or no n-3 FA), with subgroup analyses by population. In all meta-analyses, only studies that reported sufficient results data are included.

Abbreviations: CI = confidence interval, CVD = cardiovascular disease, DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid, n/N = number with outcome/number analyzed, n-3 FA = omega-3 fatty acids, Phet = P value of chi-squared test of heterogeneity across studies, PMID = PubMed Identification number.

Figure 9. n-3 FA associations with CVD death: Observational studies



Study (or cohort) level associations between n-3 FA exposure and hazard ratio (HR) for the outcome. Studies that reported associations by continuous exposure (e.g., per g/d intake or per standard deviation) could not be graphed and are omitted. P values are the study-reported P value for the trend across quantiles. Where 95% confidence intervals (vertical lines) are missing, these were not reported in the studies. The 95% confidence intervals were truncated when <0.25 and >2.

White triangles = healthy adults, white squares = healthy males, black squares = healthy females.

Abbreviations: ALA = alphalinolenic acid, CVD = cardiovascular disease, DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, EPA = eicosapentaenoic acid, , HR = hazard ratio, n-3 FA = omega-3 fatty acids, PPFA = plasma polyunsaturated fatty acids.

Table 7. Meta-analysis results of observational studies of marine oil (EPA+DHA±DPA) intake and CVD death (including stroke)

N patients	Dose range, g/d	Knot	ES, overall	ES below knot	ES above knot	P*	AIC	No. cohorts (crossing threshold)
90,778	0.066-1.58	NA	0.88 (0.82, 0.95)					5
		0.1		0.36 (0.07, 1.78)	0.92 (0.78, 1.09)	0.28	27.0	5
		0.2		0.54 (0.24, 1.22)	0.93 (0.78, 1.11)	0.26	23.6	5
		0.3		0.64 (0.37, 1.10)	0.93 (0.77, 1.13)	0.27	23.5	5
		0.4		0.70 (0.46, 1.05)	0.93 (0.77, 1.14)	0.31	27.9	3
		0.5		0.72 (0.50, 1.03)	0.94 (0.76, 1.17)	0.31	27.0	3
		0.6		0.74 (0.53, 1.01)	0.95 (0.74, 1.21)	0.33	26.9	3
		0.7		0.75 (0.56, 1.01)	0.96 (0.72, 1.28)	0.37	27.5	3
		0.8		0.78 (0.59, 1.02)	0.96 (0.69, 1.33)	0.45	28.1	3
		0.9		0.79 (0.62, 1.02)	0.97 (0.66, 1.43)	0.52	29.5	3
		1.0		0.81 (0.64, 1.03)	0.96 (0.59, 1.56)	0.62	31.8	3
		1.1		0.83 (0.67, 1.03)	0.96 (0.50, 1.82)	0.72	35.7	3
		1.2		0.83 (0.68, 1.02)	0.96 (0.33, 2.73)	0.82	44.0	3

* ES below vs. above knot

Abbreviations: AIC = Akaike information criterion (estimation of fit of regression with spline), CVD = cardiovascular disease, DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, EPA = eicosapentaenoic acid, ES = effect size, NA = not applicable.

Cardiac Death

Randomized Controlled Trials

Five RCTs reported on cardiac death (combined CHD and other cardiac death) (Table 8).[70, 74, 81, 82, 87] The trials were conducted in a total of 15,596 people with CVD including MI, arrhythmia, and CHD. Only one trial reported cardiac death to be a primary outcome (Marchioli 2002).[70]

Marine Oil Versus Placebo

CVD Population

Among people with CVD, four compared marine oil (EPA+DHA) to placebo (oleic acid or olive oil) or no intervention in a total of 12,282 participants with arrhythmia, ventricular tachycardia or fibrillation, MI, or CHD,[70, 81, 82, 87] and one compared two levels of "fish advice" (dietician to advise to increase fish and/or fish oil supplement intake) with no fish advice in a total of 3114 men with MI or angina.[74]

Among the four RCTs that compared marine oil (EPA+DHA) to placebo (oleic acid or olive oil) or no intervention EPA+DHA ranged from 0.8 to 2.6 g/d. In the two RCTs reporting sufficient details, the EPA to DHA ratio was 1.4. Compliance was generally good (>70%). The duration of follow-up ranged from 1 to 3.5 years. Three of the four RCTs found that EPA+DHA supplementation did not have significant effects on cardiac death (OR=0.39, 0.45, and 1.01).[82, 87] The third RCT found that EPA+DHA supplementation had protective effects against cardiac death (RR 0.65; 95% CI 0.51 to 0.82).[70]

In the study that compared "fish advice" (advise to increase fish intake in one subgroup and additional advise to take fish oil supplement in a second subgroup) with "no fish advice",[74] the mean EPA intake estimated by the dietary assessment was 0.45 and ≤0.85 g/d in the "fish advice" groups, and was 0.11 in the "no fish advice" group. No estimates for DHA intake levels were reported. Compliance was good (fish intake was significantly increased in the "fish advice" groups) based on the dietary assessments. The trial found that, after 9 years of followup, overall, there was a significant *increase* in cardiac death between 1571 men with angina who were advised to increase fish intake and 1543 men with angina who were not (adjusted HR 1.26; 95% CI 1.00 to 1.58; P=0.047). The effect was similar but nonsignificant in the subgroup of 1109 men given advice only about increasing fish intake (adjusted HR 1.20, 95% CI 0.93 to 1.53) but larger and statistically significant in 462 men who were advised to take a fish oil supplement (adjusted HR 1.45; 95% CI 1.05 to 1.99).[74]

RCT Subgroup Analyses

The RCT that found a significant increased risk of cardiac death with combined fish diet and EPA+DHA supplements reported subgroup analyses for cardiac death.[74] It found nonsignificant interactions between fish advice and the following five pairs of subgroups, based on whether they take nitrates, digoxin, lipid-lowering drugs, anticoagulants, or diuretics.

Observational Studies

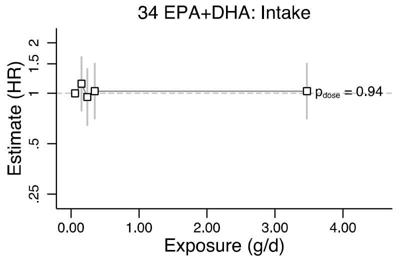
Two studies evaluated a composite outcome of fatal CHD and SCD, both in healthy adult males (Appendix F, Cardiac death section; Figure 10).[54, 155] The Health Professionals Follow-up Study found no association between EPA+DHA intake and cardiac death (Figure 10, plot #34). The Physician's Health Study found no associations between erythrocyte ALA, EPA, DHA, DPA, SDA, or EPA+DHA+DPA levels and cardiac death.[50, 155]

Table 8. Cardiac mortality: RCTs

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int n/N,%	Ctrl n/N,%	Effect Size	Reported P value
Marine oil vs. Placebo											
Brouwer 2006 16772624 N. Europe	CVD	EPA+DHA	0.96 g n-3 FA (0.464 g EPA, 0.335 g DHA) (Marine oil) [E:D]=1.4	Placebo	0 (high-oleic acid sunflower oil)	1 y	Generally good (76% reported taking 80% pills) based on pill counts and confirmed by biomarkers.	6/273, 2%	13/273, 5%	OR 0.45 (0.17, 1.20)	0.111
Leaf 2005 16267249 U.S.	CVD	EPA+DHA	EPA plus DHA of 2.6 g (Marine oil)	Placebo	0 (Olive oil)	12 mo	Pill counts and analysis of the phospholipids of red blood cells for their content of EPA and DHA	9/200, 4.5%	9/202, 4.5%	OR 1.01 (0.39, 2.60)	0.983
Marchioli 2002 11997274 Italy	CVD	EPA+DHA	EPA and DHA 0.850- 0.882 g/d) (Marine oil)	No intervention	nd	3.5 y	Followup (adherence was 72.5% at the end of study)	247/5666, 4.4%	306/5668, 5.4%	RR 0.65 (0.51, 0.82)	<0.001
Burr 2007 17343767 UK	CVD	Fish advice	EPA 0.45 g/d (diet)[a]	No fish advice	EPA 0.11 (diet)[a]	9 y	dietary charts sent by post with reply-paid envelopes	121/1109, 10.9%	139/1543, 9.0%	Adj HR 1.20 (0.93, 1.53)	0.16
	CVD	EPA+DHA (advice to take fish oil)	EPA ≤0.51 and DHA ≤0.345 (marine oil)[a]	No fish advice	EPA 0.11 (diet)[a]	9 y	dietary charts sent by post with reply-paid envelopes	59/462, 12.8%	139/1543, 9.0%	Adj HR 1.45 (1.05, 1.99)	0.024
	CVD	EPA+DHA (advice to take fish oil)	EPA ≤0.51 and DHA ≤0.345 (marine oil)[a]	Fish advice	EPA 0.45 g/d (diet)[a]	9 y	dietary charts sent by post with reply-paid envelopes	59/462, 12.8%	121/1109, 10.9%	OR 1.20 (0.86, 1.67)	nd
Raitt 2005 15956633 U.S.	CVD	EPA+DHA	EPA 0.756 g/d, DHA 0.54 g/d (fish oil) [E:D 1.4]	Placebo	0 (olive oil: 73% oleic acid, 12%)	2 y	RBC and plasma n-3 FA levels	2/100, 2.0%	5/100, 5.0%	OR 0.39 (0.07, 2.05)	0.44

Abbreviations: Ctrl = control, CVD = cardiovascular disease, DHA = docosahexaenoic acid, E:D = EPA to DHA ratio, EPA = eicosapentaenoic acid, F/up = followup, HR = hazard ratio, Int = intervention, n/N = number with outcome/number analyzed, n3 FA = omega-3 fatty acids, n6 = omega-6, OR = odds ratio, PMID = PubMed Identification number, RBC = red blood cell, RCT = randomized controlled trial, RR = relative risk.

Figure 10. n-3 FA associations with cardiac death: Observational studies



Study (or cohort) level associations between n-3 FA exposure and hazard ratio (HR) for cardiac death. Studies that reported associations by continuous exposure (e.g., per g/d intake or per standard deviation) could not be graphed and are omitted.
White squares = healthy males.

Abbreviations: DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid, HR = hazard ratio, n-3 FA = omega-3 fatty acids.

Coronary Heart Disease Death

Randomized Controlled Trials

Four RCTs evaluated CHD death (Table 9).[48, 51, 90, 119] Of these, one study was conducted in 18,645 participants with dyslipidemia (19.5% with CHD),[90] and three were conducted in a total of 6929 people with CVD including MI, arrhythmia, and CHD. Only one trial reported death to be a primary outcome (Yokoyama 2007).[90]

Marine Oil Versus Placebo

At-Risk-for-CVD Population

Among people at risk of CVD, one study compared 1.8 g/d EPA ethyl ester combined with statin with control (statin alone) in 18,645 participants with dyslipidemia (19.5% with CHD).[90] Local physicians monitored compliance with dietary advice and medication at every clinic visit but the adherence level was not reported. This study found no significant additive effect of EPA supplementation on risk of CHD death compared with statin alone (HR 0.94; 95% CI 0.57 to 1.56). When only the patients without CHD were analyzed, the study still found no significant additive effect of EPA supplementation on risk of CHD death compared with statin alone (HR 1.1; 95% CI 0.47 to 2.6).

CVD Population

The same study analyzed the small subgroups of patients with CVD separately. Among people with previous CHD, 1.8 g/d EPA ethyl ester combined with statin was compared with statin alone in 3,664 patients. No significant additive effect of EPA supplementation on risk of CHD death was found (HR 0.87; 95% CI 0.46 to 1.64). Among 223 people with peripheral artery disease, no significant additive effect of EPA supplementation on risk of CHD death compared with statin alone was found (HR 0.48; 95% CI 0.10 to 1.98).[90]

Among people with CVD, two studies compared marine oil (EPA+DHA) to placebo (oleic acid or olive oil) in a total of 4896 participants with arrhythmia, MI, or CHD,[51, 119] one was the 2-by‒2 factorial RCT described under *Major Adverse Cardiovascular Events.*[119]

A relatively small trial (with 59 participants) compared 6 g/d marine oil (2.88 g/d EPA, 1.92 g/d DHA, 1.2 g/d DPA) to olive oil placebo for 2.4 years, with 80 percent compliance in the marine oil supplement arm (and 90% compliance in the olive oil placebo arm).[51] The 2-by−2 factorial trial compared 0.4 g/d of EPA+DHA in margarine to placebo margarine for 40 months with 90 percent compliance, overall.[119] Both trials found no significant association between marine oil intake and CHD death, but the smaller trial had only one such death during its followup.

In one trial that compared "fish advice" (advise to increase fish intake) with "no fish advice" in 2033 adults,[48] the mean EPA intake estimated by the dietary assessment was 0.34 g/d in the "fish advice" group and 0.09 in the "no fish advice" group. No estimates for DHA intake levels were reported. Compliance was good based on the dietary assessments. No significant difference in risk of CHD death was found (adjusted HR = 0.92; 95% CI 0.66 to 1.29).

ALA Versus Placebo

CVD Population

The 2-by−2 factorial study compared 2 g/d ALA in margarine to control margarine.[119] The trial found no difference in risk of CHD death after 40 months (HR 0.92; 95% CI 0.66 to 1.29).

RCT Subgroup Analyses

Two RCTs reported subgroup analysis for CHD death (Table 10). The 2-by−2 factorial study found significant protective effect of EPA+DHA in subjects with diabetes (HR=0.51, P=0.04) that was not seen in subjects without diabetes (HR=1.21, P=0.32); no analysis of a statistical interaction was reported.[119] In both subgroups, the effect of ALA on CHD death was nonsignificant (HR=0.87, P=0.63 with diabetes; HR=0.97, P=0.87 without diabetes).

In the trial of participants with dyslipidemia (19.5% of whom had CHD),[90] no significant effect of EPA was found. In participants with no history of CHD (primary prevention), HR=1.00 (95% CI 0.32 to 3.11). In participants with a history of CHD (secondary prevention), HR=0.64 (95% CI 0.21 to 1.94).

Observational Studies

Ten studies evaluated associations between n-3 FA intake and biomarkers and CHD death, including the Pooling Project, which pooled data from eight large cohorts (ARIC, FMC, IWHS, NHS, VIP, WHS, ATBC, HPFS) (Appendix F, Death from coronary heart disease section; Figure 11).[47, 57, 69, 84, 98, 113, 159, 162, 175, 181, 186] The studies were all conducted in healthy adults with average followup ranging from about 6 to 24 years (median 11.3 years).

n-3 FA Intake

Eleven studies analyzed n-3 FA intake (Alpha-Tocopherol Beta-Carotene Cancer Prevention, Cardiovascular Health Study, JACC, Japan Public Health Center-Based Study - Cohort I, MORGEN, MRFIT, NIPPON DATA80, Nurses' Health Study, Pooling Project of Cohort Studies on Diet and Coronary Disease, Shanghai Women's and Men's Health Studies, Singapore Chinese Health Study).

The NIPPON DATA80, JACC studies found no associations between total n-3 FA intake (combined) and CHD death after 13 and 24 years of followup (Figure 11, plots #47 & 48).[98, 175]

The Singapore Chinese Health Study found significant associations between total n-3 FA intake and CHD death after five years of followup (P=0.04).[170]

Five studies, including the Pooling Project and thus comprising eight study cohorts, evaluated ALA intake (Alpha-Tocopherol Beta-Carotene Cancer Prevention, Cardiovascular Health Study, MRFIT, Pooling Project of Cohort Studies on Diet and Coronary Disease) (Figure 11, plots #35 & 36).[47, 57, 159, 170, 181] The Singapore Chinese Health Study found significant associations between total ALA intake and CHD death after five years of followup (P=0.001).[170] MRFIT found a statistically significant association between higher ALA intake measured as percent Kcal (energy) in men after about 10 years of followup (with possibly significant associations bound in quartiles with median values above about 0.5% Kcal), but no association with ALA intake measured as g/d.[47] The other three studies also found no association (in men, women, or all healthy adults) at 6, 12, and 4−10 years of followup.

By meta-analysis (Table 11), overall there is no statistically significant association between ALA intake and CHD death across a median dose range of 0.59 to 2.5 g/d (effect size per g/d = 0.94; 95% CI 0.85 to 1.03). Meta-analyses with the addition of a spline knot point at different dose thresholds (from 0.6 to 1.2 g/d) consistently found a stronger association (of higher dose being associated with lower risk) at *higher* doses than at lower doses (ES above knot < ES below knot); although the differences were generally small and all were nonsignificant. The best fit curve was found with a knot at 0.9 g/d. The lowest P value between lower-dose and higher-dose ES estimates was found at 1.2 g/d (P=0.44), the highest dose threshold that could be tested.

Two studies (NIPPON DATA80, Shanghai Women's and Men's Health Studies) found no associations with EPA or DHA intake (separately) and CHD death at 24 years in one study and at about 6 years in men and 11 years in women in the other study (Figure 11, plots #38, 39, 44 & 45).[162, 175]

Eight studies analyzed EPA+DHA (5 studies; Japan Public Health Center-Based Study - Cohort I, NIPPON DATA80, Nurses' Health Study, MORGEN, Shanghai Women's and Men's Health Studies Singapore Chinese Health Study[69, 84, 143, 162, 170, 175]) or EPA+DHA+DPA (2 studies; Alpha-Tocopherol Beta-Carotene Cancer Prevention, MRFIT[47, 57]) between 6 and 24 years of followup.[47] The studies found heterogeneous results (Figure 11, plots #42 & 43). Four studies (MORGEN, MRFIT, Nurses' Health Study, Singapore Chinese Health Study) found significant associations between higher EPA+DHA±DPA and lower risk of CHD death (with significant associations occurring in quantiles with median intake of at least about 0.1% Kcal or 0.25 g/d).[47, 69, 143, 170] One study found an about 80 percent increase in risk of CHD death with higher EPA+DHA intake, but this was not statistically significant (Japan Public Health Center-Based Study - Cohort I, highest vs. lowest quintiles HR=1.79; 95% CI 0.82 to 3.87; P=0.10 across quintiles).[84] The remaining three studies found no associations between EPA+DHA±DPA and CHD death risk. Meta-analysis could not be run because intake was inconsistently measured as either g/d or percent Kcal.

By meta-analysis (Table 12), overall there no significant association between marine oil intake and CHD death across a median dose range of 0.04 to 2.1 g/d (effect size per g/d = 1.09; 95% CI 0.76 to 1.57). Meta-analyses with the addition of a spline knot point at different dose thresholds (from 0.1 to 1.2 g/d) found stronger associations (of higher dose being associated with lower risk) at lower doses than at higher doses (ES below knot less than 1; ES above knot closer to 1) for knots below 0.7 g/d, but stronger associations at higher doses above 0.7 g/d. However, the differences in effect size between lower and higher doses were always highly nonsignificant, implying no difference in association. The best fit curve was found with a knot at 0.5 g/d. The lowest P value between lower-dose and higher-dose ES estimates was found at the lowest tested threshold, 0.1 g/d (P=0.46).

n-3 FA Biomarkers

The Cardiovascular Health Study was the only study to evaluate the association between n-3 FA biomarkers and CHD death.[159] At 16 years of followup, higher plasma total n-3 FA and higher plasma DHA were each significantly associated with lower risk of CHD death. No associations were found for ALA, EPA, or DPA plasma levels (Figure 11, plots #37, 40, 41, 46, and 49).

Observational Study Subgroup Analyses

The Pooling Project analysis of ALA, found a near-significant interaction by sex (P=0.07), suggesting that higher ALA intake may be protective against CHD death in men (HR=0.77; 95% CI 0.58 to 1.01) but not in women (HR=0.88; 95% CI 0.68 to 1.14).[181]

Table 9. CHD Mortality: RCTs

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int n/N,%	Ctrl n/N,%	Effect Size	Reported P value
Marine oil vs. Placebo											
Yokoyama 2007 17398308 Japan	At risk (dyslipidemia; 19.5% with CHD)	EPA+Statin	1.8 g/d (Ethyl ester)	Statin	0	5 y	Local physicians monitored but compliance level was not reported	29/9326, 0.3%	31/9319, 0.3%	HR 0.94 (0.57, 1.56)	0.812
	At risk	EPA+Statin	1.8 g/d (Ethyl ester)	Statin	0	5 y	Local physicians monitored but compliance level was not reported	11/7503 0.1%	10/7478 0.1%	HR 1.1 (0.47, 2.6)	0.822
Sacks 1995 7759696 U.S.	CVD	EPA+DHA+DPA	6 g/d (suppl) [E:D 1.5]	Placebo	0 (Olive oil)	2.4 y	Pill counting (80% for EPA+DHA; 90% for placebo)	0/31, 0.0%	1/28, 3.6%	RD −3.6% (−10.4%, 3%)	0.309
Kromhout 2010 20929341 Netherlands	CVD	EPA+DHA (±ALA)	0.4 g/d EPA+DHA and 2 g/d ALA (Marine; Plant oil) [E:D 3:2]	Placebo (±ALA)	0; 2 g/d ALA (Placebo margarine = oleic acid; Plant oil)	40 mo	90% of the patients adhered fully to the protocol; verified by biomarkers	67/2404, 2.8%	71/2433, 2.9%	HR 0.95 (0.68,1.32)	0.75
Burr 1989 2571009 UK	CVD	Fish advice, either alone or in combination with fiber advice, fat advice, or both fiber and fat advice.	EPA 0.34 g/d (diet)	No fish advice (Fat advice, fiber advice, fiber and fat advice, or no advice)	EPA 0.09 g/d (diet)	Overall years (10+ y)	Compliance was good based on dietary assessments	354/1015, 34.9%	384/1018, 37.7%	Adj HR 0.92 (0.80, 1.07)	NS

Table 9. CHD mortality: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int n/N,%	Ctrl n/N,%	Effect Size	Reported P value
Yokoyama 2007 17398308* Japan	CVD (previous CHD)	EPA+Statin	1.8 g/d (Ethyl ester)	Statin	0	5 y	Local physicians monitored but compliance level was not reported	18/1823 1.0%	21/1841 1.1%	HR 0.87 (0.46, 1.64)	0.667
	CVD (PAD at any time)	EPA+Statin	1.8 g/d (Ethyl ester)	Statin	0	5 y	Local physicians monitored but compliance level was not reported	3/117 2.6%	7/106 6.6%	HR 0.48 (0.10, 1.98)	0.308
ALA vs. Placebo											
Kromhout 2010 20929341 Netherlands	CVD	ALA (±EPA+DHA)	0.4 g/d EPA+DHA and 2 g/d ALA (Marine; Plant oil) [E:D 3:2]	Placebo (±EPA+DHA)	0; 0.4 g/d EPA-DHA (placebo = oleic acid; Marine oil) [E:D 3:2]	40 mo	90% of the patients adhered fully to the protocol; verified by biomarkers	66/2409, 2.7%	72/2428, 3.0%	HR 0.92 (0.66, 1.29)	0.64

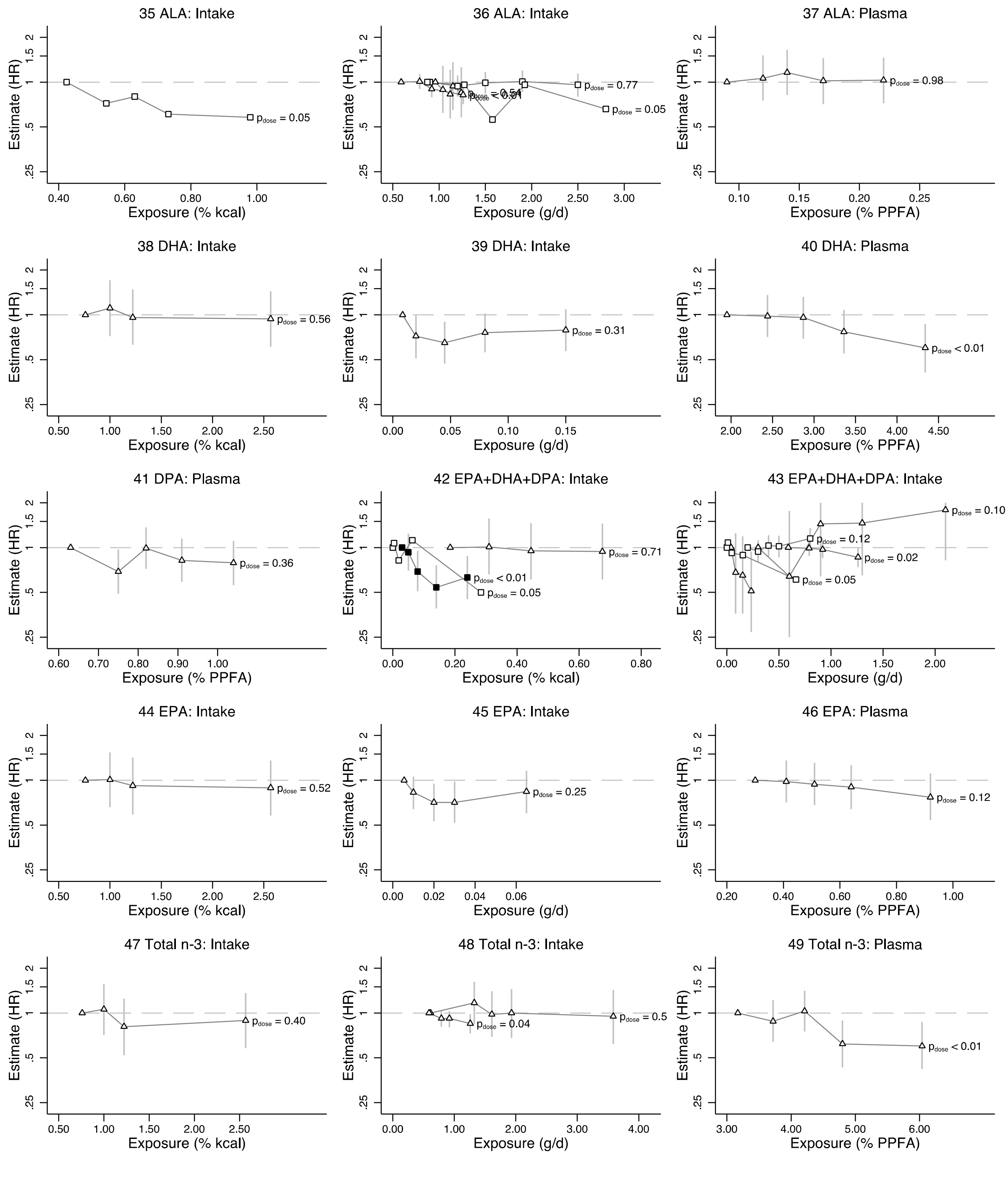
Abbreviations: ALA = alphalinolenic acid, Ctrl = control, CHD = coronary heart disease, CVD = cardiovascular disease, DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, E:D = EPA to DHA ratio, EPA = eicosapentaenoic acid, F/up = followup, Int = intervention, n/N = number with outcome/number analyzed, n3 FA = omega-3 fatty acids, NS = not significant, PAD = peripheral artery disease, PMID = PubMed Identification number, RCT = randomized controlled trial, RD = risk difference.

Table 10. CHD mortality: Subgroup analyses, randomized trials

Study Year PMID Region	Population	Subgroups	n-3 FA	Comparator	N Total	P difference	Difference	Favors
Kromhout 2010 20929341 Netherlands	CVD	Diabetes vs. no diabetes	EPA+DHA	Placebo or ALA	4837	0.04 diabetes, 0.34 no diabetes	0.51 vs. 1.21	Diabetes (possibly)
	CVD	Diabetes vs. no diabetes	ALA	Placebo or EPA+DHA	4837	NS both subgroups		
Yokoyama 2007 17398308 Japan	At risk (dyslipidemia; 19.5% with CHD)	No history of CHD vs. history of CHD	EPA + Statin	Statin	18645	NS both subgroups		

Abbreviations: ALA = alphalinolenic acid, CHD = coronary heart disease, CVD = cardiovascular disease, DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid, n-3 FA = omega-3 fatty acids, NS = not significant, PMID = PubMed Identification number.

Figure 11. n-3 FA associations with CHD death: Observational studies



Study (or cohort) level associations between n-3 FA exposure and hazard ratio (HR) for the outcome. Studies that reported associations by continuous exposure (e.g., per g/d intake or per standard deviation) could not be graphed and are omitted. P values are the study-reported P value for the trend across quantiles. Where 95% confidence intervals (vertical lines) are missing, these were not reported in the studies. The 95% confidence intervals were truncated when <0.25 and >2.

White triangles = healthy adults, white squares = healthy males, black squares = healthy females.

Abbreviations: ALA = alphalinolenic acid, CHD = coronary heart disease, DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, EPA = eicosapentaenoic acid, HR = hazard ratio, n-3 FA = omega-3 fatty acids, PPFA = plasma polyunsaturated fatty acids.

Table 11. Meta-analysis results of observational studies of ALA intake and CHD death

N patients	Dose range, g/d	Knot	ES, overall	ES below knot	ES above knot	P*	AIC	No. cohorts (crossing threshold)
84,811	0.59-2.5	NA	0.94 (0.85, 1.03)					3
		0.6		1.01 (0.78, 1.30)	0.83 (0.57, 1.21)	0.53	10.8	3
		0.7		0.98 (0.82, 1.17)	0.83 (0.57, 1.21)	0.53	10.2	3
		0.8		0.96 (0.84, 1.09)	0.83 (0.57, 1.21)	0.53	9.7	3
		0.9		0.95 (0.85, 1.05)	0.83 (0.56, 1.24)	0.56	9.3	3
		1.0		0.94 (0.86, 1.04)	0.80 (0.49, 1.31)	0.54	9.4	3
		1.1		0.94 (0.86, 1.03)	0.72 (0.34, 1.54)	0.50	10.6	3
		1.2		0.94 (0.87, 1.03)	0.42 (0.06, 3.20)	0.44	14.5	3

* ES below vs. above knot

Abbreviations: AIC = Akaike information criterion (estimation of fit of regression with spline), ALA = alphalinolenic acid, CHD = coronary heart disease, ES = effect size, NA = not applicable.

Table 12. Meta-analysis results of observational studies of marine oil (EPA+DHA±DPA) intake and CHD death

N patients	Dose range, g/d	Knot	ES, overall	ES below knot	ES above knot	P*	AIC	No. cohorts (crossing threshold)
145,148	0.04-2.1	NA	1.09 (0.76, 1.57)					4
		0.10	NA	0.38 (0.02, 6.25)	1.31 (0.78, 2.20)	0.46	31.1	4
		0.20	NA	0.66 (0.17, 2.61)	1.35 (0.73, 2.49)	0.47	29.8	4
		0.30	NA	0.88 (0.42, 1.87)	1.28 (0.71, 2.34)	0.57	30.2	3
		0.40	NA	1.03 (0.72, 1.48)	1.20 (0.73, 1.98)	0.70	29.6	3
		0.50	NA	1.06 (0.84, 1.35)	1.19 (0.71, 2.00)	0.74	29.1	3
		0.60	NA	1.06 (0.87, 1.29)	1.23 (0.66, 2.27)	0.69	30.1	3
		0.70	NA	1.07 (0.89, 1.28)	1.25 (0.55, 2.82)	0.73	32.9	3
		0.80	NA	1.10 (0.92, 1.33)	1.06 (0.56, 2.02)	0.90	97.2	3
		0.90	NA	1.10 (0.90, 1.35)	1.02 (0.52, 2.00)	0.82	36.2	2
		1.00	NA	1.10 (0.90, 1.35)	0.98 (0.45, 2.16)	0.77	37.0	2
		1.10	NA	1.10 (0.89, 1.36)	0.89 (0.31, 2.55)	0.68	38.7	2
		1.20	NA	1.10 (0.89, 1.37)	0.57 (0.06, 5.22)	0.55	44.2	2

* ES below vs. above knot

Abbreviations: AIC = Akaike information criterion (estimation of fit of regression with spline), ALA = alphalinolenic acid, CHD = coronary heart disease, ES = effect size, NA = not applicable.

Myocardial Infarction Death

Randomized Controlled Trials

No RCTs evaluated this outcome.

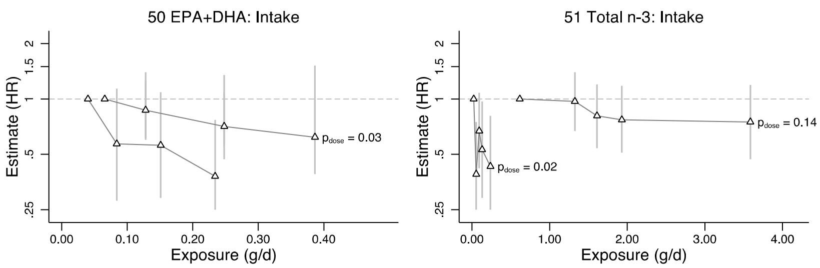
Observational Studies

Four studies evaluated n-3 FA and MI death in healthy adults (Appendix F, Death from myocardial infarction section; Figure 12).[68, 98, 113, 176] The Shanghai study found a significant association between higher total n-3 FA intake and lower risk of MI death at 12 years of followup, with significant associations found in quintiles with median intake above about 0.05 g/d).[162] In contrast, JACC found no association between total n-3 FA intake and MI death at about 13 years of followup.[98] In a single analysis of EPA+DHA intake, MORGEN found a significant association between higher EPA+DHA intake and lower risk of MI death at about 11 years of followup, with a significant association found in the quartile with intake >0.19 g/d.[143] The VITAL study found no association between higher EPA+DHA intake in CVD adults, but did find a significant association in healthy adults (P=0.029) .[176]

Observational Study Subgroup Analyses

The Shanghai study reported no difference in association (with total n-3 FA intake) by baseline total cholesterol to HDL-c ratio.[162]

Figure 12. n-3 FA associations with myocardial infarction death: Observational studies



Study (or cohort) level associations between n-3 FA exposure and hazard ratio (HR) for myocardial infarction death. P values are the study-reported P value for the trend across quantiles. The 95% confidence intervals were truncated when <0.25 and >2.
White triangles = healthy adults.

Abbreviations: DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid, HR = hazard ratio, n-3 FA = omega-3 fatty acids.

Congestive Heart Failure Death

Randomized Controlled Trials

Marine Oil Versus Placebo

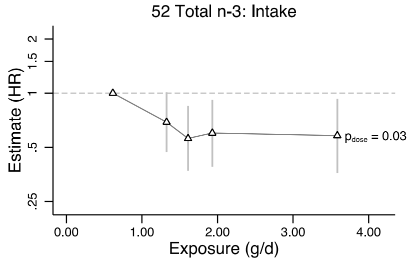
At-Risk-for-CVD Population

One trial in 12,505 participants at risk for CVD based on multiple risk factors compared a marine oil supplement with at least 0.85 g/d EPA+DHA with olive oil placebo (Table 13).[160] The EPA to DHA ratio ranged from 0.9 to 1.5. Compliance data were not reported. After 5 years of followup, no effect on congestive heart failure (CHF) death was seen (HR=1.00; 95% CI 0.53 to 1.88). CHF death was reported to be a secondary outcome.

Observational Studies

Only JACC evaluated n-3 FA and CHF death (Appendix F, Death from congestive heart failure section; Figure 13).[98] In healthy adults, the study found a significant association between higher total n-3 FA intake (combined) and lower risk of CHF death after about 13 years of followup, with significant associations found in quintiles with intake >2.1 g/d.

Figure 13. n-3 FA associations with heart failure death: Observational studies



Study (or cohort) level associations between omega-3 fatty acid (n-3 FA) exposure and hazard ratio (HR) for heart failure death. P values are the study-reported P value for the trend across quantiles.
White triangles = healthy adults.

Abbreviations: n-3 FA = omega-3 fatty acids, HR = hazard ratio

Table 13. Congestive heart failure death: RCTs

Study Year PMID Region	Population	Int (n-3 FA)	Int n-3 Dose (Source) [E:D; n-6:3]	Control	Ctrl n-3 Dose (Source) [E:D; n-6:3]	F/up Time	Compliance Verification	Int n/N,%	Ctrl n/N,%	Effect Size	Reported P value
Marine oil vs. Placebo											
Roncaglioni 2013 23656645 Italy	At risk	EPA+ DHA	≥0.85 g/d (suppl) [E:D 0.9−1.5]	Placebo	0 (Olive oil)	5 y	Self-reported (nd on level of adherence)	19/6239, 0.3%	19/6266, 0.3%	HR 1.00 (0.53, 1.88)	0.99

Abbreviations: Ctrl = control, DHA = docosahexaenoic acid, E:D = EPA to DHA ratio, EPA = eicosapentaenoic acid, F/up = followup, Int = intervention, n/N = number with outcome/number analyzed, HR = hazard ratio, n-3 FA = omega-3 fatty acids, n6:3 = omega-6 to omega-3 fatty acid ratio, PMID = PubMed Identification number, RCT = randomized controlled trial.

Stroke Death, Total (Ischemic and Hemorrhagic)

Randomized Controlled Trials

Three RCTs evaluated total stroke death (Table 14).[48, 96, 160] One trial was in 12,505 participants at risk for CVD based on multiple risk factors,[160] and the other two were in a total of 9008 participants with a history of MI,[48] or heart failure.[96] No trial reported stroke death as a primary outcome.

Marine Oil Versus Placebo

At-Risk-for-CVD Population

One RCT evaluated the effect of marine oil (EPA+DHA) on stroke death compared with placebo (olive oil) in a total of 12,505 participants with high risk for CVD.[160] The dose of EPA+DHA was at least 0.85 g/d (composition of the marine oil was not reported). Adherence was verified by participants' self-report but the level of adherence was not reported. After 5 years, the study found no significant difference in stoke death comparing EPA+DHA with placebo (HR 1.05, 95% CI 0.55 to 2.00).[160]

CVD Population

One trial compared marine oil (EPA+DHA) ethyl ester supplementation (0.85−0.88 g/d) to placebo in 6975 participants with heart failure.[96] After 3.9 years of followup, about 30 percent of participants in both study arms were not taking the supplement. No difference was found in risk of stroke death (OR = 1.13; 95% CI 0.75 to 1.71). A second trial compared fish advice (resulting in an average of 0.34 g/d EPA intake) with no fish advice (0.09 g/d EPA intake) in 2033 adults with a history of MI.[48] Compliance was not reported. After more than 10 years of followup, no significant difference in stroke death was found (OR=1.23; 95% CI 0.71 to 2.14).

Observational Studies

Five studies evaluated n-3 FA intake and biomarkers and risk of total stroke death at 5, 12 to 24 years of followup in healthy adults (Appendix F, Death from stroke section; Figure 14).[68, 98, 159, 170, 175]

n-3 FA Intake

Four studies evaluated n-3 FA intake and risk of stroke death (JACC, NIPPON DATA80, Shanghai, Singapore Chinese Health Study).[68, 98, 170, 175] All analyses were nonsignificant, including for total n-3 FA (combined) intake (all four studies) at 5, 12, 13, and 24 years of followup (Figure 14, plots #61 & 62); and EPA, DHA, and EPA+DHA intake (separately) in the NIPPON DATA80 study at 24 years of followup (Figure 14, plots #54, 57, & 59).[175] The Singapore Chinese Health Study also found no significant associations between higher ALA or EPA+DHA intake (separately) and lower risk of stroke death.[170]

n-3 FA Biomarkers

Only the Cardiovascular Health Study evaluated n-3 FA biomarkers.[159] The study found near-significant associations (P<0.10) between higher plasma total n-3 FA (Figure 14, plot #63), DHA (Figure 14, plot #55), and DPA levels (Figure 14, plot #56), separately, and lower risk of stroke death after 16 years of followup (P=0.092, 0.082, and 0.056, respectively). The study found no association with plasma EPA levels (Figure 14, plot #60).

Observational Study Subgroup Analyses

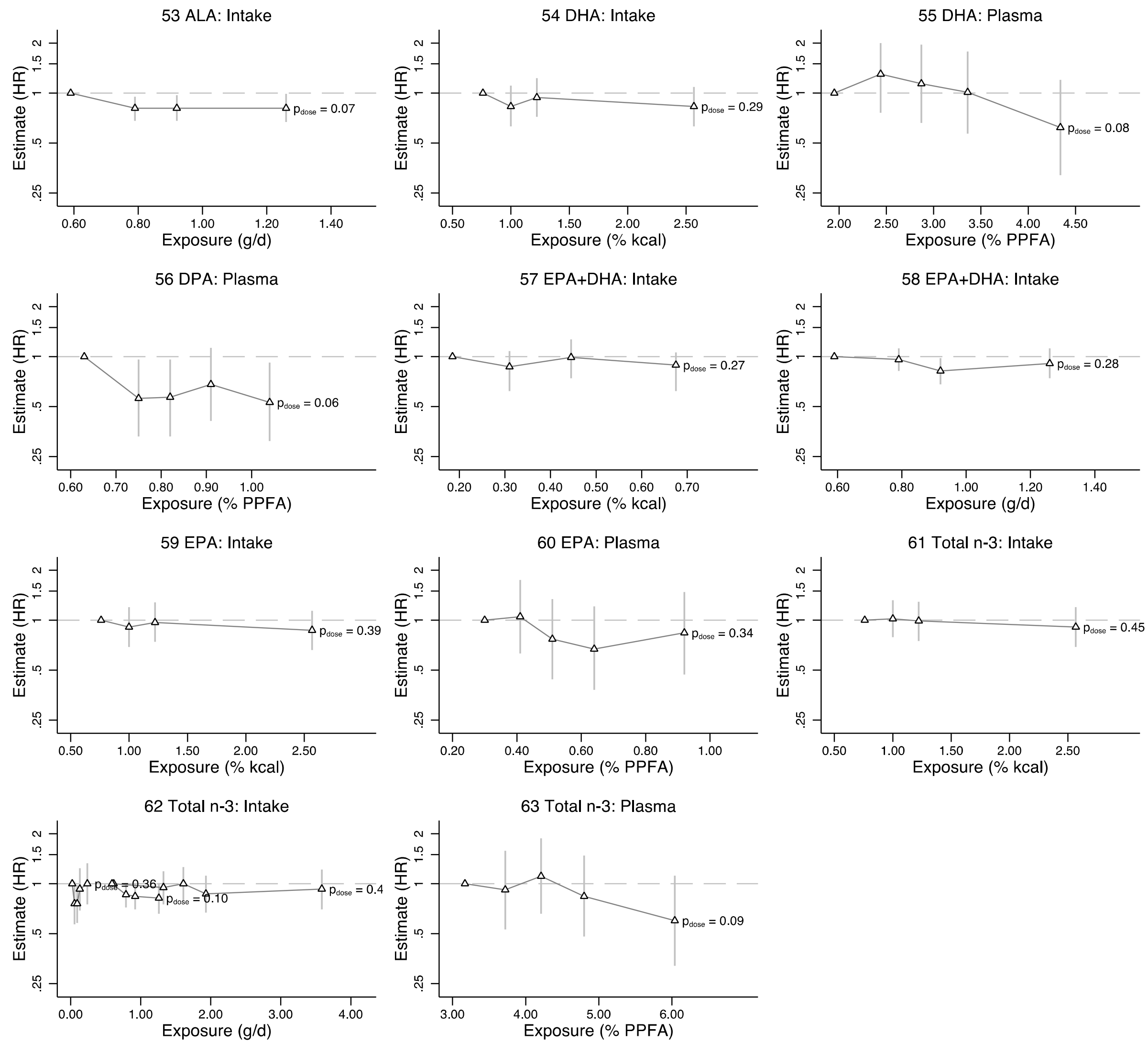
The Shanghai study found no significant difference in association (of total n-3 FA intake) by baseline total cholesterol to HDL-c ratio.[162]

Table 14. Total stroke death: RCTs

Study Year PMID Region	Population	Int (n-3 FA)	Int n-3 Dose (Source) [E:D; n-6:3]	Control	Ctrl n-3 Dose (Source) [E:D; n-6:3]	F/up Time	Compliance Verification	Int n/N,%	Ctrl n/N,%	Effect Size	Reported P value
Marine oil vs Placebo											
Roncaglioni 2013 23656645 Italy	At risk	EPA+DHA	≥0.85 g/d (marine oil) [E:D 0.9:1−1.5:1]	Placebo	0 (Olive oil)	5 y	Self-reported (nd on level of adherence)	19/6239, 0.3%	18/6266, 0.3%	HR 1.05 (0.55, 2.00)	0.88
Tavazzi 2008 18757090 Italy	CVD	EPA+DHA	0.850−0.882 g/d (Ethyl esters) [E:D 1:1.2]	Placebo	0 (nd)	3.9 y	Exam question (~30% not taking n-3 FA or placebo by the end of study)	50/3494, 1.4%	44/3481, 1.3%	OR 1.13 (0.75, 1.71)	
Burr 1989 2571009 UK	CVD	Fish advice, either alone or in combination with fiber advice, fat advice, or both fiber and fat advice.	EPA 0.34 g/d (diet)	No fish advice (Fat advice, fiber advice, fiber and fat advice, or no advice)	EPA 0.09 g/d (diet)	>10 y	Compliance was good based on dietary assessments	29/1015, 2.9%	23/1018, 2.3%	OR 1.23 (0.71, 2.14)	NS

Abbreviations: Ctrl = control, CVD = cardiovascular disease, DHA = docosahexaenoic acid, E:D = EPA to DHA ratio, EPA = eicosapentaenoic acid, F/up = followup, HR = hazard ratio, Int = intervention, n/N = number with outcome/number analyzed, n-3 FA = omega-3 fatty acids, n6:3 = omega-6 to omega-3 fatty acid ratio, NS = not significant, OR = odds ratio, PMID = PubMed Identification number, RCT = randomized controlled trial.

Figure 14. n-3 FA associations with total stroke death: Observational studies



Study (or cohort) level associations between n-3 FA exposure and hazard ratio (HR) for the outcome. Studies that reported associations by continuous exposure (e.g., per g/d intake or per standard deviation) could not be graphed and are omitted. P values are the study-reported P value for the trend across quantiles. The 95% confidence intervals were truncated when <0.25 and >2.
White triangles = healthy adults.

Abbreviations: ALA = alphalinolenic acid, DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, EPA = eicosapentaenoic acid, HR = hazard ratio, n-3 FA = omega-3 fatty acids, PPFA = plasma polyunsaturated fatty acids.

Ischemic Stroke Death

Randomized Controlled Trials

No RCTs evaluated this outcome.

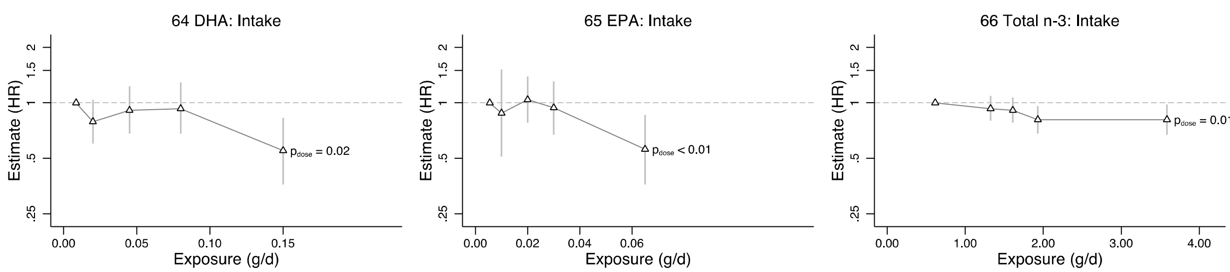
Observational Studies

Two studies evaluated the association between n-3 FA intake and risk of ischemic stroke death in healthy adults (Appendix F, Death from ischemic stroke section; Figure 15).[98, 162] Both found significant associations. JACC found an association between higher intake of total n-3 FA (combined) and lower risk of ischemic stroke death after about 13 years of followup (Figure 15, plot #66), with significant associations found in quintiles with median intake of about 2 g/d or more.[98] The Shanghai Women's and Men's Health Studies found similar significant associations with higher EPA (particularly for median intake >0.07 g/d in men an d>0.06 g/d in women), DHA (particularly for median intake >0.15 g/d), and combined EPA+DHA intake (in separate analyses) with about 11 years of followup in women and 6 years of followup in men (Figure 15, plots #64 & 65; EPA+DHA not plotted because no data were provided for median intake per quantile).[162]

Observational Study Subgroup Analyses

The Shanghai study found no significant difference in association (of total n-3 FA intake) by baseline total cholesterol to HDL-c ratio.[162]

Figure 15. n-3 FA associations with ischemic stroke death: Observational studies



Study (or cohort) level associations between n-3 FA exposure and hazard ratio (HR) for ischemic stroke death. Studies that reported associations by continuous exposure (e.g., per g/d intake or per standard deviation) could not be graphed and are omitted. P values are the study-reported P value for the trend across quantiles.
White triangles = healthy adults.

Abbreviations: DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid, HR = hazard ratio, n-3 FA = omega-3 fatty acids.

Hemorrhagic Stroke Death

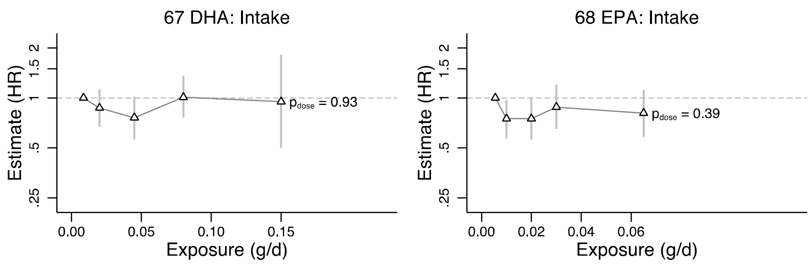
Randomized Controlled Trials

No RCTs evaluated this outcome.

Observational Studies

Only the Shanghai Women's and Men's Health Studies evaluated hemorrhagic stroke death (Appendix F, Death from hemorrhagic stroke section; Figure 16).[162] The study found no association between EPA, DHA, and EPA+DHA intake (not graphed because no data on median intake per quantile), separately, and risk of hemorrhagic stroke death after about 11 years followup in women and 6 years followup in men (combined analyses).

Figure 16. n-3 FA associations with hemorrhagic stroke death: Observational studies



Study (or cohort) level associations between n-3 FA exposure and hazard ratio (HR) for the outcome.
White triangles = healthy adults.

Abbreviations: DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid, HR = hazard ratio, n-3 FA = omega-3 fatty acids.

Death, All-Cause

Randomized Controlled Trials

Eighteen RCTs evaluated all-cause death (Table 15).[48, 49, 56, 67, 70, 74, 81, 82, 87, 90, 96, 115, 119, 121, 123, 146, 157, 160] Of these, one study was conducted in 12,716 generally healthy participants,[49] three were in a total of 13,713 participants at risk of CVD (defined as dyslipidemia,[90] hypercholesterolemia,[115] or a combination of various risk factors[160]), and 14 in a total of 50,386 participants with CVD including previous persistent AFib,[157] diabetes or a history of CVD,[146] arrhythmia,[82, 87] CHD,[56] ventricular tachycardia or fibrillation,[81] all CVD,[123] MI,[48, 67, 70, 119, 121] heart failure,[96] and angina.[74] Four of the trials reported all-cause death to be a primary outcome (Burr 2003, Kromhout 2010, Marchioli 2002, Tavazzi 2008).[70, 89, 96, 119]

Marine Oil Versus Placebo

Meta-analysis of the 17 RCTs of marine oil versus placebo yielded a nonsignificant summary effect size for risk of all-cause death: HR=0.97 (95% CI 0.92 to 1.03) (Figure 17).

At-Risk-for-CVD Population

Three RCTs compared EPA+DHA or EPA alone with placebo in participants at risk of CVD.

Among 13,068 participants, two RCTs compared marine oil (EPA+DHA) with placebo (corn or olive oil) (Figure 17).[115, 160] The doses of EPA+DHA were greater than 0.85 and 2.02 g/d, with EPA to DHA ratio ranging from 0.9 to 1.5. Compliance was greater than 90% in one study and was not reported in another. The duration of followup was 3 and 5 years. Both RCTs found that EPA+DHA had no significant effect on all-cause death compared with placebo (adjusted HR 0.53, 95% CI 0.27 to 1.04; HR 1.03, 95% CI 0.88 to 1.19).

One study of 18,645 patients with dyslipidemia compared 1.8 g/d EPA ethyl ester plus statin with statin alone. Compliance was monitored by local physicians but not reported in the study. Followup time was 4.6 years, and no significant additive effect of EPA supplementation on all-cause death was found (HR 1.09; 95% CI 0.92 to 1.28).[90]

Subgroup meta-analysis (as part of a meta-analysis of all marine oil vs. placebo trials) yielded a summary HR of 1.04 (95% CI 0.93 to 1.16) for people at risk for CVD.

CVD Population

Among the 14 RCTs that were conducted in participants with CVD (Figure 17), nine studies compared marine oil (EPA+DHA) with placebo,[67, 82, 87, 96, 121, 123, 146, 157] three compared marine oil (EPA+DHA) with no intervention,[56, 70, 81] two compared "fish advice" (advise to increase fish intake in both studies with additional advise to take fish oil supplement in later study) with "no fish advice",[48, 74] and one was the 2-by–2 factorial RCT described under *Major Adverse Cardiovascular Events* that compared EPA+DHA, EPA+DHA and ALA, ALA, and oleic acid margarines.[119]

Among the 12 studies that compared marine oil (EPA+DHA) with placebo or no intervention, a total of 44,629 participants with CVD were examined.[56, 67, 70, 81, 82, 87, 96, 119, 121, 123, 146, 157] The doses of EPA+DHA ranged from 0.4 g/d to 3.32 g/d. Among the nine RCTs reporting sufficient detail, the EPA to DHA ratio ranged from 0.5 to 2. Compliance ranged from 65 to 88 percent. The duration of follow-up ranged from 1 year to more than 6 years. Two of the 12 RCTs found that EPA+DHA had significant effect on reducing all-cause death compared with placebo or no intervention in 6975 participants with heart failure (adjusted HR 0.91; 95% CI 0.833 to 0.998) and in 11,332 participants with MI (RR 0.79; 95% CI 0.66 to 0.93). The other 10 RCTs found that EPA+DHA did not have significant effect on all-cause death with OR/HR ranging from 0.38 to 1.25.

Among the two studies that compared "fish advice" with "no fish advice",[48, 74] a total of 5147 participant with MI or angina were examined. The mean EPA intake estimated by the dietary assessment was 0.34 and 0.45 g/d in the "fish advice" groups, and was 0.09 and 0.11 in the "no fish advice" groups. No estimates for DHA intake levels were reported. Compliance was good (fish intake was significantly increased in the "fish advice" groups) based on the dietary assessments. Both RCTs found no significant difference in the risk of all-cause death between groups (HR 0.95; 95% CI 0.85 to 1.07; HR 1.15, 95% CI 0.92 to 1.32).

Across the 14 RCTs of CVD populations, the summary HR (Figure 17) was 0.96 (95% CI 0.90 to 1.02); almost identical to the nonsignificant summary HR for all RCTs, regardless of population (HR 0.97; 95% CI 0.92 to 1.03).

ALA Versus Placebo

Healthy Population

Among 12,716 healthy people, one RCT compared ALA oil (linseed oil) to control oil (sunflower seed oil).[49] The doses of ALA were 5.2 and 0.13 g/d, respectively. Compliance was not reported. After 1-year followup, there was no significant difference in all-cause death between the two groups (OR 0.93; 95% CI 0.61 to 1.44).

CVD Population

Among 4837 participants with MI, the 2-by‒2 factorial RCT found no significant difference in the risk of all-cause death compared with the groups received EPA+DHA alone or placebo margarines (HR 0.97; 95% CI 0.79 to 1.19).[119]

RCT Subgroup Analyses

Four RCTs included subgroup analysis for all causes of death (Table 16). All trials compared marine oil against placebo. One trial found no significant difference in effect between patients with and without hypertension (P interaction = 0.67).[70] Among the two analyses of diabetes vs no diabetes subgroups neither reported a statistically significant interaction between diabetes and marine oils.[70, 96] One study found no interactions between marine oil and age, left ventricular ejection fraction, ischemic cause versus nonischemic cause of existing CVD, New York Heart Association level, total cholesterol, or statin use. A third study found no significant difference in effect regardless of B vitamin supplementation.[123] The fourth study found no difference in effect between patients with history of CVD compared to patients without a history of CVD.[115]

Meta-regression of the marine oil trials found no significant interaction between n-3 FA dose (P=0.54), followup time (P=0.19), or between at risk and CVD populations (P=0.75)

Observational Studies

Seven studies evaluated the associations between n-3 FA intake or biomarker levels and all-cause death, mostly in healthy adults after 7 to 30 years of followup (Appendix F, All-cause death section; Figure 18); one study evaluated CVD patients with a history of MI after 4 years of followup.[47, 72, 95, 98, 148, 154, 159, 162, 186] Most analyses found significant associations between higher n-3 FA intake or biomarker level and reduced risk of death.

n-3 FA Intake

Six studies evaluated n-3 FA intake and the risk of death (Cardiovascular Health Study, JACC, MRFIT, Shanghai Women's and Men's Health Studies [two separate studies analyzed together], Takayama, VITAL).[47, 72, 98, 159, 162, 176]

JACC found no association between total n-3 FA intake (combined) and all-cause death in healthy adults after about 13 years of followup (Figure 18, plot #79).[98]

Two studies evaluated ALA intake. MRFIT and the Cardiovascular Health Study both found significant associations between higher ALA intake and reduced death in healthy men after about 10 years and healthy adults ≥65 years old after 12 years (Figure 18, plots # 69 & 70), with significant or larger associations found in median quantiles with intakes above about 1.6 g/d, 1 percent Kcal, or 2.4 percent of fat intake.[47, 159]

In a combined analysis (of women and men), the Shanghai Women's and Men's Health Studies found a significant associations between higher EPA and DHA intakes (separately) and reduced death after about 11 years of followup in the women and 6 years of followup in the men (Figure 18, plots #72 & 77), with significant associations found for quintiles with median intakes above 0.01 g/d of EPA and above 0.02 g/d of DHA.[162]

Four studies found heterogeneous associations between EPA+DHA (or EPA+DHA+DPA) intake and death risk (Figure 18, plots #75 & 76). MRFIT found near-significant associations between higher marine oil intake and death after 10 years of followup (P<0.10).[47] The Takayama study found no association in healthy men, but significantly lower death among women with higher marine oil intake after 7 years of followup.[72] The combined Shanghai Women's and Men's Health Studies found a significant association between higher marine oil intake and lower risk of death in women after 11 years of followup and men after 6 years of followup.[162] The VITAL study found a significant association between higher marine intake and lower risk of death in healthy adults after 6 years of followup (P=0.004).[176] Across studies, associations were large or near-significant (P<0.10) in quantiles with median intake above about 0.3 percent Kcal or about 0.7 or 1.2 g/d.

By meta-analysis (Table 17), overall there no significant association between marine oil intake and all-cause death across a median dose range of 0.066 to 1.58 g/d (effect size per g/d = 0.62; 95% CI 0.31 to 1.25). However, meta-analyses with the addition of a spline knot point at different dose thresholds (from 0.1 to 1.2 g/d) consistently found stronger associations (of higher dose being associated with lower risk) at *lower* doses than at higher doses (ES below knot less than 1; ES above knot closer to 1). This implies the possibility of a ceiling effect (where intake above a certain level adds no further benefit). For thresholds ≤0.4 g/d the associations are statistically significant at lower doses, but not statistically significant at higher doses. The difference between low- and high-dose associations is statistically significantly different at a threshold of 0.2 g/d (P=0.047). The best fit curve was found with a knot at 0.3 g/d. This analysis may suggest that marine oil intake above about 0.2 to 0.4 g/d may not further strengthen any association between higher marine oil intake and lower rate of all-cause death.

The VITAL study found a significant association between higher EPA and DHA intake (separately) and lower risk of death in healthy adults after 6 years of followup (EPA: P=0.014, DHA: P=0.004).[176]

n-3 FA Biomarkers

Three studies evaluated associations between n-3 FA biomarkers and risk of death, two in healthy adults, one in CVD patients with a history of MI.

The Cardiovascular Health Study found a significant association between higher plasma n-3 FA levels (combined) and risk of death in healthy adults ≥65 years after 16 years of followup (Figure 18, plot #80).[148]

Two studies evaluated ALA biomarkers (Figure 18, plot #71). The Cardiovascular Health Study and ULSAM found no significant associations between plasma ALA and risk of death at 16 and 31 years of followup in healthy adults.[95, 148]

Three studies evaluated EPA biomarkers (Figure 18, plot #78), one in a CVD population. The Osaka Acute Coronary Insufficiency Study found no association between blood EPA levels and death in patients with a history of MI after 4 years of followup. Similarly, ULSAM found no association with plasma EPA after 31 years of followup.[95] In contrast, the Cardiovascular Health Study found a significantly lower risk of death with higher plasma EPA levels after 16 years of followup in healthy adults ≥65 years old.[148]

The same three studies evaluated DHA biomarkers (Figure 18, plot #73). In contrast with its finding regarding blood EPA levels, the Osaka Acute Coronary Insufficiency Study found a significant association between higher blood DHA levels and reduced death. In ULSAM and the Cardiovascular Health Study, findings were concordant between blood EPA and DHA levels, such that the former found no association with death and the latter found a significant association between higher plasma DHA levels and lower death.[95, 148]

The Cardiovascular Health Study also found a significant association between higher plasma DPA levels and lower all-cause death in healthy adults (Figure 18, plot #74).

Observational Study Subgroup Analyses

Three observational studies conducted subgroup analyses of the associations between n-3 FA and all-cause death (Table 18). The Takayama study implied no difference in association of EPA+DHA intake between men and women.[72] The Cardiovascular Health Study found no difference in association of intake of or plasma ALA based on baseline fish consumption.[148] The Osaka Acute Coronary Insufficiency Study evaluated 12 sets of subgroups for both blood DHA and blood EPA, as listed in Table 18. A statistically significant interaction was found between blood EPA and hypertension (P interaction = 0.015). In participants with hypertension, no association was found between blood EPA and risk of death (HR=0.96); however, in participants with no hypertension, higher blood EPA was associated with higher risk of dying (HR=8.23). The study also found near-significant interactions between blood EPA and diabetes (P interaction = 0.089, favoring those without diabetes) and statin use (P interaction = 0.062, favoring those not using statins).

Table 15. All-cause mortality: RCTs

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int n/N,%	Ctrl n/N,%	Effect Size	Reported P value
Marine oil vs. Placebo											
Einvik 2010 20389249 Norway	At Risk	EPA+DHA+diet intervention	2.02 g/d (Marine oil) [E:D 1.4]	Placebo+diet intervention	0 (Corn oil))	3 y	>90% of the tablets were taken based on pharmacy records, and verified by biomarkers	14/282, 4.96%	24/281, 8.54%	Adj HR 0.53 (0.27, 1.04)	0.063
Roncaglioni 2013 23656645 Italy	At risk	EPA+DHA	≥0.85 g/d (suppl) [E:D 0.9−1.5]	Placebo	0 (Olive oil)	5 y	Self-reported (nd on level of adherence)	348/6239, 5.6%	337/6266, 5.4%	HR 1.03 (0.88, 1.19)	0.73
Yokoyama 2007 17398308 Japan	At risk (dyslipidemia)	EPA (+Statin)	1.8 g/d (Ethyl ester)	Placebo (+Statin)	0	4.6 y	Local physicians monitored but compliance level was not reported	286/9326, 3.1%	265/9319, 2.8%	HR 1.09 (0.92, 1.28)	0.333
Macchia 2013 23265344 Argentina and Italy	CVD	EPA+DHA	0.85−0.882 (suppl) [nd]	Placebo	0 (Olive oil)	12 mo	nd	4/289, 1.4%	5/297, 1.7%	HR 0.80 (0.21, 3.00)	NS
Bosch 2012 22686415 Canada	CVD	EPA+DHA	0.84 g/d (Marine oil) [E:D 1.24]	Placebo	0 (Olive oil)	6+ y	FFQ at baseline, 2 years, and end of study (adherence was 88% at the end of study)	951/6281, 15.1%	964/6255, 15.4%	Adj HR 0.98 (0.89, 1.07)	0.63
Brouwer 2006 16772624 N Europe	CVD	EPA+DHA	0.96 g n-3 FA (0.464 g EPA, 0.335 g DHA) (Marine oil) [E:D=1.4]	Placebo	0 (high-oleic acid sunflower oil)	1 y	Generally good (76% reported taking 80% pills) based on pill counts and confirmed by biomarkers.	8/273, 3%	14/273, 5%	OR 0.56 (0.23, 1.35)	0.142

Table 15. All-cause mortality: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int n/N,%	Ctrl n/N,%	Effect Size	Reported P value
Leaf 2005 16267249 U.S.	CVD	EPA+DHA	EPA plus DHA of 2.6 g (Marine oil)	Placebo	0 (Olive oil)	12 mo	Pill counts and analysis of the phospholipids of red blood cells for their content of EPA and DHA. Noncompliance ~35%	13/200, 6.5%	12/202, 5.9%	OR 1.10 (0.49, 2.47)	0.816
Galan 2010 21115589 France	CVD	EPA+DHA	EPA 0.4 g/d DHA 0.2 g/d (Marine oil) [E:D=2]	Placebo	0 (nd)	4.7 y	Patient reported (86% reported they took >=80% of allocated treatment)	58/1253, 4.7%	59/1248, 4.7%	Adj HR 1.03 (0.72, 1.48)	0.88
Nilsen 2001 2001 11451717 Norway	CVD	EPA+DHA	EPA-DHA 3.4−3.528 g/d (Marine oil) [E:D=0.5]	Placebo	0 (Corn oil)	median 2.4 y	nd (82% in fish oil group; 86% in the placebo group)	21/150, 14%	18/150, 12%	OR 1.19 (0.61, 2.34)	0.607
Rauch 2010 21060071 Germany	CVD	EPA+DHA	0.46 g EPA, 0.38 g DHA (Marine oil) [E:D=1.2]	Placebo	0 (Olive oil)	1 y	Pill counts at 3 months and 12 months (≥70% of study period)	88/1919, 4.6%	70/1885, 3.7%	OR 1.25 (0.90, 1.72)	0.18
Raitt 2005 15956633 U.S.	CVD	EPA+DHA	EPA 0.756 g/d, DHA 0.54 g/d (fish oil) [E:D 1.4]	Placebo	0 (olive oil: 73% oleic acid, 12%)	2 y	RBC and plasma n-3 FA levels	4/100, 4.0%	10/100, 10.0%	OR 0.38 (0.11, 1.24)	0.16
Tavazzi 2008 18757090 Italy	CVD	EPA+DHA	0.850−0.882 g/d (Ethyl esters) [E:D 0.83]	Placebo	0 (nd)	3.9 y	Exam question (~30% not taking n-3 FA or placebo by the end of study)	955/3494, 27.3%	1014/3481, 29.1%	Adj HR 0.91 (0.833, 0.998)	0.041
Kromhout 2010 20929341 Netherlands	CVD	EPA+DHA (±ALA)	0.4 g/d EPA+DHA and 2 g/d ALA (Marine; Plant oil) [E:D 3:2]	Placebo (±ALA)	0; 2 g/d ALA (Placebo margarine = oleic acid; Plant oil)	40 mo	90% of the patients adhered fully to the protocol; verified by biomarkers	186/2404, 7.7%	184/2433, 7.6%	HR 1.01 (0.82, 1.24)	0.92

Table 15. All-cause mortality: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int n/N,%	Ctrl n/N,%	Effect Size	Reported P value
Eritsland 1996 8540453 Norway	CVD	EPA+DHA	EPA 2.04 g/d, DHA 1.28 g/d (Marine oil) [E:D=1.6]	No intervention	0	1 y	Tablet and capsule accounts (88% were taken), and serum phospholipid FA	8/317, 2.5%	6/293, 2.0%	OR 1.24 (0.42, 3.61)	0.695
	CVD	EPA+DHA + Aspirin	EPA 2.04 g/d, DHA 1.28 g/d (Marine oil) [E:D=1.6]	Aspirin	0	1 y	Tablet and capsule accounts (88% were taken), and serum phospholipid FA	5/143, 3.5%	4/148, 2.7%	OR 1.3 (0.34, 4.96)	0.697
	CVD	EPA+DHA + Warfarin	EPA 2.04 g/d, DHA 1.28 g/d (Marine oil) [E:D=1.6]	Warfarin	0	1 y	Tablet and capsule accounts (88% were taken), and serum phospholipid FA	3/174, 1.7%	2/145, 1.4%	OR 1.25 (0.21, 7.61)	0.805
Marchioli 2002 11997274 Italy	CVD	EPA+DHA	0.850- 0.882 g/d (Marine oil) [E:D 0.5]	No intervention	nd	42 mo	Followup (adherence was 72.5% at the end of study)	477/5679, 8.4%	554/5653, 9.8%	RR 0.79 (0.66, 0.93)	0.0006
Burr 1989 2571009 UK	CVD	Fish advice, either alone or in combination with fiber advice, fat advice, or both fiber and fat advice.	EPA 0.34 g/d (diet)	No fish advice (Fat advice, fiber advice, fiber and fat advice, or no advice)	EPA 0.09 g/d (diet)	Overall years (10+ y)	Compliance was good based on dietary assessments	530/1015, 52.2%	553/1018, 54.3%	Adj HR 0.95 (0.85, 1.07)	NS

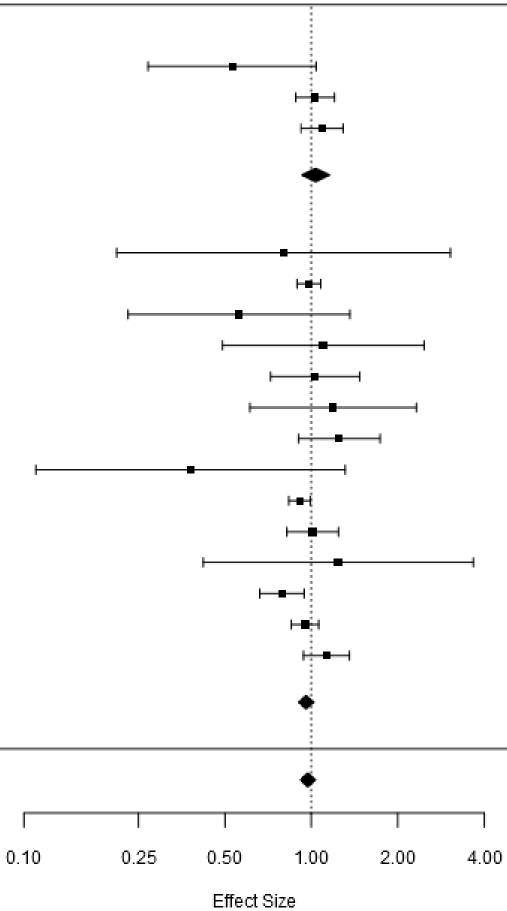
Table 15. All-cause mortality: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int n/N,%	Ctrl n/N,%	Effect Size	Reported P value
Burr 2007 17343767 UK	CVD	Fish advice	EPA 0.45 g/d (diet)[a]	No fish advice	EPA 0.11 (diet)[a]	9 y	dietary charts sent by post with reply-paid envelopes	198/1109, 11.0%	242/1543, 15.7%	Adj HR 1.13 (0.94, 1.37)	0.20
	CVD	EPA+DHA (advice to take fish oil)	EPA ≤0.51 and DHA ≤0.345 (marine oil)[a]	No fish advice	EPA 0.11 (diet)[a]	9 y	dietary charts sent by post with reply-paid envelopes	85/462, 18.4%	242/1543, 15.7%	Adj HR 1.19 (0.92, 1.54)	0.19
	CVD	EPA+DHA (advice to take fish oil)	EPA ≤0.51 and DHA ≤0.345 (marine oil)[a]	Fish advice	EPA 0.45 g/d (diet)[a]	9 y	dietary charts sent by post with reply-paid envelopes	85/462, 18.4%	198/1109, 11.0%	OR 1.04 (0.78, 1.37)	nd
ALA vs. Placebo											
Natvig 1965 5756076 Norway	Healthy	ALA	ALA 5.2 g/d (Linseed oil)	Control oil	ALA 0.13 g/d (Sunflower seed oil)	1 y	nd	40/6690, 6%	43/6716, 6%	OR 0.93 (0.61, 1.44)	0.755
Kromhout 2010 20929341 Netherlands	CVD	ALA (±EPA+DHA)	0.4 g/d EPA+DHA and 2 g/d ALA (Marine; Plant oil) [E:D 3:2]	Placebo (±EPA+DHA)	0; 0.4 g/d EPA-DHA (placebo = oleic acid; Marine oil) [E:D 3:2]	40 mo	90% of the patients adhered fully to the protocol; verified by biomarkers	182/2404, 7.6%	188/2433, 7.7%	HR 0.97 (0.79, 1.19)	0.8

Abbreviations: ALA = alphalinolenic acid, Ctrl = control, CVD = cardiovascular disease, DHA = docosahexaenoic acid, E:D = EPA to DHA ratio, EPA = eicosapentaenoic acid, F/up = followup, FFQ = food frequency questionnaire, HR = hazard ratio, Int = intervention, n/N = number with outcome/number analyzed, n6:3 = omega-6 to omega-3 fatty acid ratio, n-3 FA = omega-3 fatty acids, ND = no data, NS = not significant, OR = odds ratio, RBC = red blood cell, RCT = randomized controlled trial, RR = relative risk.

Figure 17. All-cause death: Randomized trials of marine oils

Study PMID	n-3 FA	g/day	Years	n-3 FA n/N	Placebo n/N	Effect Size [95% CI]
At risk population						
Einvik 2010 20389249	EPA+DHA	2.02	3	14/282	24/281	0.53 [0.27, 1.04]
Roncaglioni 2013 23656645	EPA+DHA	0.85	5	348/6239	337/6266	1.03 [0.88, 1.19]
Yokoyama 2007 17398308	EPA	1.8	4.6	286/9326	265/9319	1.09 [0.92, 1.28]
Summary, at risk						*1.04 [0.93 , 1.16]*
CVD population						
Macchia 2013 23265344	EPA+DHA	0.87	1	4/289	5/297	0.80 [0.21, 3.00]
Bosch 2012 22686415	EPA+DHA	0.84	6	951/6281	964/6255	0.98 [0.89, 1.07]
Brouwer 2006 16772624	EPA+DHA	0.96	1	8/273	14/273	0.56 [0.23, 1.35]
Leaf 2005 16267249	EPA+DHA	2.6	1	13/200	12/202	1.10 [0.49, 2.47]
Galan 2010 21115589	EPA+DHA	0.6	4.7	58/1253	59/1248	1.03 [0.72, 1.48]
Nilsen 2001 2001 11451717	EPA+DHA	3.46	2.4	21/150	18/150	1.19 [0.61, 2.34]
Rauch 2010 21060071	EPA+DHA	0.84	1	88/1919	70/1885	1.25 [0.90, 1.72]
Raitt 2005 15956633	EPA+DHA	1.3	2	4/100	10/100	0.38 [0.11, 1.24]
Tavazzi 2008 18757090	EPA+DHA	0.87	3.9	955/3494	1014/3481	0.91 [0.833, 0.998]
Kromhout 2010 20929341	EPA+DHA*	0.4	3.3	186/2404	184/2433	1.01 [0.82, 1.24]
Eritsland 1996 8540453	EPA+DHA	3.32	1	8/317	6/293	1.24 [0.42, 3.61]
Marchioli 2002 11997274	EPA+DHA	0.87	3.5	477/5679	554/5653	0.79 [0.66, 0.93]
Burr 1989 2571009	EPA	0.34	10	530/1015	553/1018	0.95 [0.85, 1.07]
Burr 2007 17343767	EPA	0.45	9	198/1109	242/1543	1.13 [0.94, 1.37]
Summary, CVD						*0.96 [0.90 , 1.02]*
Summary [I-squared=23.747, Phet=0.137]						**0.97 [0.92 , 1.03]**



Random effects model meta-analysis of n-3 FA versus placebo (or no n-3 FA), with subgroup analyses by population. In all meta-analyses, only studies that reported sufficient results data are included.

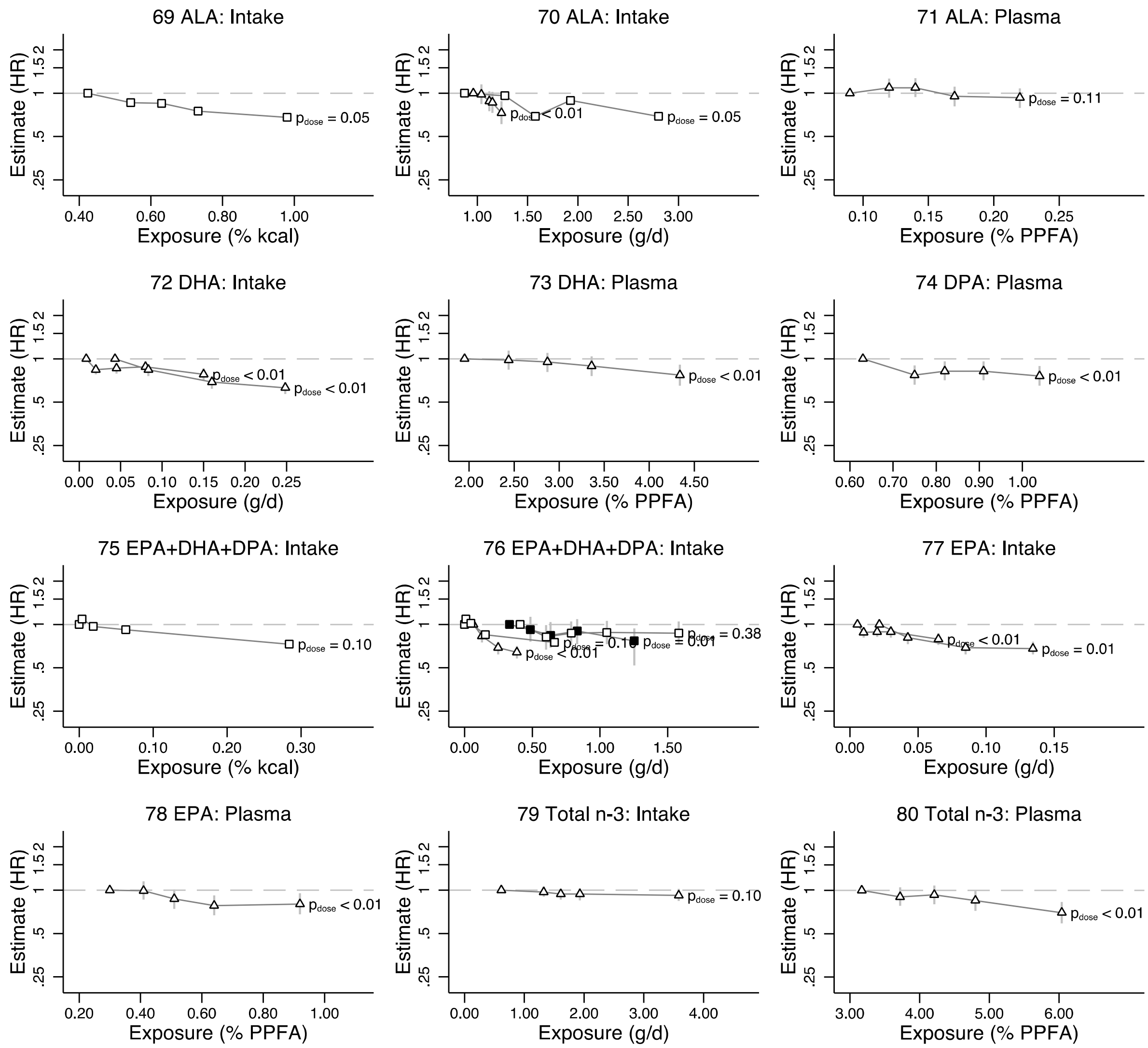
Abbreviations: CI = confidence interval, CVD = cardiovascular disease, DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid, n/N = number with outcome/number analyzed, n-3 FA = omega-3 fatty acids, Phet = P value of chi-squared test of heterogeneity across studies, PMID = PubMed Identification number.

Table 16. All-cause death: Subgroup analyses, randomized trials

Study	Population	Subgroups	n-3 FA	Comparator	N Total	P difference	Difference	Favors
Marchioli 2002 11997274 Italy	CVD	HTN vs no HTN	EPA+DHA	Placebo	11323	0.67		
		Diabetes vs no diabetes	EPA+DHA	Placebo	11323	0.50		
Tavazzi 2008 18757090 Italy	CVD	Diabetes vs no diabetes	EPA+DHA	Placebo	6975	NS		
		Age <69 vs ≥69 years	EPA+DHA	Placebo	6975	NS		
		Left ventricular ejection fraction ≤40% vs >40%	EPA+DHA	Placebo	6975	NS		
		Ischemic cause vs nonischemic cause	EPA+DHA	Placebo	6975	NS		
		New York Heart Association II vs III or IV	EPA+DHA	Placebo	6975	NS		
		Total cholesterol ≤4.87 vs >4.87 mmoL/L	EPA+DHA	Placebo	6975	NS		
		Statin vs no statin	EPA+DHA	Placebo	6975	NS		
Galan 2010 21115589 France	CVD	B vitamin vs no B vitamin	EPA+DHA	Placebo	2501	NS		
Einvik 2010 20389249 Norway	At Risk	CVD vs no CVD	EPA+DHA	Placebo	563	NS		

Abbreviations: CVD = cardiovascular disease, DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid, HTN = hypertension, n-3 FA = omega-3 fatty acids, NS = not significant, PMID = PubMed Identification number.

Figure 18. n-3 FA associations with all-cause death: Observational studies



Study (or cohort) level associations between n-3 FA exposure and hazard ratio (HR) for the outcome. Studies that reported associations by continuous exposure (e.g., per g/d intake or per standard deviation) could not be graphed and are omitted. P values are the study-reported P value for the trend across quantiles. Where 95% confidence intervals (vertical lines) are missing, these were not reported in the studies.
White triangles = healthy adults, white squares = healthy males, black squares = healthy females.

Abbreviations: ALA = alphalinolenic acid, DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, EPA = eicosapentaenoic acid, HR = hazard ratio, n-3 FA = omega-3 fatty acids, PPFA = plasma polyunsaturated fatty acids.

Table 17. Meta-analysis results of observational studies of marine oil (EPA+DHA±DPA) intake and all-cause death

N patients	Dose range, g/d	Knot	ES, overall	ES below knot	ES above knot	P*	AIC	No. cohorts (crossing threshold)
100,767	0.066-1.58	NA	0.62 (0.31, 1.25)					3
		0.1		0.24 (0.07, 0.82)	0.71 (0.38, 1.34)	0.10	20.4	3
		0.2		0.36 (0.15, 0.87)	0.82 (0.52, 1.28)	0.047	17.4	3
		0.3		0.43 (0.19, 0.98)	1.09 (0.81, 1.47)	0.09	15.1	3
		0.4		0.53 (0.28, 0.98)	1.12 (0.76, 1.65)	0.12	20.5	2
		0.5		0.55 (0.29, 1.04)	1.19 (0.69, 2.06)	0.18	20.9	2
		0.6		0.57 (0.30, 1.08)	1.25 (0.60, 2.64)	0.22	21.5	2
		0.7		0.58 (0.30, 1.12)	1.35 (0.47, 3.87)	0.28	22.4	2
		0.8		0.60 (0.30, 1.17)	1.47 (0.29, 7.54)	0.38	23.4	2
		0.9		0.60 (0.31, 1.18)	1.54 (0.10, 24.2)	0.54	24.4	2
		1.0		0.60 (0.31, 1.19)	1.19 (0.04, 36.2)	0.71	25.6	2
		1.1		0.60 (0.31, 1.20)	1.47 (0.01, 188)	0.73	27.5	2
		1.2		0.60 (0.31, 1.19)	6.17 (0.00, >999)	0.73	31.6	2

* ES below vs. above knot

Abbreviations: AIC = Akaike information criterion (estimation of fit of regression with spline), DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, EPA = eicosapentaenoic acid, ES = effect size, HTN = hypertension, n-3 FA = omega-3 fatty acids, NA = not applicable.

Table 18. All-cause death: Subgroup analyses, observational studies

Study	Subgroups	n-3 FA	N Total	P difference	Difference	Favors
Takayama[72]	Men vs Women	EPA+DHA intake	30480	NS (implied)		
Cardiovascular Health Study[148]	Fish consumption vs low or no fish consumption	ALA (Plasma or Intake)	4432	NS		
	Men vs Women			NS		
Osaka Acute Coronary Insufficiency Study[154]	Age <65 vs ≥65 years	DHA (Blood)	671	0.63		
	Male vs Female			0.83		
	Diabetes vs. no diabetes			0.21		
	Hypertension vs. no hypertension			0.30		
	Dyslipidemia vs. no dyslipidemia			0.31		
	LDL-c <100 vs ≥100 mg/dL			0.80		
	HDL-c <40 vs ≥40 mg/dL			0.81		
	Tg <150 vs. ≥ 150 mg/dL			0.56		
	eGFR <60 vs. ≥60 mL/min			0.69		
	Statin vs no statin			0.31		
	ACEi/ARB vs. no ACEi/ARB			0.40		
	Beta blocker vs. no beta blocker			0.77		
	Age <65 vs ≥65 years	EPA (Blood)	671	0.15		
	Male vs Female			0.24		
	Diabetes vs. no diabetes			0.089	HR 2.73 vs. 0.92	No diabetes
	Hypertension vs. no hypertension			0.015	HR 0.96 vs. 8.23	Hyperten sion
	Dyslipidemia vs. no dyslipidemia			0.44		
	LDL-c <100 vs ≥100 mg/dL			0.74		
	HDL-c <40 vs ≥40 mg/dL			0.94		
	Tg <150 vs. ≥ 150 mg/dL			0.56		
	eGFR <60 vs. ≥60 mL/min			0.38		
	Statin vs no statin			0.062	HR 2.64 vs. 0.83	No statin
	ACEi/ARB vs. no ACEi/ARB			0.97		
	Beta blocker vs. no beta blocker			0.72		

Abbreviations: ARB = angiotensin receptor blocker, ACEi = angiotensin-converting enzyme inhibitor, ALA = alphalinolenic acid, DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, eGFR = epidermal growth factor receptor, EPA = eicosapentaenoic acid, HDL-c = high density lipoprotein cholesterol, HR = hazard ratio, LDL-c = low density lipoprotein cholesterol, n-3 FA = omega-3 fatty acids, NS = not significant, Tg = triglycerides.

Coronary Heart Disease, Incident

Randomized Controlled Trials

No RCT evaluated incident CHD.

Observational Studies

Eleven studies evaluated the associations between intake and biomarkers of n-3 FA and incident CHD (Appendix F, Coronary heart disease section; Figure 19).[54, 57, 69, 78, 84, 127, 135, 148, 149, 171, 172, 186]. Definitions of CHD outcomes varied across studies, but mostly included both fatal and nonfatal events. All studies were conducted in generally healthy adults. The median followup duration across studies was 11.5 years (range of average followup 6 to 23 years). Studies found a mix of both significant associations between higher n-3 FA intake or biomarker levels and lower risk of CHD or a lack of associations.

n-3 FA Intake

Ten studies evaluated n-3 FA intake and risk of CHD (Alpha-Tocopherol, Beta-Carotene Cancer Prevention, Cardiovascular Health Study, Glostrup Population Studies, Health Professional Follow-up Study, Japan Public Health Center-Based Study - Cohort I, MESA, MORGEN, Nurses' Health Study, Pooling Project of Cohort Studies on Diet and Coronary Disease, Spanish EPIC).

Six studies evaluated ALA intake with 6 to 23 years of followup (Pooling Project of Cohort Studies on Diet and Coronary Disease, Alpha-Tocopherol Beta-Carotene Cancer Prevention, Cardiovascular Health Study, Glostrup Population Studies, MESA, MORGEN). One of these studies, the Pooling Project, pooled data from eight large cohorts (ARIC, FMC, IWHS, NHS, VIP, WHS, ATBC, HPFS); thus, overall 13 study cohorts were included (Figure 19, plot #81). Individually, none of the studies found associations between ALA intake and CHD.

By meta-analysis (Table 19), overall there is no association between ALA intake and CHD across a median dosage range of 0.2 to 2.5 g/d (effect size per g/d = 0.97; 95% CI 0.92 to 1.03). Meta-analyses with the addition of a spline knot point at different dose thresholds (from 0.1 to 1.4 g/d) consistently found marginally smaller ES at lower doses than at higher doses. At no dose threshold was there a statistically significant difference between the ES below the dose threshold (knot) and above the threshold. The best fit curve was found with a knot at 0.7 g/d, the threshold that also had the lowest P value (P=0.34).

For both EPA and DHA, separately, two studies evaluated associations with CHD, both at about 10 years of followup (Figure 19, plots #84 & 93). Spanish EPIC found no associations between DHA or EPA intake and CHD in either men or women (analyzed separately).[172] MESA found near-significant associations (P=0.09 DHA and 0.06 EPA) between higher DHA and EPA intake and lower risk of CHD.[171]

Only MESA evaluated DPA intake, finding significantly lower risk of CHD among those with higher DPA intake after 10 years of followup (Figure 19, plot #87).[171]

Seven studies evaluated intake of EPA+DHA (five studies) or EPA+DHA+DPA (two studies) with 6 to 23 years of followup (Alpha-Tocopherol Beta-Carotene Cancer Prevention, Glostrup Population Studies, Health Professional Follow-up Study, Japan Public Health Center-Based Study - Cohort I, MESA, Nurses' Health Study, Spanish EPIC) (Figure 19, plots #90 & 91). Individually, studies found variable associations. In two analyses of combined men and women (Japan Public Health Center-Based Study - Cohort I, MESA), neither found a significant association at 10 and 11.5 years of followup (although, MESA found a lower risk with higher EPA+DHA+DPA intake at P=0.08).[84, 171] Three studies analyzed associations in women specifically (Glostrup Population Studies, Nurses' Health Study, Spanish EPIC). The Nurses' Health Study and Glostrup Population Studies found significantly lower risk of CHD with higher EPA+DHA intake;[69, 135] the Spanish EPIC study also found lower HRs with higher intake but the association was nonsignificant.[172] Four studies analyzed men specifically (Alpha-Tocopherol Beta-Carotene Cancer Prevention, Glostrup Population Studies, Health Professional Follow-up Study, Spanish EPIC). All found no significant associations; however, in contrast with the studies of all adults or of women, the direction of the associations suggested *higher* risk of CHD among men with higher marine oil intake at baseline.[54, 57, 135, 172]

By meta-analysis (Table 20), overall there no significant association between marine oil intake and CHD across a median dose range of 0.038 to 3.47 g/d (effect size per g/d = 0.94; 95% CI 0.81 to 1.10). Meta-analyses with the addition of a spline knot point at different dose thresholds (from 0.1 to 1.4 g/d) consistently found a stronger association (of higher dose being associated with lower risk) at *lower* doses than at higher doses (ES below knot less than 1, ES above know about 1). At all knot points the differences were nonsignificant. This weakly suggests the possibility of a floor effect (where intake above a certain minimum amount is needed before any benefit accrues). The best fit curve was found with a knot at 0.4 g/d. The P values for differences between lower- and higher-dose knots were between 0.12 and 0.14 at all knots ≥0.3 g/d.

Table 19. Meta-analysis results of observational studies of ALA intake and CHD

N patients	Dose range, g/d	Knot	ES, overall	ES below knot	ES above knot	P*	AIC	No. cohorts (crossing threshold)
73,093	0.2-2.5	NA	0.97 (0.92, 1.03)	0.93 (0.82, 1.05)	0.99 (0.92, 1.06)	0.45	29.0	6
		0.1		0.93 (0.82, 1.05)	0.99 (0.92, 1.07)	0.42	25.4	6
		0.2		0.93 (0.83, 1.04)	1.00 (0.92, 1.08)	0.40	22.6	6
		0.3		0.93 (0.83, 1.04)	1.00 (0.92, 1.09)	0.38	20.3	6
		0.4		0.93 (0.84, 1.03)	1.01 (0.92, 1.10)	0.36	18.4	6
		0.5		0.93 (0.85, 1.03)	1.01 (0.92, 1.11)	0.35	17.0	6
		0.6		0.94 (0.85, 1.03)	1.01 (0.92, 1.12)	0.35	16.2	6
		0.7		0.94 (0.86, 1.02)	1.02 (0.91, 1.13)	0.34	15.4	6
		0.8		0.94 (0.87, 1.02)	1.02 (0.91, 1.13)	0.35	16.0	6
		0.9		0.95 (0.88, 1.02)	1.02 (0.91, 1.14)	0.35	20.9	6
		1.0		0.95 (0.88, 1.02)	1.02 (0.91, 1.16)	0.37	25.1	5
		1.1		0.95 (0.89, 1.02)	1.02 (0.89, 1.17)	0.43	27.6	5
		1.2		0.93 (0.82, 1.05)	0.99 (0.92, 1.06)	0.45	29.0	6
		1.3		0.93 (0.82, 1.05)	0.99 (0.92, 1.07)	0.42	25.4	6
		1.4		0.93 (0.83, 1.04)	1.00 (0.92, 1.08)	0.40	22.6	6

* ES below vs. above knot

Abbreviations: AIC = Akaike information criterion (estimation of fit of regression with spline), ALA = alphalinolenic acid, CHD = coronary heart disease, ES = effect size, NA = not applicable.

Table 20. Meta-analysis results of observational studies of marine oil (EPA+DHA±DPA) intake and CHD

N patients	Dose range, g/d	Knot	ES, overall	ES below knot	ES above knot	P*	AIC	No. cohorts (crossing threshold)
178,005	0.038−3.47	NA	0.94 (0.81, 1.10)					9
		0.1		0.85 (0.43, 1.69)	0.91 (0.74, 1.12)	0.86	64.6	8
		0.2		0.67 (0.38, 1.20)	1.00 (0.87, 1.15)	0.20	55.5	8
		0.3		0.74 (0.50, 1.10)	1.01 (0.88, 1.16)	0.14	47.6	7
		0.4		0.78 (0.57, 1.09)	1.02 (0.89, 1.17)	0.14	46.4	7
		0.5		0.80 (0.60, 1.07)	1.03 (0.90, 1.18)	0.12	47.9	7
		0.6		0.82 (0.63, 1.07)	1.04 (0.91, 1.19)	0.12	51.3	7
		0.7		0.84 (0.66, 1.07)	1.06 (0.93, 1.20)	0.13	58.0	7
		0.8		0.86 (0.69, 1.07)	1.07 (0.94, 1.21)	0.13	184.7	6
		0.9		0.88 (0.72, 1.07)	1.07 (0.94, 1.23)	0.14	79.4	5
		1.0		0.89 (0.74, 1.07)	1.08 (0.95, 1.23)	0.13	64.1	4
		1.1		0.89 (0.74, 1.07)	1.09 (0.96, 1.25)	0.13	65.7	4
		1.2		0.90 (0.75, 1.07)	1.10 (0.95, 1.27)	0.13	67.1	4
		1.3		0.91 (0.77, 1.07)	1.11 (0.95, 1.30)	0.14	68.3	4
		1.4		0.91 (0.77, 1.07)	1.12 (0.96, 1.32)	0.12	71.5	4

* ES below vs. above knot

Abbreviations: AIC = Akaike information criterion (estimation of fit of regression with spline), CHD = coronary heart disease, DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, EPA = eicosapentaenoic acid, ES = effect size, NA = not applicable.

n-3 FA Biomarkers

Three studies analyzed n-3 FA biomarkers (Cardiovascular Health Study, EPIC Norfolk, MESA) in healthy adults (men and women combined) with 10, 13, and 16 years of followup.[149, 159, 171]

The two studies that evaluated blood or plasma levels of total n-3 FA combined had conflicting findings regarding the association between total n-3 FA biomarkers and risk of CHD (Figure 19, plots #96 & 97). EPIC Norfolk found no evidence of an association between blood levels of total n-3 FA and risk of CHD at 13 years,[149] but the Cardiovascular Health Study found a significantly lower risk of CHD at 16 years with higher total n-3 FA plasma levels.[148, 159]

All three studies (Cardiovascular Health Study, EPIC Norfolk, MESA) found no association between ALA blood, plasma, or phospholipid levels and risk of CHD (Figure 19, plots #82 & 83).[149, 159, 171]

All three studies evaluated both EPA and DHA blood, plasma, or phospholipid levels (separately for each n-3 FA) and found similar associations for the two n-3 FA (Figure 19, plots #85, 86, 94, & 95). The Cardiovascular Health Study and MESA both found lower risk of CHD associated with higher baseline EPA and DHA levels.[148, 159, 171] EPIC Norfolk found no association.[149]

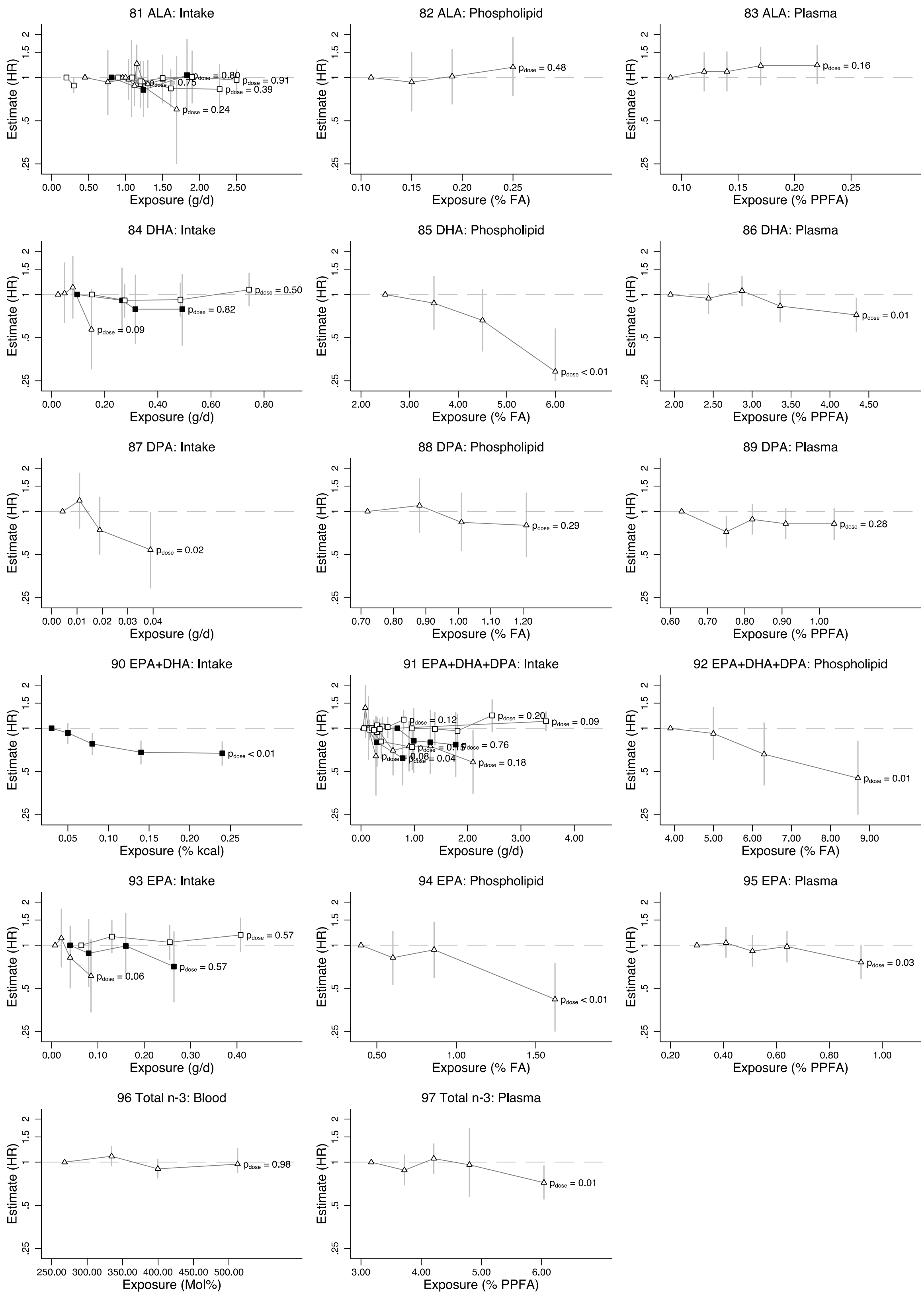
The three studies also evaluated DPA blood, plasma, or phospholipid levels, but each study had the opposite findings as for EPA and DHA biomarkers (Figure 19, plots #88 & 89). The Cardiovascular Health Study and MESA found no significant association with CHD (although the HR estimates also favored lower CHD with higher DPA levels).[148, 159, 171] EPIC Norfolk found a significantly lower risk of CHD with higher DPA blood levels.[149]

The MESA study found a significant association between combined EPA+DHA+DPA phospholipid levels and lower risk of CHD (Figure 19, plot #92).[171]

Observational Study Subgroup Analyses

The Pooling Project found a stronger, almost significant, association between ALA intake and incident CHD in men (HR=0.85; 95% CI 0.72 to 1.01) than in women (HR=1.02; 95% CI 0.65 to 1.59), but did not report whether these associations were significantly different from each other (whether there was an interaction).[181] The Cardiovascular Health Study found no difference in associations between ALA (plasma or intake) and incident CHD between men and women or between those with higher versus lower (or no) fish intake at baseline.[148]

Figure 19. n-3 FA associations with incident coronary heart disease: Observational studies



Study (or cohort) level associations between n-3 FA exposure and hazard ratio (HR) for the outcome. Studies that reported associations by continuous exposure (e.g., per g/d intake or per standard deviation) could not be graphed and are omitted. P values are the study-reported P value for the trend across quantiles. The 95% confidence intervals were truncated when <0.25 and >2.
White triangles = healthy adults, black circles = adults with dyslipidemia (at risk), white squares = healthy males, black squares = healthy females.

Abbreviations: ALA = alphalinolenic acid, DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, EPA = eicosapentaenoic acid, FA = fatty acid, HR = hazard ratio, n-3 FA = omega-3 fatty acids, PPFA = plasma polyunsaturated fatty acids.

Myocardial Infarction, Total (Fatal and Nonfatal)

Randomized Controlled Trials

Eleven RCTs evaluated risk of MI (Table 21).[48, 49, 51, 81, 87, 90, 96, 123, 146, 157, 160] Of these, one study was conducted in 12,716 generally healthy participants,[49] three were in a total of 27,938 participants at risk of CVD (defined as previous stable angina,[49] dyslipidemia,[90] or a combination of various risk factors,[160] and nine were in a total of 29,338 participants with CVD including MI,[48, 49, 160] CHD,[51, 90] diabetes, and history of CVD,[146] all CVD,[123] heart failure,[96] previous persistent AFib,[157] ventricular tachycardia or fibrillation,[81] and arrhythmia.[87] One of the marine oil trials reported separate analyses for at risk and CVD populations.[90] One of the ALA trials reported separate analyses for all three population groups.[49] Three of the trials reported incident MI to be a primary outcome (Bosch 2012, Burr 1989, Galan 2010); however Galan recorded MI as a secondary outcome in the ISRCTN registry).[48, 123, 146]

Marine Oil Versus Placebo

Meta-analysis of the 11 RCTs of marine oil versus placebo yielded a significant summary effect size for lower risk of MI: HR=0.88 (95% CI 0.77 to 1.02) (Figure 20).

At-Risk-for-CVD Population

Two RCTs comparing marine oils to control were conducted in participants at increased risk of CVD.[90, 160] One compared 1.8 g/d EPA combined with statin with control (statin alone) in 14,981 participants with dyslipidemia (without CHD),[90] and one compared marine oil (EPA+DHA) with placebo (olive oil) in 12,505 participants with a combination of various risk factors.[160] Compliance was not reported in either study. After 5-year followup, the EPA (and statin) study showed no significant additive effect of EPA on statin use to reduce the risk of MI compared with statin alone (HR 0.79; 95% CI 0.52 to 1.19). In the RCT of EPA+DHA,[160] the dose of EPA+DHA was less than 0.85 g/d with a EPA to DHA ratio between 0.9 and 1.5. After 5-year followup, this study found that EPA+DHA had no significant effect on risk of MI compared with placebo (HR 0.76; 95% CI 0.34 to 1.74)

Subgroup meta-analysis (as part of a meta-analysis of all marine oil vs. placebo trials) yielded a nonsignificant summary HR of 0.77 (95% CI 0.57 to 1.03) for people at increased risk for CVD.

CVD Population

Nine RCTs of participants with a history of CVD evaluated EPA+DHA supplementation or fish advice to placebo (or no fish advice) in a total of 28,314 participants.[48, 51, 81, 87, 90, 96, 123, 146, 157] Followup duration ranged from 1 to over 6 years. Among the nine EPA+DHA trials, total dose of marine oil ranged from 0.6 to 6 g/d; the fish advice trial compared 0.34 g/d (based on food frequency questionnaire) to 0.09 g/d. Among five of the RCTs, the ratio of EPA to DHA ranged from 0.83 to 2. None of the trials found a statistically significant effect of marine oil on risk of MI, with effect sizes ranging from 0.33 (95% CI 0.03 to 3.19) to 1.10 (95% CI 0.07 to 17.9). The RCT that compared 1.8 g/d EPA ethyl ester plus statin with statin alone also analyzed the 3,884 patients with either CHD or peripheral artery disease separately. Followup time was 5 years and compliance was not reported. There was no significant additive effect of EPA supplementation on risk of MI (HR 0.75; 95% CI 0.47 to 1.19 and OR 0.67; 95% CI 0.15 to 3.07).[90]

Across the nine RCTs of CVD populations, the summary HR (Figure 20) was 0.91 (0.78 to 1.06); almost identical to the near-significant summary HR for all RCTs, regardless of population (HR 0.88; 95% CI 0.77 to 1.02).

ALA Versus Placebo

Healthy Population

A single trial from 1965 compared linseed oil (ALA 5.2 g/d) to sunflower seed oil (ALA 0.13 g/d) in 12,716 healthy adults. After 1 year of followup, no effect of ALA was found on risk of MI (OR=0.99; 95% CI 0.67 to 1.45).[49]

At-Risk-for-CVD Population

The same trial from 1965 compared linseed oil (ALA 5.2 g/d) to sunflower seed oil (ALA 0.13 g/d) in 452 adults with previous angina pectoris but no infarction. After 1 year of followup, those on ALA supplementation had a significantly lower risk of MI (OR=0.17; 95% CI 0.04 to 0.79).[49]

CVD Population

One ALA trial from the 1960s reported analyses of the effect of ALA in participants with a history of MI in a total of 438 people. The trial used linseed oil as the source of ALA (5.2 g/d) compared with sunflower seed oil (0.13 g/d ALA). It found no significant effect of ALA on risk of a subsequent MI (OR 0.84).[49]

RCT Subgroup Analyses

One trial of EPA+DHA 0.6 g/d versus placebo, in 2501 people with a history of any CVD found no difference in effect on risk of MI of marine oil in participants also taking B vitamins or not.[123]

Meta-regression of the marine oil trials found no significant interaction between n-3 FA dose (P=0.09) or between at risk and CVD populations (P=0.40), but a significant interaction was found for followup time (P<0.01).

Observational Studies

Three studies evaluated the associations between n-3 FA intake or biomarker level and MI risk in healthy adults, mostly men, in 4 to 11. 5 years (Appendix F, Myocardial Infarction section; Figure 21).[50, 52, 54, 84, 191] Most analyses found no association. The Physicians Health Study found no association between intake of total n-3 FA (combined) and risk of MI in healthy men at 4 years of followup (Figure 21, plot #99). The two studies that evaluated marine oil

(EPA+DHA) intake had different findings (Figure 21, plot #98). The Health Professional Follow-up Study found no significant association among healthy men at 6 years of followup.[54] The Japan Public Health Center-Based Study - Cohort I study found lower risk of MI among healthy adults (men and women combined) with higher EPA+DHA intake.[84]

Only the Physicians Health Study evaluated associations of n-3 FA biomarkers and MI. The study found no associations with cholesteryl ester or phospholipid levels of EPA, DHA, or combined EPA+DHA.

Table 21. Myocardial infarction: RCTs

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int n/N,%	Ctrl n/N,%	Effect Size	Reported P value
Marine oil vs Placebo											
Roncaglioni 2013 23656645 Italy	At risk	EPA+DHA	≤0.85 g (Marine oil) [E:D 0.9−1.5]	Placebo	0 (Olive oil)	5 y	Monitored by self-report but compliance level was not reported	10/6239, 0.2%	13/6266, 0.2%	HR 0.76 (0.34, 1.74)	0.52
Yokoyama 2007 17398308 Japan	At risk	EPA+Statin	1.8 g/d (Ethyl ester)	Statin	0	5 y	Local physicians monitored but compliance level was not reported	71/9326 0.8%	93/9319 1%	HR 0.77 (0.56, 1.05)	0.091
	At risk (no previous CVD)	EPA+Statin	1.8 g/d (Ethyl ester)	Statin	0	5 y	Local physicians monitored but compliance level was not reported	40/7503, 0.7%	51/7478, 0.5%	HR 0.79 (0.52, 1.19)	0.253
Bosch 2012 22686415 Canada	CVD	EPA+DHA	0.84 g/d (Marine oil) [E:D 1.24]	Placebo	0 (Olive oil)	6+ y	FFQ at baseline, 2 years, and end of study (adherence was 88% at the end of study)	344/6281, 5.5%	316/6255, 5.1%	Adj HR 1.09 (0.93, 1.27)	0.28
Brouwer 2006 16772624 N Europe	CVD	EPA+DHA	0.96 g n-3 FA (0.464 g EPA, 0.335 g DHA) (Marine oil) [E:D]=1.4	Placebo	0 (high-oleic acid sunflower oil)	1 y	Generally good (76% reported taking 80% pills) based on pill counts and confirmed by biomarkers.	1/273, 0.4%	3/273, 1%	OR 0.33 (0.03, 3.20)	0.339
Galan 2010 21115589 France	CVD	EPA+DHA	0.6 g/d (Marine oil) [E:D 2]	Placebo	0 (nd)	4.7 y	Patient reported (86% reported they took >=80% of allocated treatment)	51/1253, 4.1%	53/1248, 4.2%	Adj HR 0.97 (0.66, 1.42)	0.87
Macchia 2013 23265344 Argentina; Italy	CVD	EPA+DHA	0.85−0.882 g/d (suppl) [nd]	Placebo	0 (Olive oil)	1 y	nd	1/289, 0.3%	1/297, 0.3%	HR 1.10 (0.07, 17.9)	nd

Table 21. Myocardial infarction: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int n/N,%	Ctrl n/N,%	Effect Size	Reported P value
Sacks 1995 7759696 U.S.	CVD	EPA+DHA+DPA	6 g/d (suppl) [E:D 1.5]	Placebo	0 (Olive oil)	2.4 y	Pill counts	1/31, 3.2%	2/28, 7.1%	OR 0.43 (0.04, 5.06)	0.505
Raitt 2005 15956633 U.S.	CVD	EPA+DHA	EPA 0.756 g/d, DHA 0.54 g/d (fish oil) [E:D 1.4]	Placebo	0 (olive oil: 73% oleic acid, 12%)	2 y	RBC and plasma n- 3 FA levels	1/100, 1.0%	3/100, 3.0%	OR 0.33 (0.03, 3.19)	0.61
Tavazzi 2008 18757090 Italy	CVD	EPA+DHA	0.850−0.882 g/d (Ethyl esters) [E:D 0.83]	Placebo	0 (nd)	3.9 y	Exam question (~30% not taking n-3 FA or placebo by the end of study)	107/3494, 3.1%	129/3481, 3.7%	Adj HR 0.82 (0.63, 1.06)	0.121
Yokoyama 2007 17398308 Japan	CVD (previous CVD)	EPA+Statin	1.8 g/d (Ethyl ester)	Statin	0	5 y	Local physicians monitored but compliance level was not reported	31/1823, 2.3%	42/1841, 1.7%	HR 0.75 (0.47, 1.19)	0.223
	CVD (PAD at any time)	EPA+Statin	1.8 g/d (Ethyl ester)	Statin	0	5 y	Local physicians monitored but compliance level was not reported	3/117 2.6%	4/106 3.8%	OR 0.67 (0.15, 3.07)	
Burr 1989 2571009 UK	CVD	Fish advice, either alone or in combination with fiber advice, fat advice, or both fiber and fat advice.	EPA 0.34 g/d (diet)	No fish advice (Fat advice, fiber advice, fiber and fat advice, or no advice)	EPA 0.09 g/d (diet)	2 y	Compliance was good based on dietary assessments	127/1015, 12.5%	149/1018, 14.6%	Adj RR 0.84 (0.66, 1.07)	0.162

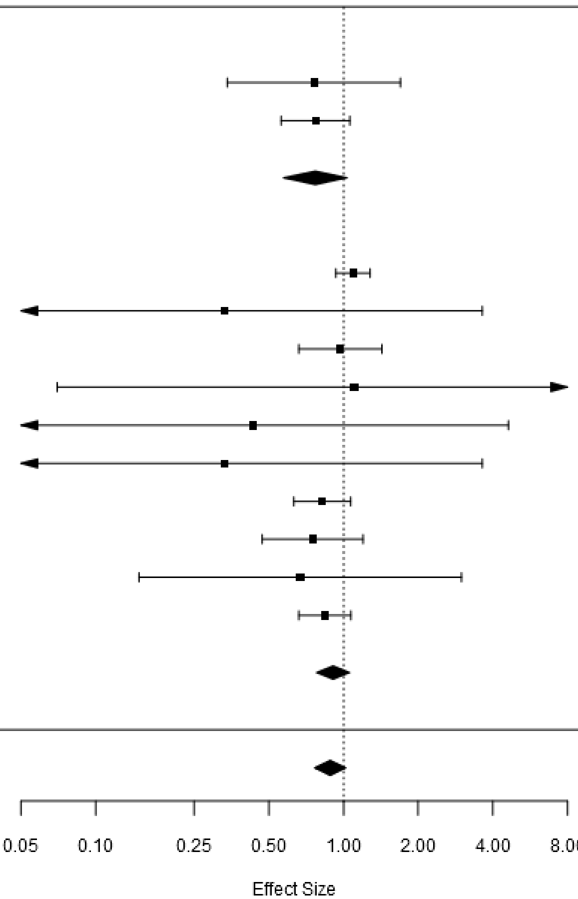
Table 21. Myocardial infarction: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int n/N,%	Ctrl n/N,%	Effect Size	Reported P value
ALA vs Placebo											
Natvig 1965 5756076 Norway	Healthy	ALA	ALA 5.2 g/d (Linseed oil)	Control oil	ALA 0.13 g/d (Sunflower seed oil)	1 y	nd	52/6352, 0.8%	53/6364, 0.8%	OR 0.99 (0.67, 1.45)	NS
	At risk	ALA	ALA 5.2 g/d (Linseed oil)	Control oil	ALA 0.13 g/d (Sunflower seed oil)	1 y	nd	2/216, 0.9%	12/236, 5.1%	OR 0.17 (0.04, 0.79)	0.02
	CVD	ALA	ALA 5.2 g/d (Linseed oil)	Control oil	ALA 0.13 g/d (Sunflower seed oil)	1 y	nd	9/122, 7.4%	10/116, 8.6%	OR 0.84 (0.33, 2.16)	0.724

Abbreviations: ALA = alphalinolenic acid, Ctrl = control, CVD = cardiovascular disease, DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, E:D = EPA to DHA ratio, EPA = eicosapentaenoic acid, F/up = followup, FFQ = food frequency questionnaire, HR = hazard ratio, Int = intervention, n/N = number with outcome/number analyzed, n6:3 = omega-6 to omega-3 fatty acid ratio, n-3 FA = omega-3 fatty acids, ND = no data, NS = not significant, OR = odds ratio, PAD = peripheral artery disease, PMID = PubMed Identification number, RBC = red blood cell, RCT = randomized controlled trial, RR = relative risk.

Figure 20. Myocardial infarction: Randomized trials of marine oils

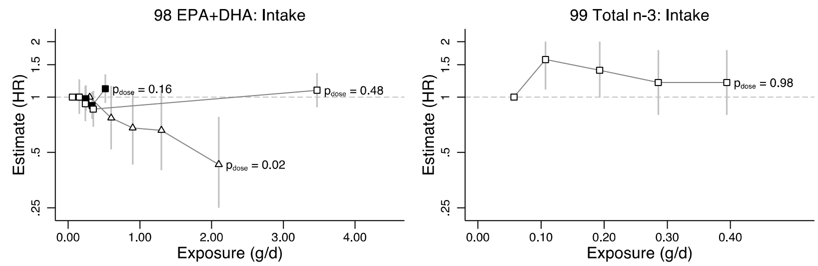
Study PMID	n-3 FA	g/day	Years	n-3 FA n/N	Placebo n/N	Effect Size [95% CI]
At risk population						
Roncaglioni 2013 23656645	EPA+DHA	0.85	5	10/6239	13/6266	0.76 [0.34, 1.74]
Yokoyama 2007 17398308	EPA	1.8	5	71/9326	93/9319	0.77 [0.56, 1.05]
Summary, at risk						*0.77 [0.57 , 1.03]*
CVD population						
Bosch 2012 22686415	EPA+DHA	0.84	6	344/6281	316/6255	1.09 [0.93, 1.27]
Brouwer 2006 16772624	EPA+DHA	0.96	1	1/273	3/273	0.33 [0.03, 3.20]
Galan 2010 21115589	EPA+DHA	0.6	4.7	51/1253	53/1248	0.97 [0.66, 1.42]
Macchia 2013 23265344	EPA+DHA	0.87	1	1/289	1/297	1.10 [0.07, 17.9]
Sacks 1995 7759696	EPA+DHA+DPA	6	2.4	1/31	2/28	0.43 [0.04, 5.06]
Raitt 2005 15956633	EPA+DHA	1.3	2	1/100	3/100	0.33 [0.03, 3.19]
Tavazzi 2008 18757090	EPA+DHA	0.87	3.9	107/3494	129/3481	0.82 [0.63, 1.06]
Tavazzi 2008 18757090	EPA	1.8	5	31/1823	42/1841	0.75 [0.47, 1.19]
Yokoyama 2007 17398308	EPA	1.8	5	3/117	4/106	0.67 [0.15, 3.07]
Burr 1989 2571009	EPA	0.34	2	127/1015	149/1018	0.84 [0.66, 1.07]
Summary, CVD						*0.91 [0.78 , 1.06]*
Summary [I-squared=23.455, Phet=0.542]						**0.88 [0.77 , 1.02]**



Random effects model meta-analysis of n-3 FA versus placebo (or no n-3 FA), with subgroup analyses by population. In all meta-analyses, only studies that reported sufficient results data are included.

Abbreviations: CI = confidence interval, CVD = cardiovascular disease, DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, EPA = eicosapentaenoic acid, n/N = number with outcome/number analyzed, n-3 FA = omega-3 fatty acids, Phet = P value of chi-squared test of heterogeneity across studies, PMID = PubMed Identification number.

Figure 21. n-3 FA associations with myocardial infarction: Observational studies



Study (or cohort) level associations between n-3 FA exposure and hazard ratio (HR) for myocardial infarction. Studies that reported associations by continuous exposure (e.g., per g/d intake or per standard deviation) could not be graphed and are omitted. P values are the study-reported P value for the trend across quantiles. The 95% confidence intervals were truncated when <0.25 and >2.
White triangles = healthy adults, black squares = healthy males.

Abbreviations: DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, EPA = eicosapentaenoic acid, HR = hazard ratio, n-3 FA = omega-3 fatty acids.

Revascularization

Randomized Controlled Trials

Six RCTs evaluated coronary revascularization as an outcome (Table 22).[67, 81, 90, 121, 123, 146] Of these, one was conducted in 18,645 hypercholesterolemic participants (19.5% with CHD),[90] and five were in a total of 20,669 participants with CVD including diabetes and history of CVD,[146] all CVD,[123] patients with implantable defibrillators,[81] and MI.[67, 121] None of the trials reported revascularization to be a primary outcome.

Marine Oil Versus Placebo

At-Risk-for-CVD Population

Among 18,645 hypercholesterolemic participants (19.5% with CHD), one RCT compared 1.8 g/d EPA ethyl ester combined with statin with control (statin alone) for a duration of 5 years.[90] Adherence was not reported. There was no significant difference in the risk of coronary artery bypass between the two groups (HR=0.86; 95% CI 0.71 to 1.05). A subgroup analysis among 14,981 hypercholesterolemic participants without previous CHD showed similar finding (HR=0.87; 95% CI 0.62 to 1.21).

CVD Population

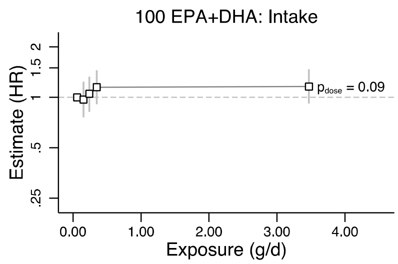
Among participants with CVD, five studies compared marine oil (EPA+DHA) to placebo (olive oil or corn oil) in a total of 19,241 participants.[67, 81, 121, 123, 146]. The dose of EPA+DHA ranged from 0.6 to 1.7 g/d, and the EPA to DHA ratio ranged from 0.5 to 2. Reported in three studies, compliance was more than 70 percent. The mean duration of followup ranged from 1 to more than 6 years. All five studies found that EPA+DHA supplementation had no significant effect on revascularization compared with placebo with HR/OR ranging from 0.49 to 0.97.

One other study compared 1.8 g/d EPA ethyl ester combined with statin with control (statin alone) in a subgroup of 3664 patients with previous CVD (HR=0.87; 95% CI 0.69 to 1.1) and 283 peripheral artery disease patients (HR=0.40; 95% CI 0.14 to 1.05) also did not find significant effect on the risk of coronary artery bypass.[90]

Observational Studies

Only the Health Professional Follow-up Study analyzed coronary revascularization (Appendix F, Coronary artery bypass graft surgery section; Figure 22).[54] The study found no significant association in healthy men between intake of combined EPA+DHA and risk of undergoing coronary artery bypass grafting after 6 years of followup (P=0.09).

Figure 22. n-3 FA associations with coronary revascularization: Observational studies



Study (or cohort) level associations between n-3 FA exposure and hazard ratio (HR) for the outcome. Studies that reported associations by continuous exposure (e.g., per g/d intake or per standard deviation) could not be graphed and are omitted. P values are the study-reported P value for the trend across quantiles.
White squares = healthy males

Abbreviations: DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid, HR = hazard ratio, n-3 FA = omega-3 fatty acids.

Table 22. Revascularization: RCTs

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	Outcome Definition	F/up Time	Compliance Verification	Int n/N,%	Ctrl n/N,%	Effect Size	Reported P value
Marine oil vs Placebo												
Yokoyama 2007 17398308 Japan	At risk	EPA	1.8 g/d (Ethyl ester)	Placebo	0	CABG or PCTA	5 y	nd	191/9326, 2%	222/9319, 2%	HR 0.86 (0.71, 1.05)	0.135
	At risk (no previous CVD)	EPA+Statin	1.8 g/d (Ethyl ester)	Statin	0	CABG or PCTA	5 y	Local physicians monitored but compliance level was not reported	64/7503, 0.9%	74/7478, 1.0%	HR 0.87 (0.62, 1.21)	0.40
Rauch 2010 21060071 Germany	CVD	EPA+DHA	0.46 g EPA, 0.38 g DHA (Marine oil) [E:D=1.2]	Placebo	0 (Olive oil)	Coronary revascularization	1 y	Pill counts at 3 mo and 12 mo (≥70% of study period)	~530/1919, 28%	~541/1885, 29%	OR 0.93 (0.80, 1.08)	
Raitt 2005 15956633 U.S.	CVD	EPA+DHA	EPA 0.756 g/d, DHA 0.54 g/d (fish oil) [E:D 1.4]	Placebo	0 (olive oil: 73% oleic acid, 12%)	Coronary revascularization	2 y	RBC and plasma n-3 FA levels	2/100, 2.0%	4/100, 4.0%	OR 0.49 (0.09, 2.74)	0.68
Bosch 2012 22686415 Canada	CVD	EPA+DHA	0.84 g/d (Marine oil) [E:D 1.24]	Placebo	0 (Olive oil)	Coronary, carotid, aortic, or peripheral revascularization	6+ y	FFQ at baseline, 2 years, and end of study (adherence was 88% at the end of study)	866/6281, 14%	869/6155, 14%	HR 0.96 (0.87, 1.05)	0.39
Galan 2010 21115589 France	CVD	EPA+DHA	0.6 g/d (Marine oil) [E:D 2]	Placebo	0 (nd)	Coronary or peripheral revascularization	4.7 y	Patient reported (86% reported they took >=80% of allocated treatment)	152/1253, 12%	156/1248, 13%	HR 0.97 (0.78, 1.22)	0.82

Table 22. Revascularization: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	Outcome Definition	F/up Time	Compliance Verification	Int n/N,%	Ctrl n/N,%	Effect Size	Reported P value
Nilsen 2001 11451717 Scandinavia	CVD	EPA+DHA	1.7−1.764 g/d (Marine oil) [E:D 0.5]	Placebo	0 (Corn oil)	Coronary (implied) revascularization	Median 2.4 y	nd (82% in fish oil group; 86% in the placebo group)	54/150, 36%	57/150, 39%	OR 0.92 (0.57, 1.47)	
Yokoyama 2007 17398308 Japan	CVD (previous CVD)	EPA+Statin	1.8 g/d (Ethyl ester)	Statin	0	CABG or PCTA	5 y	Local physicians monitored but compliance level was not reported	127/1823, 7.0%	148/1841, 8.0%	HR 0.87 (0.69, 1.1)	0.243
	CVD (PAD at any time)	EPA+Statin	1.8 g/d (Ethyl ester)	Statin	0	CABG or PCTA	5 y	Local physicians monitored but compliance level was not reported	6/117 5.1%	12/106 11.3%	HR 0.40 (0.14, 1.05)	0.064

Abbreviations: CABG = coronary artery bypass grafting, Ctrl = control, CVD = cardiovascular disease, DHA = docosahexaenoic acid, E:D = EPA to DHA ratio, EPA = eicosapentaenoic acid, F/up = followup, FFQ = food frequency questionnaire, HR = hazard ratio, Int = intervention, n/N = number with outcome/number analyzed, n6:3 = omega-6 to omega-3 fatty acid ratio, n-3 FA = omega-3 fatty acids, OR = odds ratio, PCTA = percutaneous transluminal coronary angioplasty, PMID = PubMed Identification number, RBC = red blood cell, RCT = randomized controlled trial.

Acute Coronary Syndrome

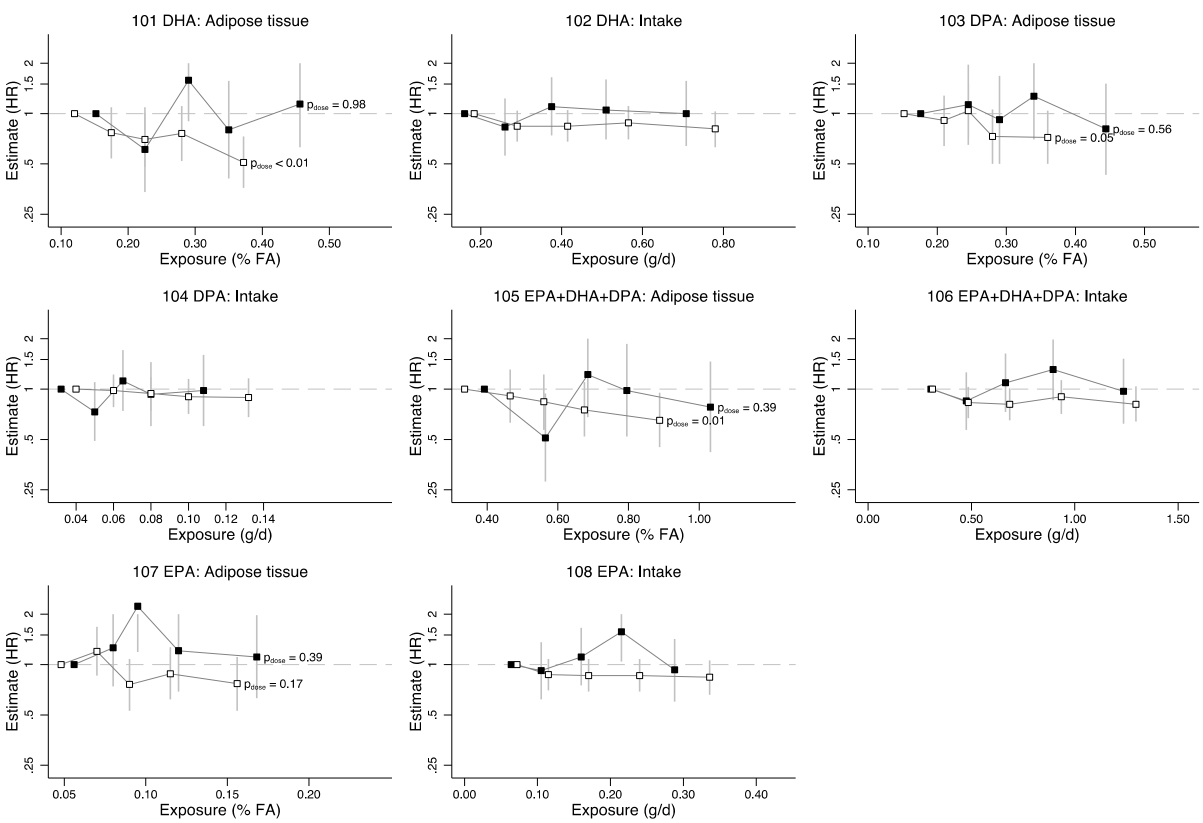
Randomized Controlled Trials

No RCT evaluated acute coronary syndrome.

Observational Studies

One study (Diet, Cancer, Health) evaluated the associations between multiple n-3 FA measures and acute coronary syndrome (MI or unstable angina) after a mean of 7.6 years in a healthy population (age 50−64 y) (Appendix F, Acute coronary syndrome section; Figure 23).[134] Analyses were conducted separately for men and women; for DHA, DPA, EPA, and EPA+DHA+DPA; and for each n-3 FA type, both intake and adipose tissue percent FA. For both men and women, the intake levels of total n-3 FA were not associated with future acute coronary ischemia (Figure 23, plots #102, 104, 106, & 108). Among men, higher baseline adipose tissue DHA, DPA, and EPA+DHA+DPA, but not EPA, were significantly associated with decreased risk of acute coronary ischemia, based on both a 0.1 percent increase in baseline measure and comparing the highest and lowest quantiles for each n-3 FA adipose tissue level (Figure 23, plots #101 103, 105, & 107). Among women, no statistically significant associations between baseline biomarker level and outcome were found.

Figure 23. n-3 FA associations with acute coronary syndrome: Observational studies



Study (or cohort) level associations between n-3 FA exposure and hazard ratio (HR) for the outcome. P values are the study-reported P value for the trend across quantiles. The 95% confidence intervals were truncated when <0.25 and >2.
White squares = healthy males, black squares = healthy females.

Abbreviations: DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, EPA = eicosapentaenoic acid, HR = hazard ratio, n-3 FA = omega-3 fatty acids.

Angina Pectoris

Randomized Controlled Trials

Seven trials evaluated angina pectoris (Table 23). Three RCTs evaluated stable angina,[49, 86, 87, 146], one evaluated hospitalization for angina,[81] and three evaluated unstable angina.[51, 67, 90] Only one trial reported unstable angina to be a primary outcome (Sacks 1995).[51] Meta-analysis was not conducted due to the heterogeneity of specific outcomes analyzed by the primary studies.

Marine Oil Versus Placebo

At-Risk-for-CVD Population

One study compared 1.8 g/d purified EPA combined with statin with control (statin alone) to placebo with statin in 18,645 participants with dyslipidemia (19.5% with CHD).[90] Adherence was verified by local physicians at every clinic visit but the level was not reported. After 5 years of followup, the trial found a significant risk reduction in unstable angina pectoris events (HR 0.76 95% CI 0.62 to 0.95) in participants who were assigned to the EPA+statin group compared to those in the statin alone group.

CVD Population

Five trials were conducted in a total of 13,641 patients with documented CVD, CHD or MI.[51, 67, 81, 86, 146] The dose of EPA+DHA ranged from 0.84 to 6 g/d, and the EPA to DHA ratio ranged from 1.24 to 2. Reported in two studies, compliance was more than 80 percent, and one study used n-3 FA biomarkers to monitor the adherence. The mean duration of followup ranged from 1 to more than 6 years. All five studies found that EPA+DHA supplementation had no significant effect on the risk for angina compared with placebo with HR/OR ranging from 0.64 to 1.18.

One other study compared 1.8 g/d EPA ethyl ester combined with statin with control (statin alone) found that EPA had significant additive effect on reducing the risk of unstable angina in a subgroup of 3664 patients with previous CVD (HR=0.72; 95% CI 0.55 to 0.95), but the effect was not significant in a subgroup of 283 peripheral artery disease patients (HR=0.56; 95% CI 0.17 to 1.71).[90]

ALA Versus Placebo

Healthy Population

One trial compared linseed oil (5.2 g/d ALA) to a control oil (sunflower seed oil, 0.13 g/d ALA) for a duration of 1 year among 13,628 generally healthy participants.[49] Adherence was verified at follow-up by participating physicians but level was not reported. This study found no significant effect on stable angina between the two groups (OR 1.58 95% CI 0.77 to 3.26).

Observational Studies

No observational studies evaluated angina pectoris, per se.

Table 23. Angina pectoris: RCTs

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	Outcome Definition	F/up Time	Compliance Verification	Int n/N,%	Ctrl n/N,%	Effect Size	Reported P value
Marine oil vs. Placebo												
Yokoyama 2007 17398308 Japan	At risk (dyslipidemia)	EPA+Statin	1.8 g/d (Ethyl ester)	Statin	0	Unstable Angina	5 y	Local physicians monitored compliance at every clinic visit (nd)	147 / 9326, 1.6%	193 / 9319, 2.1%	HR 0.76 (0.62, 0.95)	0.014
	At risk (no previous CVD)	EPA+Statin	1.8 g/d (Ethyl ester)	Statin	0	Unstable Angina	5 y	Local physicians monitored but compliance level was not reported	59/7503, 0.8%	70/7478, 0.9%	HR 0.85 (0.60, 1.19)	0.338
Bosch 2012 22686415§ Canada	CVD (or diabetes)	EPA+DHA	0.84 g/d (Marine oil) [E:D 1.24]	Placebo	0 (Olive oil)	Angina included new, worsening, or unstable disease	6+ y	FFQ at baseline, 2 years, and end of study (adherence was 88% at the end of study)	724/6281, 11.5%	725/6255, 11.6%	HR 1.00 (0.90, 1.10)	0.94
Brouwer 2006 16772624 N. Europe	CVD	EPA+DHA	0.96 g n-3 FA (0.464 g EPA, 0.335 g DHA) (Marine oil) [E:D]=1.4	Placebo	0 (high-oleic acid sunflower oil)	Angina	1 y	Generally good (76% reported taking 80% pills) based on pill counts and confirmed by biomarkers.	10/273, 4%	12/273, 4%	OR 0.83 (0.35, 1.95)	nd
Nilsen 2001 11451717	CVD	EPA+DHA	3.52 g/d (marine oil) [E:D 2]	Placebo	0 (Corn oil)	Unstable Angina	Median 2.4 y	nd	32/150, 21.3%	28/150, 18.7%	OR 1.18 (0.67, 2.08)	0.564

Table 23. Angina pectoris: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	Outcome Definition	F/up Time	Compliance Verification	Int n/N,%	Ctrl n/N,%	Effect Size	Reported P value
Raitt 2005 15956633 U.S.	CVD	EPA+DHA	EPA 0.756 g/d, DHA 0.54 g/d (fish oil) [E:D 1.4]	Placebo	0 (olive oil: 73% oleic acid, 12%)	Hospitalization for angina	2 y	RBC and plasma n-3 FA levels	10/100, 10.0%	7/100, 7.0%	OR 1.48 (0.54, 4.05)	0.61
Sacks 1995 7759696	CVD	EPA+DHA+DPA	6 g/d (suppl) [E:D 1.5]	Placebo	0 (Olive oil, potassium tablets)	Unstable Angina	2.4 y	Mean compliance determined by pill count	3 / 31, 9.6%	4 / 28, 14.3%	OR 0.64 (0.13, 3.16)	0.59
Yokoyama 2007 17398308 Japan	CVD (previous CVD)	EPA+Statin	1.8 g/d (Ethyl ester)	Statin	0	Unstable Angina	5 y	Local physicians monitored but compliance level was not reported	88/1823, 4.8%	123/1841, 6.7%	HR 0.72 (0.55, 0.95)	0.019
	CVD (PAD at any time)	EPA+Statin	1.8 g/d (Ethyl ester)	Statin	0	Unstable Angina	5 y	Local physicians monitored but compliance level was not reported	5/117 4.3%	8/106 7.5%	HR 0.56 (0.17, 1.71)	0.310
ALA vs. Placebo												
Natvig 1968 5756076 Norway	Healthy	ALA	ALA 5.2 g/d (Linseed oil)	Control oil	ALA 0.13 g/d (Sunflower seed oil)	Stable Angina	1 y	Participating physicians assessed compliance at follow-up (nd)	19 / 6641, 0.29%	12 / 6627, 0.18%	OR 1.58 (0.77, 3.26)	0.214

Abbreviations: ALA = alphalinolenic acid, Ctrl = control, CVD = cardiovascular disease, DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, E:D = EPA to DHA ratio, EPA = eicosapentaenoic acid, F/up = followup, FFQ = food frequency questionnaire, HR = hazard ratio, Int = intervention, n/N = number with outcome/number analyzed, n6:3 = omega-6 to omega-3 fatty acid ratio, n-3 FA = omega-3 fatty acids, ND = no data, OR = odds ratio, PAD = peripheral artery disease, PMID = PubMed Identification number, RBC = red blood cell, RCT = randomized controlled trial.

Stroke, Total (Ischemic and Hemorrhagic, Fatal and Nonfatal)

Randomized Controlled Trials

Eight RCTs evaluated total stroke (Table 24).[49, 51, 70, 90, 96, 123, 146, 157] One was conducted in 13,406 healthy participants,[49] 18,645 participants with dyslipidemia (19.5% with CHD),[90], and the other six included a total of 33,981 participants with CVD and/or diabetes,[123, 146] MI,[51, 70] persistent AFib,[157] and heart failure.[96] None of the trials reported total stroke to be a primary outcome.

Marine Oil Versus Placebo

Meta-analysis of the seven RCTs of marine oil versus placebo yielded a nonsignificant summary effect size for risk of MI: HR=0.98 (95% CI 0.88 to 1.09) (Figure 24).[51, 70, 90, 96, 123, 146, 157]

At-Risk-for-CVD Population

One study compared 1.8 g/d purified EPA combined with statin with control (statin alone) to placebo with statin in 18,645 participants with dyslipidemia (19.5% with CHD).[90] Adherence was verified by local physicians at every clinic visit but the level was not reported. After 5 years of followup, the trial did not find significant difference in the risk of total stroke between participants who were assigned to the EPA+statin group and those in the statin alone group (HR=1.02; 95% CI 0.91 to 1.13).

CVD Population

Seven RCTs of participants with a history of CVD evaluated EPA±DHA supplementation.[51, 70, 90, 96, 123, 146, 157] Followup duration ranged from 1 to at least 6 years. The total dose of marine oil ranged from 0.6 to 6 g/d. Among four of the studies the EPA to DHA ratio ranged from 0.8 to 2. The six studies of EPA+DHA found a statistically significant effect of marine oil on risk of stroke, mostly with wide confidence intervals, and with effect sizes ranging from 0.92 (95% CI 0.79 to 1.08) to 2.8 (95% CI 0.11 to 71.6). The one study that compared 1.8 g/d EPA ethyl ester combined with statin with control (statin alone) found that EPA had significant additive effect on reducing the risk of total stroke in a subgroup of 942 patients with previous CHD (HR=0.80; 95% CI 0.64 to 0.997).[90]

Across the seven RCTs of CVD populations, the summary HR (Figure 24) was 0.97 (95% CI 0.83 to 1.13).

ALA Versus Placebo

Healthy Population

One RCT of 13,406 healthy participants compared linseed oil (5.2 g/d ALA) to a control oil (sunflower seed oil with 0.13 g/d ALA).[49] Adherence was not reported. After 1 year of follow up, the trial found no significant effect of ALA on stroke (OR=1.33; 95% CI 0.56 to 3.16).

RCT Subgroup Analyses

Meta-regression of the marine oil trials found no significant interaction between n-3 FA dose (P=0.06), followup time (P=0.08), or between at risk and CVD populations (P=0.08)

Observational Studies

Six studies evaluated the associations between n-3 FA intake or biomarker level and risk of total stroke in healthy adults in 4 to 16 years (Appendix F, Stroke section; Figure 25).[50, 65, 73, 138, 143, 145, 159, 186] Most analyses found no association between n-3 FA intake and total stroke risk and all found no significant association with n-3 FA biomarker level.

n-3 FA Intake

All six studies evaluated n-3 FA intake (Cardiovascular Health Study, Health Professional Follow-up Study, MORGEN, Nurses' Health Study, Physician's Health Study, Swedish Mammography Study). Among analyses the only significant associations were found in women.

In a study of healthy men, the Physicians Health Study found no significant association between intake of total n-3 FA (combined) and total stroke after 4 years of followup (Figure 25, plot #115)

Three studies evaluated ALA intake (Figure 25, plot #109). Two studies (Cardiovascular Health Study, Swedish Mammography Study) found no significant association after 10 and 12 years. The third study, MORGEN, did not report a P value for trend across quintiles, but found lower risk for stroke in all quintiles (at 10 years) compared with the lowest, the middle three of which were statistically significant (with median intake above about 1.25 g/d).

Four studies evaluated combined EPA+DHA intake (Figure 25, plot #113). Three analyses were conducted in women and two in men. In analyses of women, MORGEN and the Swedish Mammography Study found significant associations between higher EPA+DHA (particularly with median intake of at least 0.56 g/d or >0.19 g/d) and lower risk of stroke at 10 years of followup, but the Nurses' Health Study found no significant association. Both the Health Professional Follow-up Study and the MORGEN analysis of men found no significant association.

n-3 FA Biomarkers

Two studies (Cardiovascular Health Study, MORGEN) evaluated plasma n-3 FA levels in healthy adults at 10 and 16 years. All analyses were not statistically significant. The Cardiovascular Health Study found no association with total n-3 FA plasma levels (combined, Figure 25, plot #116). Both studies found no association with plasma ALA (Figure 25, plot #110). In contrast with all other analyses, MORGEN found a near-significant *increased* risk ($P<0.10$) of total stroke among adults with higher EPA+DHA levels measured as a continuous variable (OR=1.16 per percentage unit FA; 95% CI 0.94 to 1.45; $P=0.07$). The Cardiovascular Health Study found no associations for EPA, DHA, and DPA plasma levels (separately, Figure 25, plots #111, 112, & 114).

By meta-analysis (Table 25), overall there is a statistically significant association between marine oil intake and total stroke across a median dosage range of 0.025 to 0.6 g/d (effect size per g/d = 0.68; 95% CI 0.53 to 0.87). Meta-analyses with the addition of a spline knot point at different dose thresholds (from 0.1 to 0.5 g/d) consistently found a much stronger association (of higher dose being associated with lower risk) at *lower* doses than at higher doses (ES below know less than 1; ES above know greater than 1); although, the difference in effect sizes above and below the knots were never statistically significant This implies a possible ceiling effect ceiling effect (where intake above a certain level adds no further benefit). However, given that the differences between lower and higher dose ES remained large across the range of testable dose thresholds, the actual ceiling dose threshold may be above the analyzable range (i.e., >0.5 g/d). The best fit curve was found with the lowest knot at 0.1 g/d. The P values for differences between lower- and higher-dose effect sizes ranged from 0.14 to 0.20.

Observational Study Subgroup Analyses

The Cardiovascular Health Study found no difference in associations of ALA intake or plasma values and total stroke by amount of fish consumption at baseline or by sex. The Health Professional Follow-up Study found no difference in association between EPA+DHA intake and ischemic stroke based on whether participants used fish oil supplements.

Table 24. Stroke, total: RCTs

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int n/N,%	Ctrl n/N,%	Effect Size	Reported P value
Marine oil vs Placebo											
Yokoyama 2007 17398308 Japan	At risk (dyslipidemia)	EPA (+Statin)	1.8 g/d (Ethyl ester)	Placebo (+Statin)	0	4.6 y	Local physicians monitored but compliance level was not reported	166/9326, 1.8%	162/9319, 1.7%	1.02 (0.91, 1.13)	0.785
	At risk (no previous CHD)	EPA (+Statin)	1.8 g/d (Ethyl ester)	Placebo (+Statin)	0	4.6 y	Local physicians monitored but compliance level was not reported	133/8841 1.5%	114/8862 1.3%	HR 1.08 (0.95, 1.22)	0.244
	CVD (previous CHD)	EPA (+Statin)	1.8 g/d (Ethyl ester)	Placebo (+Statin)	0	4.6 y	Local physicians monitored but compliance level was not reported	33/485 6.8%	48/457 10.5%	HR 0.80 (0.64, 0.997)	0.047
Bosch 2012 22686415 Canada	CVD	EPA+DHA	EPA 0.465 g/d, DHA 0.375 g/d (marine oil) [E:D 1:1.24]	Placebo	0 (Olive oil)	≥6 y	FFQ at baseline, 2 years, and end of study (adherence was 88% at the end of study)	314/6281, 5.0%	336/6255, 5.4%	HR 0.92 (0.79, 1.08)	0.32
Galan 2010 21115589 France	CVD	EPA+DHA	0.6 g/d (Marine oil) [E:D 2:1]	Placebo	0 (nd)	4.7 y	Patient reported (86% reported they took >=80% of allocated treatment)	29/1253, 2.3%	28/1248, 2.2%	HR 1.04 (0.62, 1.75)	0.88
Marchioli 2002 11997274 Italy	CVD	EPA+DHA	0.850−0.882 g/d (marine oil)	No intervention	nd	3.5 y	Followup (adherence was 72.5% at the end of study)	62/5666, 1.1%	57/5658, 1.0%	RR 1.22 (0.75, 1.97)	
Sacks 1995 7759696 U.S.	CVD	EPA+DHA+DPA	6 g/d (suppl) [E:D 1.5]	Placebo	0 (Olive oil)	2.4 y	Biomarker at followup	1/31, 3.2%	0/28, 0%	OR 2.8 (0.11, 71.63)	
Tavazzi 2008 18757090 Italy	CVD	EPA+DHA	0.850−0.882 g/d (Ethyl esters) [E:D 1:1.2]	Placebo	0 (nd)	3.9 y	Exam question (~30% not taking n-3 FA or placebo by the end of study)	122/3494, 3.5%	103/3481, 3.0%	HR 1.16 (0.89, 1.51)	0.271

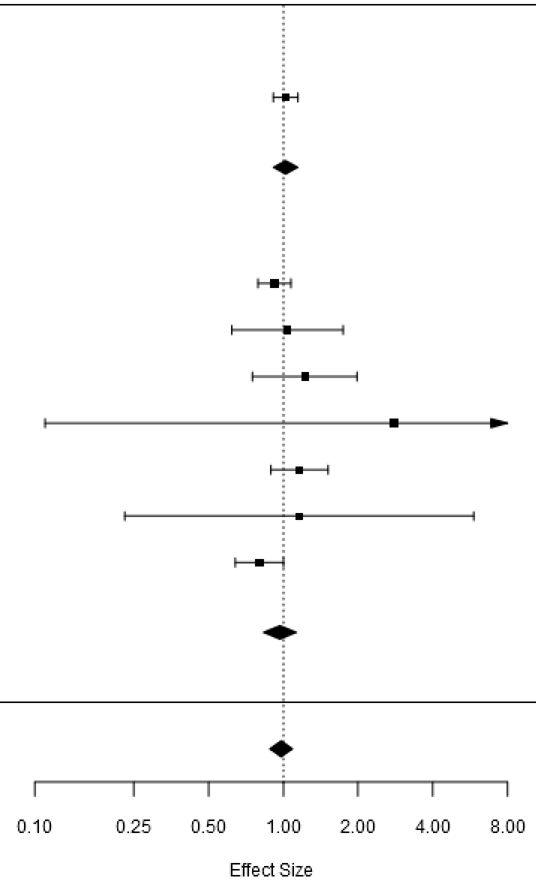
Table 24. Stroke, total: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int n/N,%	Ctrl n/N,%	Effect Size	Reported P value
Macchia 2013 23265344 Argentina and Italy	CVD	EPA+DHA	0.85−0.882 (suppl) [nd]	Placebo	0 (Olive oil)	1 y	nd	3/289, 1.0%	3/297, 1.0%	HR 1.16 (0.23, 5.78)	
Yokoyama 2007 17398308 Japan	CVD (previous CHD)	EPA (+Statin)	1.8 g/d (Ethyl ester)	Placebo (+Statin)	0	4.6 y	Local physicians monitored but compliance level was not reported	33/485 6.8%	48/457 10.5%	HR 0.80 (0.64, 0.997)	0.047
ALA vs Placebo											
Natvig 1968 5756076 Norway	Healthy	ALA	5.2 g/d (linseed oil)	Control oil	ALA 0.13 g/d (Sunflower seed oil)	1 y	nd	12/6716, 0.2%	9/6690, 0.1%	OR 1.33 (0.56, 3.16)	NS

Abbreviations: ALA = alphalinolenic acid, CHD = coronary heart disease, Ctrl = control, CVD = cardiovascular disease, DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, E:D = EPA to DHA ratio, EPA = eicosapentaenoic acid, F/up = followup, FFQ = food frequency questionnaire, HR = hazard ratio, Int = intervention, n/N = number with outcome/number analyzed, n6:3 = omega-6 to omega-3 fatty acid ratio, OR = odds ratio, PMID = PubMed Identification number, RR = relative risk.

Figure 24. Total stroke: Randomized trials of marine oils

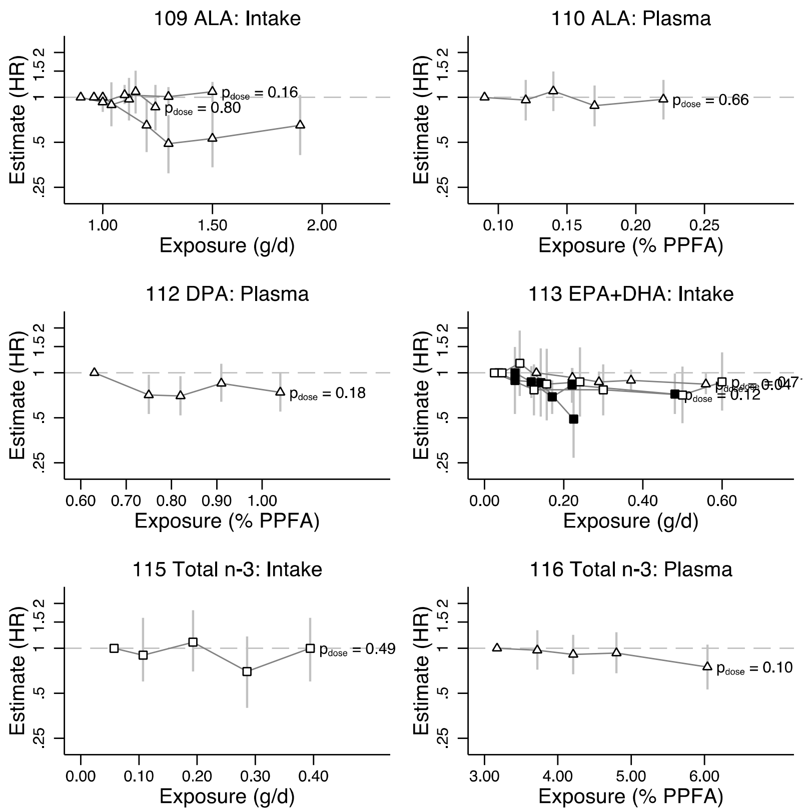
Study PMID	n-3 FA	g/day	Years	n-3 FA n/N	Placebo n/N	Effect Size [95% CI]
At risk population						
Yokoyama 2007 17398308	EPA	1.8	4.6	166/9326	162/9319	1.02 [0.91, 1.13]
Summary, at risk						*1.02 [0.91 , 1.14]*
CVD population						
Bosch 2012 22686415	EPA+DHA	0.84	6	314/6281	336/6255	0.92 [0.79, 1.08]
Galan 2010 21115589	EPA+DHA	0.6	4.7	29/1253	28/1248	1.04 [0.62, 1.75]
Marchioli 2002 11997274	EPA+DHA	0.87	3.5	62/5666	57/5658	1.22 [0.75, 1.97]
Sacks 1995 7759696	EPA+DHA+DPA	6	2.4	1/31	0/28	2.8 [0.11, 71.63]
Tavazzi 2008 18757090	EPA+DHA	0.87	3.9	122/3494	103/3481	1.16 [0.89, 1.51]
Macchia 2013 23265344	EPA+DHA	0.87	1	3/289	3/297	1.16 [0.23, 5.78]
Yokoyama 2007 17398308	EPA	1.8	4.6	33/485	48/457	0.80 [0.64, 0.997]
Summary, CVD						*0.97 [0.83 , 1.13]*
Summary [I-squared=20.59, Phet=0.414]						**0.98 [0.88 , 1.09]**



Random effects model meta-analysis of n-3 FA versus placebo (or no n-3 FA), with subgroup analyses by population. In all meta-analyses, only studies that reported sufficient results data are included.

Abbreviations: CI = confidence interval, CVD = cardiovascular disease, DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, EPA = eicosapentaenoic acid, n/N = number with outcome/number analyzed, n-3 FA = omega-3 fatty acids, Phet = P value of chi-squared test of heterogeneity across studies, PMID = PubMed Identification number.

Figure 25. n-3 FA associations with total stroke: Observational studies



Study (or cohort) level associations between n-3 FA exposure and hazard ratio (HR) for the outcome. Studies that reported associations by continuous exposure (e.g., per g/d intake or per standard deviation) could not be graphed and are omitted. P values are the study-reported P value for the trend across quantiles.
White triangles = healthy adults, white squares = healthy males, black squares = healthy females.

Abbreviations: ALA = alphalinolenic acid, DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, EPA = eicosapentaenoic acid, HR = hazard ratio, n-3 FA = omega-3 fatty acids, PPFA = plasma polyunsaturated fatty acids.

Table 25. Meta-analysis results of observational studies of marine oil (EPA+DHA±DPA) intake and total stroke

N patients	Dose range, g/d	Knot	ES, overall	ES below knot	ES above knot	P*	AIC	No. cohorts (crossing threshold)
178,249	0.025−0.60		0.68 (0.53, 0.87)					5
		0.1		0.26 (0.07, 0.99)	0.82 (0.57, 1.19)	0.14	37.1	5
		0.2		0.35 (0.14, 0.90)	0.95 (0.55, 1.65)	0.15	38.6	5
		0.3		0.43 (0.20, 0.91)	1.16 (0.50, 2.68)	0.19	45.0	3
		0.4		0.44 (0.21, 0.90)	2.43 (0.33, 18.0)	0.20	51.7	3
		0.5		0.58 (0.43, 0.79)	3.83 (0.38, 38.4)	0.14	59.9	2

* ES below vs. above knot

Abbreviations: AIC = Akaike information criterion (estimation of fit of regression with spline), DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, EPA = eicosapentaenoic acid, ES = effect size.

Stroke, Ischemic (Fatal and Nonfatal)

Randomized Controlled Trials

Two RCTs evaluated ischemic stroke (Table 26).[90, 96] One was conducted in 18,645 participants with dyslipidemia (19.5% with CHD) and performed a subgroup analysis in 942 patients with previous CHD,[90] and the other was conducted in 6975 participants with heart failure.[96] Both trials evaluated n-3 FA ethyl esters. Neither of the trials reported ischemic stroke to be a primary outcome.

At-Risk-for-CVD Population

One study compared 1.8 g/d purified EPA combined with statin with control (statin alone) to placebo with statin in 18,645 participants with dyslipidemia (19.5% with CHD).[90] Adherence was verified by local physicians at every clinic visit but the level was not reported. After 5 years of followup, the trial did not find significant difference in the risk of ischemic stroke between participants who were assigned to the EPA+statin group and those in the statin alone group (HR=0.97; 95% CI 0.85 to 1.10).

CVD Population

One study of 6975 participants with heart failure compared marine oil ethyl esters (EPA+DHA 0.850-0.882 g/d) with placebo.[96] The adherence was about 70% by the end of the 3.9-year study. There was no significant difference in the risk of ischemic stroke between the two groups (OR=1.23; 95% CI 0.91 to 1.66)

One other study compared 1.8 g/d EPA ethyl ester combined with statin with control (statin alone) also did not find significant additive effect of EPA on reducing the risk of ischemic stroke in a subgroup of 942 patients with previous CHD (HR=1.04; 95% CI 0.67 to 1.62).[90]

Observational Studies

Five studies evaluated the associations between n-3 FA intake or biomarker level and risk of ischemic stroke in healthy adults after 10 to 22 years of followup (Appendix F, Ischemic stroke section; Figure 26).[65, 73, 127, 144, 145, 159, 164, 186] All but one analysis across studies were nonsignificant for an association. All but two analyses across studies were nonsignificant for an association.

n-3 FA Intake

The five studies all evaluated n-3 FA intake (Atherosclerosis Risk in Communities Study, Cardiovascular Health Study, Health Professional Follow-up Study, MORGEN, Nurses' Health Study). All found no association with ischemic stroke. This included two studies of ALA intake (Cardiovascular Health Study, MORGEN) in healthy adults after 10 and 12 years of followup (Figure 26, plot #117), one study of EPA and DHA intake, separately, measured as continuous variables (Atherosclerosis Risk in Communities Study) in healthy adults at 18 years followup, and four studies of combined EPA+DHA intake (Figure 26, plot #122) in one analysis of all healthy adults (Atherosclerosis Risk in Communities Study), two analyses in men (Health Professionals Follow-up Study, MORGEN), and two analyses in women (Nurses' Health Study, MORGEN).

By meta-analysis (Table 27), overall there is a statistically significant association between higher marine oil intake and *lower* risk of ischemic stroke across a median dosage range of 0.025 to 0.6 g/d (effect size per g/d = 0.51; 95% CI 0.29 to 0.89). Meta-analyses with the addition of a spline knot point at different dose thresholds (from 0.1 to 0.4 g/d) consistently found a much stronger association (of higher dose being associated with lower risk) at *lower* doses than at higher doses (ES below knot less than 1; ES above knot near or greater than 1). All effect sizes below the knots were statistically significant and all above the knots were nonsignificant. The differences between lower- and higher-dose effect sizes were all statistically significant (P=0.03-0.049). This implies a ceiling effect (where intake above a certain level adds no further benefit). However, it is unclear what the threshold may be, as it may be greater than the highest threshold tested (0.4 g/d). The best fit curve was found with a knot at either 0.3 or 0.4 g/d. The difference between lower-dose and higher-dose ES estimates was statistically significant with a knot at 0.1 g/d.

n-3 FA Biomarkers

Three studies evaluated the association between n-3 FA biomarkers and risk of ischemic stroke (Atherosclerosis Risk in Communities Study, Cardiovascular Health Study, MORGEN) in healthy adults.

The Cardiovascular Health Study found a significant association between plasma levels of total n-3 FA (combined) and lower risk of ischemic stroke in healthy adults ≥65 years of age after 16 years of followup (Figure 26, plot #125).

All three studies found no significant associations between plasma, cholesteryl ester, or phospholipid ALA levels and risk of ischemic stroke in healthy adults after 10, 16, and 22 years of followup (Figure 26, plot #118).

The Atherosclerosis Risk in Communities Study and the Cardiovascular Health Study found no associations between plasma, cholesteryl ester, or phospholipid EPA levels and risk of ischemic stroke in healthy adults after 16 to 22 years of follow-up (Figure 26, plot #124).

The same two studies evaluated DHA biomarkers (Figure 26, plot #119). The Atherosclerosis Risk in Communities Study found that those in the in the highest quintiles of DHA cholesteryl ester and phospholipid levels (separately) had lower risk of ischemic stroke with near-statistical significance (P=0.07 and 0.08, respectively). The Cardiovascular Health Study also found the same association across quintiles with plasma DHA with near statistical significance (P=0.052).

The Cardiovascular Health study also evaluated plasma DPA levels and found no significant association with ischemic stroke (Figure 26, plot #120).

The Atherosclerosis Risk in Communities Study found no significant association with cholesteryl ester or phospholipid EPA+DHA+DPA and ischemic stroke at 22 years of followup (Figure 26, plots #121 & 123), and also with phospholipid EPA+DHA at 18 years. MORGEN, however, found a statistically significant association between higher plasma EPA+DHA and ischemic stroke after 10 years.

Observational Study Subgroup Analyses

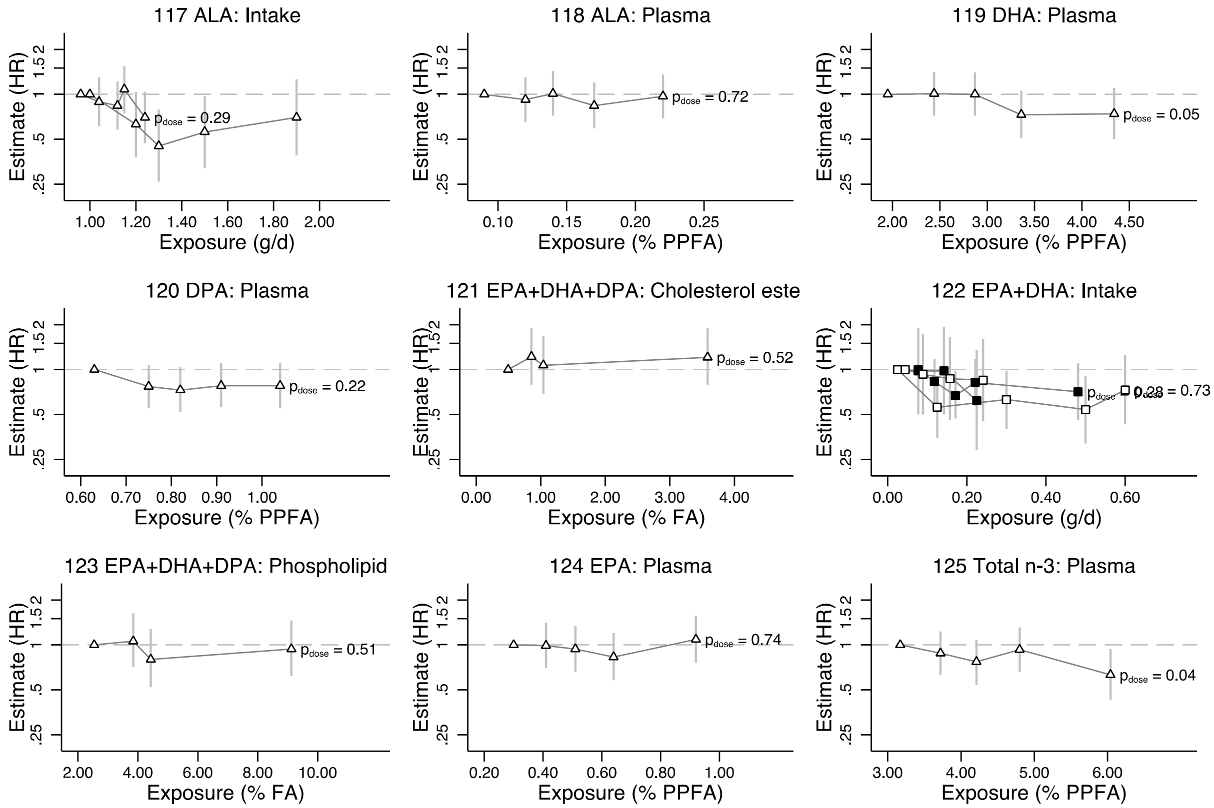
The Cardiovascular Health Study found no difference in associations of ALA intake or plasma values and ischemic stroke by amount of fish consumption at baseline or by sex.

Table 26. Stroke, ischemic: RCTs

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int n/N,%	Ctrl n/N,%	Effect Size	Reported P value
Marine oil vs Placebo											
Yokoyama 2007 17398308 Japan	At risk (dyslipidemia)	EPA (+Statin)	1.8 g/d (Ethyl ester)	Placebo (+Statin)	0	4.6 y	Local physicians monitored but compliance level was not reported	115/9326, 1.2%	123/9319, 1.3%	0.97 (0.85, 1.10)	0.632
Tavazzi 2008 18757090 Italy	CVD	EPA+DHA	0.850−0.882 g/d (Ethyl esters) [E:D 1:1.2]	Placebo	0 (nd)	3.9 y	Exam question (~30% not taking n-3 FA or placebo by the end of study)	97/3494, 2.8%	79/3481, 2.3%	OR 1.23 (0.91, 1.66)	nd
Yokoyama 2007 17398308 Japan	CVD (previous CHD)	EPA (+Statin)	1.8 g/d (Ethyl ester)	Placebo (+Statin)	0	4.6 y	Local physicians monitored but compliance level was not reported	45/485 9%	41/457 9%	OR 1.04 (0.67, 1.62)	0.871

Abbreviations: CHD = coronary heart disease, Ctrl = control, CVD = cardiovascular disease, DHA = docosahexaenoic acid, E:D = EPA to DHA ratio, EPA = eicosapentaenoic acid, F/up = followup, Int = intervention, n/N = number with outcome/number analyzed, n6:3 = omega-6 to omega-3 fatty acid ratio, n-3 FA = omega-3 fatty acids, OR = odds ratio, PMID = PubMed Identification number, RCT = randomized controlled trial.

Figure 26. n-3 FA associations with ischemic stroke: Observational studies



Study (or cohort) level associations between n-3 FA exposure and hazard ratio (HR) for the outcome. Studies that reported associations by continuous exposure (e.g., per g/d intake or per standard deviation) could not be graphed and are omitted. P values are the study-reported P value for the trend across quantiles.
White triangles = healthy adults, white squares = healthy males, black squares = healthy females.

Abbreviations: ALA = alphalinolenic acid, DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, EPA = eicosapentaenoic acid, HR = hazard ratio, n-3 FA = omega-3 fatty acids, PPFA = plasma polyunsaturated fatty acids.

Table 27. Meta-analysis results of observational studies of marine oil (EPA+DHA±DPA) intake and ischemic stroke

N patients	Dose range, g/d	Knot	ES, overall	ES below knot	ES above knot	P*	AIC	No. cohorts (crossing threshold)
143,579	0.025−0.60		0.51 (0.29, 0.89)					4
		0.1		0.05 (0.01, 0.46)	0.87 (0.41, 1.81)	0.03	34.9	4
		0.2		0.16 (0.05, 0.53)	1.17 (0.46, 3.00)	0.03	37.0	4
		0.3		0.24 (0.09, 0.61)	1.72 (0.46, 6.50)	0.049	43.2	2
		0.4		0.25 (0.11, 0.60)	7.08 (0.55, 90.8)	0.04	48.9	2

* ES below vs. above knot

Abbreviations: AIC = Akaike information criterion (estimation of fit of regression with spline), DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, EPA = eicosapentaenoic acid, ES = effect size.

Stroke, Hemorrhagic (Fatal and Nonfatal)

Randomized Controlled Trials

Two RCTs evaluated hemorrhagic stroke (Table 28).[90, 96] One was conducted in 18,645 participants with dyslipidemia (19.5% with CHD),[90] and the other was conducted in 6975 participants with heart failure.[96] Both evaluated n-3 FA ethyl esters. Neither of the trials reported hemorrhagic stroke to be a primary outcomes.

At-Risk-for-CVD Population

One study compared 1.8 g/d purified EPA combined with statin with control (statin alone) to placebo with statin in 18,645 participants with dyslipidemia (19.5% with CHD).[90] Adherence was verified by local physicians at every clinic visit but the level was not reported. After 5 years of followup, the trial did not find significant difference in the risk of hemorrhagic stroke between participants who were assigned to the EPA+statin group and those in the statin alone group (HR=1.12; 95% CI 0.91 to 1.39).

CVD Population

One study of 6975 participants with heart failure compared marine oil ethyl esters (EPA+DHA 0.850-0.882 g/d) with placebo.[96] The adherence was about 70% by the end of the 3.9-year study. There was no significant difference in the risk of hemorrhagic stroke between the two groups (OR=1.30; 95% CI 0.57 to 2.96)

Observational Studies

Five studies evaluated the associations between n-3 FA intake or biomarker levels and risk of hemorrhagic stroke in healthy adults after 10 to 16 years of followup (Appendix F, Hemorrhagic stroke section; Figure 27).[65, 73, 112, 143, 145, 159, 186] All but one analysis across studies were nonsignificant for an association.

n-3 FA Intake

The five studies all evaluated n-3 FA intake (Cardiovascular Health Study, Health Professional Follow-up Study, MORGEN, Nurses' Health Study, Swedish Mammography Study).

The Cardiovascular Health Study (in adults ≥65 years) and the Swedish Mammography Study in women both found no association between ALA intake and risk of hemorrhagic stroke (Figure 27, plot #126).

Four studies (Health Professional Follow-up Study, MORGEN, Nurses' Health Study, Swedish Mammography Study) evaluated EPA+DHA intake (Figure 27, plot #130). Only MORGEN, in a subgroup of men (<65 years old), found an association between higher EPA+DHA intake and *lower* risk of hemorrhagic stroke. No such association was found in women in MORGEN or the other three studies.

By meta-analysis (Table 29), overall there is no significant association between marine oil intake and hemorrhagic stroke across a median dosage range of 0.025 to 0.6 g/d (effect size per g/d = 0.61; 95% CI 0.34 to 1.11). Meta-analyses with the addition of a spline knot point at different dose thresholds (from 0.1 to 0.5 g/d) consistently found similar associations above and below the knots. At no threshold was the difference in effect sizes statistically significant. The best fit curve was found with a knot at 0.1 g/d. The lowest P value between lower-dose and higher-dose ES estimates was found at 0.5 g/d (P=0.78).

n-3 FA Biomarkers

The Cardiovascular Health Study and MORGEN evaluated plasma n-3 FA and risk of hemorrhagic stroke. Both analyses found no significant associations, including total n-3 FA (combined, Cardiovascular Health Study, Figure 27, plot #132); ALA (both studies, Figure 27, plot #126); EPA (Figure 27, plot #131), DHA (Figure 27, plot #128), and DPA (Figure 27, plot #129) (Cardiovascular Health Study); and EPA+DHA (MORGEN).

Observational Study Subgroup Analyses

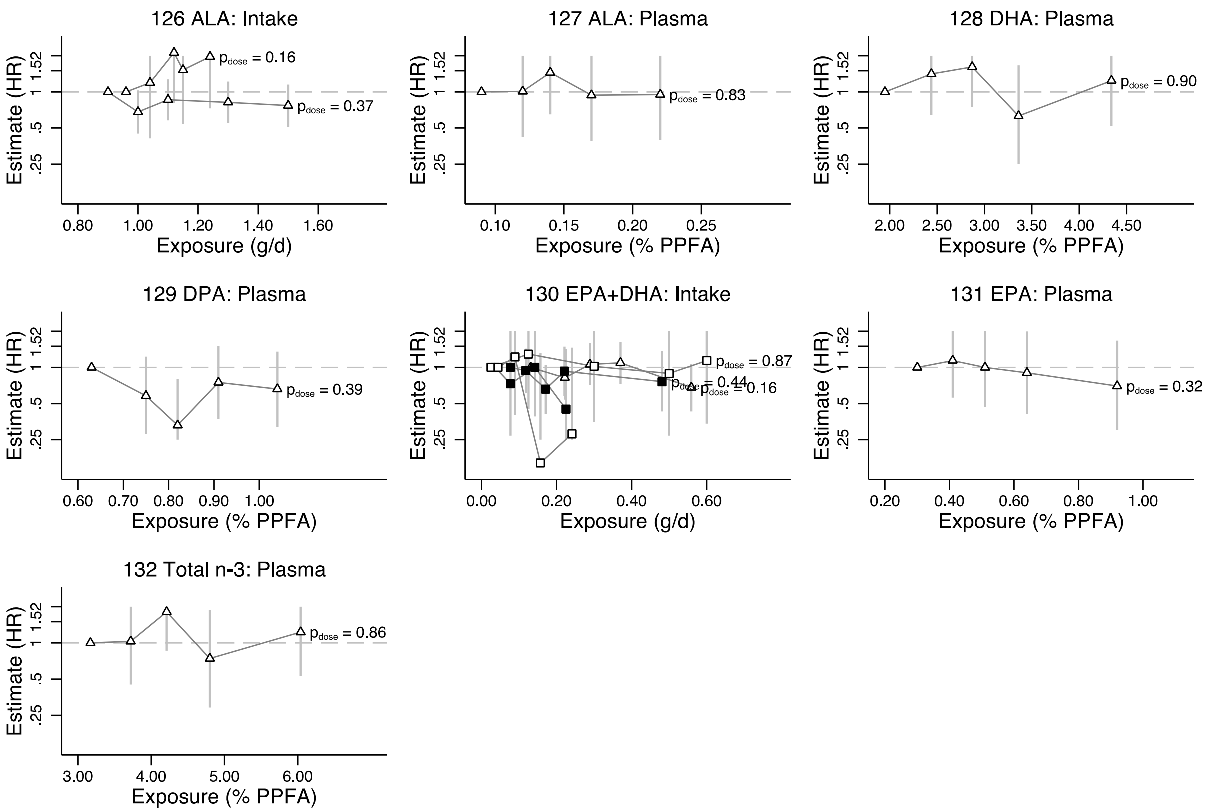
The Cardiovascular Health Study found no difference in associations of ALA intake or plasma values and hemorrhagic stroke by amount of fish consumption at baseline or by sex.

Table 28. Stroke, hemorrhagic: RCTs

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int n/N,%	Ctrl n/N,%	Effect Size	Reported P value
Marine oil vs Placebo											
Tavazzi 2008 18757090 Italy	CVD	EPA+DHA	0.850−0.882 g/d (Ethyl esters) [E:D 1:1.2]	Placebo	0 (nd)	3.9 y	Exam question (~30% not taking n-3 FA or placebo by the end of study)	13/3494, 0.4%	10/3481, 0.3%	OR 1.30 (0.57, 2.96)	nd
Yokoyama 2007 17398308 Japan	At risk (dyslipidemia)	EPA (+Statin)	1.8 g/d (Ethyl ester)	Placebo (+Statin)	0	4.6 y	Local physicians monitored but compliance level was not reported	49/9326, 0.5%	39/9319, 0.4%	1.12 (0.91, 1.39)	0.272

Abbreviations: Ctrl = control, CVD = cardiovascular disease, DHA = docosahexaenoic acid, E:D = EPA to DHA ratio, EPA = eicosapentaenoic acid, F/up = followup, Int = intervention, n/N = number with outcome/number analyzed, n6:3 = omega-6 to omega-3 fatty acid ratio, n-3 FA = omega-3 fatty acids, ND = no data, PMID = PubMed Identification number, RCT = randomized controlled trial.

Figure 27. n-3 FA associations with hemorrhagic stroke: Observational studies



Study (or cohort) level associations between n-3 FA exposure and hazard ratio (HR) for the outcome. Studies that reported associations by continuous exposure (e.g., per g/d intake or per standard deviation) could not be graphed and are omitted. P values are the study-reported P value for the trend across quantiles. The 95% confidence intervals were truncated when <0.25 and >2.
White triangles = healthy adults, white squares = healthy males, black squares = healthy females

Abbreviations: ALA = alphalinolenic acid, DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, EPA = eicosapentaenoic acid, HR = hazard ratio, n-3 FA = omega-3 fatty acids, PPFA = plasma polyunsaturated fatty acids.

Table 29. Meta-analysis results of observational studies of marine oil (EPA+DHA±DPA) intake and hemorrhagic stroke

N patients	Dose range, g/d	Knot	ES, overall	ES below knot	ES above knot	P*	AIC	No. cohorts (crossing threshold)
178,249	0.035−0.6		0.61 (0.34, 1.11)	NA	NA			5
		0.1	NA	0.55 (0.04, 7.31)	0.63 (0.27, 1.44)	0.94	49.2	5
		0.2	NA	0.52 (0.14, 1.94)	0.68 (0.26, 1.81)	0.79	51.1	5
		0.3	NA	0.64 (0.14, 2.90)	0.55 (0.08, 4.02)	0.93	57.9	3
		0.4	NA	0.63 (0.15, 2.73)	0.49 (<0.01, 53.9)	0.93	64.0	3
		0.5	NA	0.68 (0.28, 1.63)	0.17 (<0.01, 1336)	0.78	75.7	2

* ES below vs. above knot

Abbreviations: AIC = Akaike information criterion (estimation of fit of regression with spline), DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, EPA = eicosapentaenoic acid, ES = effect size, NA = not applicable.

Sudden Cardiac Death

Randomized Controlled Trials

Nine RCTs evaluated SCD (Table 30).[81, 82, 87, 89, 90, 96, 121, 146, 160] Of these, two studies were conducted in 31,150 participants at risk of CVD (defined as dyslipidemia [19.5% with CHD][90] or with multiple risk factors[160]), and eight in a total of 24,463 participants with CVD including diabetes and history of CVD,[146] arrhythmia,[81, 82, 87] MI,[89, 121] CHD or peripheral artery disease,[90] and heart failure.[96] One study reported on both at-risk and CVD populations.[90] No trial reported SCD to be a primary outcome.

Marine Oil Versus Placebo

Meta-analysis of the nine trials of marine oil yielded a nonsignificant summary HR=1.04 (95% CI 0.92 to 1.17) (Figure 28).[81, 82, 87, 90, 96, 121, 146, 160]

At-Risk-for-CVD Population

Among people at risk for CVD, one study compared 1.8 g/d EPA ethyl ester combined with statin with control (statin alone) in 18,645 participants with dyslipidemia,[90] and one compared marine oil (EPA+DHA) or EPA to placebo in 12,505 participants with multiple risk factors.[160] The dose of EPA+DHA was at least 0.85 g/d. Neither study reported adherence level. The durations of followup was 4.6 and 5 years. Both studies found no significant differences in SCD between groups (HR 1.06, 95% CI 0.55 to 2.07; OR 1.28, 95% CI 0.80 to 1.85). Because the study that combined EPA with statin also included a percentage of patients with CHD, the authors reported the results of a subgroup analysis of patients without previous CHD, though the results were still nonsignificant (HR 1.25; 95% CI 0.34 to 4.67).[90]

Subgroup meta-analysis yielded a nonsignificant summary HR of 1.17 (95% CI 0.82 to 1.67) for people at risk for CVD.

CVD Population

Among people with existing CVD, eight studies compared marine oil (EPA+DHA) to placebo (olive oil or oleic acid sunflower oil),[81, 82, 87, 89, 90, 96, 121, 146] Overall, these trials followed 24,463 people with existing CVD. The EPA+DHA doses ranged from 0.84 to 2.6 g/d. The duration of followup ranged from 0.8 years to 6.2 years. Compliance, when reported, ranged from 70 to 88 percent. All trials found no significant association, with effect sizes ranging from 0.94 to 3.06.

The study described above that combined 1.8 g/d EPA ethyl ester also reported separate analyses for the patients with CHD and peripheral artery disease at any time. There was no significant additive effect of EPA supplementation on SCD in either group of patients (HR 1.02, 95% CI 0.47 to 2.19; HR 0.19, 95% CI 0.01 to 1.33).[90]

One study compared two levels of “fish advice” (dietician to advise to increase fish and/or fish oil supplement intake) with no fish advice in a total of 3114 men with MI or angina.[89] The mean EPA intake estimated by the dietary assessment was 0.45 and ≤0.85 g/d in the “fish advice” groups, and was 0.11 in the “no fish advice” group. No estimates for DHA intake levels were reported. Compliance was good (fish intake was significantly increased in the “fish advice” groups) based on the dietary assessments. The trial found that, after 9 years of followup, overall, there was no significant difference in SCD between 1109 men with angina who were advised to increase fish intake and 1543 men with angina who were not (adjusted HR 1.43; 95% CI 0.95 to

2.15; P=0.086). The effect was significant in the subgroup of 462 men given advice about taking a fish oil supplement (adjusted HR 1.84, 95% CI 1.11 to 3.05). There was no significant difference between the two groups (OR 1.19; 95% CI 0.72 to 1.96). Across the four RCTs of CVD populations, the summary HR was 1.03 (95% CI 0.92 to 1.17).

RCT Subgroup Analyses

No trial reported a direct within-study subgroup analysis. By meta-regression of the marine oil trials, effect sizes did not vary across studies by dose (P=0.93) or population (P=0.48), but did vary across studies by followup time (P=0.04)

Observational Studies

Four studies evaluated the associations between multiple n-3 FA measures and SCD after about 11 to 18 years of follow-up in mostly healthy adults of varying ages, and also, in one study, women with a history of prior CVD (Appendix F, Sudden coronary death section; Figure 29).[60, 78, 83, 84, 159, 186] Analyses and studies found a mix of nonsignificant associations and associations favoring higher n-3 FA quantiles.

n-3 FA Intake

The Physician's Health Study found no association between total n-3 FA intake (combined) and risk of SCD at 11 years in healthy men (Figure 29, plot #140). Two studies analyzed ALA intake (Figure 29, plots #133 & 134). The Nurses' Health Study found a significant association between higher ALA intake and lower risk of SCD after 18 years. The Cardiovascular Health Study found no significant association with 16 years of followup. The Japan Public Health Center-Based Study - Cohort I also found no association between EPA+DHA intake and risk of SCD at about 11.5 years (Figure 29, plot #138).

n-3 FA Biomarkers

The Cardiovascular Health Study found a significant association between plasma levels of total n-3 FA combined (implicitly ALA, DHA, DPA, and EPA) and lower risk of SCD with 16 years of followup (Figure 29, plot #141). The Cardiovascular Health Study, however, found no association between plasma ALA level and risk of SCD (Figure 29, plot #135). Regarding marine oils, this same study found a significant association between plasma DHA (Figure 29, plot #136) and risk of SCD, but no significant associations with plasma DPA (Figure 29, plot #137) or EPA (Figure 29, plot #139).

Observational Study Subgroup Analyses

In the Nurses' Health Study, the subgroup of women with no history of CVD at baseline had a significant association between higher ALA intake and lower risk of SCD after 18 years; in the smaller subgroup of women with a history of CVD, the effect estimates across quintiles were similar, but not statistically significant.[83] The Cardiovascular Health Study reported no significant difference (without details) in association of total n-3 FA and SCD between participants with high, low, or no fish consumption and between men and women.[186]

Table 30. Sudden cardiac death: RCTs

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int n/N,%	Ctrl n/N,%	Effect Size	Reported P value
Marine oil vs Placebo											
Roncaglioni 2013 23656645 Italy	At risk	EPA+DHA	>= 0.85 g/d (marine oil) [E:D 0.9:1−1.5:1]	Placebo	0 (Olive oil)	5 y	Self-reported (nd on level of adherence)	49/6239 0.8%	40/6266 0.6%	HR 1.22 (0.80, 1.85)	0.36
Yokoyama 2007 17398308 Japan	At risk	EPA (+Statin)	1.8 g/d (Ethyl ester)	Placebo (+Statin)	0	4.6 y	Local physicians monitored but compliance level was not reported	18/9326 0.2%	17/9319 0.2%	HR 1.06 (0.55, 2.07)	0.854
	At risk (no previous CHD)	EPA+Statin	1.8 g/d (Ethyl ester)	Statin	0	5 y	Local physicians monitored but compliance level was not reported	4/7503 0.1%	5/7478 0.1%	HR 1.25 (0.34, 4.67)	0.736
Bosch 2012 22686415 Canada	CVD	EPA+DHA	EPA 0.465 g/d, DHA 0.375 g/d (Marine oil) [E:D 1.24]	Placebo	0 (Olive oil)	6.2 y	FFQ at baseline, 2 years, and end of study (adherence was 88% at the end of study)	288/6281 4.6%	259/6255 4.1%	OR 1.10 (0.93, 1.30)	0.26
Brouwer 2006 16772624 Europe	CVD	EPA+DHA	0.96 g n-3 PUFA (0.464 g EPA, 0.335 g DHA) (Marine oil) [E:D=1.4]	Placebo	0 (high-oleic acid sunflower oil)	1 y	Generally good (76% reported taking 80% pills) based on pill counts and confirmed by biomarkers.	81/273 29.7%	90/273 33%	0.86 (0.6, 1.23)	0.33
Leaf 2005 16267249 U.S.	CVD	EPA+DHA	2.6 g/d (Marine oil)	Placebo	0 (Olive oil)	1 y	Pill counts and analysis of the phospholipids of red blood cells for their content of EPA and DHA. Noncompliance ~35%	3/200 1.5%	1/202 0.5%	3.06 (0.32, 29.68)	0.334
Rauch 2010 21060071 Germany	CVD	EPA+DHA	0.46 g EPA, 0.38 g DHA (Marine oil) [E:D 1.2]	Placebo	0 (Olive oil)	1 y	Pill counts at 3 months and 12 months (≥70% of study period)	28/1919 1.5%	29/1885 1.5%	0.95 (0.56, 1.6)	0.84
Raitt 2005 15956633 U.S.	CVD	EPA+DHA	EPA 0.756 g/d, DHA 0.54 g/d (fish oil) [E:D 1.4]	Placebo	0 (olive oil: 73% oleic acid, 12%)	2 y	RBC and plasma n-3 FA levels	2/100 2%	0/100 0%	OR 5.1 (0.24, 107.64)	0.47
Tavazzi 2008 18757090 Italy	CVD	EPA+DHA	0.850−0.882 g/d (Ethyl esters) [E:D 0.83]	Placebo	0 (NR)	3.9 y	Exam question (~30% not taking n-3 FA or placebo by the end of study)	307/3494	325/3481	Adj. HR 0.93 (0.79, 1.08)	0.333

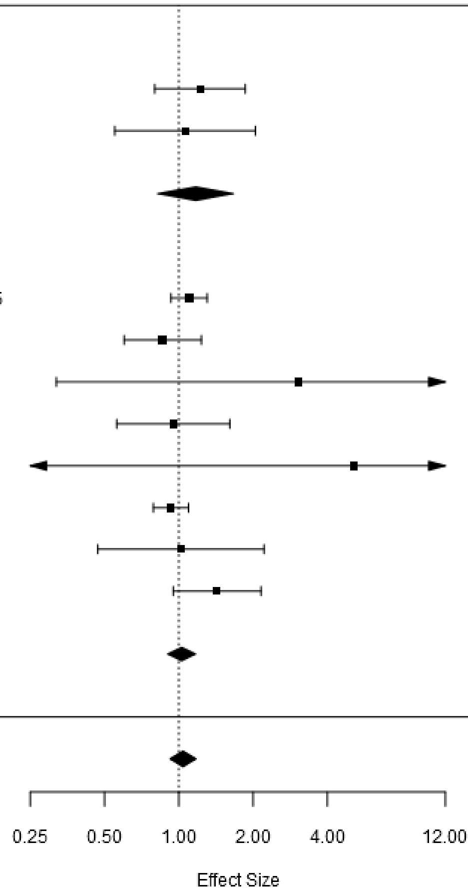
Table 30. Sudden cardiac death: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int n/N,%	Ctrl n/N,%	Effect Size	Reported P value
Yokoyama 2007 17398308 Japan	CVD (previous CHD)	EPA+Statin	1.8 g/d (Ethyl ester)	Statin	0	5 y	Local physicians monitored but compliance level was not reported	13/1823 0.7%	13/1841 0.7%	HR 1.02 (0.47, 2.19)	0.967
	CVD (PAD at any time)	EPA+Statin	1.8 g/d (Ethyl ester)	Statin	0	5 y	Local physicians monitored but compliance level was not reported	1/117 0.9%	4/106 3.8%	HR 0.19 (0.01, 1.33)	0.099
Burr 2007 17343767 UK	CVD	Fish advice	EPA 0.45 g/d (diet)[a]	No fish advice	EPA 0.11 (diet)[a]	9 y	dietary charts sent by post with reply-paid envelopes	49/1109, 4.4%	47/1543, 3.0%	Adj HR 1.43 (0.95, 2.15)	0.086
	CVD	EPA+DHA (advice to take fish oil)	EPA ≤0.51 and DHA ≤0.345 (marine oil)[a]	No fish advice	EPA 0.11 (diet)[a]	9 y	dietary charts sent by post with reply-paid envelopes	24/462, 5.2%	47/1543, 3.0%	Adj HR 1.84 (1.11, 3.05)	0.018
	CVD	EPA+DHA (advice to take fish oil)	EPA ≤0.51 and DHA ≤0.345 (marine oil)[a]	Fish advice	EPA 0.45 g/d (diet)[a]	9 y	dietary charts sent by post with reply-paid envelopes	24/462, 5.2%	49/1109, 4.4%	OR 1.19 (0.72, 1.96)	nd

Abbreviations: CHD = coronary heart disease, Ctrl = control, CVD = cardiovascular disease, DHA = docosahexaenoic acid, E:D = EPA to DHA ratio, EPA = eicosapentaenoic acid, F/up = followup, FFQ = food frequency questionnaire, HR = hazard ratio, Int = intervention, n/N = number with outcome/number analyzed, n6:3 = omega-6 to omega-3 fatty acid ratio, n-3 FA = omega-3 fatty acids, ND = no data, OR = odds ratio, PAD = peripheral artery disease, PMID = PubMed Identification number, RBC = red blood cell, RCT = randomized controlled trial.

Figure 28. Sudden cardiac death: Randomized trials of marine oils

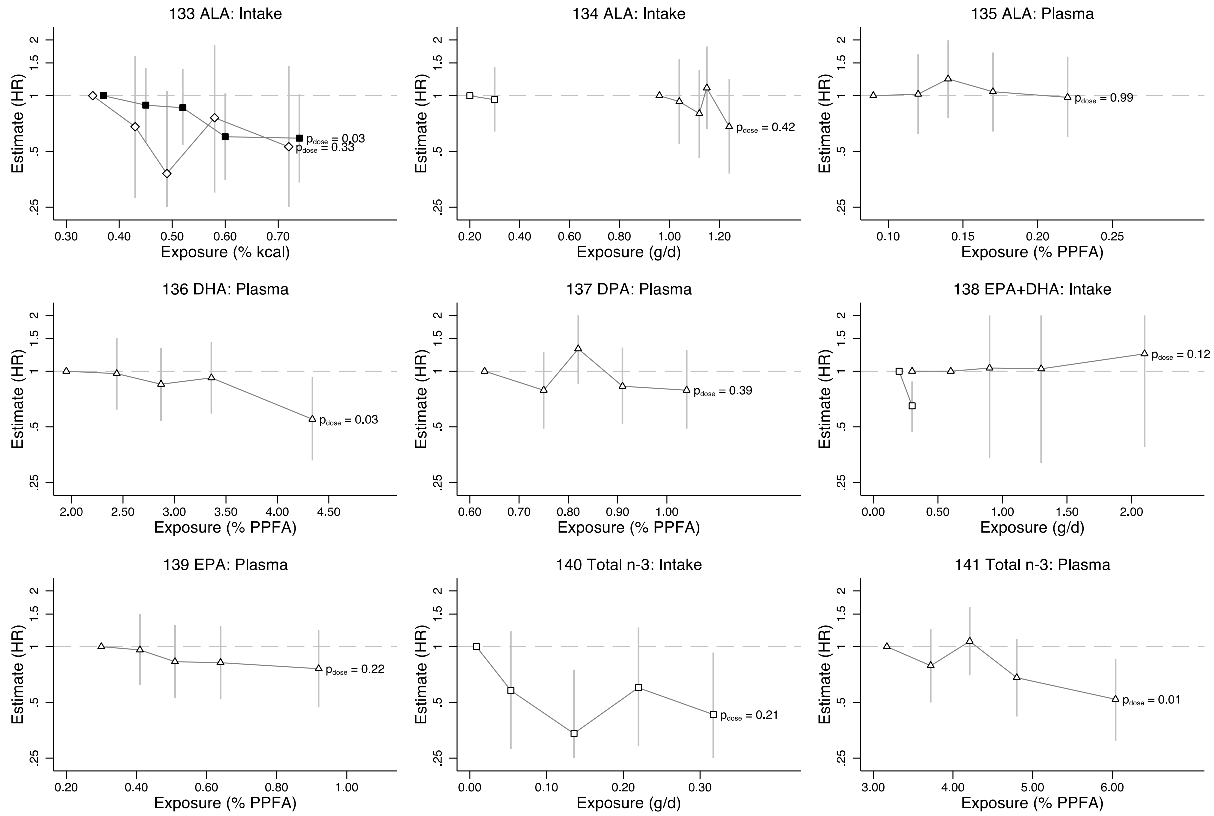
Study PMID	n-3 FA	g/day	Years	n-3 FA n/N	Placebo n/N	Effect Size [95% CI]
At risk population						
Roncaglioni 2013 23656645	EPA+DHA	0.85	5	49/6239	40/6266	1.22 [0.80, 1.85]
Yokoyama 2007 17398308	EPA	1.8	4.6	18/9326	17/9319	1.06 [0.55, 2.07]
Summary, at risk						*1.17 [0.82 , 1.67]*
CVD population						
Bosch 2012 22686415	EPA+DHA	0.84	6.2	288/6281	259/6255	1.10 [0.93, 1.30]
Brouwer 2006 16772624	EPA+DHA	0.96	1	81/273	90/273	0.86 [0.6, 1.23]
Leaf 2005 16267249	EPA+DHA	2.6	1	3/200	1/202	3.06 [0.32, 29.68]
Rauch 2010 21060071	EPA+DHA	0.84	1	28/1919	29/1885	0.95 [0.56, 1.6]
Raitt 2005 15956633	EPA+DHA	1.3	2	2/100	0/100	5.1 [0.24, 107.64]
Tavazzi 2008 18757090	EPA+DHA	0.87	3.9	307/3494	325/3481	0.93 [0.79, 1.08]
Yokoyama 2007 17398308	EPA	1.8	5	13/1823	13/1841	1.02 [0.47, 2.19]
Burr 2007 17343767	EPA	0.45	9	49/1109	47/1543	1.43 [0.95, 2.15]
Summary, CVD						*1.03 [0.90 , 1.17]*
Summary [I-squared=11.039, Phet=0.515]						**1.04 [0.92 , 1.17]**



Random effects model meta-analysis of n-3 FA versus placebo (or no n-3 FA), with subgroup analyses by population. In all meta-analyses, only studies that reported sufficient results data are included.

Abbreviations: CI = confidence interval, CVD = cardiovascular disease, DHA = docosahexaenoic acid

Figure 29. n-3 FA associations with sudden cardiac death: Observational studies



Study (or cohort) level associations between n-3 FA exposure and hazard ratio (HR) for the outcome. Studies that reported associations by continuous exposure (e.g., per g/d intake or per standard deviation) could not be graphed and are omitted. P values are the study-reported P value for the trend across quantiles. The 95% confidence intervals were truncated when <0.25 and >2.
White triangles = healthy adults, white squares = healthy males, black squares = healthy females

Abbreviations: ALA = alphalinolenic acid, DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, EPA = eicosapentaenoic acid, HR = hazard ratio, n-3 FA = omega-3 fatty acids, PPFA = plasma polyunsaturated fatty acids.

Atrial Fibrillation

Randomized Controlled Trials

Three RCTs evaluated supraventricular tachycardias, specifically AFib.[96, 133, 157] All were conducted among people with CVD (Table 31). Specifically, two studies were conducted in a total of 785 people who had previous persistent AFib,[133, 157] and one in 5835 heart failure patients without AFib at study entry.[96] No study reported AFib to be a primary outcome.

Marine Oil Versus Placebo

CVD Population

Among 785 people with previous persistent AFib, two RCTs compared marine oil (EPA+DHA) to placebo (olive oil).[133, 157] The same dose of EPA+DHA (0.850 to 0.882 g/d) was used in both studies for a duration of 1 year, but the EPA to DHA ratio was 0.5 in one study and 1.2 in another. Compliance was not reported. Both studies found that EPA+DHA supplementation had no significant effect on the recurrence of AFib (HR 1.28; 95% CI 0.90 to 1.83; OR 0.52, 95% 0.26 to 1.06).

Among 5835 heart failure patients without AFib at study entry, one RCT compared marine oil ethyl esters (EPA+DHA) to placebo.[96] The dose of EPA+DHA was 0.850 to 0.882 g/d with a EPA to DHA ratio of 1.2. Compliance was about 70 percent. This study found no significant effect on incidence of AFib comparing EPA+DHA ethyl esters to placebo after a mean 3.9 years of followup (HR 1.10 95% CI 0.96 to 1.25).[96]

RCT Subgroup Analyses

Two RCTs reported subgroup analysis for AFib (Table 32). In one trial of AFib recurrence in people with a history of persistent AFib,[157] no differences in effect were found between subgroups based on sex, age (at a threshold of 60 years), or duration of prior AFib (at a threshold of 48 hours). In the trial of incident AFib (history of heart failure),[96] no differences in effect were found between subgroups based on age (threshold 70 years), left ventricular ejection fraction (threshold 40%), ischemic versus nonischemic heart failure, New York Heart Association class (I&II vs. III&IV), diabetes, total cholesterol (200 mg/dL threshold), glomerular filtration rate (60 mL/min threshold), or fish intake (2 servings per week threshold).

Observational Studies

Five studies evaluated the associations between multiple n-3 FA measures and supraventricular tachycardias (specifically AFib) after 6.4 to 18 years of followup in healthy adults (mostly over age 50 or 65 years) (Appendix F, Atrial fibrillation section; Figure 30).[79, 86, 110, 111, 140, 158] Most specific analyses found no significant association and the three studies with significant associations were inconsistent.

n-3 FA Intake

Four studies evaluated n-3 FA intake. The Cardiovascular Health Study found no significant association with ALA intake (Figure 30, plot #142), overall and, separately, in men and women. The other three studies (Women's Health Initiative, Rotterdam, and the Diet, Cancer, Health study) evaluated marine oil (EPA+DHA±DPA) intake (Figure 30, plot #148).

Over a relatively low and narrow range of marine oil intake (less than about 0.3 g/d), the Women's Health Initiative and Rotterdam studies found no significant association. In contrast, the Diet, Cancer, Health study found that after a mean of 8.1 years, higher EPA+DHA+DPA intake, particularly in the quintile with median intake of 1.3 g/d, was associated with lower risk of AFib in healthy women (age 50 to 64 years).

n-3 FA Biomarkers

The Cardiovascular Health Study and the Kuopio Ischemic Heart Disease Risk Factor Study evaluated biomarkers. The Cardiovascular Health Study found significantly lower risks of AFib (after 14 years) with higher plasma levels of total n-3 FA combined (not plotted because median quantile values not reported), and DHA (Figure 30, plot #144) in healthy adults at least 65 years of age. No significant associations were found with plasma ALA (Figure 30, plot #143), DPA (Figure 30, plot #146), or EPA (Figure 30, plot #150). The Kupio study found statistically significant associations for both higher serum fatty acid combined EPA+DHA+DPA (Figure 30, plot #149) and higher serum fatty acid DHA (plot #145) with lower risk of AFib at a mean 17.7 years, but no significant associations for serum fatty acid EPA (Figure 30, plot #151) or DPA (Figure 30, plot #147).

Observational Study Subgroup Analyses

In the Cardiovascular Health Study, no differences were found (in a lack of association) for either plasma levels or intake of ALA and AFib between men and women.

Table 31. Atrial fibrillation: RCTs

Study Year PMID Region	Population	Int (n-3 FA)	Int n-3 Dose (Source) [E:D; n-6:3]	Control	Ctrl n-3 Dose (Source) [E:D; n-6:3]	F/up Time	Compliance Verification	Int n/N, %	Ctrl n/N,%	Effect Size	Reported P value
Marine oil vs. Placebo											
Macchia 2013 23265344 Italy & Argentina	CVD (previous persistent AFib)	EPA+DHA	0.850−0.882 g/d (marine oil) [E:D 0.5]	Placebo	0 (Olive oil)	1 y	NR	56 / 297, 18.9%	69 / 289, 23.9%	HR 1.28 (0.90, 1.83)	0.17
Nodari 2011 21844082 Italy	CVD (previous persistent AFib)	EPA+DHA	0.850−0.882 g/d (marine oil) [E:D 1.2]	Placebo	0 (Olive oil)	1 y	NR	15 / 100, 15%	25 / 99, 25%	OR 0.52 (0.26, 1.06)[a]	NR
Tavazzi 2008 18757090 Italy	CVD (heart failure, no history of AFib)	EPA+DHA	0.850−0.882 g/d (Ethyl esters) [E:D 0.83]	Placebo	0 (NR)	3.9 y	Exam question (~30% not taking n-3 FA or placebo by the end of study)	444/2921, 15.2%	408/2914, 14.0%	HR 1.10 (0.96, 1.25)	0.11

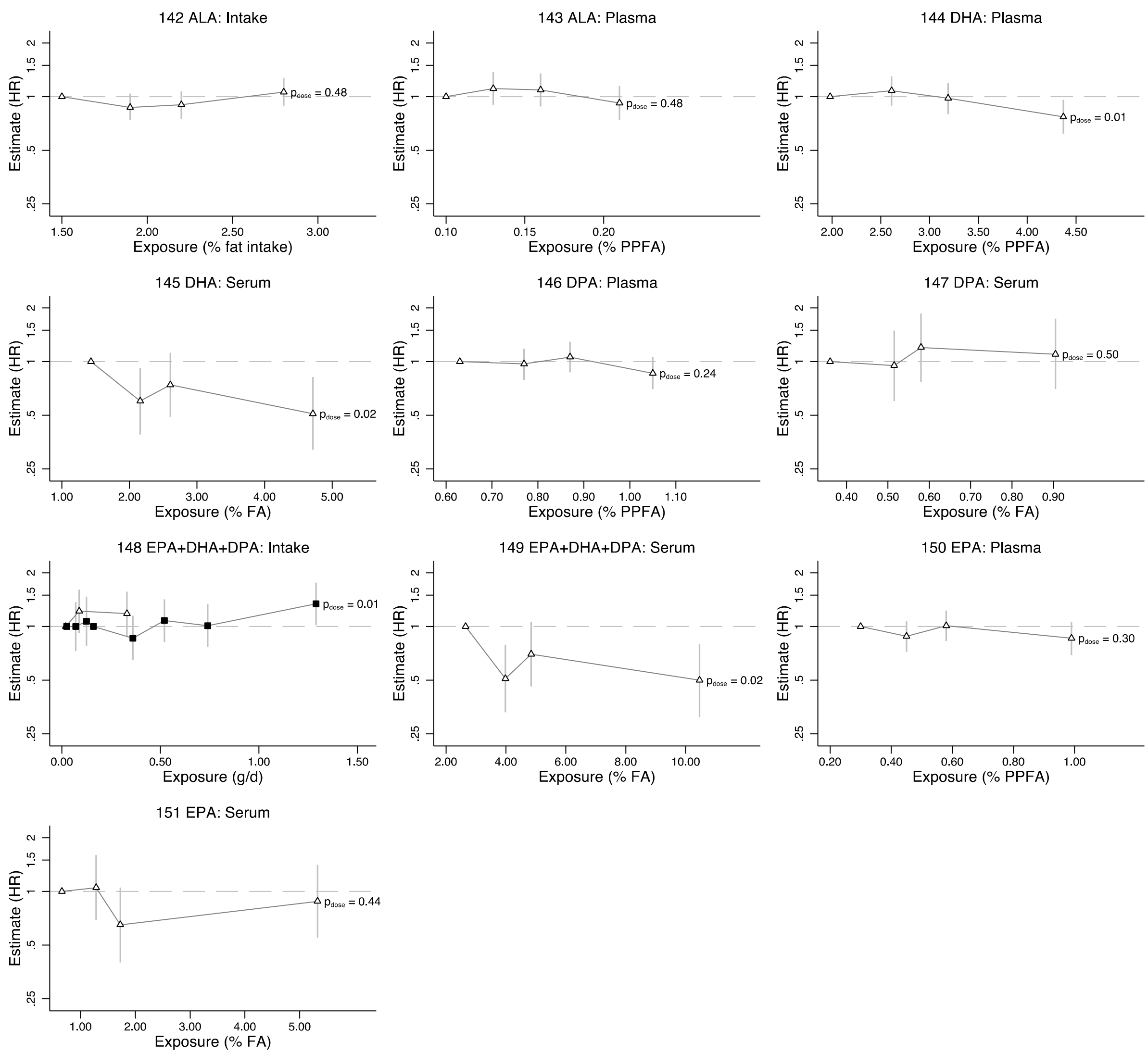
Abbreviations: AFib = atrial fibrillation, Ctrl = control, CVD = cardiovascular disease, DHA = docosahexaenoic acid, E:D = EPA to DHA ratio, EPA = eicosapentaenoic acid, F/up = followup, HR = hazard ratio, Int = intervention, n/N = number with outcome/number analyzed, n6:3 = omega-6 to omega-3 fatty acid ratio, n-3 FA = omega-3 fatty acids, NR = not reported, OR = odds ratio, PMID = PubMed Identification number, RCT = randomized controlled trial.

Table 32. Atrial fibrillation: Subgroup analyses, randomized trials

Study	Population	Subgroups	n-3 FA	Comparator	N Total	P difference	Difference	Favors
Macchia 2013 23265344 Italy & Argentina	CVD (previous persistent AFib)	Age: <60 vs >= 60	EPA+DHA	Placebo oil	586	0.12		
		Men vs women	EPA+DHA	Placebo oil	586	0.70		
		Duration of AF <48 hours vs. >= 48 hours	EPA+DHA	Placebo oil	586	0.12		
Tavazzi 2008 18757090 Italy	CVD (heart failure, no history of AFib)	Age: <=70 vs. >70	EPA+DHA	Placebo	5835	0.55		
		LVEF <=40% vs. >40%	EPA+DHA	Placebo	5835	0.46		
		Ischemic etiology vs. nonischemic etiology	EPA+DHA	Placebo	5835	0.95		
		NYHA II vs. NYHA III-IV	EPA+DHA	Placebo	5835	0.55		
		Diabetes vs. no diabetes	EPA+DHA	Placebo	5835	0.51		
		Total cholesterol <=200 mg/dL vs. >200 mg/dL	EPA+DHA	Placebo	5835	0.57		
		eGFR <60 ml/min/1.73 m^2 vs. >= 60 ml/min/1.73 m^2	EPA+DHA	Placebo	5835	0.99		
		History of AFib vs. no history of AFib	EPA+DHA	Placebo	5835	0.24		
		Fish intake <2 per week vs. >= 2 per week	EPA+DHA	Placebo	5835	0.16		

Abbreviations: AFib = atrial fibrillation, CVD = cardiovascular disease, DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, EGFR = epidermal growth factor receptor, EPA = eicosapentaenoic acid, LVEF = left ventricular ejection fraction, n-3 FA = omega-3 fatty acids, NYHA = New York Heart Association class, PMID = PubMed Identification number.

Figure 30. n-3 FA associations with atrial fibrillation: Observational studies



Study (or cohort) level associations between n-3 FA exposure and hazard ratio (HR) for the outcome. Studies that reported associations by continuous exposure (e.g., per g/d intake or per standard deviation) could not be graphed and are omitted. P values are the study-reported P value for the trend across quantiles. The 95% confidence intervals were truncated when <0.25 and >2.
White triangles = healthy adults, white squares = healthy males, black squares = healthy females

Abbreviations: ALA = alphalinolenic acid, DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, EPA = eicosapentaenoic acid, HR = hazard ratio, n-3 FA = omega-3 fatty acids, PPFA = plasma polyunsaturated fatty acids.

Ventricular Arrhythmia

Randomized Controlled Trials

One 2-by‒2 factorial study evaluated ventricular arrhythmia, described as “ventricular arrhythmia–related events (SCD, fatal and nonfatal cardiac arrest, and placement of implantable cardioverter–defibrillators)” (Table 33).[193] The RCT compared the effects of a margarine supplemented with EPA+DHA alone (0.4 g/d), a combination of both EPA+DHA and ALA margarines, and ALA alone (2 g/d) with placebo margarine (oleic acid) in 4837 participants with a history of MI.[119] (The 2-by‒2 factorial trial reported only analyses of EPA+DHA vs. placebo and ALA vs. placebo.) Ventricular arrhythmia was a secondary outcome in the trial.

Marine Oil Versus Placebo

CVD Population

The 2-by‒2 factorial trial compared 0.4 g/d of EPA+DHA in margarine to placebo margarine for 40 months with 90 percent compliance, overall.[193] The study found no significant effect of marine oil intake on ventricular arrhythmia (HR 0.90; 95% CI 0.65 to 1.26).

ALA Versus Placebo

CVD Population

The 2-by‒2 factorial study compared 2 g/d ALA in margarine to control margarine.[193] The trial found no difference in risk of ventricular arrhythmia after 40 months (HR 0.79; 95% CI 0.57 to 1.10).

RCT Subgroup Analyses

The same 2-by‒2 factorial RCT analyzed subgroups based on history of diabetes (Table 34).[193] For patients with diabetes, EPA+DHA supplementation resulted in a nonsignificant halving of ventricular arrhythmia risk (HR=0.51, P=0.09) in contrast to no effect in those without diabetes (HR=1.04, P=0.83); no test for interaction was reported. The effect of ALA on CVD death was significant in patients with diabetes (HR=0.39, P=0.02) and nonsignificant for those without diabetes (HR=0.93, P=0.71).

Observational Studies

No observational studies evaluated ventricular arrhythmias, per se.

Table 33. Ventricular arrhythmia: RCTs

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int n/N, %	Ctrl n/N,%	Effect Size	Reported P value
Marine oil vs. Placebo											
Kromhout 2010 20929341 Netherlands	CVD	EPA+DHA	0.4 g/d EPA+DHA and 2 g/d ALA (Marine; Plant oil) [E:D 3:2]	Placebo (±ALA)	0; 2 g/d ALA (Placebo margarine = oleic acid; Plant oil)	40 mo	90% of the patients adhered fully to the protocol; verified by biomarkers	67/2404, 2.8%	74/2433, 3.0%	HR 0.90 (0.65, 1.26)	0.55
ALA vs. Placebo											
Kromhout 2010 20929341 Netherlands	CVD	ALA	0.4 g/d EPA+DHA and 2 g/d ALA (Marine; Plant oil) [E:D 3:2]	Placebo (±EPA+DHA)	0; 0.4 g/d EPA-DHA (placebo = oleic acid; Marine oil) [E:D 3:2]	40 mo	90% of the patients adhered fully to the protocol; verified by biomarkers	62/2409, 2.6%	79/2428, 3.3%	HR 0.79 (0.57, 1.10)	0.16

Abbreviations: ALA = alphalinolenic acid, Ctrl = control, CVD = cardiovascular disease, DHA = docosahexaenoic acid, E:D = EPA to DHA ratio, EPA = eicosapentaenoic acid, F/up = followup, HR = hazard ratio, Int = intervention, n/N = number with outcome/number analyzed, n6:3 = omega-6 to omega-3 fatty acid ratio, PMID = PubMed Identification number, RCT = randomized controlled trial.

Table 34. Ventricular arrhythmia: Subgroup analyses, randomized trials

Study Year PMID Region	Population	Subgroups	n-3 FA	Comparator	N Total	P difference	Difference	Favors
Kromhout 2010 20929341 Netherlands	CVD	Diabetes vs. no diabetes	EPA+DHA	Placebo or ALA	4837	0.09 diabetes, 0.83 no diabetes	0.51 vs. 1.04	Diabetes (possibly)
			ALA	Placebo or EPA+DHA	4837	0.02 diabetes, 0.71 no diabetes	0.39 vs. 0.93	Diabetes (possibly)

Abbreviations: ALA = alphalinolenic acid, CVD = cardiovascular disease, DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid, HR = hazard ratio, PMID = PubMed Identification number.

Congestive Heart Failure

Randomized Controlled Trials

Six RCTs evaluated CHF, all of which evaluated marine oils and had as an endpoint CHF hospitalization (Table 35).[51, 81, 87, 146, 157, 160] None of the trials reported CHF to be a primary outcome.

Marine Oil Versus Placebo

At-Risk-for-CVD Population

Among 12,505 people with multiple risk factors for CHF, one RCT compared marine oil (EPA+DHA) to placebo for a median duration of 5 years.[160] The dose of EPA and DHA was at least 0.85 g/d (composition of the marine oil was not reported). Adherence was verified by participants' self-report but the level of adherence was not reported. The trial found a significant risk reduction in CHF hospitalizations in participants who were assigned to marine oil group compared with those in placebo group (HR 0.67; 95% CI 0.52 to 0.87).

CVD Population

Among people with CVD, five RCTs compared marine oil (EPA+DHA) to placebo.[51, 81, 87, 146, 157] The RCTs included a total of 13,927 patients. The dose of EPA+DHA ranged from 0.84 g/d to 6 g/d; adherence ranged from 76 to 90 percent in the four studies that reported compliance. The duration of followup ranged from 1 to over 6 years. None of the studies found a significant effect on CHF hospitalizations comparing marine oil to placebo, with effect sizes ranging from 0.86 (95% CI 0.26 to 2.81) to 1.19 (95% CI 0.52 to 2.73).

Observational Studies

Eight studies evaluated the associations between intake and biomarkers of n-3 FA and CHF (Appendix F, Congestive heart failure section; Figure 31).[86, 100, 102, 112, 129, 132, 148, 153, 154] Definitions of CHF outcomes varied across studies, including incident CHF and CHF hospitalization. One study analyzed only people with a history of MI; the Cohort of Swedish Men also reported a subgroup analysis in people with either diabetes of a history of MI. The remaining analyses were conducted in generally healthy populations. The median followup duration across studies was 9.5 years (range of average followup 4 to 16 years). Studies found a mix of both significant associations between higher n-3 FA intake or biomarker levels and lower risk of CHF and lack of association.

n-3 FA Intake

Six studies evaluated n-3 FA intake and CHF (Cardiovascular Health Study, Cohort of Swedish Men, Physician's Health Study, Rotterdam, Swedish Mammography Study, Women's Health Initiative). All but one analysis found no associations between n-3 FA intake and CHF.

The four studies assessing ALA intake (Cardiovascular Health Study, Physician's Health Study, Swedish Mammography Study, Women's Health Initiative) found no association with incident CHF or CHF hospitalization or death across 4 to 12 years of followup of healthy adults (Figure 31, plot #152).

Among the five studies evaluating EPA+DHA or EPA+DHA+DPA intake (Cohort of Swedish Men, Physician's Health Study, Rotterdam, Swedish Mammography Study, Women's Health Initiative), only the Swedish Mammography Study found an association between higher marine oil intake at baseline and CHF (hospitalization or death) in healthy women after 9 years of followup (Figure 31, plot #157). The Cohort of Swedish Men study, in contrast found no association after 7 years of followup, including in a subgroup analysis of men with a history of MI or diabetes at baseline.

By meta-analysis (Table 36), overall there is a just-significant association between higher marine oil intake and decreased risk of CHF across a median dosage range of 0.014 to 0.71 g/d (effect size per g/d = 0.76; 95% CI 0.58 to 1.00). Meta-analyses with the addition of a spline knot point at different dose thresholds (from 0.1 to 0.5 g/d) consistently found a stronger association (of higher dose being associated with lower risk) at *lower* doses than at higher doses (ES below knot less than 1; ES above knot closer to 1). This implies the possibility of a ceiling effect (where intake above a certain level adds no further benefit). However, given that the differences between lower and higher dose ES remained large across the range of testable dose thresholds, the actual ceiling dose threshold may be above the analyzable range (i.e., >0.5 g/d). At thresholds of 0.1 and 0.2 g/d, the difference in effect size at lower and higher doses were statistically significant (P values 0.04 and 0.03, respectively). But the most significant difference was found at the highest threshold tested, 0.5 g/d (P=0.02). The best fit curve was found with the lowest knot tested, 0.1 g/d.

n-3 FA Biomarkers

Four studies conducted numerous analyses of n-3 FA biomarkers (Atherosclerosis Risk in Communities Study, Cardiovascular Health Study, Osaka Acute Coronary Insufficiency Study, Physician's Health Study) in healthy adults (3 studies) and adults with a history of MI (Osaka Acute Coronary Insufficiency Study) with 4 or 14 years of followup.

One study (Cardiovascular Health Study) found lower incidence of CHF in adults ≥65 years old after 14 years of followup with higher plasma levels of total n-3 FA combined, but the association was not statistically significant (P=0.062).

Three studies analyzed plasma, cholesteryl ester, and phospholipid ALA (Atherosclerosis Risk in Communities Study, Cardiovascular Health Study, Physician's Health Study) (Figure 31, plots #153 & 154). Only the Physicians Health study found an association of lower risk of CHF in men with higher plasma ALA levels after 4 years of followup; the Cardiovascular Health Study found no such association in adults ≥65 years at 14 years of followup and the Atherosclerosis Risk in Communities Study found no association with either cholesteryl ester or phospholipid ALA in younger adults (45−64 years old) also at 14 years of followup.

Three studies analyzed blood, plasma, cholesteryl ester, and phospholipid EPA (Atherosclerosis Risk in Communities Study, Cardiovascular Health Study, Osaka Acute Coronary Insufficiency Study). The studies had heterogeneous findings. The Cardiovascular Health Study found that higher plasma EPA levels were associated with lower risk of CHF in older adults (>65 y) with 14 years of followup (Figure 31, plot #159), in contrast to a lack of association for DHA (Figure 31, plot #155). The Osaka Acute Coronary Insufficiency Study also found a significant association between higher blood EPA levels and lower risk of CHF in adults with a history of MI (4 year followup), also in contrast with their finding for DHA (no association). The third study, the Atherosclerosis Risk in Communities Study, found no significant associations with either cholesteryl ester phospholipid DHA and CHF, with no difference in associations between men and women. These findings were also in contrast to their finding for DHA.

The same three studies analyzed the same DHA biomarkers, with heterogeneous findings. The Cardiovascular Health Study found no association with plasma DHA in healthy older adults (≥65 years, 14 year followup) (Figure 31, plot #155), in contrast with an association found for plasma EPA. The Osaka Acute Coronary Insufficiency Study also found no association with blood DHA in adults with a history of MI (4 year followup), in contrast to an association found for EPA. found a significant difference in association between men and women for both cholesteryl ester and phospholipid DHA.

Only the Cardiovascular Health Study evaluated plasma DPA (Figure 31, plot #156), in healthy older adults (≥65 years) with 14 years of followup. CHF risk was lower in participants with higher plasma DPA levels with near statistical significance (P=0.057).

Two studies analyzed biomarkers for combined marine oils. The Physicians Health Study found no association between plasma EPA+DHA+DPA and CHF risk in healthy men at 4 years (Figure 31, plot #158). The Atherosclerosis Risk in Communities Study also found no association with cholesteryl ester or phospholipid EPA+DHA+DPA and CHF in healthy men after 14 years. In women, no association was found with cholesteryl ester EPA+DHA+DPA, but higher levels of phospholipid EPA+DHA+DPA were associated with lower CHF risk.

Observational Study Subgroup Analyses

The Cardiovascular Health Study found no differences in associations between ALA plasma or intake levels and CHF in subgroups based on age, sex, diabetes, or fish consumption (Table 37).[148]

The Osaka Acute Coronary Insufficiency Study conducted multiple subgroup analyses for the associations between blood DHA, blood EPA, and CHF.[154] For both biomarkers, no significant interaction between subgroups and associations were found for use of angiotensin receptor blocker drugs, use of beta blocker drugs, diabetes, dyslipidemia, hypertension, glomerular filtration function (threshold = 60 mL/min), or hypertriglyceridemia (threshold = 150 mg/dL). Statistically significant interactions were found for statin use. In participants taking statins, risk of CHF was not associated with blood DHA (HR=0.74) or EPA (HR=1.45) levels, in contrast with significant associations among participants not taking statins: DHA HR=6.65 (P interaction = 0.003); EPA HR=6.40 (P interaction = 0.048). Similarly for baseline HDL-c level, a significant interaction was found for blood EPA (P interaction = 0.034) and a nonsignificant interaction for blood DHA (P interaction = 0.096), such that significant associations were seen in participants with low HDL-c (<40 mg/dL), but not among those with higher HDL-c. Subgroup analyses by sex found a significant interaction (P interaction = 0.008) with blood EPA, but not blood DHA, such that in men there was a significant association between EPA and CHF risk (HR=3.48) but not among women (HR=0.88). Near-significant interactions were found for blood DHA and age (P interaction = 0.051, significant association found for those ≥65 years old) and LDL-c (P interaction = 0.068, significant association found for those with LDL-c <100 mg/dL) (Table 37). No interactions were found for blood EPA.

The Cohort of Swedish Men found no differences in associations of EPA+DHA intake and CHF between men with histories of diabetes or MI and healthy men, or between those who used marine oil supplements or not.[102]

Table 35. Congestive heart failure hospitalization: RCTs

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int n/N,%	Ctrl n/N,%	Effect Size	Reported P value
Marine oil vs. Placebo											
Roncaglioni 2013 23656645 Italy	At risk	EPA+ DHA	≥0.85 g/d (suppl) [E:D 0.9−1.5]	Placebo	0 (Olive oil)	5 y	Self-reported (nd on level of adherence)	96/6239, 5%	142/6266, 2.3%	HR 0.67 (0.52, 0.87)	0.002
Bosch 2012 22686415 Canada	CVD	EPA+ DHA	0.84 g/d (Marine oil) [E:D 1.24]	Placebo	0 (Olive oil)	6+ y	FFQ at baseline, 2 years, and end of study (adherence was 88% at the end of study)	331/6281, 5.3%	320/6255, 5.1%	Adj HR 1.02 (0.88, 1.19)	0.76
Brouwer 2006 16772624 N. Europe	CVD	EPA+ DHA	0.96 g n-3 FA (0.464 g EPA, 0.335 g DHA) (Marine oil) [E:D]=1.4	Placebo	0 (high-oleic acid sunflower oil)	1 y	Generally good (76% reported taking 80% pills) based on pill counts and confirmed by biomarkers.	22/273, 8%	19/273, 7%	OR 1.17 (0.62, 2.22)	nd
Macchia 2013 23265344 Argentina; Italy	CVD	EPA+ DHA	0.85−0.882 g/d (suppl) [nd]	Placebo	0 (Olive oil)	1 y	nd	5/289, 1.7%	6/297, 2.0%	HR 0.86 (0.26, 2.81)	nd
Raitt 2005 15956633 U.S.	CVD	EPA+ DHA	EPA 0.756 g/d, DHA 0.54 g/d (fish oil) [E:D 1.4]	Placebo	0 (olive oil: 73% oleic acid, 12%)	2 y	RBC and plasma n-3 FA levels	14/100, 14.0%	12/100, 12.0%	OR 1.19 (0.52, 2.73)	0.83
Sacks 1995 7759696 U.S.	CVD	EPA+ DHA+ DPA	6 g/d (suppl) [E:D 1.5]	Placebo	0 (Olive oil)	2.4 y	Pill counting (80% for EPA+DHA; 90% for placebo)	0/31, 0%	1/28, 3.6%	nd	nd

Abbreviations: Ctrl = control, CVD = cardiovascular disease, DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, E:D = EPA to DHA ratio, EPA = eicosapentaenoic acid, F/up = followup, FFQ = food frequency questionnaire, HR = hazard ratio, Int = intervention, n/N = number with outcome/number analyzed, n6:3 = omega-6 to omega-3 fatty acid ratio, n-3 FA = omega-3 fatty acids, ND = no data, OR = odds ratio, PMID = PubMed Identification number, RCT = randomized controlled trial.

Table 36. Meta-analysis results of observational studies of marine oil (EPA+DHA±DPA) intake and CHF

N patients	Dose range, g/d	Knot	ES, overall	ES below knot	ES above knot	P*	AIC	No. cohorts (crossing threshold)
184,491	0.014−0.71	NA	0.76 (0.58, 1.00)					5
		0.1		0.29 (0.12, 0.74)	1.00 (0.67, 1.50)	0.04	28.6	5
		0.2		0.43 (0.26, 0.73)	1.17 (0.70, 1.96)	0.03	32.6	4
		0.3		0.55 (0.38, 0.80)	1.32 (0.61, 2.84)	0.07	44.0	4
		0.4		0.64 (0.47, 0.86)	1.31 (0.37, 4.64)	0.29	46.8	2
		0.5		0.64 (0.49, 0.85)	2.58 (0.93, 7.11)	0.02	53.2	2

* ES below vs. above knot

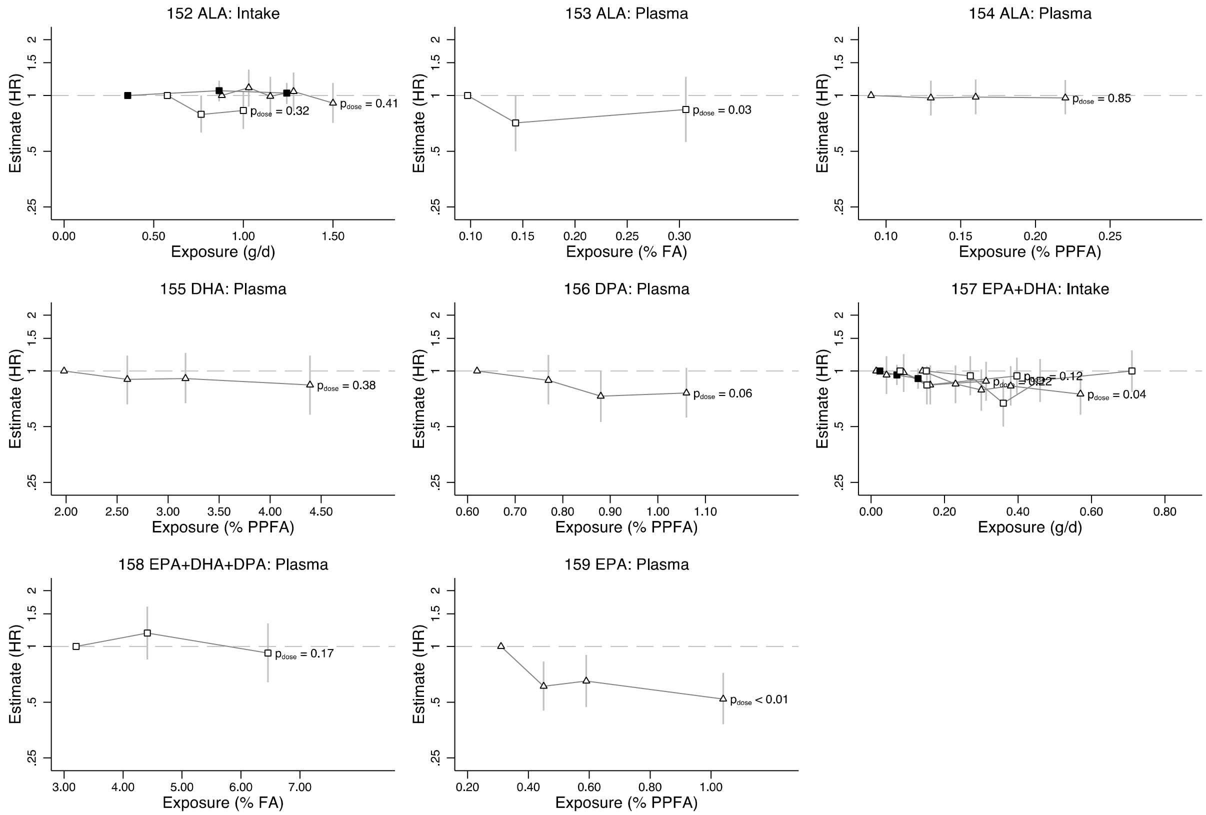
Abbreviations: AIC = Akaike information criterion (estimation of fit of regression with spline), CHF = congestive heart failure, DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, EPA = eicosapentaenoic acid, ES = effect size, NA = not applicable.

Table 37. Congestive heart failure: Subgroup analyses, observational studies

Study	Subgroups	n-3 FA	N Total	P difference	Difference*	Favors
Cardiovascular Health Study[148]	Fish consumption vs low or no fish consumption (<0.6 servings/week)	ALA (Plasma or Intake)	4432	NS		
	Men vs Women			NS		
	Age, continuous			NS		
	Diabetes vs. no diabetes			NS		
	Body mass index, continuous			NS		
	Plasma linoleic acid, continuous			NS		
Osaka Acute Coronary Insufficiency Study[154]	Age <65 vs ≥65 years	DHA (Blood)	671	0.051	0.52 vs. 3.00	≥65 y
	Male vs Female			0.37		
	Diabetes vs. no diabetes			0.61		
	Hypertension vs. no hypertension			0.13		
	Dyslipidemia vs. no dyslipidemia			0.15		
	LDL-c <100 vs ≥100 mg/dL			0.068	3.48 vs. 0.88	Low LDL-c
	HDL-c <40 vs ≥40 mg/dL			0.096	4.50 vs. 1.17	Low HDL-c
	Tg <150 vs. ≥ 150 mg/dL			0.66		
	eGFR <60 vs. ≥60 mL/min			0.27		
	Statin vs no statin			0.003	0.74 vs. 6.65	No statin
	ACEi/ARB vs. no ACEi/ARB			0.39		
	Beta blocker vs. no beta blocker			0.37		
	Age <65 vs ≥65 years	EPA (Blood)	671	0.44		
	Male vs Female			0.008	5.82 vs. 0.69	Male
	Diabetes vs. no diabetes			0.98		
	Hypertension vs. no hypertension			0.84		
	Dyslipidemia vs. no dyslipidemia			0.14		
	LDL-c <100 vs ≥100 mg/dL			0.68		
	HDL-c <40 vs ≥40 mg/dL			0.034	15.7 vs. 1.44	Low HDL-c
	Tg <150 vs. ≥ 150 mg/dL			0.97		
	eGFR <60 vs. ≥60 mL/min			0.94		
	Statin vs no statin			0.048	1.45 vs. 6.40	No statin
	ACEi/ARB vs. no ACEi/ARB			0.17		
	Beta blocker vs. no beta blocker			0.27		
Cohort of Swedish Men[102]	History of DM or MI vs. healthy	EPA+DHA (Intake)	5234	NS		
	Supplement use vs. no supplement			NS		

* Hazard ratios refer to the association between low EPA and risk of CHF (i.e. higher HRs are better).
Abbreviations: ACEi = angiotensin-converting enzyme inhibitor, ALA = alphalinolenic acid, ARB = angiotensin receptor blocker, DHA = docosahexaenoic acid, DM = diabetes mellitus, eGFR = epidermal growth factor receptor, EPA = eicosapentaenoic acid, HDL-c = high density lipoprotein cholesterol, LDL-c = low density lipoprotein cholesterol, MI = myocardial infarction, NS = not significant, Tg = triglycerides.

Figure 31. n-3 FA associations with congestive heart failure: Observational studies



Study (or cohort) level associations between n-3 FA exposure and hazard ratio (HR) for the outcome. Studies that reported associations by continuous exposure (e.g., per g/d intake or per standard deviation) could not be graphed and are omitted. P values are the study-reported P value for the trend across quantiles. The 95% confidence intervals were truncated when <0.25 and >2.
White triangles = healthy adults, white squares = healthy males, black squares = healthy females

Abbreviations: ALA = alphalinolenic acid, DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, EPA = eicosapentaenoic acid, HR = hazard ratio, n-3 FA = omega-3 fatty acids, PPFA = plasma polyunsaturated fatty acids.

Hypertension, Incident

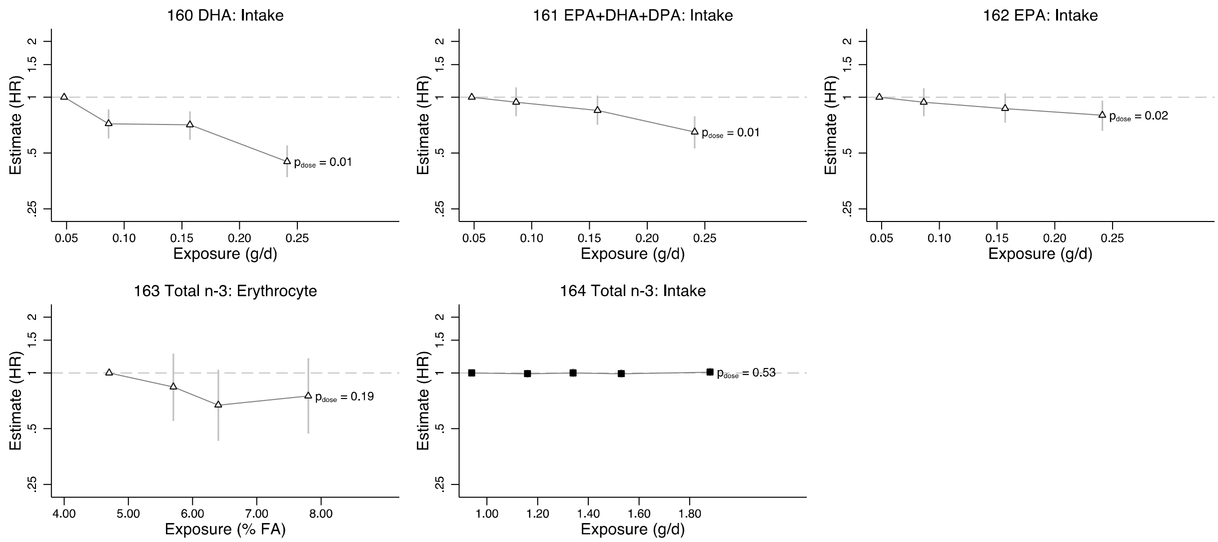
Randomized Controlled Trials

No trial evaluated incident hypertension.

Observational Studies

Two studies evaluated the associations between intake of multiple n-3 FA or erythrocyte FA and new-onset hypertension after about 13 or 20 years of followup in health adults (Appendix F, Hypertension section; Figure 32).[118, 124] Statistically significant associations were found for younger, but not older, adults (with one exception). The Women's Health Study found that overall total n-3 FA intake and erythrocyte levels were not significantly associated with risk of hypertension (Figure 32, plots #163 & 164). Among women 55 to 89 years old at baseline, there were also no significant associations with ALA, DHA, and EPA intake, and with erythrocyte total n-3 FA, ALA, DPA, and DHA levels, but higher erythrocyte EPA levels were associated with lower hypertension incidence. Among younger women, 39 to 54 years old at baseline, higher DHA intake and higher erythrocyte total n-3 FA, DPA, and DHA levels , but not ALA or EPA levels, were associated with lower hypertension risk. Similarly, the CARDIA study, all in 18 to 30 year old adults, with 20 year followup, higher EPA (Figure 32, plot #162), DHA (Figure 32, plot #160), and EPA+DHA+DPA (Figure 32, plot #161) intake were all significantly associated with lower hypertension incidence.

Figure 32. n-3 FA associations with incident hypertension: Observational studies



Study (or cohort) level associations between n-3 FA exposure and hazard ratio (HR) for the outcome. Studies that reported associations by continuous exposure (e.g., per g/d intake or per standard deviation) could not be graphed and are omitted. P values are the study-reported P value for the trend across quantiles. The 95% confidence intervals were truncated when <0.25 and >2.
White triangles = healthy adults, black squares = healthy females

Abbreviations: ALA = alphalinolenic acid, DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, EPA = eicosapentaenoic acid, HR = hazard ratio, n-3 FA = omega-3 fatty acids.

Blood Pressure, Systolic and Diastolic

Randomized Controlled Trials

Thirty-five RCTs provided data on effect of n-3 FA on systolic blood pressure (BP) (Table 38). Twenty-eight RCTs provided data on effect of n-3 FA on diastolic BP (Table 39). Only five of the trials reported BP to be a primary outcome (Carter 2012, Finnegan 2003, Harrison 2004, Lungershausen 1994, Vasquez 2014); however, Vasquez reported BP to be a secondary outcome in the ClinicalTrials.gov registry.[53, 75, 80, 147, 174]

Total n-3 FA Versus Placebo

Two RCTs evaluated supplementation with combined ALA and marine oil (1.2 or 2 g ALA, and 3.6 or 0.4 g EPA+DHA) versus placebo in people with at least one of several risk factors for CVD in one trial[180] or with CVD in the second trial.[119] In the at-risk population, at 1 month followup, no differences in systolic or diastolic BP were seen, and the confidence intervals were wide (systolic net change = −1.9 mmHg; 95% CI −44.7 to 40.9; diastolic net change = −2.5 mmHg; 95% CI −31.3 to 26.3). In the CVD population, the study found nonsignificant increases in systolic (2.3 mmHg; 95% CI −0.1 to 4.6) and diastolic (0.5 mmHg; 95% CI −0.7 to 1.7) BPs.

Marine Oil Versus Placebo

Twenty-nine RCTs compared marine oil versus placebo (or control) and reported on changes in systolic BP in populations of healthy people, those at risk for CVD primarily related to a diagnosis of hypertension, and those with existing CVD (Table 38, Figure 33).[48, 51, 53, 55, 61, 62, 75, 80, 85, 90, 96, 99, 103, 105, 115, 119, 120, 123, 133, 136, 146, 147, 160, 173, 174, 179, 180, 189, 190] Across the 29 trials, no significant effect was found on systolic BP: summary net change = 0.10 mmHg (95% CI −0.20 to 0.40).

All but one of these trials also reported diastolic BP.[179] Across the 28 trials (Table 39, Figure 34), no significant effect was found on diastolic BP: summary net change = −0.19 mmHg (95% CI −0.43 to 0.05).

Healthy Population

Ten RCTs contributed to a pooled analysis of marine oils (EPA+DHA) against placebo for systolic BP, comprising data from 2,156 healthy individuals with mean baseline systolic BP ranging between 107 to 140.5 mmHg.[51, 61, 75, 85, 136, 147, 173, 174, 189, 190] One study compared both EPA (3.8 g/d) and DHA (3.6 g/d) ethyl esters, separately, to placebo;[61] all other evaluated supplements with both EPA+DHA. Marine oil dosage ranged from 0.64 to 3.8 g/d, and follow-up duration from 2 months to 1 year. Five studies reported their compliance verification methods (including self-report, food records, pill count, and plasma measurement). All RCTs found no significant effect of EPA+DHA on systolic BP; net systolic BP varied between −3.0 and 1.2 mmHg. The pooled effect size was a nonsignificant −0.63 mmHg (95% CI −1.45 to 0.18).

Ten RCTs contributed to a pooled analysis of marine oils (EPA+DHA) against placebo for diastolic BP, comprising data from 2,240 healthy individuals with mean baseline diastolic BP ranging between 65 to 85.3 mmHg.[51, 61, 75, 85, 136, 147, 173, 174, 189, 190] RCTs found no significant effect of EPA+DHA on diastolic BP; net diastolic BP varied between −5.7 and 1.9 mmHg. The pooled effect size was a nonsignificant −0.97 mmHg (95% CI −1.82 to −0.13).

At-Risk-for-CVD Population

Thirteen RCTs contributed to a pooled analysis for systolic BP of marine oils (EPA+DHA) against placebo in those at risk for CVD, comprising data from 45,150 individuals, primarily due to hypertension, with mean baseline systolic BP ranging between 120 and 149 mmHg.[53, 80, 90, 99, 103, 105, 115, 120, 133, 146, 160, 179, 180] One study compared DHA (2 g/d) to placebo;[80] the rest evaluated supplements with EPA+DHA. Dosage ranged from 0.30 to 6 g/d, and follow-up duration from 1 month to 6 years. Eight RCTs reported their compliance verification methods (including self-report, pill count, and plasma measurements). Across trials, the net change in systolic BP varied from −5.3 and 3.8 mmHg, all of which were nonsignificant. The pooled effect size was a nonsignificant 0.22 mmHg (95% CI −0.14 to 0.59).

Twelve RCTs contributed to a pooled analysis for diastolic BP of marine oils (EPA+DHA) against placebo in those at risk for CVD, comprising data from 45,072 individuals, primarily due to hypertension, with mean baseline diastolic BP ranging between 76 and 85.5 mmHg.[53, 80, 90, 99, 103, 105, 115, 120, 133, 146, 160, 180] Across trials, the net change in diastolic BP varied from −4.5 and 0.7 mmHg, all of which were nonsignificant. The pooled effect size was a nonsignificant 0.01 mmHg (95% CI −0.26 to 0.27).

CVD Population

Six RCTs contributed to a pooled analysis for systolic BP of marine oils (EPA+DHA) against placebo, comprising data from 11,791 individuals with CVD (mean baseline systolic BP 126 to 133 mmHg).[48, 51, 62, 90, 119, 123] A sixth trial reported only that no significant effect on BP was found.[96] Dosage ranged from 0.36 to 6 g/d, and follow-up durations from 1 and 4.7 years. They reported a variety of compliance verification methods (self-report, dietary questionnaire, pill count/audit, and plasma measurements). None of the RCTs found a significant effect of EPA+DHA on systolic BP, with net change ranging from −1 to 0.4 mmHg. The pooled effect size was a nonsignificant 0.17 mmHg (95% CI −0.48 to 0.82).

Six RCTs contributed to a pooled analysis for diastolic BP of marine oils (EPA+DHA) against placebo (mean baseline diastolic BP 77 to 83 mmHg).[48, 51, 62, 90, 119, 123] None of the RCTs found a significant effect of EPA+DHA on diastolic BP, with net change ranging from −0.5 to 1.0 mmHg. The pooled effect size was a nonsignificant −0.11 mmHg (95% CI −0.52 to 0.30).

RCT Subgroup Analyses

Carter 2012 found no differences in effect on BP between two subpopulations of those with prehypertension or normal BP.[147]

By meta-regression, no differences in effect were found based on population (at risk P=0.99 systolic, P=0.24 diastolic; CVD P=0.99 systolic, P=0.97 diastolic), n-3 FA dose (P=0.56 systolic, P=0.42 diastolic), baseline systolic BP (P=0.91 systolic) or diastolic BP (P=0.21 diastolic), or followup duration (P=0.38 systolic, P=0.37 diastolic).

ALA Versus Placebo

Five trials compared ALA supplementation to placebo, one in a healthy population,[75] three in at risk populations,[152, 167, 180] and one in a population with CVD (Tables 38 and 39).[119] The trials evaluated ALA doses ranging from 1.38 to 5.9 g/d; Jones 2014 evaluated these two doses of ALA versus placebo.[180] Followup ranged from 1 to 40 months. Compliance was confirmed in four trials and was >90 percent in one (Finnegan 2003). All five trials found no significant effect of ALA supplementation on systolic BP, ranging from −7.3 to 5.2 mmHg, or on diastolic BP, ranging from −7.3 to 4.5 mmHg, or on diastolic BP, ranging from −3.9 to 1.0 mmHg, mostly with wide confidence intervals.

RCT Subgroup Analyses

Rodriguez-Leyva 2013 also found no differences in effect on systolic or diastolic BP in a subpopulation with systolic hypertension (>140 mmHg) compared with the study population as a whole.[167]

Marine Oil, Comparison of Different Doses

Four trials directly compared different doses of EPA+DHA, three in healthy populations,[75, 136, 190] one in an at risk population (Tables 38 and 39).[169] All found no differences in effects on systolic or diastolic BP between higher and lower EPA+DHA doses (1.7 vs. 0.8 g/d; 1.8 vs. 0.9 or 0.45 g/d; 3.4 vs. 1.7 g/d).

ALA, Comparison of Different Doses

One trial directly compared different doses of ALA (1.38 and 5.9 g/d) in an at risk population (Tables 38 and 39).[180] No differences in effects on systolic or diastolic BP were found, with wide confidence intervals, between higher and lower ALA doses (5.9 vs. 1.4 g/d).

Marine Oils, Comparison of Different Specific n-3 FA

Grimsgaard 1998 directly compared EPA 3.8 g/d and DHA 3.6 g/d ethyl ester supplementation, finding no differences in effect at 2 months (Tables 38 and 39).[61] Tatsuno 2013 compared two doses of EPA+DHA (3.4 and 1.7 g/d) and EPA 1.8 g/d (all ethyl esters); they did not report full data but stated there were no "clinically relevant changes" at 1 year.[169]

Marine Oil Versus ALA

Finnegan 2003 compared two doses of EPA+DHA (1.7 and 0.8 g/d) and ALA 4.5 g/d in a healthy population.[75] (The study also tested ALA 9 g/d but that dose was excluded here because it did not meet eligibility criteria.) The comparisons between either dose of EPA+DHA and ALA found no differences in effect on systolic or diastolic BP at 4 months (Tables 38 and 39). Kromhout 2010 also compared EPA+DHA 0.4 g/d to ALA 2 g/d in a population with CVD. Neither systolic nor diastolic BP were significantly different between study arms.

SDA Versus Placebo

Pieters 2015 compared 1.2 g/d SDA to placebo in 32 patients at risk for CVD. At 1.5 month followup, no significant differences in change in systolic or diastolic BP were found.[188]

SDA Versus Marine Oil

Kuhnt 2014 compared 2.0 g/d SDA and 1.9 g/d EPA+DHA+DPA in 59 healthy people (broken into cohorts based on body mass index and age). At 2 month followup, no significant differences in change in systolic or diastolic BP were found.[178]

Observational Studies

One study (Guangzhou) evaluated the associations between erythrocyte FA and change in systolic and diastolic BP in healthy men and women (age of 40 to 75) after about 3 years (Appendix F, Blood pressure section; Figure 35, Figure 36). Statistically significant decreases in systolic BP were found in those who took higher doses of EPA erythrocyte (Figure 35, plot #168), DHA erythrocyte (Figure 35, plot #166) and DPA erythrocyte (Figure 35, plot #167). Nonsignificant changes in systolic BP were found in those who took higher levels of ALA erythrocyte (Figure 35, plot #165). Statistically significant decreases in diastolic BP were found in those who took higher doses of EPA erythrocyte (Figure 36, plot #172), DHA erythrocyte (Figure 36, plot #170) and DPA erythrocyte (Figure 36, plot #171). Higher doses of ALA erythrocyte (Figure 36, plot #169) were not associated with a decrease in diastolic BP.

Table 38. Systolic blood pressure: RCTs

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline, mmHg	Ctrl N	Ctrl Baseline, mmHg	Net Chg, mmHg	Reported P value
Total n-3 FA vs. Placebo													
Jones 2014 24829493 Canada	At risk	ALA + EPA+DHA	3.48 DHA g/d+1.2 g/d ALA+0.12 EPA g/d+1.44 g/d DPA (suppl: CanolaDHA)	Placebo	0	1 mo	nd	130	120.62	130	120.62	−1.9 (−44.7, 40.9)	nd
Kromhout 2010 20929341 Netherlands	CVD	ALA + EPA+DHA	0.4 g/d EPA+DHA; 2 g/d ALA (Marine oil, plant oil) [E:D 3:2]	Placebo	0	40 mo	Audit of unused margarine tubs returned	1212	140.9	1236	141.9	2.3 (−0.1, 4.6)	NS
Marine oil vs. Placebo													
Grimsgaard 1998 9665096 Norway	Healthy	EPA	3.8 g/d (Ethyl ester)	Placebo	0	2 mo	nd	75	123.2	77	122.2	−1.2 (−2.9, 0.5)	nd
	Healthy	DHA	3.6 g/d (Ethyl ester)	Placebo	0	2 mo	nd	72	121.3	77	122.2	−0.2 (−1.8, 1.4)	nd
Harrison 2004 15853118 UK	At risk	DHA+/- soy protein	2 g/d (suppl: marine oil)	Placebo+/- soy protein	0	1.25 mo	Food diaries, biomarker check	101	130.9	112	134.7	3.8 (−1.7, 9.3)	nd
Carter 2012 22707560 U.S.	Healthy (normotensive)	EPA+DHA	1.6 EPA g/d+1.1 DHA g/d (suppl: marine oil)	Placebo	0	2 mo	Pill diary	19	110	19	107	−3 (−7, 1)	nd
	Healthy (pre-hypertensive)	EPA+DHA	1.6 EPA g/d+1.1 DHA g/d (suppl: marine oil)	Placebo	0			15	127	14	126	1 (−4.2, 6.2)	nd
Finnegan 2003 12663273 UK	Healthy	EPA+DHA	1.7 g/d (suppl: marine oil, diet: marine oil margarine	Placebo	0	4 mo	Pill count, plasma measurement	31	118.4	30	123.2	0.2 (−5.6, 6.1)	nd
	Healthy	EPA+DHA	0.8 g/d (suppl: marine oil)	Placebo	0			30	119.6	30	123.2	2.8 (−4.1, 9.8)	nd

Table 38. Systolic blood pressure: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline, mmHg	Ctrl N	Ctrl Baseline, mmHg	Net Chg, mmHg	Reported P value
Grieger 2014 24454276 Australia	Healthy	EPA+DHA	0.8 g/d (diet: fish)	Low n-3 FA diet (usual diet)	0.017 g/d EPA and 0.004 g/d DHA (diet)	2 mo	Food Records	43	126	37	126	−2.0 (−9.3, 5.3)	nd
Rasmussen 2006 16469978 Europe and Australia	Healthy	EPA+DHA	2.4 g/d EPA+DHA	Placebo	0	3 mo	nd	80	122.6	82	122.3	−0.4 (−2.6, 1.8)	0.76
Sacks 1994 8021472 U.S.	Healthy	EPA+DHA	1.44 EPA g/d+0.96 DHA g/d+0.6 DPA g/d (suppl: marine oil)	Placebo	0	6 mo	FA measurement and pill count	175	122.9	175	122.6	−0.1 (−1.5, 1.3)	NS
Sanders 2011 21865334 UK	Healthy	EPA+DHA	1.8 g/d (suppl: marine oil) EPA:DHA : 1.51	Placebo	0	1 y	Pill Count, Plasma Check	80	119.1	71	122.6	−0.3 (−4.3, 3.7)	nd
		EPA+DHA	0.9 g/d (suppl: marine oil) EPA:DHA : 1.51	Placebo	0	1 y	Pill Count, Plasma Check	79	123.5	71	122.6	−0.8 (−4.8, 3.2)	nd
		EPA+DHA	0.45 g/d (suppl: marine oil) EPA:DHA : 1.51	Placebo	0	1 y	Pill Count, Plasma Check	80	122.6	71	122.6	0 (−4, 4)	nd
Tardivo 2015 25394692 Brazil	Healthy	EPA+DHA	0.9 g/d [E:D 3:2]	Placebo	0	6 mo	Pill count	44	138.3	43	134.5	−13.9 (−20.9, −6.9)	nd
Vazquez 2014 24462043 Spain	Healthy	EPA+DHA	0.64 g/d [E:D 1:3]	Placebo	0	2 mo	Assessed by trained dieticians at each visit	273	140.5	273	140.5	−0.28 (−2.6, 2.1)	0.787
Pase 2015 25565485 Australia	Healthy	EPA+DHA± DPA	480 mg/d EPA + 480 mg/d DHA [E:D 1:1]	Placebo	0	4 mo	nd	38	117	32	109.8	−6.9 (−0.2, 14.0)	nd

continued

Table 38. Systolic blood pressure: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline, mmHg	Ctrl N	Ctrl Baseline, mmHg	Net Chg, mmHg	Reported P value
Bosch 2012 22686415 Canada	At risk	EPA+DHA	EPA+DHA 0.84 g/d (suppl: marine oil)	Placebo	0	6 y	FFQ at baseline, 2 years, and end of study (adherence was 88% at the end of study)	6281	145.6	6255	146.0	0.1 (−0.6, 0.9)	0.75
Tierney 2011 20938439 Northern Europe	At risk	EPA+DHA	EPA 0.26 g/d, DHA 0.19 g/d (suppl) [E:D 1.5]	Placebo	0	3 mo	Pill Count and plasma FA	100	137.73	106	139.53	0.1 (−4, 4.2)	NS
Derosa 2009 19397392 Italy	At risk	EPA+DHA	0.9 g/d EPA+1.5 g/d DHA (suppl: marine oil) E:D : 0.6	Placebo	0	6 mo	Pill Count	168	128.4	165	129.6	0 (−1.4, 1.4)	nd
Ebrahimi 2009 19593941 Iran	At risk	EPA+DHA	0.18 g/d EPA+0.12 g/d DHA (suppl: marine oil)	Placebo	0	6 mo	nd	47	130.7	42	129.6	−5.3 (−13.4, 2.8)	nd
Einvik 2010 20389249 Norway	At risk	EPA+DHA (no diet intervention)	2.4 g n-3 FA (1.17 g EPA and 0.84 g DHA) (Suppl: marine oil), E:D: 2:1	Placebo (no diet intervention)	0	3 y	Pharmacy records of remaining capsules, and measurements of serum n-3 FA	70	150	68	148	−2 (−8.7, 4.7)	nd
		EPA+DHA (diet intervention)	2.4 g n-3 FFA (1.17 g EPA and 0.84 g DHA) (Suppl: marine oil), E:D: 2:1	Placebo (diet intervention)	0			69	149	71	149	−1 (−7.7, 5.7)	nd
Holman 2009 19002433 UK	At risk	EPA+DHA (+/− atorvastatin)	EPA+DHA 1.68 g/d (suppl: marine oil) E:D : 1.2	Placebo (+/- atorvastatin)	0	4 mo	Pill count	371	137	361	139	0.39 (−1.88, 2.66)	0.82

Table 38. Systolic blood pressure: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline, mmHg	Ctrl N	Ctrl Baseline, mmHg	Net Chg, mmHg	Reported P value
Lungershausen 1994 7852747 Australia	At risk	EPA+DHA	1.9 g/d EPA, 1.5 g/d DHA (suppl) E:D : 1.27	Placebo	0	1.5 mo	Interview and Pill Count	42	132	42	132	−3.1 (−8.3, 2.1)	0.012
Nodari 2011 21215550 Italy	At risk	EPA+DHA	4.25 − 4.41 g/d EPA+DHA daily for the first month followed by 1.7 – 1.764 g/d (suppl: marine oil) EPA:DHA : 0.6	Placebo	0	1 y	nd	67	119	66	120	3 (−0.4, 6.4)	0.015
Roncaglioni 2013 23656645 Italy	At risk	EPA+DHA	EPA+DHA <0.85 g/d (suppl: marine oil) (E:D 1]	Placebo	0	5 y	Patient Self−Report	6244	140.3	6269	140.1	0.2 (−0.4, 0.7)	0.57
Soares 2014 24652053 Brazil	At risk	EPA+DHA (and dietary intervention)	3 g/d (suppl: marine oil)	Placebo and dietary intervention	0	3 mo	nd	20	130.2	18	134.4	0.6 (−1.5, 2.7)	0.702 (overall)
		EPA+DHA (and dietary intervention +exercise)	3 g/d (suppl: marine oil)	Placebo and dietary intervention and exercise	0			17	131.6	15	131.1	3.8 (1.2, 6.4)	0.702 (overall)
Jones 2014 24829493 Canada	At risk	EPA+DHA+ ALA (Canola DHA)	3.48 DHA g/d+1.2 g/d ALA+0.12 EPA g/d+1.44 g/d DPA (suppl: CanolaDHA)	ALA (Canola Oleic)	1.38 g/d	1 mo	nd	130	120.6	130	120.6	−1.2 (−44, 41.7)	nd
Yokoyama 2007 17398308 Japan	At risk (no previous CHD)	EPA+Statin	1.8 g/d (Ethyl ester)	Statin	0	4.6 y	Local physicians monitored but compliance level was not reported	8841	135	8862	135	0 (−0.9, 0.9)	0.575

Table 38. Systolic blood pressure: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline, mmHg	Ctrl N	Ctrl Baseline, mmHg	Net Chg, mmHg	Reported P value
Burr 1989 2571009 UK	CVD	EPA+DHA	0.357 EPA g/d+nd DPA (suppl: marine oil, diet: fish)	No intervention	0	2 y	Dietary Questionnaire	1015	129.7	1018	130.1	0.4 (−1.3, 2.1)	nd
Galan 2010 21115589 France	CVD	EPA+DHA (+/− B vitamin)	0.6 g/d (suppl: marine oil) [E:D 2:1]	Placebo (+/− B vitamin	0	4.7 y	Self−Report	1253	134	1248	133	−0.06 (−0.9, 0.8)	nd
Tavazzi 2008 18757090 Italy	CVD	EPA+DHA	EPA+DHA 0.75 – 0.882 g/d (Ethyl esters) (E:D : 0.833]	Placebo	0	3.9 y	Pill count	3494	126	3481	126	nd	0.47
Sacks 1995 7759696 U.S.	CVD	EPA+DHA	2.88 g/d EPA and 3.12 g/d DHA (suppl: marine oil) (E:D 0.923)	Placebo	0	2.4 y	Pill Count	31	126	28	133	−1.0 (−14, 12.0)	nd
von Schacky 1999 10189324 Canada	CVD	EPA+DHA	EPA+DHA 3.3 g/d for 3 months then 1.65 g/d for 21 months (suppl: marine oil)	Placebo	0	1 y	Interrogation, Pill Count, and analysis of FA	112	132.0	111	129.6	−0.1 (−4.9, 4.7)	NS
Kromhout 2010 20929341 Netherlands	CVD	EPA+DHA	0.4 g/d (Marine oil) [E:D 3:2]	Placebo	0	40 mo	Audit of unused margarine tubs returned	1192	142.3	1236	141.9	1.7 (−0.6, 3.9)	NS
		EPA+DHA (+ALA)	0.4 g/d (Marine oil) [E:D 3:2]	(ALA)	0			1212	140.9	1197	141.4	0.2 (−2.0, 2.5)	nd
Yokoyama 2007 17398308 Japan	CVD	EPA+Statin	1.8 g/d (Ethyl ester)	Statin	0	4.6 y	Local physicians monitored but compliance level was not reported	485	139	457	139	0 (−2.6, 2.6)	0.607

Table 38. Systolic blood pressure: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline, mmHg	Ctrl N	Ctrl Baseline, mmHg	Net Chg, mmHg	Reported P value
EPA+DHA vs. EPA+DHA (doses)													
Pase 2015 25565485 Australia	Healthy	EPA+DHA± DPA + Multivitamin	480 mg/d EPA + 480 mg/d DHA [E:D 1:1]	EPA+DHA±DPA + Multivitamin	280 mg/d EPA + 280 mg/d DHA	4 mo	nd	36	112.8	38	116.5	−1 (−9.0, 7.0)	nd
Finnegan 2003 12663273 UK	Healthy	EPA+DHA	1.7 g/d	EPA+DHA	0.8 g/d	4 mo	Pill count, plasma measurement	31	118.4	30	119.6	−2.6 (−7.9, 2.7)	nd
Sanders 2011 21865334 UK	Healthy	EPA+DHA	1.8 g/d (suppl: marine oil) EPA:DHA : 1.51	EPA+DHA	0.9 g/d (suppl: marine oil)	1 y	Pill Count, Plasma Check	80	119.1	79	123.5	0.5 (−3.5, 4.5)	nd
		EPA+DHA	1.8 g/d (suppl: marine oil) EPA:DHA : 1.51	EPA+DHA	0.45 g/d (suppl: marine oil)	1 y	Pill Count, Plasma Check	80	119.1	80	122.6	−0.3 (−4.3, 3.7)	nd
		EPA+DHA	0.9 g/d (suppl: marine oil)	EPA+DHA	0.45 g/d (suppl: marine oil)	1 y	Pill Count, Plasma Check	79	123.5	80	122.6	−0.8 (−4.8, 3.2)	nd
Tatsuno 2013 24314359 Japan	At risk	EPA+DHA	3.36 g/d (Ethyl esters) E:D 1.24	EPA+DHA	1.68 g/d (Ethyl esters) E:D 1.24	1 y	nd	171	nd	165	nd	1.6 (nd)	nd
Marine oil vs. marine oil (miscellaneous)													
Grimsgaard 1998 9665096 Norway	Healthy	EPA	3.8 g/d (Ethyl ester)	DHA	3.6 g/d (Ethyl ester)	2 mo	nd	77	122.2	72	121.3	−1.0 (−2.8, 0.8)	nd
Tatsuno 2013 24314359 Japan	At risk	EPA+DHA	3.36 g/d (Ethyl esters) E:D 1.24	EPA	1.8 g/d (Ethyl ester)	1 y	nd	171	nd	167	nd	2.6 (nd)	nd
		EPA+DHA	1.68 g/d (Ethyl esters) E:D 1.24	EPA	1.8 g/d (Ethyl ester)	1 y	nd	165	nd	167	nd	1.0 (nd)	nd

Table 38. Systolic blood pressure: RCTs (continued)

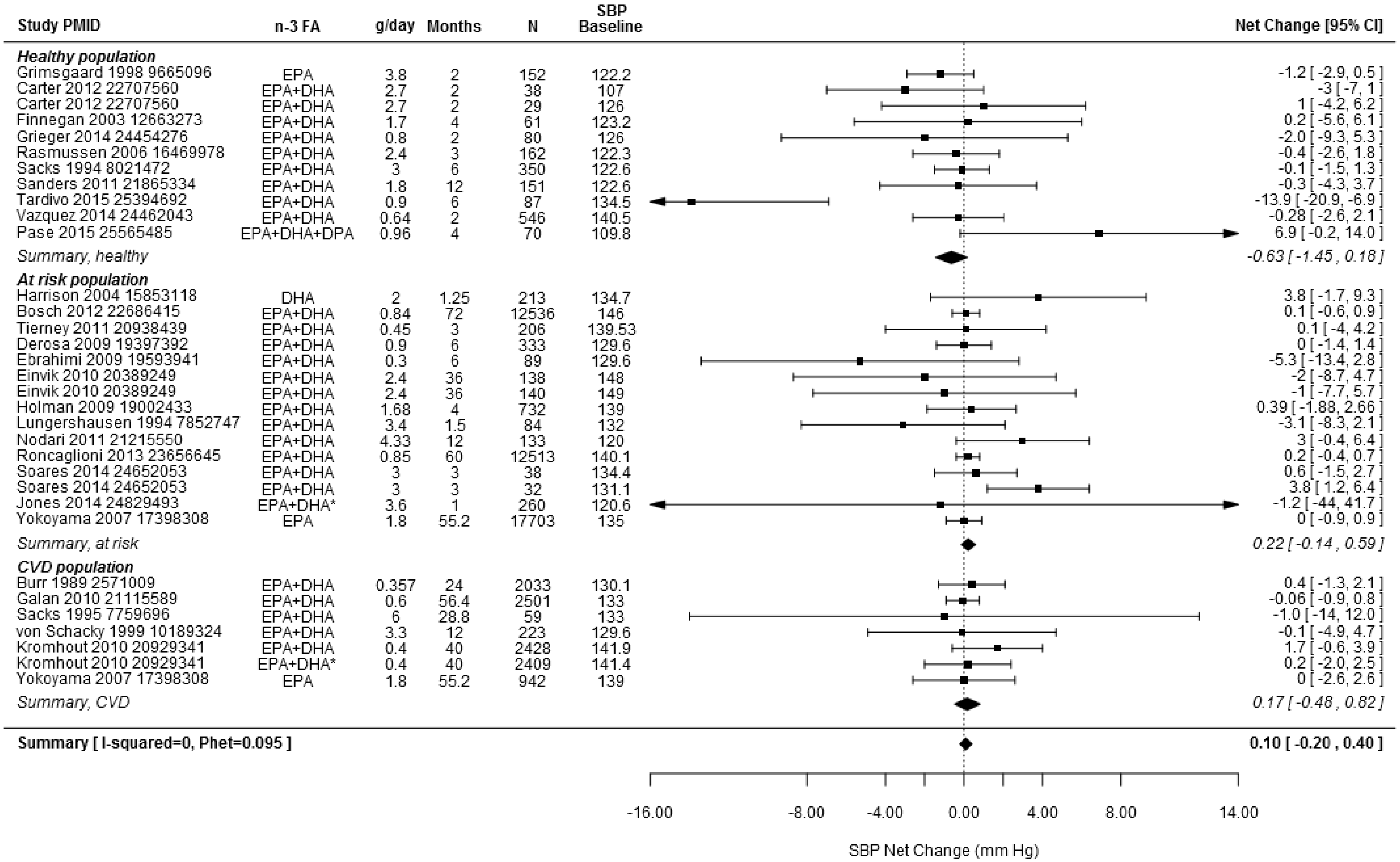
Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline, mmHg	Ctrl N	Ctrl Baseline, mmHg	Net Chg, mmHg	Reported P value
ALA vs. Placebo													
Finnegan 2003 12663273 UK	Healthy	ALA	4.5 g/d (rapeseed oil margarine)	Placebo	0	4 mo	Return of margarine pots (>90%)	30	118.2	30	123.2	4.5 (−0.6, 9.6)	nd
Rodriguez-Leyva 2013 24126178 Canada	At risk	ALA	5.9 g/d (flaxseed)	Placebo	0	1 y	Plasma ALA and enterolignan levels	45	143.3	41	142.4	−7.3 (−15.4, 0.80)	nd
Baxheinrich 2012 22894911 Germany	At risk	ALA	3.46 g/d (suppl: plant oil)	Placebo	0	6 mo	Dietary records	40	142.4	41	140.1	−1.8 (−8.3, 4.7)	0.697
Jones 2014 24829493 Canada	At risk	ALA	5.9 g/d (canola)	Placebo	0	1 mo	nd	130	120.6	130	120.6	−1.1 (−43.9, 41.8)	nd
		ALA	1.38 g/d (canola)	Placebo	0			130	120.6	130	120.6	−1.0 (−43.8, 41.8)	nd
Kromhout 2010 20929341 Netherlands	CVD	ALA	2 g/d (plant oil)	Placebo	0	40 mo	Audit of unused margarine tubs returned	1197	141.4	1236	141.9	2.1 (−0.2, 4.3)	NS
		ALA (+EPA+DHA)	2 g/d (plant oil)	(EPA+DHA)	0			1212	140.9	1192	142.3	0.6 (−1.6, 2.9)	nd
ALA vs. ALA (doses)													
Jones 2014 24829493 Canada	At risk	ALA	5.9 g/d (canola)	ALA	1.38 g/d (canola)	1 mo	nd	130	120.6	130	120.6	−0.1 (−42.9, 42.8)	nd

Table 38. Systolic blood pressure: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline, mmHg	Ctrl N	Ctrl Baseline, mmHg	Net Chg, mmHg	Reported P value
Marine oil vs. ALA													
Finnegan 2003 12663273 UK	Healthy	EPA+DHA	1.7 g/d	ALA	4.5 g/d (rapeseed oil margarine)			31	118.4	30	118.2	−4.3 (−9.4, 0.9)	nd
		EPA+DHA	0.8 g/d	ALA	4.5 g/d (rapeseed oil margarine)			30	119.6	30	118.2	−1.7 (−6.1, 2.8)	nd
Kromhout 2010 20929341 Netherlands	CVD	EPA+DHA	0.4 g/d (Marine oil) [E:D 3:2]	ALA	2 g/d (plant oil)	40 mo	Audit of unused margarine tubs returned	1192	142.3	1197	141.4	−0.4 (−2.6, 1.8)	nd

Abbreviations: ALA = alphalinolenic acid, Ctrl = control, CVD = cardiovascular disease, DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, E:D = EPA to DHA ratio, EPA = eicosapentaenoic acid, F/up = followup, FFQ = food frequency questionnaire, Int = intervention, n/N = number with outcome/number analyzed, n6:3 = omega-6 to omega-3 fatty acid ratio, n-3 FA = omega-3 fatty acids, ND = no data, NS = not significant, PMID = PubMed Identification number, RCT = randomized controlled trial.

Figure 33. Systolic blood pressure: Randomized trials of marine oils



Random effects model meta-analysis of n-3 FA versus placebo (or no n-3 FA), with subgroup analyses by population. In all meta-analyses, only studies that reported sufficient results data are included.

Abbreviations: CI = confidence interval, CVD = cardiovascular disease, DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, EPA = eicosapentaenoic acid, n-3 FA = omega-3 fatty acids

Table 39. Diastolic blood pressure: RCTs

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline, mmHg	Ctrl N	Ctrl Baseline, mmHg	Net Chg, mmHg	Reported P value
Total n-3 FA vs. Placebo													
Jones 2014 24829493 Canada	At risk	ALA + EPA+DHA	3.48 DHA g/d+1.2 g/d ALA+0.12 EPA g/d+1.44 g/d DPA (suppl: CanolaDHA)	Placebo	0	1 mo	nd	130	77.0	130	77.0	−2.5 (−31.3, 26.3)	nd
Kromhout 2010 20929341 Netherlands	CVD	ALA + EPA+DHA	0.4 g/d EPA+DHA; 2 g/d ALA (Marine oil, plant oil) [E:D 3:2]	Placebo	0	40 mo	Audit of unused margarine tubs returned	1212	nd	1236	nd	0.5 (−0.7, 1.7)	NS
Marine oil vs. Placebo													
Pase 2015 25565485 Australia	Healthy	EPA+DHA±DPA	480 mg/d EPA + 480 mg/d DHA [E:D 1:1]	Placebo	0	4 mo	nd	38	78.3	36	74.1	−3.5 (−8.2, 1.2)	nd
Grimsgaard 1998 9665096 Norway	Healthy	EPA	3.8 g/d (Ethyl ester)	Placebo	0	2 mo	nd	75	78.1	77	76.9	−0.6 (−1.9, 0.7)	nd
	Healthy	DHA	3.6 g/d (Ethyl ester)	Placebo	0	2 mo	nd	72	76.1	77	76.9	−0.4 (−1.8, 1.0)	nd

Table 39. Diastolic blood pressure: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline, mmHg	Ctrl N	Ctrl Baseline, mmHg	Net Chg, mmHg	Reported P value
Carter 2012 22707560 U.S.	Healthy (normotensive)	EPA+DHA	1.6 EPA g/d+1.1 DHA g/d (suppl: marine oil)	Placebo	0	2 mo	Pill diary	19	66	19	65	−1.0 (−3.6, 1.6)	nd
	Healthy (pre-hypertensive)	EPA+DHA	1.6 EPA g/d+1.1 DHA g/d (suppl: marine oil)	Placebo	0			15	68	14	74	0 (−5.2, 5.2)	nd
Finnegan 2003 12663273 UK	Healthy	EPA+DHA	1.7 g/d (suppl: marine oil, diet: marine oil margarine	Placebo	0	4 mo	Pill count, plasma measurement	31	74.8	30	76.0	−0.1 (−5, 4.7)	nd
	Healthy	EPA+DHA	0.8 g/d (suppl: marine oil)	Placebo	0			30	74.6	30	76.0	1.9 (−3.7, 7.6)	nd
Grieger 2014 24454276 Australia	Healthy	EPA+DHA	0.8 g/d (diet: fish)	Low n-3 FA diet (usual diet)	0.017 g/d EPA and 0.004 g/d DHA (diet)	2 mo	Food Records	43	69	37	67	0 (−3.9, 3.9)	nd
Rasmussen 2006 16469978 Europe and Australia	Healthy	EPA+DHA	2.4 g/d EPA+DHA	Placebo	0	3 mo	nd	80	76	82	77	−0.6 (−2.8, 0.8)	nd
Sacks 1994 8021472 U.S.	Healthy	EPA+DHA	1.44 EPA g/d+0.96 DHA g/d+0.6 DPA g/d (suppl: marine oil)	Placebo	0	6 mo	FA measurement	175	81.0	175	81.1	−0.4 (−1.5, 0.6)	NS

Table 39. Diastolic blood pressure: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline, mmHg	Ctrl N	Ctrl Baseline, mmHg	Net Chg, mmHg	Reported P value
Sanders 2011 21865334 UK	Healthy	EPA+DHA	1.8 g/d (suppl: marine oil) EPA:DHA : 1.51	Placebo	0	1 y	Pill Count, Plasma Check	80	71.8	71	74.1	0.6 (−1.4, 2.6)	nd
	Healthy	EPA+DHA	0.9 g/d (suppl: marine oil) EPA:DHA : 1.51	Placebo	0	1 y	Pill Count, Plasma Check	79	73.9	71	74.1	0.6 (−1.5, 2.7)	nd
	Healthy	EPA+DHA	0.45 g/d (suppl: marine oil) EPA:DHA : 1.51	Placebo	0	1 y	Pill Count, Plasma Check	80	71.2	71	74.1	1.2 (−0.9, 3.3)	nd
Tardivo 2015 25394692 Brazil	Healthy	EPA+DHA	0.9 g/d [E:D 3:2]	Placebo	0	6 mo	Pill count	44	86.2	43	85.3	−5.7 (−8.5, −2.9)	nd
Vazquez 2014 24462043 Spain	Healthy	EPA+DHA	0.64 g/d [E:D 1:3]	Placebo	0	2 mo	Assessed by trained dieticians at each visit	273	83.9	273	83.9	−1.32 (−2.5, −0.1)	0.014
Bosch 2012 22686415 Canada	At risk	EPA+DHA	EPA+DHA 0.84 g/d (suppl: marine oil)	Placebo	0	6 y	FFQ at baseline, 2 years, and end of study (adherence was 88% at the end of study)	6281	84.1	6255	84.2	0.1 (−0.3, 0.5)	0.91
Tierney 2011 20938439 Northern Europe	At risk	EPA+DHA	EPA 0.26 g/d, DHA 0.19 g/d (suppl) [E:D 1.5]	Placebo	0	3 mo	Pill Count and plasma FA	100	85.5	106	85.52	0.7 (−1.7, 3.1)	NS

Table 39. Diastolic blood pressure: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline, mmHg	Ctrl N	Ctrl Baseline, mmHg	Net Chg, mmHg	Reported P value
Derosa 2009 19397392 Italy	At risk	EPA+DHA	0.9 g/d EPA+1.5 g/d DHA (suppl: marine oil) E:D : 0.6	Placebo	0	6 mo	Pill Count	168	80.6	165	81.4	0.2 (−1.3, 1.7)	nd
Ebrahimi 2009 19593941 Iran	At risk	EPA+DHA	0.18 g/d EPA+0.12 g/d DHA (suppl: marine oil)	Placebo	0	6 mo	nd	47	81.7	42	78.3	−4.5 (−9, 0.03)	nd
Einvik 2010 20389249 Norway	At risk	EPA+DHA (no diet intervention)	2.4 g n-3 FA (1.17 g EPA and 0.84 g DHA) (Suppl: marine oil), E:D: 2:1	Placebo (no diet intervention)	0	3 y	Pharmacy records of remaining capsules, and measurements of serum n-3 FA	70	83	68	83	0 (−3.9, 3.9)	nd
	At risk	EPA+DHA (diet intervention)	2.4 g n-3 FA (1.17 g EPA and 0.84 g DHA) (Suppl: marine oil), E:D: 2:1	Placebo (diet intervention)	0			69	85	71	83	−1.0 (−5.0, 3.0)	nd
Harrison 2004 15853118 UK	At risk	DHA +/- soy protein	2 g/d (suppl: marine oil)	Placebo +/- soy protein	0	1.25 mo	Food diaries, biomarker check	101	81.1	112	81.8	−1.0 (−4.5, 2.4)	nd
Holman 2009 19002433 UK	At risk	EPA+DHA (+/− atorvastatin)	EPA+DHA 1.68 g/d (suppl: marine oil) E:D : 1.2	Placebo (+/- atorvastatin)	0	4 mo	Pill count	371	77	361	78	0.6 (−1.09, 2.29)	0.34

Table 39. Diastolic blood pressure: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline, mmHg	Ctrl N	Ctrl Baseline, mmHg	Net Chg, mmHg	Reported P value
Jones 2014 24829493 Canada	At risk	ALA + EPA+DHA (Canola DHA)	3.48 DHA g/d+1.2 g/d ALA+0.12 EPA g/d+1.44 g/d DPA (suppl: CanolaDHA)	ALA (Canola Oleic)	1.38 g/d	1 mo	nd	130	77.0	130	77.0	−2.2 (−30.9, 26.6)	nd
Lungershausen 1994 7852747 Australia	At risk	EPA+DHA	1.9 g/d EPA, 1.5 g/d DHA (suppl) E:D : 1.27	Placebo	0	1.5 mo	Interview and Pill Count	42	76.2	42	76.2	−1.8 (−4.8, 1.2)	0.006
Nodari 2011 21215550 Italy	At risk	EPA+DHA	4.25 − 4.41 g/d EPA+DHA daily for the first month followed by 1.7 – 1.764 g/d (suppl: marine oil) EPA:DHA : 0.6	Placebo	0	1 y	nd	67	76	66	76	−1.0 (−2.6, 0.6)	0.015
Roncaglioni 2013 23656645 Italy	At risk	EPA+DHA	EPA+DHA <0.85 g/d (suppl: marine oil) (E:D 1]	Placebo	0	5 y	Patient Self−Report	6239	82.9	6266	82.5	−0.26 (−25.2, 24.7)	0.57
Yokoyama 2007 17398308 Japan	At risk (no previous CHD)	EPA+Statin	1.8 g/d (Ethyl ester)	Statin	0	4.6 y	Local physicians monitored but compliance level was not reported	8841	78	8862	78	0 (−0.4, 0.4)	0.986

Table 39. Diastolic blood pressure: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline, mmHg	Ctrl N	Ctrl Baseline, mmHg	Net Chg, mmHg	Reported P value
Burr 1989 2571009 UK	CVD	EPA+DHA	0.357 EPA g/d+nd DPA (suppl: marine oil, diet: fish)	No intervention	0	2 y	Dietary Questionnaire	1015	79.3	1018	80.2	0.2 (−0.9, 1.3)	nd
Galan 2010 21115589 France	CVD	EPA+DHA (+/− B vitamin)	0.6 g/d (suppl: marine oil) [E:D 2:1]	Placebo (+/− B vitamin	0	4.7 y	Self−Report	1253	84	1248	83	0.06 (−0.5, 0.6)	nd
Kromhout 2010 20929341 Netherlands	CVD	EPA+DHA	0.4 g/d (Marine oil) [E:D 3:2]	Placebo	0	40 mo	Audit of unused margarine tubs returned	1192	nd	1236	nd	−0.4 (−1.6, 0.7)	NS
	CVD	EPA+DHA (+ALA)	0.4 g/d (Marine oil) [E:D 3:2]	ALA	0			1212	nd	1197	nd	−0.5 (−1.6, 0.7)	nd
Sacks 1995 7759696 U.S.	CVD	EPA+DHA	2.88 g/d EPA and 3.12 g/d DHA (suppl: marine oil) (E:D 0.923)	Placebo	0	2.4 y	Pill Count	31	76	28	77	1 .0(−4.6, 6.6)	nd
Tavazzi 2008 18757090 Italy	CVD	EPA+DHA	EPA+DHA 0.75 – 0.882 g/d (Ethyl esters) (E:D : 0.833]	Placebo	0	3.9 y	Pill count	3494	77	3481	77	nd	0.43

Table 39. Diastolic blood pressure: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline, mmHg	Ctrl N	Ctrl Baseline, mmHg	Net Chg, mmHg	Reported P value
von Schacky 1999 10189324 Canada	CVD	EPA+DHA	EPA+DHA 3.3 g/d for 3 months then 1.65 g/d for 21 months (suppl: marine oil)	Placebo	0	1 y	Interrogation, Pill Count, and analysis of FA	112	80.7	111	79.8	0.2 (−2.8, 3.2)	NS
Yokoyama 2007 17398308 Japan	CVD	EPA+Statin	1.8 g/d (Ethyl ester)	Statin	0	4.6 y	Local physicians monitored but compliance level was not reported	485	80	457	79	−1 (−2.6, 0.6)	0.538
EPA+DHA vs. EPA+DHA (doses)													
Pase 2015 25565485 Australia	Healthy	EPA+DHA±DPA + Multivitamin	480 mg/d EPA + 480 mg/d DHA [E:D 1:1]	EPA+DHA±DPA + Multivitamin	280 mg/d EPA + 280 mg/d DHA	4 mo	nd	36	76.5	38	78.2	−1.5 (−7.0, 4.0)	nd
Finnegan 2003 12663273 UK	Healthy	EPA+DHA	1.7 g/d	EPA+DHA	0.8 g/d	4 mo	Pill count, plasma measurement	31	74.8	30	74.6	−2.1 (−6.6, 2.4)	nd

Table 39. Diastolic blood pressure: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline, mmHg	Ctrl N	Ctrl Baseline, mmHg	Net Chg, mmHg	Reported P value
Sanders 2011 21865334 UK	Healthy	EPA+DHA	1.8 g/d (suppl: marine oil) EPA:DHA : 1.51	EPA+DHA	0.9 g/d (suppl: marine oil)	1 y	Pill Count, Plasma Check	80	71.8	79	73.9	0 (−2.0, 2.0)	nd
		EPA+DHA	1.8 g/d (suppl: marine oil) EPA:DHA : 1.51	EPA+DHA	0.45 g/d (suppl: marine oil)	1 y	Pill Count, Plasma Check	80	71.8	80	71.2	−0.6 (−2.5, 1.3)	nd
		EPA+DHA	0.9 g/d (suppl: marine oil)	EPA+DHA	0.45 g/d (suppl: marine oil)	1 y	Pill Count, Plasma Check	79	73.9	80	71.2	−0.6 (−2.7, 1.5)	nd
Tatsuno 2013 24314359 Japan	At risk	EPA+DHA	3.36 g/d (Ethyl esters) E:D 1.24	EPA+DHA	1.68 g/d (Ethyl esters) E:D 1.24	1 y	nd	171	nd	165	nd	0.4 (nd)	nd
Marine oil vs. marine oil (miscellaneous)													
Grimsgaard 1998 9665096 Norway	Healthy	EPA	3.8 g/d (Ethyl ester)	DHA	3.6 g/d (Ethyl ester)	2 mo	nd	77	78.1	72	76.1	−0.2 (−1.6, 1.2)	nd
Tatsuno 2013 24314359 Japan	At risk	EPA+DHA	3.36 g/d (Ethyl esters) E:D 1.24	EPA	1.8 g/d (Ethyl ester)	1 y	nd	171	nd	167	nd	−0.8 (nd)	nd
		EPA+DHA	1.68 g/d (Ethyl esters) E:D 1.24	EPA	1.8 g/d (Ethyl ester)			165	nd	167	nd	−1.2 (nd)	nd
ALA vs. Placebo													
Finnegan 2003 12663273 UK	Healthy	ALA	4.5 g/d (rapeseed oil margarine)	Placebo	0	4 mo	Return of margarine pots (>90%)	30	76.0	30	76.0	0.6 (−3.5, 4.7)	nd

Table 39. Diastolic blood pressure: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline, mmHg	Ctrl N	Ctrl Baseline, mmHg	Net Chg, mmHg	Reported P value
Rodriguez-Leyva 2013 24126178 Canada	At risk	ALA	5.9 g/d (flaxseed)	Placebo	0	6 mo	Plasma ALA and enterolignan levels	45	77	41	79	−2.1 (−7.2, 3.0)	nd
Baxheinrich 2012 22894911 Germany	At risk	ALA	3.46 g/d (suppl: plant oil)	Placebo	0	6 mo	Dietary records	40	91.8	41	90.2	−3.9 (−8.1, 0.3)	0.026
Jones 2014 24829493 Canada	At risk	ALA	5.9 g/d (canola)	Placebo	0	1 mo	nd	130	77.0	130	77.0	0.1 (−28.8, 28.8)	nd
		ALA	1.38 g/d (canola)	Placebo	0			130	77.04	130	77.04	−0.3 (−29.1, 28.5)	nd
Kromhout 2010 20929341 Netherlands	CVD	ALA	2 g/d (plant oil)	Placebo	0	40 mo	Audit of unused margarine tubs returned	1197	nd	1236	nd	1.0 (−0.2, 2.1)	NS
		ALA (+EPA+DHA)	2 g/d (plant oil)	(EPA+DHA)	0			1212	nd	1192	nd	0.9 (−0.3, 2.1)	nd
ALA vs. ALA (doses)													
Jones 2014 24829493 Canada	At risk	ALA	5.9 g/d (canola)	ALA	1.38 g/d (canola)	1 mo	nd	130	77.04	130	77.04	0.3 (−28.5, 29.1)	nd
Marine oil vs. ALA													
Finnegan 2003 12663273 UK	Healthy	EPA+DHA	1.7 g/d	ALA	4.5 g/d (rapeseed oil margarine)			31	74.8	30	76.0	−0.7 (−5.3, 3.8)	nd
		EPA+DHA	0.8 g/d	ALA	4.5 g/d (rapeseed oil margarine)			30	74.6	30	76.0	1.3 (−2.4, 5.1)	nd

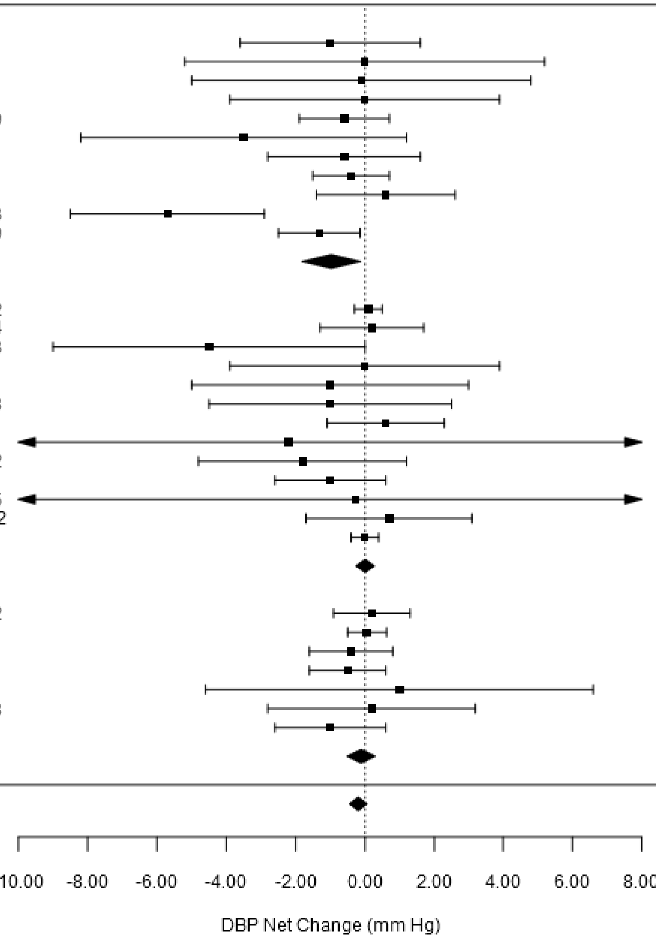
Table 39. Diastolic blood pressure: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline, mmHg	Ctrl N	Ctrl Baseline, mmHg	Net Chg, mmHg	Reported P value
Kromhout 2010 20929341 Netherlands	CVD	EPA+DHA	0.4 g/d (Marine oil) [E:D 3:2]	ALA	2 g/d (plant oil)	40 mo	Audit of unused margarine tubs returned	1192	nd	1197	nd	−1.4 (−2.5, −0.2)	nd

Abbreviations: ALA = alphalinolenic acid, Ctrl = control, CVD = cardiovascular disease, DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, E:D = EPA to DHA ratio, EPA = eicosapentaenoic acid, F/up = followup, Int = intervention, n/N = number with outcome/number analyzed, n6:3 = omega-6 to omega-3 fatty acid ratio, ND = no data, NS = not significant, PMID = PubMed Identification number, RCT = randomized controlled trial.

Figure 34. Diastolic blood pressure: Randomized trials of marine oils

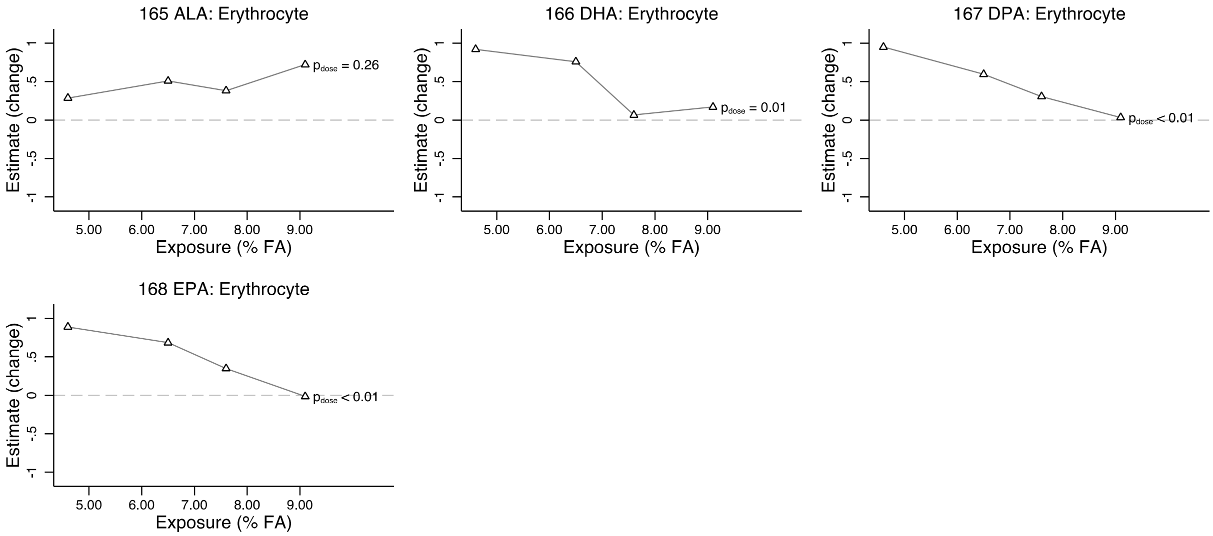
Study PMID	n-3 FA	g/day	Months	N	DBP Baseline	Net Change [95% CI]
Healthy population						
Carter 2012 22707560	EPA+DHA	2.7	2	38	65	-1.0 [-3.6, 1.6]
Carter 2012 22707560	EPA+DHA	2.7	2	29	74	0 [-5.2, 5.2]
Finnegan 2003 12663273	EPA+DHA	1.7	4	61	76	-0.1 [-5, 4.7]
Grieger 2014 24454276	EPA+DHA	0.8	2	80	67	0 [-3.9, 3.9]
Grimsgaard 1998 9665096	EPA	3.8	2	152	76.9	-0.6 [-1.9, 0.7]
Pase 2015 25565485	EPA+DHA+DPA	0.96	4	74	74.1	-3.5 [-8.2, 1.2]
Rasmussen 2006 16469978	EPA+DHA	2.4	3	162	77	-0.6 [-2.8, 0.8]
Sacks 1994 8021472	EPA+DHA	3	6	350	81.1	-0.4 [-1.5, 0.6]
Sanders 2011 21865334	EPA+DHA	1.8	12	151	74.1	0.6 [-1.4, 2.6]
Tardivo 2015 25394692	EPA+DHA	0.9	3	87	85.3	-5.7 [-8.5, -2.9]
Vazquez 2014 24462043	EPA+DHA	0.64	2	546	83.9	-1.32 [-2.5, -0.1]
Summary, healthy						*-0.97 [-1.82 , -0.13]*
At risk population						
Bosch 2012 22686415	EPA+DHA	0.84	72	12536	84.2	0.1 [-0.3, 0.5]
Derosa 2009 19397392	EPA+DHA	2.4	6	333	81.4	0.2 [-1.3, 1.7]
Ebrahimi 2009 19593941	EPA+DHA	0.3	6	89	78.3	-4.5 [-9, 0.03]
Einvik 2010 20389249	EPA+DHA	2.4	36	138	83	0 [-3.9, 3.9]
Einvik 2010 20389249	EPA+DHA	2.4	36	140	83	-1.0 [-5.0, 3.0]
Harrison 2004 15853118	DHA	2	1.25	213	81.8	-1.0 [-4.5, 2.4]
Holman 2009 19002433	EPA+DHA	1.68	4	732	78	0.6 [-1.09, 2.29]
Jones 2014 24829493	EPA+DHA*	5	1	260	77	-2.2 [-30.9, 26.6]
Lungershausen 1994 7852747	EPA+DHA	3.4	1.5	84	76.2	-1.8 [-4.8, 1.2]
Nodari 2011 21215550	EPA+DHA	4.3	12	133	76	-1.0 [-2.6, 0.6]
Roncaglioni 2013 23656645	EPA+DHA	0.85	60	12505	82.5	-0.26 [-25.2, 24.7]
Tierney 2011 20938439	EPA+DHA	0.45	3	206	85.52	0.7 [-1.7, 3.1]
Yokoyama 2007 17398308	EPA	1.8	55	17703	78	0 [-0.4, 0.4]
Summary, at risk						*0.01 [-0.26 , 0.27]*
CVD population						
Burr 1989 2571009	EPA+DHA	0.36	24	2033	80.2	0.2 [-0.9, 1.3]
Galan 2010 21115589	EPA+DHA	0.6	56	2501	83	0.06 [-0.5, 0.6]
Kromhout 2010 20929341	EPA+DHA	0.4	40	2428	nd	-0.4 [-1.6, 0.7]
Kromhout 2010 20929341	EPA+DHA*	0.4	40	2409	nd	-0.5 [-1.6, 0.7]
Sacks 1995 7759696	EPA+DHA	6	29	59	77	1.0 [-4.6, 6.6]
von Schacky 1999 10189324	EPA+DHA	1.65	12	223	79.8	0.2 [-2.8, 3.2]
Yokoyama 2007 17398308	EPA	1.8	55	942	79	-1 [-2.6, 0.6]
Summary, CVD						*-0.11 [-0.52 , 0.30]*
Summary [I-squared=6, Phet=0.238]						**-0.19 [-0.43 , 0.05]**



Random effects model meta-analysis of n-3 FA versus placebo (or no n-3 FA), with subgroup analyses by population. In all meta-analyses, only studies that reported sufficient results data are included.

Abbreviations: CI = confidence interval, CVD = cardiovascular disease, DBP = diastolic blood pressure, DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, EPA = eicosapentaenoic acid, n-3 FA = omega-3 fatty acids, Phet = P value of chi-squared test of heterogeneity across studies, PMID = PubMed Identification number.

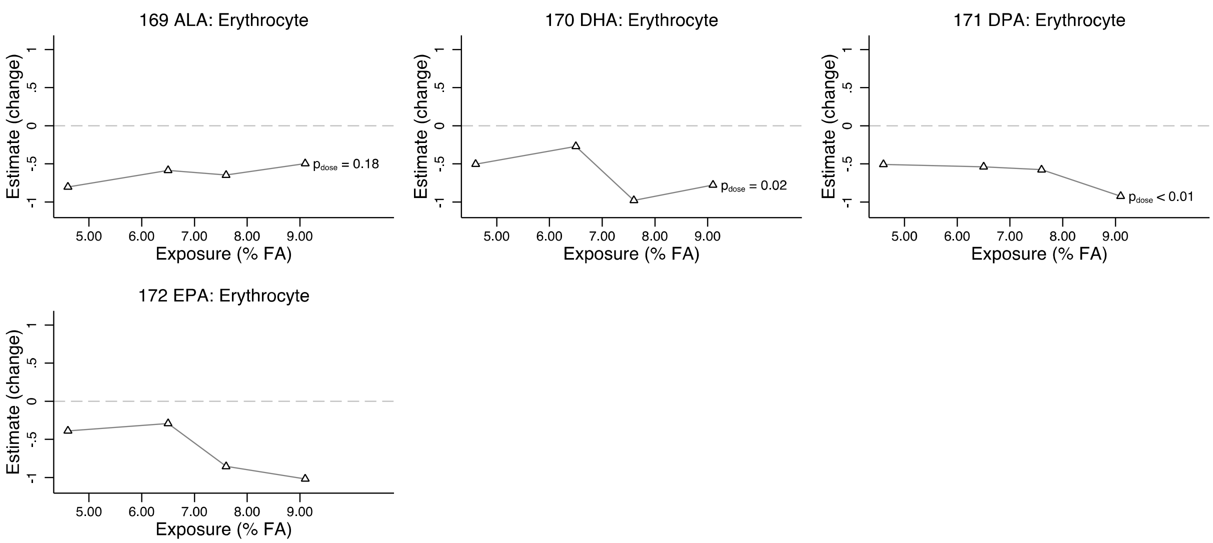
Figure 35. n-3 FA associations with systolic blood pressure: Observational studies



Study (or cohort) level associations between n-3 FA exposure and hazard ratio (HR) for the outcome. P values are the study-reported P value for the trend across quantiles. Where 95% confidence intervals (vertical lines) are missing, these were not reported in the studies. The 95% confidence intervals were truncated when <0.25 and >2.
White triangles = healthy adults

Abbreviations: ALA = alphalinolenic acid, DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, EPA = eicosapentaenoic acid, FA = fatty acid, HR = hazard ratio, n-3 FA = omega-3 fatty acids.

Figure 36. n-3 FA associations with diastolic blood pressure: Observational studies



Study (or cohort) level associations between n-3 FA exposure and hazard ratio (HR) for the outcome. P values are the study-reported P value for the trend across quantiles. Where 95% confidence intervals (vertical lines) are missing, these were not reported in the studies. The 95% confidence intervals were truncated when <0.25 and >2.
White triangles = healthy adults

Abbreviations: ALA = alphalinolenic acid, DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, EPA = eicosapentaenoic acid, FA = fatty acid, HR = hazard ratio, n-3 FA = omega-3 fatty acids.

Mean Arterial Pressure

Randomized Controlled Trials

Four RCTs reported on mean arterial pressure (MAP), all of which evaluated only marine oils (Table 40).[61, 123, 136, 147] One of the trials reported MAP among its primary outcomes (Carter 2012).[147]

Marine Oil Versus Placebo

Healthy Population

Three trials evaluated healthy populations, including the previously described trial that compared EPA 3.8 g/d and DHA 3.6 g/d ethyl esters to placebo,[61] the trial of 2.7 g/d EPA+DHA in two healthy subgroups (with normotension or prehypertension),[147] and the comparison of 1.8 g/d, 0.9 g/d, and 0.45 g/d versus placebo.[136] Followup was either 2 months or 1 year. Baseline MAP ranged from 79 to 92 mmHg. All trials found no significant effect on MAP, with estimates of net change ranging from −1 to 2 mmHg.

CVD Population

One trial of 0.6 g/d EPA+DHA versus placebo (with or without B vitamin) was conducted in 2501 people with a history of CVD.[123] At 4.7 years, there was no difference in MAP between the two groups.

RCT Subgroup Analyses

Carter 2012 found no differences in effect between two subpopulations of those with prehypertension or normal BP.[147]

Marine Oil, Comparison of Different Doses

One trial directly compared different doses of EPA+DHA in healthy populations.[136] Sanders 2011 found no differences in effects on MAP between higher and lower EPA+DHA doses (1.8, 0.9 or 0.45 g/d).

Marine Oils, Comparison of Different Specific n-3 FA

Grimsgaard 1998 directly compared EPA 3.8 g/d and DHA 3.6 g/d ethyl ester supplementation, finding no differences in effect at 2 months.[61]

Observational Studies

Observational studies did not evaluate MAP.

Table 40. Mean arterial pressure: RCTs

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline, mg/dL	Ctrl N	Ctrl Baseline, mg/dL	Net Chg, mg/dL	Reported P value
Marine oil vs Placebo													
Grimsgaard 1998 9665096 Norway	Healthy	EPA	3.8 g/d (Ethyl ester)	Placebo	0	2 mo	nd	75	92.9	77	91.8	−0.4 (−1.9, 1.1)	nd
		DHA	3.6 g/d (Ethyl ester)	Placebo	0	2 mo	nd	72	90.6	77	91.8	0.4 (−1.3, 2.1)	nd
Carter 2012 22707560 U.S.	Healthy (normotensive)	EPA+DHA	1.6 EPA g/d + 1.1 DHA g/d (suppl=marine oil)	Placebo	0	2 mo	Pill diary	19	80	19	79	−1 (−3.8, 1.8)	nd
	Healthy (prehypertensive)	EPA+DHA	1.6 EPA g/d + 1.1 DHA g/d (suppl=marine oil)	Placebo	0	2 mo	Pill diary	15	88	14	92	1 (−3.8, 5.8)	nd
Sanders 2011 21865334 UK	Healthy	EPA+DHA	1.8 g/d (suppl=marine oil)	Placebo	0	1 y	Pill Count, Plasma Check	80	91	71	93	2 (−1.4, 5.4)	nd
		EPA+DHA	0.9 g/d (suppl=marine oil)	Placebo	0	1 y	Pill Count, Plasma Check	79	94	71	93	1 (−2.4, 4.4)	nd
		EPA+DHA	0.45 g/d (suppl=marine oil)	Placebo	0	1 y	Pill Count, Plasma Check	80	93	71	93	−1 (−4.5, 2.5)	nd
Galan 2010 21115589 France	CVD	EPA+DHA (+/- B vitamin)	0.6 g/d (suppl=marine oil) [E:D 2:1]	Placebo (+/- B vitamin	0	4.7 y	Self-Report	1253	nd	1248	nd	0.007(nd)	NS

Table 40. Mean arterial pressure: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline, mg/dL	Ctrl N	Ctrl Baseline, mg/dL	Net Chg, mg/dL	Reported P value
Marine oil vs Marine oil (doses)													
Sanders 2011 21865334 UK	Healthy	EPA+DHA	1.8 g/d(suppl=marine oil)	EPA+DHA	0.9 g/d (marine oil)	1 y	Pill Count, Plasma Check	80	91	79	94	1 (−2.2, 4.2)	nd
		EPA+DHA	1.8 g/d (marine oil)	EPA+DHA	0.45 g/d (marine oil)	1 y	Pill Count, Plasma Check	80	91	80	93	3 (−0.4, 6.4)	nd
		EPA+DHA	0.9 g/d (marine oil)	EPA+DHA	0.45 g/d (marine oil)	1 y	Pill Count, Plasma Check	79	94	80	93	1.0 (−2.7, 4.7)	nd
EPA vs DHA													
Grimsgaard 1998 9665096 Norway	Healthy	EPA	3.8 g/d (Ethyl ester)	DHA	3.6 g/d (Ethyl ester)	2 mo	nd	75	92.9	72	90.6	−0.8 (−2.5, 0.9)	nd

Abbreviations: Ctrl = control, CVD = cardiovascular disease, DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, E:D = EPA to DHA ratio, EPA = eicosapentaenoic acid, F/up = followup, Int = intervention, n/N = number with outcome/number analyzed, n6:3 = omega-6 to omega-3 fatty acid ratio, ND = no data, NS = not significant, PMID = PubMed Identification number, RCT = randomized controlled trial.

Low Density Lipoprotein Cholesterol

Randomized Controlled Trials

Forty-five RCTs provided data on effect of n-3 FA on LDL-c (Table 41).[46, 51, 53, 56, 58, 61, 62, 70, 75, 76, 80, 85, 90, 94, 96, 97, 99, 103, 105, 107, 116, 119-121, 128, 136, 146, 151, 152, 156, 160, 161, 166, 167, 169, 173, 174, 177, 178, 180, 184, 187-189, 194] Only six of the trials reported LDL-c among their primary outcomes (Caslake 2008, Damsgaard 2008, Lungershausen 1994, Olano-Martin 2010, Rasmussen 2006, Sirtori 1997).[53, 58, 85, 94, 97, 107]

Total n-3 FA Versus Placebo

Two trials compared total n-3 FA (ALA+EPA+DHA) versus placebo, following 2708 patients for 1 and 40 months; one in people at increased risk for CVD,[180] one in people with CVD.[119] Baseline LDL-c measurements were 100 and 129 mg/dL. Compliance was measured in all studies, but not reported. One trial in an at risk population found a statistically significant increase in LDL-c with combined ALA 1.2 g/d (canola oil) and EPA+DHA+DPA (11.3 mg/dL; 95% CI 1.7 to 20.8).[180] . The trial in a CVD population found no significant effect on LDL-c with ALA 2 g/d and EPA+DHA 0.4 g/d.[119]

Marine Oil Versus Placebo

Thirty-nine trials evaluated the effect of marine oils versus placebo on LDL-c.[46, 51, 53, 56, 58, 61, 62, 70, 75, 76, 80, 85, 90, 94, 96, 97, 99, 103, 105, 107, 116, 119-121, 128, 136, 146, 151, 156, 160, 166, 173, 174, 177, 180, 184, 187, 189, 194] Doses of EPA+DHA±DPA ranged from 0.3 to 6 g/d (median 2.4 g/d) and followup time ranged from 1 month to 6 years (median 3 months). Across populations, the meta-analyzed summary net difference in LDL-c with EPA+DHA versus placebo (or equivalent) was a statistically significant 1.98 mg/dL (95% CI 0.38 to 3.58) (Figure 37).

Healthy Population

Sixteen of the trials of marine oils versus placebo were conducted in healthy populations, comprising data from 3,749 individuals with mean baseline LDL-c ranging from 100 to 218 and followup duration from 1 to 12 months.[61, 75, 80, 85, 94, 97, 103, 107, 128, 136, 146, 173, 174, 187, 189] Two studies compared both purified EPA (3.3 and 3.8 g/d) and DHA (3.6 and 3.7 g/d) ethyl esters, separately, to placebo;[61, 107] all other evaluated supplements with both EPA+DHA, with doses ranging from 0.45 to 6 g/d. Compliance was verified with pill counts, dietary records, or biomarker confirmation in six of the studies. All but one RCT found no significant effect of EPA+DHA on LDL-c; net LDL-c varied between −5.4 and 12.7 mg/dL. The pooled effect size was a nonsignificant 2.70 mg/dL (95% CI −0.64 to 6.03).

At-Risk-for-CVD Population

Twenty of the trials were conducted in populations at increased risk of CVD, comprising data from 48,762 individuals with mean baseline LDL-c ranging from 78.2 to 191.1 and followup duration from 1 month to 6 years.[46, 53, 58, 76, 80, 90, 99, 103, 105, 116, 120, 146, 156, 160, 166, 177, 180, 187, 194, 195] One study compared purified DHA (2 g/d) to placebo;[80] all other evaluated supplements with both EPA+DHA, with doses ranging from 0.3 to 6 g/d. Compliance was verified with pill counts, dietary records, self-report or biomarker confirmation in 11 of the studies. All but two RCTs found no significant effect of EPA+DHA on LDL-c; net change LDL-c varied between

−27.4 and 10.4 mg/dL. The pooled effect size was a nonsignificant 2.34 mg/dL (95% CI −0.82 to 5.49).

CVD Population

Eight of the trials were conducted in people with CVD, comprising data from 28,699 individuals with mean baseline LDL-c ranging from 99 to 181 mg/dL and followup duration from 9 months to 4.6 years.[51, 56, 62, 70, 90, 96, 119, 121] Compliance was verified in four of the studies, by pill count or equivalent. All trials found no significant effect on LDL-c; net change LDL-c varied from −0.8 to 5.8 mg/dL. The pooled effect size was a nonsignificant 1.92 mg/dL (95% CI −1.05 to 4.89).

RCT Subgroup Analyses

Eight of the trials compared effects of marine oils in different subgroups of participants; five reported statin vs no statin,[46, 99, 119, 128, 156] one with or without vitamin C,[76] one men vs women,[97] one older vs younger age,[97] and one saturated FA diet vs monosaturated FA diet.[85] All found (or reported) no significant interactions (differences in effect) by subgroup or cointervention.

By meta-regression, across studies there were no significant differences in effect (interactions) by LDL-c baseline (P=0.93), n-3 FA dose (P=0.93), followup duration (P=0.29), or population (at risk P=0.51; CVD P=0.98).

Marine Oil, Comparison of Different Doses

Ten RCTs directly compared different doses of marine oils (EPA+DHA),[75, 97, 136, 151, 161, 166, 169, 177, 184, 194, 195] between 0.9 and 4 g/d. All comparisons were nonsignificant for effect on LDL-c, with estimates of differences ranging from −11.6 mg/dL (95% CI −22.5 to −0.66; 1.8 vs. 0.45 g/d) to 14 mg/dL (95% CI 0.4 to 27.7; 1.7 vs. 0.8 g/d).

ALA Versus Placebo

Five trials compared ALA to placebo (or equivalent) in a healthy population,[75] at-risk populations,[152, 167, 180] and a population with CVD.[119] In total, there were 5,452 participants followed for 1 to 40 months, with ALA doses of 0.4 to 5.9 g/d. None of the trials found a significant effect of ALA on LDL-c, with net changes ranging from −1.2 to 14.5 mg/dL, mostly with wide confidence intervals.

ALA, Comparison of Different Doses

One trial compared ALA 5.9 and 1.4 g/d and found no difference in effect on LDL-c with wide confidence intervals (1.3 mg/dL; 95% CI −8.3 to 11).[180]

Comparison of Different Specific n-3 FA

Two trials directly compared EPA (3.8 or 3.3 g/d) to DHA (3.6 or 3.7 g/d),[61, 107] one of which evaluated EPA and DHA ethyl esters,[61] the other evaluated EPA- and DHA-enriched oils.[107] Both found larger, but nonsignificant, relative reductions in LDL-C with EPA than DHA (net difference −5.8 [95% CI −11.7 to 0.1]; −6.2 [95% CI −21.8 to 9.4]). One trial compared two doses of EPA+DHA (3.4 and 1.7 g/d) to EPA 1.8 g/d (all ethyl esters),[169] with no significant differences between marine oil formulations. Two trials compared EPA+DHA to ALA, one comparing two doses of EPA+DHA (1.7 and 0.8 g/d) to ALA 4.5 g/d,[75] one comparing 0.4 g/d

EPA+DHA to 2 g/d ALA.[119] All comparisons were reported as nonsignificant, but the comparison of the higher dose marine oil in Finnegan 2003 found a large relative increase in LDL-c with a significant estimated CI (14.0 mg/dL; 95% CI 0.4 to 27.7).

SDA Versus Placebo

Pieters 2015 compared 1.2 g/d SDA to placebo in 32 patients at risk for CVD. At 1.5 month followup, no significant differences in change in LDL-c were found.[188]

SDA Versus Marine Oil

Kuhnt 2014 compared 2.0 g/d SDA and 1.9 g/d EPA+DHA+DPA in 59 healthy people (broken into cohorts based on body mass index and age). At 2 month followup, no significant differences in change in LDL-c ratios were found.[178]

Observational Studies

Observational studies did not evaluate LDL-c.

Table 41. Low density lipoprotein cholesterol: RCTs

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline, mg/dL	Ctrl N	Ctrl Baseline, mg/dL	Net Chg, mg/dL (95% CI)	Reported P value
Total n-3 FA vs Placebo													
Jones 2014 24829493 Canada	At risk	ALA + EPA+DHA	ALA: 1.2 g/d, EPA: 0.1 g/d, DHA: 3.5 g/d, DPA: 1.4 g/d (canola+DHA)	Placebo	0	4 wk	Assessed by coordinators	130	129.3	130	129.3	11.3 (1.7, 20.8)	<0.05
Kromhout 2010 20929341 Netherlands	CVD	ALA + EPA+DHA	0.4 g/d EPA+DHA; 2 g/d ALA (Marine oil, plant oil) [E:D 3:2]	Placebo	0	40 mo	Audit of unused margarine tubs returned	1212	98	1236	100	0.8 (−2.4, 4.0)	NS
Marine oil vs Placebo													
Ras 2014 25122648 Scandinavia	Healthy	EPA+DHA±DPA	0.9 g/d EPA+DHA	Placebo	0	1 mo	nd	64	153.7	64	145.6	−1.9 (nd)	nd
	Healthy	EPA+DHA±DPA	1.3 g/d EPA+DHA	Placebo	0	1 mo	nd	62	151.7	64	145.6	−1.5 (nd)	nd
	Healthy	EPA+DHA±DPA	1.8 g/d EPA+DHA	Placebo	0	1 mo	nd	62	145.6	64	145.6	−3.1 (nd)	nd
Grimsgaard 1998 9665096 Norway	Healthy	EPA	3.8 g/d (Ethyl ester)	Placebo	0	2 mo	pill count	75	156.8	77	156.0	−5.4 (−11.3, 0.5)	nd
		DHA	3.6 g/d (Ethyl ester)	Placebo	0	2 mo	pill count	72	156.8	77	156.0	0.4 (−5.4, 6.2)	nd
Olano-Martin 2010 19748619 UK	Healthy	EPA	3.3 g/d (Marine oil)	Placebo	0	1 mo	nd	38	136.3	38	136.7	3.1 (−12, 18.2)	NS
		DHA	3.7 g/d (Marine oil)	Placebo	0	1 mo	nd	38	139.4	38	136.7	6.2 (−5.1, 17.5)	NS
Harrison 2004 15853118 Scotland, UK	At risk	DHA+/- soy protein	Placebo+/- soy protein	Placebo+/- soy protein	0	1.25 mo	Food diary (biomarker confirmation)	101	218.1	112	191.1	−27.4 (−63.8, 8.9)	

Table 41. Low density lipoprotein cholesterol: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline, mg/dL	Ctrl N	Ctrl Baseline, mg/dL	Net Chg, mg/dL (95% CI)	Reported P value
Carrepeiro 2011 21561620 Brazil	Healthy	EPA+DHA + Statin	2.4 g/d (Marine oil)	Placebo + Statin	0	6 mo	nd	20	133.4	20	116.9	−1.5 (−3.5, 0.4)	0.128
		EPA+DHA	2.4 g/d (Marine oil)	Placebo	0	6 mo	nd	23	136	23	144.5	−0.8 (−2.8, 1.2)	0.431
Caslake 2008 18779276 UK	Healthy	EPA+DHA	1.8 g/d (Marine oil)	Placebo	0	2 mo	Pill count	312	148.5	312	147.2	2.7 (−3.0, 8.4)	<0.017
		EPA+DHA	0.7 g/d (Marine oil)	Placebo	0	2 mo	Pill count	312	148.5	312	147.2	2.7 (−2.6, 8.1)	<0.017
Damsgaard 2008 18492834 Scandinavia	Healthy	EPA+DHA + high LA	3.1 g/d (Marine oil) [E:D 1.64]	Placebo + high LA	0	2 mo	nd	17	99.6	16	90	3.5 (−9, 15.9)	
		EPA+DHA + low LA	3.1 g/d (Marine oil) [E:D 1.64]	Placebo + low LA	0	2 mo	nd	14	102.1	17	104.6	5.4 (−15.1, 25.9)	
Finnegan 2003 12663273 UK		EPA+DHA	1.7 g/d (marine oil capsule and marine oil margarine)	Placebo	0	6 mo	Pill count	31	132.05	30	140.15	11.7 (−3.2, 26.7)	nd
	Healthy	EPA+DHA	0.8 g/d (marine oil margarine)	Placebo	0	6 mo	Pill count	30	131.66	30	140.15	−2.3 (−11.0, 6.4)	nd
Grieger 2014 24454276 Australia	Healthy	EPA+DHA	0.8 g/d (fish diet)	Placebo	EPA: 0.017 g/d, DHA: 0.004 g/d (red meat diet)	8 wk	Weighed food records	43	123.55	37	127.41	11.6 (0.9, 22.3)	nd
Rasmussen 2006 16469978 Scandinavia, Australia	Healthy	EPA+DHA (MUFA diet)	EPA 3.6 g/d, 2.4 g/d DHA (Marine oil)	Placebo (MUFA diet)	0	3 mo	Dietary records (biomarker confirmation)	39	141	40	141	5% (nd)	nd
	Healthy	EPA+DHA (SFA diet)	EPA 3.6 g/d, 2.4 g/d DHA (Marine oil)	Placebo (SFA diet)	0	3 mo		41	141	42	141	7.1% (nd)	nd

Table 41. Low density lipoprotein cholesterol: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline, mg/dL	Ctrl N	Ctrl Baseline, mg/dL	Net Chg, mg/dL (95% CI)	Reported P value
Sanders 2011 21865334 UK	Healthy	EPA+DHA	1.8 g/d (suppl=marine oil)	Placebo	0	1 y	Pill Count, Plasma Check	80	123.6	71	127.4	3.9 (−5.6, 13.6)	nd
		EPA+DHA	0.9 g/d (suppl=marine oil)	Placebo	0	1 y	Pill Count, Plasma Check	81	123.6	71	127.4	0 (−10.2, 10.2)	nd
		EPA+DHA	0.45 g/d (suppl=marine oil)	Placebo	0	1 y	Pill Count, Plasma Check	80	123.6	71	127.4	7.7 (−2.5, 17.9)	nd
Shaikh 2014 25185754 U.S.	Healthy	EPA+DHA	3.6 g/d [E:D 6:1]	Placebo	0	2 mo	Pill count	36	115.4	32	103.1	12.7 (−3.3, 28.8)	0.12
Tardivo 2015 25394692 Brazil	Healthy	EPA+DHA	0.9 g/d [E:D 3:2]	Placebo	0	6 mo	Pill count	44	134.8	43	134.3	−5.7 (−20.7, 9.3)	nd
Vazquez 2014 24462043 Spain	Healthy	EPA+DHA	0.64 g/d [E:D 1:3]	Placebo	0	2 mo	Assessed by trained dieticians at each visit	273	119.8	273	119.8	−3.01 (−7.2, 1.1)	0.046
Bosch 2012 22686415 Canada	At risk	EPA+DHA	EPA: 0.465 g/d, DHA: 0.375 g/d (Marine oil) [E:D 1.24]	Placebo	0	6 y	FFQ at baseline, 2 years, and end of study (adherence was 88% at the end of study)	6281	112	6255	112	0.6 (−1.6, 2.8)	0.44
Ballantyne 2012 22819432 U.S.	At risk	EPA+DHA	4 g/d (marine oil)	Placebo	0	3 mo	nd	225	82	226	84	−6.3 (−11.6, −1.0)	0.007
		EPA+DHA	2 g/d (marine oil)	Placebo	0	3 mo	nd	233	82	226	84	−3.8 (−9, 1.4)	0.09
Derosa 2009 19397392 Italy	At risk	EPA+DHA	EPA: 0.9 g/d, DHA: 1.5 g/d (marine oil)	Placebo	0	6 mo	Pill count	168	148.5	165	149.9	0.7 (−0.8, 2.2)	nd
Ebrahimi 2009 19593941 Iran	At risk	EPA+DHA	EPA: 0.18, DHA: 0.12 (marine oil)	Placebo	0	6 mo	nd	47	145.6	42	143.2	5.4 (−7.2, 18.0)	nd

Table 41. Low density lipoprotein cholesterol: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline, mg/dL	Ctrl N	Ctrl Baseline, mg/dL	Net Chg, mg/dL (95% CI)	Reported P value
Holman 2009 19002433 UK	At risk	EPA+DHA	2 g/d	Placebo	0	4 mo	Pill count	371	123.6	361	121.6	−1.2 (−11.1, 8.8)	0.82
Jones 2014 24829493 Canada	At risk	EPA+DHA (+ALA)	EPA: 0.1 g/d, DHA: 3.5 g/d, DPA: 1.4 g/d (canola+DHA)	(ALA)	0	4 wk	Assessed by coordinators	130	129.3	130	129.3	6.9 (−2.7, 16.5)	<0.05
Kastelein 2014 24528690 Europe	At risk	EPA+DHA	EPA: 2.20 g/d, DHA: 0.80 g/d	Placebo	0	12 wk	Pill count	99	90.3	98	78.2	15.2 (7.1, 23.2)	<0.001
		EPA+DHA	EPA: 1.65 g/d, DHA: 0.60 g/d	Placebo	0	12 wk	Pill count	97	81.0	98	78.2	9.2 (1.9, 16.6)	NS
		EPA+DHA	EPA: 1.10 g/d, DHA: 0.40 g/d	Placebo	0	12 wk	Pill count	99	77.3	98	78.2	12.5 (5.2, 19.8)	<0.01
Liu 2003 Sweden	At risk	EPA+DHA	EPA: 1.7 g/d, DHA: 1.1 g/d	Placebo	0	12 wk	Pill count	29	180.31	22	173.75	5.4 (−13.3, 24.1)	NS
		EPA+DHA + simvastatin	EPA: 1.7 g/d, DHA: 1.1 g/d	Placebo + simvastatin	0	12 wk	Pill count	19	173.36	18	172.20	5.0 (−17, 27.1)	NS
Lungershausen 1994 7852747 Australia	At risk	EPA+DHA	EPA: 1.9 g/d, DHA: 1.5 g/d (marine oil)	Placebo	0	6 wk	Pill count	42	155.98	42	155.98	6.6 (−7.4, 20.6)	0.359
Maki 2010 20451686 U.S.	At risk	EPA+DHA (+simvastatin)	EPA: 1.86 g/d, DHA: 1.5 g/d	Placebo (+simvastatin)	0	8 wk	Pill count	122	89.2	132	92.3	3.4 (−2.1, 8.9)	0.052
Maki 2013 23998969 U.S.	At risk	EPA+DHA	4 g/d total oil (free FA oil) [nd]	Placebo	0	1.5 mo	Biomarker confirmation	207	93.6	211	91.7	−0.5 (−4.1, 3.1)	NS
		EPA+DHA	2 g/d total oil (free FA oil) [nd]	Placebo	0	1.5 mo	Biomarker confirmation	209	92.3	211	91.7	3.2 (−0.4, 6.8)	<0.05

Table 41. Low density lipoprotein cholesterol: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline, mg/dL	Ctrl N	Ctrl Baseline, mg/dL	Net Chg, mg/dL (95% CI)	Reported P value
Oh, 2014, 25147070 Korea	At risk	EPA+DHA	4 g/d (Marine oil)	Placebo	0	2 mo	Pill count	44	110	42	111	1.0 (−13.2, 15.2)	
		EPA+DHA	2 g/d (Marine oil)	Placebo	0	2 mo	Pill count	43	109	42	111	6.0 (8.1, 20.1)	
		EPA+DHA	1 g/d (Marine oil)	Placebo	0	2 mo	Pill count	44	109	42	111	3.0 (11.1, 17.1)	
Roncaglioni 2013 23656645 Italy	At risk	EPA+DHA	0.85 g/d (Marine oil)	Placebo	0	5 y	Self-reported	6239	131.8	6266	132.5	−0.4 (−1.8, 1.1)	0.63
Shaikh 2014 25185754 U.S.	At risk	EPA+DHA	3.6 g/d [E:D 6:1]	Placebo	0	2 mo	Pill count	20	115.4	22	101.93	13.9 (−2.2, 30.0)	0.12
Shidfar 2003 12847992 Iran	At risk	EPA+DHA	EPA 0.5 g/d, DHA 0.31 g/d (suppl) [E:D 1.6]	Placebo	0	2.5 mo	nd	16	159.6	19	167.4	−4.2 (−34.9, 26.5)	
		EPA+DHA +vitamin C	EPA 0.5 g/d, DHA 0.31 g/d (suppl) [E:D 1.6]	Placebo + vitamin C	0	2.5 mo	nd	16	150.8	17	160.6	10.3 (−18.8, 39.4)	
Sirtori 1997 9174486 Italy	At risk	EPA+DHA	2.57 g/d (Marine oil) [E:D 1.45]	Placebo	0	6 mo	nd	470	135.1	465	135.1	6.6 (6.3, 6.8)	
Tierney 2011 20938439 Europe	At risk	EPA+DHA	EPA 0.26 g/d, DHA 0.19 g/d (suppl) [E:D 1.5]	Placebo	0	3 mo	Pill count and plasma FA	100	127.80	106	122.39	−5.41 (−17.73, 6.91)	nd
Vecka 2012 23183517 Czech	At risk	EPA+DHA	2.58 g/d (Marine oil) [E:D 2.74]	Placebo	0	1.5 mo	nd	60	nd	60	nd	10.4 (9.8, 11.1) [difference of final values]	<0.01
Yokoyama 2007 17398308 Japan	At risk (no previous CHD)	EPA+Statin	1.8 g/d (Ethyl ester)	Statin	0	4.6 y	Local physicians monitored but compliance level was not reported	8841	181.5	8862	181.5	0 (−0.9, 0.9)	0.493

Table 41. Low density lipoprotein cholesterol: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline, mg/dL	Ctrl N	Ctrl Baseline, mg/dL	Net Chg, mg/dL (95% CI)	Reported P value
Eritsland 1996 8540453 Norway	CVD	EPA+DHA	3.4 g/d (Marine Oil)	Placebo	0	9 mo	nd	260	180	251	181	3.8 (−3.4, 11.4)	nd
Kromhout 2010 20929341 Netherlands	CVD	EPA+DHA	0.4 g/d (Marine oil) [E:D 3:2]	Placebo	0	40 mo	Audit of unused margarine tubs returned	1192	102	1236	100	−0.8 (−4.0, 2.4)	NS
		EPA+DHA (+ALA)	0.4 g/d (Marine oil) [E:D 3:2]	(ALA)	0			1212	98	1197	99	0.4 (−2.8, 3.6)	nd
Marchioli 2002 11997274 Italy	CVD	EPA+DHA	0.850−0.882 g/d (Marine Oil)	Placebo	0	42 mo	Measured at followup times	5666	136	5668	137	2 (nd)	nd
Rauch 2010 21060071 Germany	CVD	EPA+DHA	1 g/d (Marine oil) [E:D ratio 0.460:0.380]	Placebo	0	1 y	Pill count	1925	Not reported	1893	Not reported	0 (nd)	'Did not differ significantly between the study groups'
Sacks 1995 7759696 U.S.	CVD	EPA+DHA	EPA: 2.88 g/d DHA: 3.12 g/d (Marine oil)	Placebo	0	2.4 y	Pill count (80% n3, 90% placebo)	31	122	28	117	5.0 (−9.1, 19.1)	Nd
Tavazzi 2008 18757090 Italy	CVD	EPA+DHA	EPA: 0.386−0.401 g/d DHA: 0.464−0.481 g/d (Ethyl esters) [E:D 0.83]	Placebo	0	3.9 y	Measured at clinical exams, patient was compliant if drug administered for 80% of days. Both groups had ~30% compliance	3494	nd	3481	nd	"no differences"	Nd
Von Schacky 1999 10189324 Canada	CVD	EPA+DHA	3.3 g/d	Placebo	0	12 mo	Pill count	112	158.3	111	154.4	5.8 (−5.7, 17.2)	NS

Table 41. Low density lipoprotein cholesterol: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline, mg/dL	Ctrl N	Ctrl Baseline, mg/dL	Net Chg, mg/dL (95% CI)	Reported P value
Yokoyama 2007 17398308 Japan	CVD	EPA+Statin	1.8 g/d (Ethyl ester)	Statin	0	4.6 y	Local physicians monitored but compliance level was not reported	485	179.5	457	179.5	0.7 (−2.5, 4.1)	0.602
Marine oil vs Marine oil (doses)													
Ras 2014 25122648 Scandinavia	Healthy	EPA+DHA±DPA	1.8 g/d EPA+DHA	EPA+DHA±DPA	0.9 g/d EPA+DHA	1 mo	nd	62	145.6	64	153.7	−1.2 (nd)	nd
	Healthy	EPA+DHA±DPA	1.8 g/d EPA+DHA	EPA+DHA±DPA	1.3 g/d EPA+DHA	1 mo	nd	62	145.6	62	151.7	−1.5 (nd)	nd
	Healthy	EPA+DHA±DPA	1.3 g/d EPA+DHA	EPA+DHA±DPA	0.9 g/d EPA+DHA	1 mo	nd	62	151.7	62	153.7	0.39 (nd)	nd
Finnegan 2003 12663273 UK	Healthy	EPA+DHA	1.7 g/d (marine oil capsule and marine oil margarine)	EPA+DHA	0.8 g/d (marine oil margarine)	6 mo	Pill count	31	132.05	30	131.66	14.0 (0.4, 27.7)	nd
Caslake 2008 18779276 UK	Healthy	EPA+DHA	1.8 g/d (Marine oil)	EPA+DHA	0.7 g/d (Marine oil)	2 mo	Pill count	312	148.5	312	148.5	0 (−6.3, 6.3)	NS
Sanders 2011 21865334 UK	Healthy	EPA+DHA	1.8 g/d (Marine oil)	EPA+DHA	0.9 g/d (marine oil)	1 y	Pill Count, Plasma Check	80	123.6	81	123.6	3.9 (−6.4, 14.1)	nd
		EPA+DHA	1.8 g/d (Marine oil)	EPA+DHA	0.45 g/d (marine oil)	1 y	Pill Count, Plasma Check	80	123.6	80	123.6	−11.6 (−22.5, −0.66) −3.9 (−13.5, 5.8)	nd
		EPA+DHA	0.9 g/d (Marine oil)	EPA+DHA	0.45 g/d (marine oil)	1 y	Pill Count, Plasma Check	81	123.6	80	123.6	−7.7 (−18.6, 3.2)	nd

Table 41. Low density lipoprotein cholesterol: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline, mg/dL	Ctrl N	Ctrl Baseline, mg/dL	Net Chg, mg/dL (95% CI)	Reported P value
Ballantyne 2012 22819432 U.S.	At risk	EPA+DHA	4 g/d (marine oil)	EPA+DHA	2 g/d (Marine oil)	3 mo	nd	225	82	233	82	−4	
Kastelein 2014 24528690 Europe	At risk	EPA+DHA	3 g/d (Marine oil) [E:D 2.75]	EPA+DHA	2.25 g/d (Marine oil) [E:D 2.75]	3 mo	Pill count	99	90.3	97	81.0	5.9 (−2.6, 14.5)	nd
		EPA+DHA	3 g/d (Marine oil) [E:D 2.75]	EPA+DHA	1.5 g/d (Marine oil) [E:D 2.75]	3 mo	Pill count	99	90.3	99	77.3	2.7 (−5.9, 11.2)	nd
		EPA+DHA	2.25 g/d (Marine oil) [E:D 2.75]	EPA+DHA	1.5 g/d (Marine oil) [E:D 2.75]	3 mo	Pill count	97	81.0	99	77.3	−3.3 (−11.1, 4.6)	nd
Oh, 2014, 25147070 Korea	At risk	EPA+DHA	4 g/d (Marine oil)	EPA+DHA	2 g/d (Marine oil)	2 mo	Pill count	44	110	43	109	−5 (18.7, 8.8)	
		EPA+DHA	4 g/d (Marine oil)	EPA+DHA	1 g/d (Marine oil)	2 mo	Pill count	44	110	44	109	1 (−13.1, 15.1)	
		EPA+DHA	2 g/d (Marine oil)	EPA+DHA	1 g/d (Marine oil)	2 mo	Pill count	43	109	44	109	6 (−8.1, 20.1)	
Tatsuno 2013 23725919 Japan	At Risk	EPA+DHA	3.36 g/d (Ethyl esters) E:D 1.24	EPA+DHA	1.68 g/d (Ethyl esters) E:D 1.24	12 wk	Pill count	210	125.7	206	127.4	1.3 (−4.4, 7.0)	nd
		EPA+DHA	3.36 g/d (Ethyl esters) E:D 1.24	EPA+DHA	1.68 g/d (Ethyl esters) E:D 1.24	1 y	nd	170	nd	165	nd	2.8% (−1.3, 6.9)	
Maki 2013 23998969 U.S.	At risk	EPA+DHA	4 g/d total oil (free FA oil) [nd]	EPA+DHA	2 g/d total oil (free FA oil) [nd]	1.5 mo	Biomarker confirmation	207	93.6	209	92.3	−3.7 (−7.3, −0.1)	
Marine oil vs Marine oil (miscellaneous)													
Grimsgaard 1998 9665096 Norway	Healthy	EPA	3.8 g/d (Ethyl ester)	DHA	3.6 g/d (Ethyl ester)	2 mo	pill count	72	156.8	77	156.8	−5.8 (−11.7, 0.1)	nd
Olano-Martin 2010 19748619 UK	Healthy	EPA	3.3 g/d (Marine oil)	DHA	3.7 g/d (Marine oil)	1 mo	nd	38	136.3	38	139.4	3.1 (−12.5, 18.7)	

Table 41. Low density lipoprotein cholesterol: RCTs (continued)

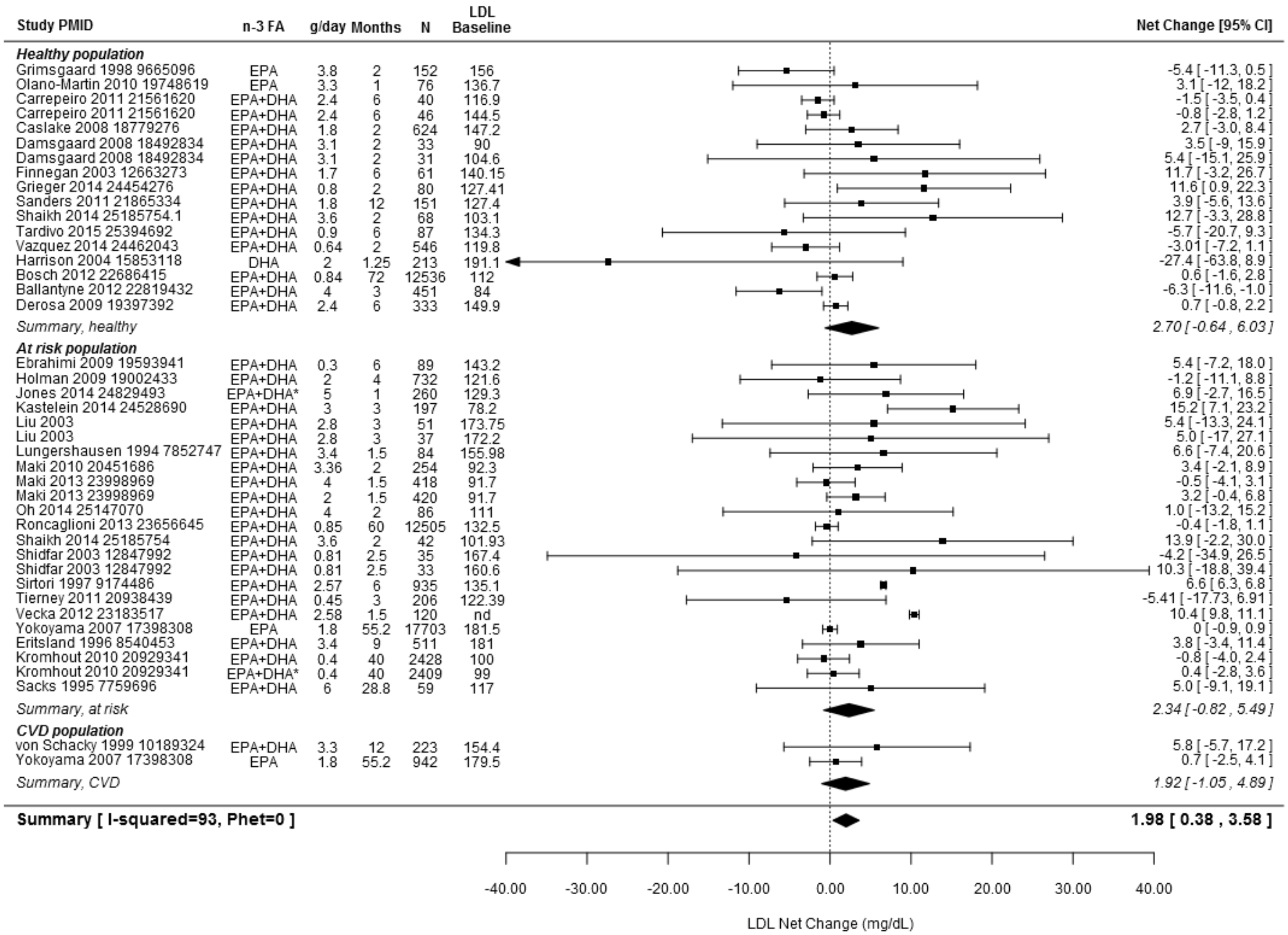
Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline, mg/dL	Ctrl N	Ctrl Baseline, mg/dL	Net Chg, mg/dL (95% CI)	
Tatsuno 2013 24314359 Japan	At risk	EPA+DHA	3.36 g/d (Ethyl esters) E:D 1.24	EPA	1.68 g/d (Ethyl ester)	1 y	nd	170	nd	165	nd	3.8% (−0.1, 7.9)	nd
		EPA+DHA	1.8 g/d (Ethyl esters) E:D 1.24	EPA	1.68 g/d (Ethyl ester)	1 y	nd	170	nd	165	nd	1.1% (−2.6, 4.7)	nd
ALA vs Placebo													
Finnegan 2003 12663273 UK	Healthy	EPA+DHA	1.7 g/d (marine oil capsule and marine oil margarine)	ALA	4.5 g/d (ALA margarine)	6 mo	Pill count	31	132.05	30	137.07	14.5 (0.4, 28.6)	NS
Finnegan 2003 12663273 UK	Healthy	EPA+DHA	0.8 g/d (marine oil margarine)	ALA	4.5 g/d (rapeseed oil margarine)	6 mo	Pill count	30	131.66	30	137.07	0.4 (−10.8, 11.6)	NS
Baxheinrich 2012 22894911 Germany	At risk	ALA	3.46 g/d (plant oil)	Placebo	ALA: 0.78 g/d	6 mo	Dietary records	40	132.05	41	134.75	1.9 (−12.0, 15.8)	0.181
Jones 2014 24829493 Canada	At risk	ALA	5.9 g/d (canola)	Placebo	0.2 g/d (CornSaff)	4 wk	Assessed by coordinators	130	129.3	130	129.3	5.7 (−3.9, 15.3)	NS
		ALA	1.4 g/d (canolaOleic)	Placebo	0.2 g/d (CornSaff)	4 wk	Assessed by coordinators	130	129.3	130	129.3	4.4 (−5.4, 14.2)	NS
Rodriguez-Leyva 2013 24126178 Canada	At risk	ALA	5.9 g/d (flaxseed)	Placebo	0	1 y	Plasma ALA and enterolignan levels	43	96.5	41	100.4	0 (−16.6, 16.6)	0.19
Kromhout 2010 20929341 Netherlands	CVD	ALA	2 g/d (plant oil)	Placebo	0	40 mo	Audit of unused margarine tubs returned	1197	99	1236	100	0.4 (−2.8, 3.6)	NS
		ALA (+EPA+DHA)	2 g/d (plant oil)	(EPA+DHA)	0			1212	98	1192	102	1.5 (−1.7, 4.8)	nd

Table 41. Low density lipoprotein cholesterol: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline, mg/dL	Ctrl N	Ctrl Baseline, mg/dL	Net Chg, mg/dL (95% CI)	Reported P value
EPA+DHA vs ALA													
Finnegan 2003 12663273 UK	Healthy	EPA+DHA	0.8 g/d (marine oil margarine)	ALA	4.5 g/d (rapeseed oil margarine)	6 mo	Pill count	30	131.66	30	137.07	14.5 (0.4, 28.6)	NS
		EPA+DHA	1.7 g/d (marine oil capsule and marine oil margarine)	ALA	4.5 g/d (ALA margarine)	6 mo	Pill count	31	132.05	30	137.07	0.4 (−10.8, 11.6)	NS
Kromhout 2010 20929341 Netherlands	CVD	EPA+DHA	0.4 g/d (Marine oil) [E:D 3:2]	ALA	2 g/d (plant oil)	40 mo	Audit of unused margarine tubs returned	1192	102	1197	99	−1.2 (−4.4, 2.1)	nd
ALA vs ALA (doses)													
Jones 2014 24829493 Canada	At risk	ALA	5.9 g/d (canola)	ALA	1.4 g/d (canolaOleic)	4 wk	Assessed by coordinators	130	129.34	130	129.34	1.3 (−8.3, 11)	.
SDA vs Placebo													
Pieters 2015 25226826 Netherlands	At risk	SDA	1.2 g/d (suppl)	Placebo	0	1.5 mo	nd	32	141.31	32	143.47	−1.55 (−6.20, 3.10)	0.46
SDA vs Marine oil													
Kuhnt 2014 24553695 Germany	Healthy	SDA	2.0 g/d (suppl)	EPA+DHA+DPA	1.9 g/d (suppl: marine oil)	2 mo	nd	20	98.07	10	96.29	−3.87 (−14.74, 22.48)	
Kuhnt 2014 24553695 Germany	Healthy	SDA	2.0 g/d (suppl)	EPA+DHA+DPA	1.9 g/d (suppl: marine oil)	2 mo	nd	20	136.68	9	118.92	−10.44 (−13.29, 34.17)	

Abbreviations: ALA = alphalinolenic acid, Ctrl = control, CVD = cardiovascular disease, DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, E:D = EPA to DHA ratio, EPA = eicosapentaenoic acid, F/up = followup, FA = fatty acid(s), FFQ = food frequency questionnaire, Int = intervention, MUFA = monounsaturated fatty acid, n/N = number with outcome/number analyzed, n6:3 = omega-6 to omega-3 fatty acid ratio, PMID = PubMed Identification number, RCT = randomized controlled trial, SDA = stearidonic acid, SFA = saturated fatty acids.

Figure 37. Low density lipoprotein cholesterol: Randomized trials of marine oils



Random effects model meta-analysis of n-3 FA versus placebo (or no n-3 FA), with subgroup analyses by population. In all meta-analyses, only studies that reported sufficient results data are included.

Abbreviations: CI = confidence interval, CVD = cardiovascular disease, DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid, LDL = low density lipoprotein, n-3 FA = omega-3 fatty acids, Phet = P value of chi-squared test of heterogeneity across studies, PMID = PubMed Identification number.

High Density Lipoprotein Cholesterol

Randomized Controlled Trials

Forty-six RCTs provided data on effect of n-3 FA on HDL-c (Table 42). [46, 48, 51, 53, 55, 56, 58, 61, 62, 67, 70, 75, 76, 80, 90, 94, 96, 97, 99, 103, 105, 107, 115, 116, 119, 120, 128, 136, 146, 151, 152, 156, 160, 167, 173, 174, 177-180, 184, 187-189, 194] Only four of the trials reported HDL-c among their primary outcomes (Damsgaard 2008, Harrison 2004, Lungershausen 1994, Sirtori 1997).[53, 58, 80, 94]

Total n-3 FA Versus Placebo

Two trials compared total n-3 FA (ALA+EPA+DHA) versus placebo, following 2708 patients for 1 and 40 months; one in people at increased risk for CVD,[180] one in people with CVD.[119] Baseline HDL-c measurements were 47 and 50 mg/dL. Compliance was measured in both studies, but not reported. The trial in an at risk population found a statistically significant increase in HDL-c with combined ALA 1.2 g/d (canola oil) and EPA+DHA+DPA 5 g/d (3.9 mg/dL; 95% CI 1.5 to 6.2).[180] The trial in a CVD population found no significant effect on HDL-c with ALA 2 g/d and EPA+DHA 0.4 g/d.[119]

Marine Oil Versus Placebo

Thirty-four trials evaluated the effect of marine oils versus placebo on HDL-c.[46, 51, 53, 56, 58, 61, 62, 67, 70, 75, 76, 80, 94, 96, 97, 99, 103, 105, 107, 115, 116, 119, 120, 128, 146, 156, 160, 166, 173, 177, 179, 180, 194, 195] Doses of EPA+DHA ranged from 0.3 to 6 g/d (median 6 g/d) and followup time ranged from 1 month to 6 years (median 3 months). Across populations, by meta-analysis (Figure 38), the summary net difference in HDL-c with EPA+DHA versus placebo (or equivalent) was a statistically significant, but small, 0.88 mg/dL (95% CI 0.20 to 1.57).

Healthy Population

Thirteen of the trials of marine oils versus placebo were conducted in healthy populations, comprising data from 3,755 individuals with mean baseline HDL-c ranging from 45 to 57.9 mg/dL and followup duration from 1 to 12 months.[55, 61, 75, 80, 94, 97, 107, 128, 136, 173, 174, 187, 189] Two studies compared both EPA (3.3 and 3.8 g/d) and DHA (3.6 and 3.7 g/d), separately, to placebo, one of which evaluated EPA and DHA ethyl esters,[61], one of which evaluated EPA- and DHA-enriched oils.[107] All other evaluated supplements with both EPA+DHA, with doses ranging from 0.45 to 3.8 g/d. Compliance was verified with pill counts, dietary records, or biomarker confirmation in six of the studies. One trial found significant net increases in HDL-c with marine oil (at two different doses, 0.7 and 1.8 g/d) of 2.3 mg/dL (95% CI 0.2 to 4.5). One study, of DHA 3.6 g/d alone, found a significant net increase in HDL-c (2.7 mg/dL; 95% CI 1.2 to 4.2), but not with EPA 3.8 g/d. The pooled effect size was nonsignificant: 0.87 mg/dL (95% CI −0.11 to 1.84) (Figure 38).[187]

At-Risk-for-CVD Population

Twenty-two of the trials were conducted in populations at increased risk of CVD, comprising data from 48,293 individuals with mean baseline HDL-c ranging from 28.7 to 65.6 mg/dL and followup duration from 1 month to 6 years.[46, 53, 58, 76, 80, 90, 99, 103, 105, 115, 116, 120, 146, 156, 160, 166, 177, 179, 180, 187, 194, 195] One study compared DHA (2 g/d) to placebo;[80] all other evaluated supplements with both EPA+DHA, with doses ranging from 0.3 to 6 g/d. Compliance was verified with pill counts, dietary records, self-report or biomarker confirmation in 11 of the studies. Thirteen of the 17 trials found no significant effects of EPA+DHA on HDL-c; net change HDL-c varied between 14.9 and 9.3 mg/dL. The pooled effect size was nonsignificant, 0.81 mg/dL (95% CI −0.41 to 2.03) (Figure 38).

CVD Population

Nine of the trials were conducted in people with CVD, comprising data from 27,080 individuals with mean baseline HDL-c ranging from 39 to 50.2 mg/dL and followup duration from 9 months to 6 years.[48, 51, 56, 62, 67, 70, 90, 96, 119] Doses ranged from 0.36 g/d to 6 g/d; compliance was verified in four of the studies, by pill count or equivalent. Two of the nine trials found significant net increases in HDL-c, but net change HDL-c varied from −1.2 to 3.1 mg/dL. The pooled effect size was a statistically significant, but small, 0.72 mg/dL (95% CI 0.16 to 1.28) (Figure 38).

RCT Subgroup Analyses

Eight of the trials compared effects of marine oils in different subgroups of participants; three reported statin vs no statin,[46, 99, 156] one with or without vitamin C,[76] two men vs women,[97, 179] one older vs younger age,[97] and one impaired glucose tolerance versus normoglycemia.[58] One study found a larger effect of marine oil among participants who were also exercising (men 9.3 mg/dL; women 7.6 mg/dL) than in groups not exercising (men 1.7 mg/dL; women −0.9 mg/dL), although it was unclear whether these differences were significantly different from each other.[179] Another study found a small but significantly different effect (P<0.05) of marine oil 2.6 g/d in men with impaired glucose tolerance (0.8 mg/dL) than those with normoglycemia (0.4 mg/dL).[58] Other subgroup analyses found no differences in effect between subgroups.

By meta-regression, across studies there were no significant differences in effect (interactions) by HDL-c baseline (P=0.16), n-3 FA dose (P=0.62), followup duration (P=0.24), or population (at risk P=0.29; CVD P=0.82).

Marine Oil, Comparison of Different Doses

Eight RCTs directly compared different doses of marine oils (EPA+DHA),[75, 97, 136, 151, 161, 169, 177, 194] between 0.9 and 4 g/d. All comparisons were nonsignificant for effect on HDL-c, with estimates of differences ranging from −3.9 mg/dL (95% CI −9.3 to 1.6; 0.9 vs. 0.45 g/d) to 3.9 mg/dL (95% CI −1.6 to 9.3; 1.8 vs. 0.9 g/d).

ALA Versus Placebo

Five trials compared ALA versus placebo (or equivalent) in 661 people at increased risk of CVD and one trial of 4837 people with CVD.[75, 119, 152, 167, 180] ALA doses ranged from 1.4 to 5.9 g/d and followup ranged from 1 to 40 months. All studies assessed compliance. Effect on HDL-c ranged from −0.3 to 2.3 mg/d, all but one study were statistically nonsignificant.

ALA, Comparison of Different Doses

One trial compared ALA 5.9 and 1.4 g/d and found no difference in effect on HDL-c.[180]

Comparison of Different Specific n-3 FA

Two trials directly compared EPA (3.8 or 3.3 g/d) to DHA (3.6 or 3.7 g/d), one of which evaluated EPA and DHA ethyl esters,[61] one of which evaluated EPA- and DHA-enriched oils.[107]

Both found similar (nonsignificant) effects on HDL-c with EPA or DHA. One trial compared two doses of EPA+DHA (3.4 and 1.7 g/d) to EPA 1.8 g/d (all ethyl esters),[169] with no differences between marine oil formulations. Two trials compared EPA+DHA to ALA. One compared two doses of EPA+DHA (1.7 and 0.8 g/d) to ALA 4.5 g/d;[75] both comparisons were nonsignificant with similar net differences (1.5 and 2.3 mg/dL). The second trial compared EPA+DHA 0.2 g/d to ALA 2 g/d; the study did not report a significant difference, but a calculated net difference was statistically significant favoring EPA+DHA (net difference 1.9 mg/dL; 95% CI 0.9 to 3.0).[119]

SDA Versus Placebo

Pieters 2015 compared 1.2 g/d SDA to placebo in 32 patients at risk for CVD. At 1.5 month followup, no significant differences in change in HDL-c were found.[188]

SDA Versus Marine Oil

Kuhnt 2014 compared 2.0 g/d SDA and 1.9 g/d EPA+DHA+DPA in 59 healthy people (broken into cohorts based on body mass index and age). At 2 month followup, no significant differences in change in HDL-c were found.[178]

Observational Studies

Observational studies did not evaluate HDL-c.

Table 42. High density lipoprotein cholesterol: RCTs

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline, mg/dL	Ctrl N	Ctrl Baseline, mg/dL	Net Chg, mg/dL (95% CI)	Reported P value
Total n-3 FA vs. Placebo													
Jones 2014 24829493 Canada	At risk	ALA + EPA+DHA	ALA: 1.2 g/d, EPA: 0.1 g/d, DHA: 3.5 g/d, DPA: 1.4 g/d (canola+DHA)	Placebo	0.2 g/d (CornSaff)	4 wk	Assessed by coordinators	130	47.1	130	47.1	3.9 (1.5, 6.2)	<0.05
Kromhout 2010 20929341 Netherlands	CVD	ALA + EPA+DHA	0.4 g/d EPA+DHA; 2 g/d ALA (Marine oil, plant oil) [E:D 3:2]	Placebo	0	40 mo	Audit of unused margarine tubs returned	1212	50	1236	50	−0.4 (−1.5, 0.7)	NS
Marine oil vs Placebo													
Ras 2014 25122648 Scandinavia	Healthy	EPA+DHA±DPA	0.9 g/d EPA+DHA	Placebo	0	1 mo	nd	64	61.0	64	64.9	0.7 (nd)	nd
	Healthy	EPA+DHA±DPA	1.3 g/d EPA+DHA	Placebo	0	1 mo	nd	62	63.7	64	64.9	3.5 (nd)	nd
	Healthy	EPA+DHA±DPA	1.8 g/d EPA+DHA	Placebo	0	1 mo	nd	62	63.3	64	64.9	3.9 (nd)	nd
Grimsgaard 1998 9665096 Norway	Healthy	EPA	3.8 g/d (Ethyl ester)	Placebo	0	2 mo	pill count	75	51.35	77	54.44	0.8 (−0.6, 2.2)	0.4
		DHA	3.6 g/d (Ethyl ester)	Placebo	0	2 mo	pill count	72	52.51	77	54.44	2.7 (1.2, 4.2)	0.0005
Olano-Martin 2010 19748619 UK	Healthy	EPA	3.3 g/d (Marine oil)	Placebo	0	1 mo	nd	38	51.0	38	51.4	−0.4 (−6.0, 5.3)	
		DHA	3.7 g/d (Marine oil)	Placebo	0	1 mo	nd	38	50.6	38	51.4	1.2 (−2.7, 5.0)	

Table 42. High density lipoprotein cholesterol: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline, mg/dL	Ctrl N	Ctrl Baseline, mg/dL	Net Chg, mg/dL (95% CI)	Reported P value
Harrison 2004 15853118 Scotland	At risk	DHA+/- soy protein	2 g/d (food fortification)	Placebo+/- soy protein	0	1.25 mo	Food diary (biomarker confirmation)	101	63.7	112	63.7	2.3 (−3.9, 8.5)	nd
Carrepeiro 2011 21561620 Brazil	Healthy	EPA+DHA + Statin	2.4 g/d (Marine oil)	Placebo + Statin	0	6 mo	nd	20	50.1	20	50.6	1.9 (nd)	
		EPA+DHA	2.4 g/d (Marine oil)	Placebo	0	6 mo	nd	23	52.4	23	49.6	−1.3 (nd)	
Caslake 2008 18779276 UK	Healthy	EPA+DHA	1.8 g/d (Marine oil)	Placebo	0	2 mo	Pill count	312	65.6	312	65.6	2.3 (0.2, 4.5)	<0.017
		EPA+DHA	0.7 g/d (Marine oil)	Placebo	0	2 mo	Pill count	312	65.2	312	65.6	2.3 (0.2, 4.5)	<0.017
Damsgaard 2008 18492834 Scandinavia	Healthy	EPA+DHA + high LA	3.1 g/d (Marine oil) [E:D 1.64]	Placebo + high LA	0	2 mo	nd	17	57.1	16	52.5	0.4 (−5.7, 6.4)	
		EPA+DHA + low LA	3.1 g/d (Marine oil) [E:D 1.64]	Placebo + low LA	0	2 mo	nd	14	57.9	17	57.9	3.1 (−7.8, 14)	
Finnegan 2003 12663273 UK	Healthy	EPA+DHA	1.7 g/d (marine oil capsule and marine oil margarine)	Placebo	0	6 mo	Pill count	31	51.74	30	52.12	1.4 (−2.1, 4.8)	nd
		EPA+DHA	0.8 g/d (marine oil margarine)	Placebo	0	6 mo	Pill count	30	52.90	30	52.12	2.8 (−0.2, 5.7)	nd
Grieger 2014 24454276 Australia	Healthy	EPA+DHA	0.8 g/d (fish diet)	Placebo	EPA: 0.017 g/d, DHA: 0.004 g/d (red meat diet)	8 wk	Weighed food records	43	65.64	37	61.776	0 (−10.7, 10.7)	nd

Table 42. High density lipoprotein cholesterol: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline, mg/dL	Ctrl N	Ctrl Baseline, mg/dL	Net Chg, mg/dL (95% CI)	Reported P value
Sacks 1994 8021472 U.S.	Healthy	EPA+DHA	3 g/d (Marine oil) [E:D 1.44:0.96]]	Placebo	0	6 mo	Pill count	84	46	84	45	1.8 (−1.0, 4.5)	NS
Sanders 2011 21865334 UK	Healthy	EPA+DHA	1.8 g/d (suppl=marine oil)	Placebo	0	1 y	Pill Count, Plasma Check	80	65.6	71	61.8	3.9 (−1.6, 9.3)	nd
		EPA+DHA	0.9 g/d (suppl=marine oil)	Placebo	0	1 y	Pill Count, Plasma Check	81	65.6	71	61.8	0 (−5.5, 5.5)	nd
		EPA+DHA	0.45 g/d (suppl=marine oil)	Placebo	0	1 y	Pill Count, Plasma Check	80	61.8	71	61.8	3.9 (−1.6, 9.3)	nd
Shaikh 2014 25185754 U.S.	Healthy	EPA+DHA	3.6 g/d [E:D 6:1]	Placebo	0	2 mo	Pill count	36	40.9	32	45.6	2.3 (−3.3, 7.9)	0.42
Tardivo 2015 25394692 Brazil	Healthy	EPA+DHA	0.9 g/d [E:D 3:2]	Placebo	0	6 mo	Pill count	44	45.7	43	44.9	0 (−3.5, 3.5)	nd
Vazquez 2014 24462043 Spain	Healthy	EPA+DHA	0.64 g/d [E:D 1:3]	Placebo	0	2 mo	Assessed by trained dieticians at each visit	273	46.2	273	46.2	−0.7 (−2.2, 0.8)	0.16
Bosch 2012 22686415 Canada	At risk	EPA+DHA	EPA: 0.465 g/d, DHA: 0.375 g/d (Marine oil) [E:D 1.24]	Placebo	0	6 y	FFQ at baseline, 2 years, and end of study (adherence was 88% at the end of study)	6281	46	6255	46	0.1 (−0.7, 0.9)	0.78

Table 42. High density lipoprotein cholesterol: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline, mg/dL	Ctrl N	Ctrl Baseline, mg/dL	Net Chg, mg/dL (95% CI)	Reported P value
Ballantyne 2012 22819432 U.S.	At risk	EPA+DHA	4 g/d (Marine oil)	Placebo	0	3 mo	nd	226	37	227	39	−5.0 (−8.8, −1.2)	0.0013
		EPA+DHA	2 g/d (Marine oil)	Placebo	0	3 mo	nd	234	38	227	39	−2.3 (−5.6, 1.0)	0.1265
Derosa 2009 19397392 Italy	At risk	EPA+DHA	EPA: 0.9 g/d, DHA: 1.5 g/d (marine oil)	Placebo	0	6 mo	Pill count	168	38.4	165	39.7	3.9 (2.7, 5.1)	nd
Ebrahimi 2009 19593941 Iran	At risk	EPA+DHA	EPA: 0.18, DHA: 0.12 (marine oil)	Placebo	0	6 mo	nd	47	45.6	42	43.2	−0.4 (−3.0, 2.2)	nd
Einvik 2010 20389249 Norway	At risk	EPA+DHA	2.4 g/d (Marine oil) [E:D 1.176:0.84]	Placebo	0	3 y	Pharmacy records/pill count	70	54.8	68	55.2	2.6 (−2.5, 7.8)	ns
		EPA+DHA + diet	2.4 g/d (Marine oil) [E:D 1.176:0.84]	Placebo + diet	0	3 y	Pharmacy records/pill count	69	54.8	71	54.1	0.8 (−5.0, 6.5)	
Holman 2009 19002433 UK	At risk	EPA+DHA	2 g/d	Placebo	0	4 mo	Pill count	371	nd	361	nd	0.8 (−0.1, 1.6)	0.082
Jones 2014 24829493 Canada	At risk	EPA+DHA (+ALA)	EPA: 0.1 g/d, DHA: 3.5 g/d, DPA: 1.4 g/d	(ALA)	0	4 wk	Assessed by coordinators	130	47.10	130	47.10	4.1 (1.9, 6.4)	nd

Table 42. High density lipoprotein cholesterol: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline, mg/dL	Ctrl N	Ctrl Baseline, mg/dL	Net Chg, mg/dL (95% CI)	Reported P value
Kastelein 2014 24528690 Europe	At risk	EPA+DHA	EPA: 2.20 g/d, DHA: 0.80 g/d	Placebo	0	12 wk	Pill count	99	28.7	98	28.7	1.1 (−0.5, 2.8)	NS
		EPA+DHA	EPA: 1.65 g/d, DHA: 0.60 g/d	Placebo	0	12 wk	Pill count	97	28.0	98	28.7	0.5 (−1.1, 2.2)	NS
		EPA+DHA	EPA: 1.10 g/d, DHA: 0.40 g/d	Placebo	0	12 wk	Pill count	99	27.3	98	28.7	1.5 (−0.2, 3.1)	NS
Liu 2003 Sweden	At risk	EPA+DHA	EPA: 1.7 g/d, DHA: 1.1 g/d	Placebo	0	12 wk	Pill count	29	59.07	22	59.07	2.3 (−7.3, 12.0)	NS
		EPA+DHA + simvastatin	EPA: 1.7 g/d, DHA: 1.1 g/d	Placebo + simvastatin	0	12 wk	Pill count	19	55.21	18	64.09	2.3 (−9.3, 14.0)	NS
Lungershausen 1994 7852747 Australia	At risk	EPA+DHA	EPA: 1.9 g/d, DHA: 1.5 g/d (marine oil)	Placebo	0	6 wk	Pill count	42	39.8	42	39.8	0.8 (−2.7, 4.3)	0.664
Maki 2010 20451686 U.S.	At risk	EPA+DHA (+simvastatin)	EPA: 1.86 g/d, DHA: 1.5 g/d	Placebo (+simvastatin)	0	8 wk	Pill count	122	47.3	132	44.7	2.5 (−0.2, 5.2)	<0.001
Maki 2013 23998969 U.S.	At risk	EPA+DHA	4 g/d total oil (free FA oil) [nd]	Placebo	0	1.5 mo	Biomarker confirmation	207	38.8	211	38.8	0.5 (−1.5, 2.5)	NS
	At risk	EPA+DHA	2 g/d total oil (free FA oil) [nd]	Placebo	0	1.5 mo	Biomarker confirmation	209	38.7	211	38.8	0.1 (−1.75, 1.95)	NS
Oh, 2014, 25147070 Korea	At risk	EPA+DHA	4 g/d (Marine oil)	Placebo	0	2 mo	Pill count	44	40	42	42	−1.0 (4.1, 2.2)	
		EPA+DHA	2 g/d (Marine oil)	Placebo	0	2 mo	Pill count	43	43	42	42	−2.0 (5.1, 1.2)	
		EPA+DHA	1 g/d (Marine oil)	Placebo	0	2 mo	Pill count	44	41	42	42	1.0 (2.4, 4.4)	

Table 42. High density lipoprotein cholesterol: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline, mg/dL	Ctrl N	Ctrl Baseline, mg/dL	Net Chg, mg/dL (95% CI)	Reported P value
Roncaglioni 2013 23656645 Italy	At risk	EPA+DHA	0.85 g/d (Marine oil)	Placebo	0	5 y	Self-reported	6239	50.9	6266	51.2	0.5 (0.03, 1.1)	0.04
Shaikh 2014 25185754 U.S.	At risk	EPA+DHA	3.6 g/d [E:D 6:1]	Placebo	0	2 mo	Pill count	20	39.0	22	39.0	1.9 (0.5, 3.3)	0.0069
Shidfar 2003 12847992 Iran	At risk	ALA + EPA+DHA	EPA 0.5 g/d, DHA 0.31 g/d (suppl) [E:D 1.6]	Placebo	0	2.5 mo	nd	16	39.1	19	39.2	−0.3 (−6.8, 6.2)	
		ALA + EPA+DHA + vitamin C	EPA 0.5 g/d, DHA 0.31 g/d (suppl) [E:D 1.6]	Placebo + vitamin C	0	2.5 mo	nd	16	53.3	17	37.2	−14.9 (−20.2, −9.6)	
Sirtori 1997 9174486 Italy	At risk	EPA+DHA	2.57 g/d (Marine oil) [E:D 1.45]	Placebo	0	6 mo	nd	470	39.8	465	39.8	0.4 (0.3, 0.5)	
Soares 2014 24652053 Brazil	At risk (male)	EPA+DHA (+diet)	1 g/d (Marine oil) unspecified n-3 FA composition	Placebo	0	3 mo	Not reported	6	43.0	6	37.3	1.7 (−3.9, 7.3)	NS
	At risk (female)	EPA+DHA (+diet)	1 g/d (Marine oil) unspecified n-3 FA composition	Placebo	0	3 mo	Not reported	17	48.6	18	48.5	−0.9 (−3.0, 1.2)	NS
	At risk (male)	EPA+DHA (+diet/exercise)	1 g/d (Marine oil) unspecified n-3 FA composition	Placebo	0	3 mo	Not reported	4	36.0	6	34.8	9.3 (2.0, 16.6)	NS
	At risk (female)	EPA+DHA (+diet/exercise)	1 g/d (Marine oil) unspecified n-3 FA composition	Placebo	0	3 mo	Not reported	17	44.1	13	48.1	7.6 (5.2, 10.0)	NS

Table 42. High density lipoprotein cholesterol: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline, mg/dL	Ctrl N	Ctrl Baseline, mg/dL	Net Chg, mg/dL (95% CI)	Reported P value
Tierney 2011 20938439 Europe	At risk	EPA+DHA	EPA 0.26 g/d, DHA 0.19 g/d (suppl) [E:D 1.5]	Placebo	0	3 mo	Pill count and plasma FA	100	42.86	106	42.08	0.77 (−2.439, 3.983)	nd
Vecka 2012 23183517 Czech	At risk	EPA+DHA	2.58 g/d (Marine oil) [E:D 2.74]	Placebo	0	1.5 mo	nd	60	nd	60	nd	1.9 (−25.4, 29.2) [difference of final values]	<0.01
Yokoyama 2007 17398308 Japan	At risk (no previous CHD)	EPA+Statin	1.8 g/d (Ethyl ester)	Statin	0	4.6 y	Local physicians monitored but compliance level was not reported	8841	58.7	8862	58.3	−0.4 (−0.9, 0.1)	0.836
Burr 1989 2571009 UK	CVD	EPA+DHA	0.357 EPA g/d+nd DPA (suppl: marine oil, diet: fish)	No intervention	0	2 y	Dietary Questionnaire	982	37.1	978	37.8	0.4 (−0.6, 1.4)	NS
Eritsland 1996 8540453 Norway	CVD	EPA+DHA	3.4 g/d (Marine Oil)	Placebo	0	9 mo	nd	260	40.93	251	38.6	2.0 (0.1, 3.9)	nd
Kromhout 2010 20929341 Netherlands	CVD	EPA+DHA	0.4 g/d (Marine oil) [E:D 3:2]	Placebo	0	40 mo	Audit of unused margarine tubs returned	1192	50	1236	50	1.2 (0.1, 2.2)	NS
		EPA+DHA (+ALA)	0.4 g/d (Marine oil) [E:D 3:2]	(ALA)	0			1212	50	1197	50	0.4 (−0.7, 1.5)	nd

Table 42. High density lipoprotein cholesterol: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline, mg/dL	Ctrl N	Ctrl Baseline, mg/dL	Net Chg, mg/dL (95% CI)	Reported P value
Marchioli 2002 11997274 Italy	CVD	EPA+DHA	0.850−0.882 g/d (Marine Oil)	Placebo	0	42 mo	Measured at followup times	5666	41	5668	41	0 (nd)	nd
Nilsen 2001 11451717 Norway	CVD	EPA+DHA	4 g/d (Marine oil) [E:D 1:2]	Placebo	0	Median 1 y	nd	119	41.7	120	44.8	11.9% (nd)	0.0016
Sacks 1995 7759696 U.S.	CVD	EPA+DHA	EPA: 2.88 g/d DHA: 3.12 g/d (Marine oil)	Placebo	0	2.4 y	Pill count (80% n3, 90% placebo)	31	41	28	40	−1.0 (−6.9, 4.9)	nd
Tavazzi 2008 18757090 Italy	CVD	EPA+DHA	EPA: 0.386−0.401 g/d DHA: 0.464−0.481 g/d (Ethyl esters) [E:D 0.83]	Placebo	0	3.9 y	Measured at clinical exams, patient compliant if drug administered for 80% of days. Both groups had ~30% compliance	3494	nd	3481	nd	"no differences"	nd
Von Schacky 1999 10189324 Canada	CVD	EPA+DHA	3.3 g/d	Placebo	0	12 mo	Pill count	112	51.0	111	50.2	3.1 (−1.0, 7.2)	NS
Yokoyama 2007 17398308 Japan	CVD	EPA+Statin	1.8 g/d (Ethyl ester)	Statin	0	4.6 y	Local physicians monitored but compliance level not reported	485	58.3	457	58.3	−1.2 (−3.9, 1.6)	0.882

Table 42. High density lipoprotein cholesterol: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline, mg/dL	Ctrl N	Ctrl Baseline, mg/dL	Net Chg, mg/dL (95% CI)	Reported P value
Marine oil vs Marine oil (miscellaneous)													
Grimsgaard 1998 9665096 Norway	Healthy	EPA	3.8 g/d (Ethyl ester)	DHA	3.6 g/d (Ethyl ester)	2 mo	pill count	72	52.51	77	51.35	−1.9 (−3.5, −0.4)	0.009
Olano-Martin 2010 19748619 UK	Healthy	EPA	3.3 g/d (Marine oil)	DHA	3.7 g/d (Marine oil)	1 mo	nd	38	136.3	38	139.4	1.5 (−3.8, 6.9)	
Tatsuno 2013 24314359 Japan	At risk	EPA+DHA	3.36 g/d (Ethyl esters) E:D 1.24	EPA	1.8 g/d (Ethyl ester)	1 y	nd	170	nd	165	nd	2.3% (−0.9, 5.6)	
	At risk	EPA+DHA	1.68 g/d (Ethyl esters) E:D 1.24	EPA	1.8 g/d (Ethyl ester)	1 y	nd	170	nd	165	nd	2.1% (−1.1, 5.3)	
Marine oil vs Marine oil (doses)													
Ras 2014 25122648 Scandinavia	Healthy	EPA+DHA±DPA	1.8 g/d EPA+DHA	EPA+DHA± DPA	0.9 g/d EPA+DHA	1 mo	nd	62	63.3	64	61.0	3.1 (nd)	nd
	Healthy	EPA+DHA±DPA	1.8 g/d EPA+DHA	EPA+DHA± DPA	1.3 g/d EPA+DHA	1 mo	nd	62	63.3	62	63.7	0.39 (nd)	nd
	Healthy	EPA+DHA±DPA	1.3 g/d EPA+DHA	EPA+DHA± DPA	0.9 g/d EPA+DHA	1 mo	nd	62	63.7	62	61.0	2.7 (nd)	nd
Caslake 2008 18779276 UK	Healthy	EPA+DHA	1.8 g/d (Marine oil)	EPA+DHA	0.7 g/d (Marine oil)	2 mo	Pill count	312	65.6	312	65.2	0 (−2.5, 2.5)	NS
Finnegan 2003 12663273 UK	Healthy	EPA+DHA	1.7 g/d (marine oil capsule and margarine)	EPA+DHA	0.8 g/d (marine oil margarine)	6 mo	Pill count	31	51.74	30	52.90	−1.4 (−5.2, 2.5)	nd

Table 42. High density lipoprotein cholesterol: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline, mg/dL	Ctrl N	Ctrl Baseline, mg/dL	Net Chg, mg/dL (95% CI)	Reported P value
Sanders 2011 21865334 UK	Healthy	EPA+DHA	1.8 g/d(suppl=marine oil)	EPA+DHA	0.9 g/d (marine oil)	1 y	Pill Count, Plasma Check	80	65.6	81	65.6	3.9 (−1.6, 9.3)	nd
		EPA+DHA	1.8 g/d (marine oil)	EPA+DHA	0.45 g/d (marine oil)	1 y	Pill Count, Plasma Check	80	65.6	80	61.8	0 (−5.5, 5.5)	nd
		EPA+DHA	0.9 g/d (marine oil)	EPA+DHA	0.45 g/d (marine oil)	1 y	Pill Count, Plasma Check	81	65.6	80	61.8	−3.9 (−9.3, 1.6)	nd
Ballantyne 2012 22819432 U.S.	At risk	EPA+DHA	4 g/d (Marine oil)	EPA+DHA	2 g/d (Marine oil)	3 mo	nd	226	37	234	38	0 (nd)	
Kastelein 2014 24528690 Europe	At risk	EPA+DHA	3 g/d (Marine oil) [E:D 2.75]	EPA+DHA	2.25 g/d (Marine oil) [E:D 2.75]	3 mo	Pill count	99	28.7	97	28.0	0.6 (−1.1, 2.3)	nd
		EPA+DHA	3 g/d (Marine oil) [E:D 2.75]	EPA+DHA	1.5 g/d (Marine oil) [E:D 2.75]	3 mo	Pill count	99	28.7	99	27.3	−0.4 (−2.0, 1.3)	nd
		EPA+DHA	2.25 g/d (Marine oil) [E:D 2.75]	EPA+DHA	1.5 g/d (Marine oil) [E:D 2.75]	3 mo	Pill count	97	28.0	99	27.3	−1.0 (−2.6, 0.7)	nd
Oh, 2014, 25147070 Korea	At risk	EPA+DHA	4 g/d (Marine oil)	EPA+DHA	2 g/d (Marine oil)	2 mo	Pill count	44	40	43	43	1 (−2.2, 4.2)	
		EPA+DHA	4 g/d (Marine oil)	EPA+DHA	1 g/d (Marine oil)	2 mo	Pill count	44	40	44	41	0 (3.5, 3.5)	
		EPA+DHA	2 g/d (Marine oil)	EPA+DHA	1 g/d (Marine oil)	2 mo	Pill count	43	43	44	41	−3 (6.4, .4)	
Tatsuno 2013 24314359 Japan	At risk	EPA+DHA	3.36 g/d (Ethyl esters) E:D 1.24	EPA+DHA	1.68 g/d (Ethyl esters) E:D 1.24	1 y	Pill count	206	45.8	210	45.7	1 (−0.1, −1.2)	nd
Maki 2013 23998969 U.S.	At risk	EPA+DHA	4 g/d total oil (free FA oil)	EPA+DHA	4 g/d total oil (free FA oil)	1.5 mo	Biomarker confirmation	207	38.8	209	38.7	0.4 (−1.67, 2.47)	NS

Table 42. High density lipoprotein cholesterol: RCTs (continued)

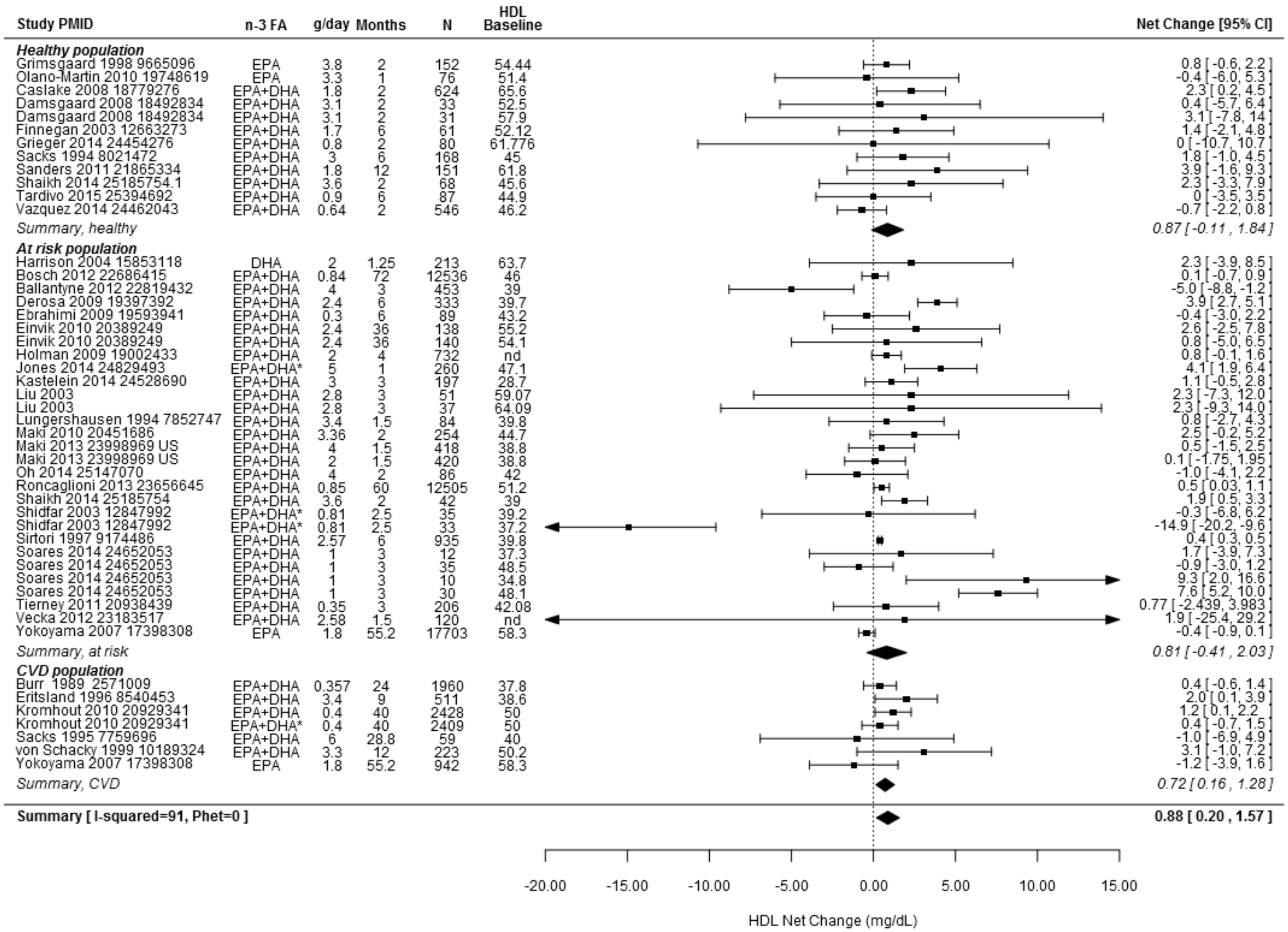
Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline, mg/dL	Ctrl N	Ctrl Baseline, mg/dL	Net Chg, mg/dL (95% CI)	Reported P value
ALA vs Placebo													
Finnegan 2003 12663273 UK	Healthy	ALA	4.5 g/d (rapeseed oil margarine)	Placebo	0	6 mo	Pill count	30	49.81	30	52.12	0.5 (−3.1, 4.1)	nd
Baxheinrich 2012 22894911 Germany	At risk	ALA	3.46 g/d (plant oil)	Placebo	ALA: 0.78 g/d	6 mo	Dietary records	40	52.90	41	55.21	2.3 (−3.0, 7.6)	0.235
Jones 2014 24829493 Canada	At risk	ALA	5.9 g/d (canola)	Placebo	0.2 g/d (CornSaff)	4 wk	Assessed by coordinators	130	47.10	130	47.10	0.1 (−2.3, 2.4)	NS
		ALA	1.4 g/d (canolaOleic)	Placebo	0.2 g/d (CornSaff)	4 wk	Assessed by coordinators	130	47.10	130	47.10	−0.3 (−2.6, 2.1)	NS
Rodriguez-Leyva 2013 24126178 Canada	At risk	ALA	5.9 g/d (flaxseed)	Placebo	0	1 y	Plasma ALA and enterolignan levels	43	46.3	41	46.7	−3.5 (−8.2, 1.2)	0.13
Kromhout 2010 20929341 Netherlands	CVD	ALA	2 g/d (plant oil)	Placebo	0	40 mo	Audit of unused margarine tubs returned	1197	49	1236	49	−0.8 (−1.8, 0.3)	NS
		ALA (+EPA+DHA)	2 g/d (plant oil)	(EPA+DHA)	0			1212	50	1192	50	−1.5 (−2.6, −0.5)	nd
ALA vs ALA (doses)													
Jones 2014 24829493 Canada	At risk	ALA	5.9 g/d (canola)	ALA	1.4 g/d (canolaOleic)	4 wk	Assessed by coordinators	130	47.10	130	47.10	0.3 (−2, 2.6)	NS

Table 42. High density lipoprotein cholesterol: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline, mg/dL	Ctrl N	Ctrl Baseline, mg/dL	Net Chg, mg/dL (95% CI)	Reported P value
Marine oil vs ALA													
Finnegan 2003 12663273 UK	Healthy	EPA+DHA	1.7 g/d (marine oil capsule and marine oil margarine)	ALA	4.5 g/d (rapeseed oil margarine)	6 mo	Pill count	31	51.74	30	49.81	0.9 (−2.8, 4.7)	nd
		EPA+DHA	0.8 g/d (marine oil margarine)	ALA	4.5 g/d (ALA margarine)	6 mo	Pill count	30	52.90	30	49.81	2.3 (−1.7, 6.3)	nd
Kromhout 2010 20929341 Netherlands	CVD	EPA+DHA	0.4 g/d (Marine oil) [E:D 3:2]	ALA	2 g/d (plant oil)	40 mo	Audit of unused margarine tubs returned	1192	50	1197	49	1.9 (0.9, 3.0)	nd
SDA vs Placebo													
Pieters 2015 25226826 Netherlands	At risk	SDA	1.2 g/d (suppl)	Placebo	0	1.5 mo	nd	32	52.51	32	51.43	1.16 (−0.39,2.71)	0.18
SDA vs Marine oil													
Kuhnt 2014 24553695 Germany	Healthy	SDA	2.0 g/d (suppl)	EPA+DHA+DPA	1.9 g/d (suppl: marine oil)	2 mo	nd	20	55.21	10	63.81	−4.25 (−15.69, 7.19)	
Kuhnt 2014 24553695 Germany	Healthy	SDA	2.0 g/d (suppl)	EPA+DHA+DPA	1.9 g/d (suppl: marine oil)	2 mo	nd	20	61.00	9	74.25	−2.71 (−18.99, 13.58)	

Abbreviations: ALA = alphalinolenic acid, Ctrl = control, CVD = cardiovascular disease, DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, E:D = EPA to DHA ratio, EPA = eicosapentaenoic acid, F/up = followup, FA = fatty acid(s), FFQ = food frequency questionnaire, Int = intervention, n/N = number with outcome/number analyzed, n6:3 = omega-6 to omega-3 fatty acid ratio, n-3 FA = omega-3 fatty acids, ND = no data, NS = not significant, PMID = PubMed Identification number, RCT = randomized controlled trial.

Figure 38. High density lipoprotein cholesterol: Randomized trials of marine oils



Random effects model meta-analysis of n-3 FA versus placebo (or no n-3 FA), with subgroup analyses by population. In all meta-analyses, only studies that reported sufficient results data are included.

Abbreviations: CI = confidence interval, CVD = cardiovascular disease, DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid, HDL = high density lipoprotein cholesterol, n-3 FA = omega-3 fatty acid, Phet = P value of chi-squared test of heterogeneity across studies, PMID = PubMed Identification number.

Triglycerides

Randomized Controlled Trials

Forty-six RCTs provided data on effect of n-3 FA on Tg (Table 43).[46, 51, 53, 56, 58, 61, 62, 67, 70, 75, 76, 90, 94, 96, 97, 99, 103, 105, 107, 115, 116, 119-121, 125, 128, 136, 146, 150-152, 156, 160, 167, 169, 173, 174, 177, 178, 180, 184, 187-189, 194] Compared with other outcomes, a relatively large number of trials, 11, but still a minority, reported Tg among their primary outcome (Brinton 2013, Caslake 2008, Damsgaard 2008, Kastelein 2014, Lungershausen 1994, Pieters 2015, Ras 2014, Rauch 2010, Shidfar 2003, Sirtori 1997, Vazquez 2014); however, Rauch 2010 reported Tg to be a secondary outcome in the ClinicalTrials.gov registry.

Total n-3 FA Versus Placebo

Two trials compared total n-3 FA (ALA+EPA+DHA) versus placebo, following 2708 patients for 1 and 40 months; one in people at increased risk for CVD,[180] one in people with CVD.[119] Baseline Tg measurements were 147.8 and 150 mg/dL. Compliance was measured in both studies, but not reported. The trial in an at risk population found a statistically significant decrease in Tg with combined ALA 1.2 g/d (canola oil) and EPA+DHA+DPA 5 g/d (−27 mg/dL; 95% CI −37.5 to −7.6).[180] The trial in a CVD population found no significant effect on Tg with ALA 2 g/d and EPA+DHA 0.4 g/d.[119]

Marine Oil Versus Placebo

Forty-one trials evaluated the effect of marine oils versus placebo on Tg.[46, 51, 53, 56, 58, 61, 62, 67, 70, 75, 76, 90, 94, 96, 97, 99, 103, 105, 107, 115, 116, 119-121, 125, 128, 136, 146, 150, 151, 156, 160, 166, 173, 174, 177, 180, 187, 189, 194] Doses of EPA+DHA±DPA ranged from 0.3 to 6 g/d (median 2.4 g/d) and followup time ranged from 1 month to 6 years (median 3 months). All but two studies found net decreases in Tg with EPA+DHA. Across populations, the summary net difference in Tg with EPA+DHA versus placebo (or equivalent) was a statistically significant −24 mg/dL (95% CI −31 to −18) among studies reporting sufficient data to be included in meta-analysis. As will be described below, net change Tg varied across studies by mean baseline Tg and, possibly, by EPA+DHA dose, but did not vary significantly by population (Figure 39).

Healthy Population

Fourteen of the trials were conducted in 3,560 generally healthy participants.[61, 75, 94, 97, 103, 107, 128, 136, 146, 151, 173, 174, 187, 189] Two of the trials evaluated both purified EPA and DHA separately (3.3 to 3.8 g/d); the rest evaluated EPA+DHA (0.45 to 3.1 g/d). Followup ranged from 1 to 12 months. Four studies evaluated compliance with pill count or weighed food records. Baseline Tg ranged from 80 to 188 mg/dL. Net difference between marine oil and placebo varied widely across studies from −42 to 7.7 mg/dL. The pooled effect size was a significant −13.2 mg/dL (95% CI −20.2 to −6.2) (Figure 39).

At-Risk-for-CVD Population

Twenty-three trials compared EPA+DHA to placebo (or equivalent) in 48,648 people at increased risk of CVD.[46, 53, 56, 58, 76, 90, 99, 103, 105, 115, 116, 119, 120, 146, 150, 156, 160, 166, 177, 180, 187, 194, 195] EPA+DHA dosages ranged from 0.3 to 5 g/d and followup ranged from 1 month to 6 years. Eleven of the studies measured compliance by pill count, coordinator “assessment,” or self-report. Mean baseline Tg ranged from 111 to 315 mg/d in 15 of the trials, was 682 mg/d in one study that included only people with severe hypertriglyceridemia (≥500 mg/d),[177] and was not reported in four trials. Excluding the trial of severe hypertriglyceridemia, net change Tg with EPA+DHA ranged from −109 (difference between final values) to 15 mg/dL. The study of people with hypertriglyceridemia found large, significant net reductions of Tg with EPA+DHA doses of 1.5, 2.25, and 3 g/d of −156 mg/d (lower two doses) and −173 mg/d (3 g/d). The pooled effect size (with the hypertriglyceridemia study) was a significant −45.1 mg/dL (95% CI −61.2 to −29.0) (Figure 39); without Kastelein, the pooled net difference was identical.

CVD Population

Ten trials compared EPA+DHA to placebo in 29,018 people with CVD.[51, 56, 62, 67, 70, 90, 96, 119, 121, 125] EPA+DHA dosages ranged from 0.4 to 6 g/d and followup ranged from 9 months to 4.6 y. All but one study measured, but few reported, compliance. Mean baseline Tg ranged from 137 to 191 mg/d when reported. Across trials, net change Tg with EPA+DHA ranged from −50 to −3 mg/dL. The pooled effect size was a significant −20.1 mg/dL (95% CI −33.5 to −6.7) (Figure 39).

RCT Subgroup Analyses

The four studies that examined subgroup effects of EPA+DHA on Tg based on statin use all found no significant interaction between marine oil and statins (Carrepeiro 2011, Holman 2009, Liu 2003, Vecka 2012).[46, 99, 128, 156] In one study each, no significant differences in effect were seen in those on high or low linoleic acid diets (Damsgaard 2008),[94] in those receiving or not general diet counseling (Einvik 2010),[115] or in older or younger age groups (Caslake 2008).[97] One study found a significantly larger effect in people also taking a multivitamin (−76 mg/dL) than in those without the multivitamin (−28 mg/dL; P interaction <0.05), but Tg increased in only the group taking multivitamins and placebo (Earnest 2012).[150] In contrast, one found a net increase in Tg concentration in people also taking vitamin C (15 mg/dL, due to a smaller decrease in Tg concentration than in the vitamin C alone group) and a large net decrease in people not taking vitamin C (−109 mg/dL), but this difference in effect was not reported to be significantly different.[76] One study examined gender effect and found that men on higher dose EPA+DHA (1.8 g/d) had a larger effect than women (P<0.038; difference not reported), but similar effects at lower dose (0.7 g/d) (Caslake 2008).[97] One study found no difference in effect of EPA between people with either impaired glucose tolerance or noninsulin dependent diabetes or normoglycemia (Sirtori 1997), but among those with diabetes, those with lower HDL-c (≤35 mg/dL) had a greater effect of EPA+DHA on Tg (−23.3%) than those with higher HDL-c (−16.9%; P interaction <0.05).[58] This difference in effect by HDL-c levels, however, was not seen among those with normoglycemia. One study of people with diabetes (Brinton 2013) found that with higher dose EPA+DHA (4 g/d) there was no difference in change in Tg by hemoglobin A1c level, but at 2 g/d, those with higher A1c levels (>6.8%) had a smaller effect that was nonsignificant (−5% net change) compared to those with lower A1c levels (−15%, P<0.01), although the study did not analyze whether the interaction was significant.[195]

By meta-regression, across studies there were no significant differences in effect (interactions) by population (at risk P=0.30; CVD P=0.52) or followup duration (P=0.49). However, both mean baseline Tg level and EPA+DHA dose across studies were significantly associated with net change Tg. The primary metaregression was conducted excluding an outlier study (Kastelein 2014) of people with severe hypertriglyceridemia (Tg >500 mg/dL at baseline), who were found to have large net changes with EPA+DHA 3, 2.25, and 1.5 g/d.[177] Analyses with this study, however, yielded similar results. Controlling for both variables, each increase in mean baseline Tg level by 1 mg/dL was associated with a greater net change Tg of −0.15 mg/dL (95% CI −0.22 to −0.08; P<0.0001) (Figure 40). Each increase of EPA+DHA dose by 1 g/d was also associated with a greater net change Tg of −5.9 mg/dL (95% CI −9.9 to −2.0; P=0.003) (Figure 41). By spline analysis of the meta-regression, there was no clear inflection point where the association between dose and net change Tg substantially changed.

Marine Oil, Comparison of Different Doses

Six RCTs directly compared different doses of marine oils (EPA+DHA),[75, 97, 169, 177, 194, 195] between 0.7 and 4 g/d. The trials compared EPA+DHA doses between 0.7 and 4 g/d. Only one of the six trials found a significant difference between higher (3.4 g/d) and lower (1.7 g/d) EPA+DHA (ethyl esters).[169] Although, most trials found no significant difference, the differences in effect on Tg between doses ranged from −39 to 6 mg/dL. A possible pattern could be discerned such that higher doses of 3.4 or 4 g/d reduced Tg by at least 30 mg/dL more than lower doses of 1 to 2 g/d (Brinton 2013: 4 vs. 2 g/d; Oh 2014: 4 vs 2 g/d and 2 vs. 1 g/d; Tatsuno 2013: 3.4 vs. 1.7 g/d). Higher doses ≤3 g/d (1.7−3 g/d) yielded much smaller relative differences in Tg change compared to lower doses (0.7−2.25 g/d) (−17 to 6 mg/dL) (Caslake 2008: 1.8 vs. 0.7 g/d; Finnegan 2003: 1.7 vs. 0.8 g/d; Kastelein 2014: 3 vs. 2.25 g/d, 3 vs. 1.5 g/d, and 2.25 vs. 1.5 g/d; Oh 2014: 2 vs. 1 g/d).

ALA Versus Placebo

Five trials compared ALA supplementation versus placebo (or equivalent), following 4940 patients for 1 to 40 months; one in healthy people,[75] three in people at increased risk for CVD,[152, 167, 180] and one in people with CVD.[119] Doses of ALA ranged from 1.4 to 5.9 g/d, and baseline Tg measurements ranged from 144 to 150 mg/dL. Compliance was measured in all studies, but not reported. All trials found no significant effect of total n-3 FA supplementation on Tg; the estimates of the net differences ranged from −22 to 22, mostly with wide confidence intervals.

SDA Versus Placebo

Pieters 2015 compared 1.2 g/d SDA to placebo in 32 patients at risk for CVD. At 1.5 month followup, no significant differences in change in Tg were found.[188]

SDA Versus Marine Oil

Kuhnt 2014 compared 2.0 g/d SDA and 1.9 g/d EPA+DHA+DPA in 59 healthy people (broken into cohorts based on body mass index and age). At 2 month followup, no significant differences in change in Tg were found.[178]

Comparison of Different Specific n-3 FA

Two trials directly compared EPA (3.8 or 3.3 g/d) to DHA (3.6 or 3.7 g/d), one of which evaluated EPA and DHA ethyl esters,[61] one of which evaluated EPA- and DHA-enriched oils.[107] Neither found a significant difference in effect on Tg between EPA and DHA. One trial compared two doses of EPA+DHA (3.4 and 1.7 g/d) to EPA 1.8 g/d (all ethyl esters),[169] finding significantly larger net reductions in Tg with either dose of EPA+DHA than EPA alone. Two trials compared EPA+DHA to ALA, one comparing two doses of EPA+DHA (1.7 and 0.8 g/d) to

ALA 4.5 g/d,[75] one comparing 0.4 g/d EPA+DHA to 2 g/d ALA.[119] A possible dose effect of EPA+DHA was found in that the comparison with the highest dose of EPA+DHA (1.7 g/d) found a significantly greater effect of EPA+DHA than ALA (−28 mg/dL; 95% CI −49 to −7) (Finnegan 2003), while in the same study a lower dose (0.8 g/d) had a smaller nonsignificant difference (−14 mg/dL), and the other study (Kromhout 2010), with EPA+DHA 0.4 g/d had no differential effect (2.7 mg/dL).

Observational Studies

Observational studies did not evaluate Tg.

Table 43. Triglycerides: RCTs

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline, mg/dL	Ctrl N	Ctrl Baseline, mg/dL	Net Chg, mg/dL (95% CI)	Reported P value
Total n-3 FA vs Placebo													
Jones 2014 24829493 Canada	At risk	ALA + EPA+DHA	ALA: 1.2 g/d, EPA: 0.1 g/d, DHA: 3.5 g/d, DPA: 1.4 g/d (canola+DHA)	Placebo	0.2 g/d (CornSaff)	4 wk	Assessed by coordinators	130	147.8	130	147.8	−22.5 (−37.5, −7.6)	<0.05
Kromhout 2010 20929341 Netherlands	CVD	ALA + EPA+DHA	0.4 g/d EPA+DHA; 2 g/d ALA (Marine oil, plant oil) [E:D 3:2]	Placebo	0	40 mo	Audit of unused margarine tubs returned	1212	145	1236	150	−8 (−16.6, 0.7)	
Marine oil vs Placebo													
Ras 2014 25122648 Scandinavia	Healthy	EPA+DHA±DPA	0.9 g/d EPA+DHA	Placebo	0	1 mo	nd	64	93.0	64	94.0	−2.5 (nd)	nd
	Healthy	EPA+DHA±DPA	1.3 g/d EPA+DHA	Placebo	0	1 mo	nd	62	91.2	64	94.0	−4.8 (nd)	nd
	Healthy	EPA+DHA±DPA	1.8 g/d EPA+DHA	Placebo	0	1 mo	nd	62	94.0	64	94.0	−10.7 (nd)	nd
Grimsgaard 1998 9665096 Norway	Healthy	EPA	3.8 g/d (Ethyl ester)	Placebo	0	2 mo	pill count	75	108.85	77	107.96	−23 (−33.5, −12.6)	0.0001
		DHA	3.6 g/d (Ethyl ester)	Placebo	0	2 mo	pill count	72	109.73	77	107.96	−29.2 (−38.4, −20.0)	0.0001
Olano-Martin 2010 19748619 UK	Healthy	EPA	3.3 g/d (Marine oil)	Placebo	0	1 mo	nd	38	143.4	38	123.0	−41.6 (−69.9, −13.3)	
		DHA	3.7 g/d (Marine oil)	Placebo	0	1 mo	nd	38	132.7	38	123.0	−27.4 (−45.3, −9.5)	

Table 43. Triglycerides: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline, mg/dL	Ctrl N	Ctrl Baseline, mg/dL	Net Chg, mg/dL (95% CI)	Reported P value
Carrepeiro 2011 21561620 Brazil	Healthy	EPA+DHA	2.4 g/d (Marine oil)	Placebo	0	6 mo	nd	23	101.2	23	112.9	−1.8 (−3.8, 0.2)	0.077
		EPA+DHA + Statin	2.4 g/d (Marine oil)	Placebo + Statin	0	6 mo	nd	20	140.1	20	120.8	−2.0 (−4.0, 0)	0.054
Caslake 2008 18779276 UK	Healthy	EPA+DHA	1.8 g/d (Marine oil)	Placebo	0	2 mo	Pill count	312	113.3	312	112.4	−1.4 (−10.8, 7.9)	<0.017
		EPA+DHA	0.7 g/d (Marine oil)	Placebo	0	2 mo	Pill count	312	110.6	312	112.4	−8.0 (−17.3, 1.3)	<0.017
Damsgaard 2008 18492834 Scandinavia	Healthy	EPA+DHA + high LA	3.1 g/d (Marine oil) [E:D 1.64]	Placebo + high LA	0	2 mo	nd	17	71.7	16	79.6	−7.3 (−14.3, −0.4)	
		EPA+DHA + low LA	3.1 g/d (Marine oil) [E:D 1.64]	Placebo + low LA	0	2 mo	nd	14	113.3	17	89.4	−18.1 (−27.8, −8.5)	
Finnegan 2003 12663273 UK	Healthy	EPA+DHA	1.7 g/d (marine oil capsule and marine oil margarine)	Placebo	0	6 mo	Pill count	31	141.59	30	149.56	−5.7 (−24.0, 12.7)	nd
		EPA+DHA	0.8 g/d (marine oil margarine)	Placebo	0	6 mo	Pill count	30	146.02	30	149.56	7.7 (−3.6, 19.0)	nd
Grieger 2014 24454276 Australia	Healthy	EPA+DHA	0.8 g/d (fish diet)	Placebo	EPA: 0.017 g/d, DHA: 0.004 g/d (red meat diet)	8 wk	Weighed food records	43	97.35	37	123.89	0 (−24.5, 24.5)	nd

Table 43. Triglycerides: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline, mg/dL	Ctrl N	Ctrl Baseline, mg/dL	Net Chg, mg/dL (95% CI)	Reported P value
Sanders 2011 21865334 UK	Healthy	EPA+DHA	1.8 g/d (suppl=marine oil)	Placebo	0	1 y	Pill Count, Plasma Check	80	97.3	71	102.6	−15.0 (−27.4, −2.7)	nd
		EPA+DHA	0.9 g/d (suppl=marine oil)	Placebo	0	1 y	Pill Count, Plasma Check	81	100	71	102.6	−3.5 (−16.5, 9.4)	nd
		EPA+DHA	0.45 g/d (suppl=marine oil)	Placebo	0	1 y	Pill Count, Plasma Check	80	100.9	71	102.6	−2.7 (−15.8, 10.5)	nd
Shaikh 2014 25185754 U.S.	Healthy	EPA+DHA	3.6 g/d [E:D 6:1]	Placebo	0	2 mo	Pill count	36	154.9	32	131.0	−28.3 (−63.0, 6.4)	0.11
Tardivo 2015 25394692 Brazil	Healthy	EPA+DHA	0.9 g/d [E:D 3:2]	Placebo	0	6 mo	Pill count	44	192.5	43	187.6	−26 (−50.9, −1.1)	nd
Vazquez 2014 24462043 Spain	Healthy	EPA+DHA	0.64 g/d [E:D 1:3]	Placebo	0	2 mo	Assessed by trained dieticians at each visit	273	170.6	273	170.6	−4.0 (−15.1, 7.2)	0.368
Bosch 2012 22686415 Canada	At risk	EPA+DHA	EPA: 0.465 g/d, DHA: 0.375 g/d (Marine oil) [E:D 1.24]	Placebo	0	6 y	FFQ at baseline, 2 y, and end of study (adherence 88% at end of study)	6281	142	6255	140	−14.5 (−22.8, −6.2)	<0.001
Ballantyne 2012 22819432 U.S.	At risk	EPA+DHA	4 g/d (marine oil)	Placebo	0	3 mo	nd	226	264.8	227	259	−23.2 (−34.9, −11.5)	<0.0001
		EPA+DHA	2 g/d (marine oil)	Placebo	0	3 mo	nd	234	254	227	259	−9.8 (−17.3, −2.3)	0.0005

Table 43. Triglycerides: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline, mg/dL	Ctrl N	Ctrl Baseline, mg/dL	Net Chg, mg/dL (95% CI)	Reported P value
Derosa 2009 19397392 Italy	At risk	EPA+DHA	EPA: 0.9 g/d, DHA: 1.5 g/d (marine oil)	Placebo	0	6 mo	Pill count	168	182.6	165	189.3	−59.2 (−67.4, −51.0)	nd
Earnest 2012 22811376 U.S.	At risk	EPA+DHA	2 g/d EPA+DHA (Marine oil) [E:D ratio 0.76:0.44]	Placebo	0	3 mo	Pill count	21	111	23	111	−27.7 (−51.4, −4.0)	
		EPA+DHA + multivitamin	2 g/d EPA+DHA + (Marine oil) [E:D ratio 0.76:0.44]	Placebo + multivitamin	0	3 mo	Pill count	25	116	23	113	−75.7 (−98.5, −52.9)	
Ebrahimi 2009 19593941 Iran	At risk	EPA+DHA	EPA: 0.18, DHA: 0.12 (marine oil)	Placebo	0	6 mo	nd	47	155.8	42	145.1	−7.1 (nd)	nd
Einvik 2010 20389249 Norway	At risk	EPA+DHA +/- diet	2.4 g/d EPA+DHA (Marine oil) [E:D ratio 0.66:1.1]	Placebo +/- diet	0	3 y	Pharmacy records/pill count	282	141.6	281	132.7	−35.4 (−97.5, 26.7)	
	At risk	EPA+DHA	2.4 g/d EPA+DHA (Marine oil) [E:D ratio 0.66:1.1]	Placebo	0	3 y	Pharmacy records/pill count	70	152.2	68	151.3	−15.0 (−41.3, 11.2)	--
		EPA+DHA + diet	2.4 g/d EPA+DHA (Marine oil) [E:D ratio 0.66:1.1]	Placebo + diet	0	3 y	Pharmacy records/pill count	69	154.9	71	154.0	−20.4 (−44.3, 3.6)	
Holman 2009 19002433 UK	At risk	EPA+DHA	2 g/d	Placebo	0	4 mo	Pill count	371	132.7	361	137.2	−6.2 (−15.6, 3.2)	0.003

Table 43. Triglycerides: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline, mg/dL	Ctrl N	Ctrl Baseline, mg/dL	Net Chg, mg/dL (95% CI)	Reported P value
Jones 2014 24829493 Canada	At risk	EPA+DHA (+ALA)	EPA: 0.1 g/d, DHA: 3.5 g/d, DPA: 1.4 g/d (canola+DHA)	(ALA)	0	4 wk	Assessed by coordinators	130	147.8	130	147.8	−28 (−42.6, −13.4)	<0.05
Liu 2003 Sweden	At risk	EPA+DHA	EPA: 1.7 g/d, DHA: 1.1 g/d	Placebo	0	12 wk	Pill count	29	146.90	22	142.48	−39.8 (−76.4, −3.3)	<0.05
		EPA+DHA + simvastatin	EPA: 1.7 g/d, DHA: 1.1 g/d	Placebo + simvastatin	0	12 wk	Pill count	19	154.87	18	136.28	−35.4 (−79.6, 8.8)	<0.05
Lungershausen 1994 7852747 Australia	At risk	EPA+DHA	EPA: 1.9 g/d, DHA: 1.5 g/d (marine oil)	Placebo	0	6 wk	Pill count	42	141.59	42	141.59	−28.3 (−54.8, −1.8)	0.05
Kastelein 2014 24528690 Europe	At risk	EPA+DHA	EPA: 2.20 g/d, DHA: 0.80 g/d	Placebo	0	12 wk	Pill count	99	655	98	682	−173.1 (−250.3, −95.8)	<0.001
		EPA+DHA	EPA: 1.65 g/d, DHA: 0.60 g/d	Placebo	0	12 wk	Pill count	97	728	98	682	−156.3 (−238.8, −73.8)	<0.01
		EPA+DHA	EPA: 1.10 g/d, DHA: 0.40 g/d	Placebo	0	12 wk	Pill count	99	717	98	682	−156.4 (−238.1, −74.6)	<0.01
Maki 2010 20451686 U.S.	At risk	EPA+DHA (+simvastatin)	EPA: 1.86 g/d, DHA: 1.5 g/d	Placebo (+simvastatin)	0	8 wk	Pill count	122	282	132	286.7	−68.8 (−89.3, −48.3)	<0.001
Maki 2013 23998969 U.S.	At risk	EPA+DHA	4 g/d total oil (free FA oil) [nd]	Placebo	0	1.5 mo	Biomarker confirmation	207	287	211	280	−42 (−59.3, −24.7)	<0.001
	At risk	EPA+DHA	2 g/d total oil (free FA oil) [nd]	Placebo	0	1.5 mo	Biomarker confirmation	209	284	211	280	−28 (−44.0, −12.0)	<0.001

Table 43. Triglycerides: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline, mg/dL	Ctrl N	Ctrl Baseline, mg/dL	Net Chg, mg/dL (95% CI)	Reported P value
Oh, 2014, 25147070 Korea	At risk	EPA+DHA	4 g/d (Marine oil)	Placebo	0	2 mo	Pill count	44	287	42	281	−62.0 (−102.5, −21.5)	
		EPA+DHA	2 g/d (Marine oil)	Placebo	0	2 mo	Pill count	43	267	42	281	−30.0 (−73.1, 13.1)	
		EPA+DHA	1 g/d (Marine oil)	Placebo	0	2 mo	Pill count	44	286	42	281	−23.0 (−60.6, 14.6)	
Roncaglioni 2013 23656645 Italy	At risk	EPA+DHA	0.85 g/d (Marine oil)	Placebo	0	5 y	Self-reported	6239	150	6266	150	−8.1 (−11.6, −4.5)	<0.0001
Shaikh 2014 25185754 U.S.	At risk	EPA+DHA	3.6 g/d [E:D 6:1]	Placebo	0	2 mo	Pill count	20	274.3	22	263.7	−95.6 (−149.4, −41.8)	0.0005
Shidfar 2003 12847992 Iran	At risk	EPA+DHA	EPA 0.5 g/d, DHA 0.31 g/d (suppl) [E:D 1.6]	Placebo	0	2.5 mo	nd	16	304	19	311.5	−109.1 (−176.9, −41.4)	
		EPA+DHA + vitamin C	EPA 0.5 g/d, DHA 0.31 g/d (suppl) [E:D 1.6]	Placebo + vitamin C	0	2.5 mo	nd	16	297.3	17	315	15.2 (−43.9, 74.3)	
Sirtori 1997 9174486 Italy	At risk	EPA+DHA	2.57 g/d (Marine oil) [E:D 1.45]	Placebo	0	6 mo	nd	470	293.8	465	297.3	−37.2 (−51.0, −23.3)	
Tierney 2011 20938439 Europe	At risk	EPA+DHA	EPA 0.26 g/d, DHA 0.19 g/d (suppl) [E:D 1.5]	Placebo	0	3 mo	Pill count and plasma FA	100	148.67	106	147.79	−19.47 (−44.664, 5.726)	nd

Table 43. Triglycerides: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline, mg/dL	Ctrl N	Ctrl Baseline, mg/dL	Net Chg, mg/dL (95% CI)	Reported P value
Vecka 2012 23183517 Czech	At risk	EPA+DHA	2.58 g/d (Marine oil) [E:D 2.74]	Placebo	0	1.5 mo	nd	60	nd	60	nd	−82.3 (−852.6, 688) [difference of final values]	<0.001
Yokoyama 2007 17398308 Japan	At risk (no previous CHD)	EPA+Statin	1.8 g/d (Ethyl ester)	Statin	0	4.6 y	Local physicians monitored but compliance level was not reported	8841	153.1	8862	153.1	−8.9 (−11.0, −6.7)	<0.0001
Eritsland 1996 8540453 Norway	CVD	EPA+DHA	3.4 g/d (Marine oil)	Placebo	0	9 mo	nd	260	171.62	251	184.96	−32.0 (−48.4, −15.6)	<0.001
Kromhout 2010 20929341 Netherlands	CVD	EPA+DHA	0.4 g/d (Marine oil) [E:D 3:2]	Placebo	0	40 mo	Audit of unused margarine tubs returned	1192	144	1236	150	−2.7 (−13.8, 8.5)	
		EPA+DHA (+ALA)	0.4 g/d (Marine oil) [E:D 3:2]	(ALA)	0			1212	145	1197	146	−2.7 (−11.3, 6.0)	
Marchioli 2002 11997274 Italy	CVD	EPA+DHA	0.850−0.882 g/d (Marine Oil)	Placebo	0	42 mo	Measured at followup times	5666	162	5668	162	−10 (nd)	
Nilsen 2001 11451717 Norway	CVD	EPA+DHA	4 g/d (Marine oil) [E:D 1:2]	Placebo	0	Median 1.5 y	nd	120	145.1	121	137.2	−37.42 % (nd)	nd

Table 43. Triglycerides: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline, mg/dL	Ctrl N	Ctrl Baseline, mg/dL	Net Chg, mg/dL (95% CI)	Reported P value
Nodari 2011 21215550 Italy	CVD	EPA+DHA	2 g/d EPA+DHA (Marine oil) [E:D ratio 0.9:1.5]	Placebo	0	1 y	Pill count	67	149	66	154	−7.0 (−29.0, 15.0)	--
Rauch 2010 21060071 Germany	CVD	EPA+DHA	1 g/d (Marine oil) [E:D ratio 0.460:0.380]	Placebo	0	1 y	Pill count	1925	Not reported	1893	Not reported	−5 (nd)	<0.01
Sacks 1995 7759696 U.S.	CVD	EPA+DHA	EPA: 2.88 g/d DHA: 3.12 g/d (Marine oil)	Placebo	0	2.4 y	Pill count (80% n3, 90% placebo)	31	128	28	137	−33.0 (−66.6, 0.6)	
Tavazzi 2008 18757090 Italy	CVD	EPA+DHA	EPA: 0.386−0.401 g/d DHA: 0.464−0.481 g/d (Ethyl esters) [E:D 0.83]	Placebo	0	3.9 y	Measured at clinical exams, patient was compliant if drug administered for 80% of days. Both groups had ~30% compliance	3494	1.42(median)	3481	nd	−7.1 (nd)	<0.0001
Von Schacky 1999 10189324 Canada	CVD	EPA+DHA	3.3 g/d	Placebo	0	12 mo	Pill count	112	194.7	111	191.2	−49.6 (−81.4, −17.7)	<0.01

Table 43. Triglycerides: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline, mg/dL	Ctrl N	Ctrl Baseline, mg/dL	Net Chg, mg/dL (95% CI)	Reported P value
Yokoyama 2007 17398308 Japan	CVD	EPA+Statin	1.8 g/d (Ethyl ester)	Statin	0	4.6 y	Local physicians monitored but compliance level not reported	485	159.3	457	159.3	−15.1 (−23.7, −6.4)	<0.001
Marine oil vs Marine oil (dose)													
Ras 2014 25122648 Scandinavia	Healthy	EPA+DHA±DPA	1.8 g/d EPA+DHA	EPA+DHA±DPA	0.9 g/d EPA+DHA	1 mo	nd	62	94.0	64	93.0	−8.3 (nd)	nd
	Healthy	EPA+DHA±DPA	1.8 g/d EPA+DHA	EPA+DHA±DPA	1.3 g/d EPA+DHA	1 mo	nd	62	94.0	62	91.2	−5.9 (nd)	nd
	Healthy	EPA+DHA±DPA	1.3 g/d EPA+DHA	EPA+DHA±DPA	0.9 g/d EPA+DHA	1 mo	nd	62	91.2	62	93.0	−2.3 (nd)	nd
Caslake 2008 18779276 UK	Healthy	EPA+DHA	1.8 g/d (Marine oil)	EPA+DHA	0.7 g/d (Marine oil)	2 mo	Pill count	312	113.3	312	110.6	6.2 (−2.6, 15.0)	NS
Finnegan 2003 12663273 UK	Healthy	EPA+DHA	1.7 g/d (marine oil capsule and marine oil margarine)	6 mo	0.8 g/d (marine oil margarine)	EPA+DHA	Pill count	31	141.59	30	146.02	−13.4 (−30.8, 4.0)	nd
Sanders 2011 21865334 UK	Healthy	EPA+DHA	1.8 g/d(suppl=marine oil)	EPA+DHA	0.9 g/d (marine oil)	1 y	Pill Count, Plasma Check	80	97.3	81	100	−11.5 (−24.2, 1.2)	nd
		EPA+DHA	1.8 g/d (marine oil)	EPA+DHA	0.45 g/d (marine oil)	1 y	Pill Count, Plasma Check	80	97.3	80	100.9	−12.4 (−88.4, 63.7)	nd
		EPA+DHA	0.9 g/d (marine oil)	EPA+DHA	0.45 g/d (marine oil)	1 y	Pill Count, Plasma Check	81	100	80	100.9	−0.9 (−77.0, 75.3)	nd

Table 43. Triglycerides: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline, mg/dL	Ctrl N	Ctrl Baseline, mg/dL	Net Chg, mg/dL (95% CI)	Reported P value
Ballantyne 2012 22819432 23835245 U.S.	At risk	EPA+DHA	4 g/d (marine oil)	EPA+DHA	2 g/d (Marine oil)	3 mo	nd	226	264.8	234	254	−32.1 (nd)	
Kastelein 2014 24528690 Europe	At risk	EPA+DHA	3 g/d (Marine oil) [E:D 2.75]	EPA+DHA	2.25 g/d (Marine oil) [E:D 2.75]	3 mo	nd	99	655	99	728	−16.8 (−86.1, 52.6)	nd
		EPA+DHA	3 g/d (Marine oil) [E:D 2.75]	EPA+DHA	1.5 g/d (Marine oil) [E:D 2.75]	3 mo	nd	99	655	99	717	−16.7 (−85.1, 51.8)	nd
		EPA+DHA	2.25 g/d (Marine oil) [E:D 2.75]	EPA+DHA	1.5 g/d (Marine oil) [E:D 2.75]	3 mo	nd	97	728	99	717	0.1 (−74.3, 74.4)	nd
Oh, 2014, 25147070 Korea	At risk	EPA+DHA	4 g/d (Marine oil)	EPA+DHA	2 g/d (Marine oil)	2 mo	Pill count	44	287	43	267	−32 (−77.2, 13.2)	
		EPA+DHA	4 g/d (Marine oil)	EPA+DHA	1 g/d (Marine oil)	2 mo	Pill count	44	287	44	286	−39 (−79.1, 1.1)	
		EPA+DHA	2 g/d (Marine oil)	EPA+DHA	1 g/d (Marine oil)	2 mo	Pill count	43	267	44	286	−7.0 (−49.7, 35.7)	
Tatsuno 2013 23725919 Japan	At Risk	EPA+DHA	3.36 g/d (Ethyl esters) E:D 1.24	EPA+DHA	1.68 g/d (Ethyl esters) E:D 1.24	12 wk	Pill count	210	277.5	206	269	−37.2 (−53.9, −20.5)	nd
	At risk	EPA+DHA	3.36 g/d (Ethyl esters) E:D 1.24	EPA+DHA	1.68 g/d (Ethyl esters) E:D 1.24	1 y	nd	170	nd	165	nd	−11.6% (−17.9, −5.3)	
Maki 2013 23998969 U.S.	At risk	EPA+DHA	4 g/d total oil (free FA oil) [nd]	EPA+DHA	4 g/d total oil (free FA oil) [nd]	1.5 mo	Biomarker confirmation	207	287	209	284	−14 (−31.3, 3.3)	nd

Table 43. Triglycerides: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline, mg/dL	Ctrl N	Ctrl Baseline, mg/dL	Net Chg, mg/dL (95% CI)	Reported P value
Marine oil vs Marine oil (miscellaneous)													
Olano-Martin 2010 19748619 UK	Healthy	EPA	3.3 g/d (Marine oil)	DHA	3.7 g/d (Marine oil)	1 mo	nd	38	143.4	38	132.7	14.2 (−14.1, 42.5)	
Grimsgaard 1998 9665096 Norway	Healthy	EPA	3.8 g/d (Ethyl ester)	DHA	3.6 g/d (Ethyl ester)	2 mo	pill count	77	108.85	72	109.73	6.2 (−4.0, 16.4)	0.14
Tatsuno 2013 23725919 Japan	At Risk	EPA+DHA	3.36 g/d (Ethyl esters) E:D 1.24	EPA	1.8 g/d (Ethyl ester)	12 wk	Pill count	210	277.5	195	271.8	−35 (−53.3, −16.7)	nd
		EPA+DHA	1.68 g/d (Ethyl esters) E:D 1.24	EPA	1.8 g/d (Ethyl ester)	12 wk	Pill count	206	269	195	271.8	1.7 (−15.7, 19.1)	nd
		EPA+DHA	3.36 g/d (Ethyl esters) E:D 1.24	EPA	1.8 g/d (Ethyl ester)	1 y	nd	170	nd	165	nd	−13.5% (−20.9, −6.0)	
		EPA+DHA	1.68 g/d (Ethyl esters) E:D 1.24	EPA	1.8 g/d (Ethyl ester)	1 y	nd	170	nd	165	nd	−1.9% (−9.6, 5.8)	
ALA vs Placebo													
Finnegan 2003 12663273 UK	Healthy	ALA	4.5 g/d (rapeseed oil margarine)	Placebo	0	6 mo	Pill count	30	146.90	30	149.56	22.0 (2.1, 41.9)	NS
Baxheinrich 2012 22894911 Germany	At risk	ALA	3.46 g/d (plant oil)	Placebo	ALA: 0.78 g/d	6 mo	Dietary records	40	171.68	41	145.13	−22.1 (−59.0, 14.8)	0.020

Table 43. Triglycerides: RCTs (continued)

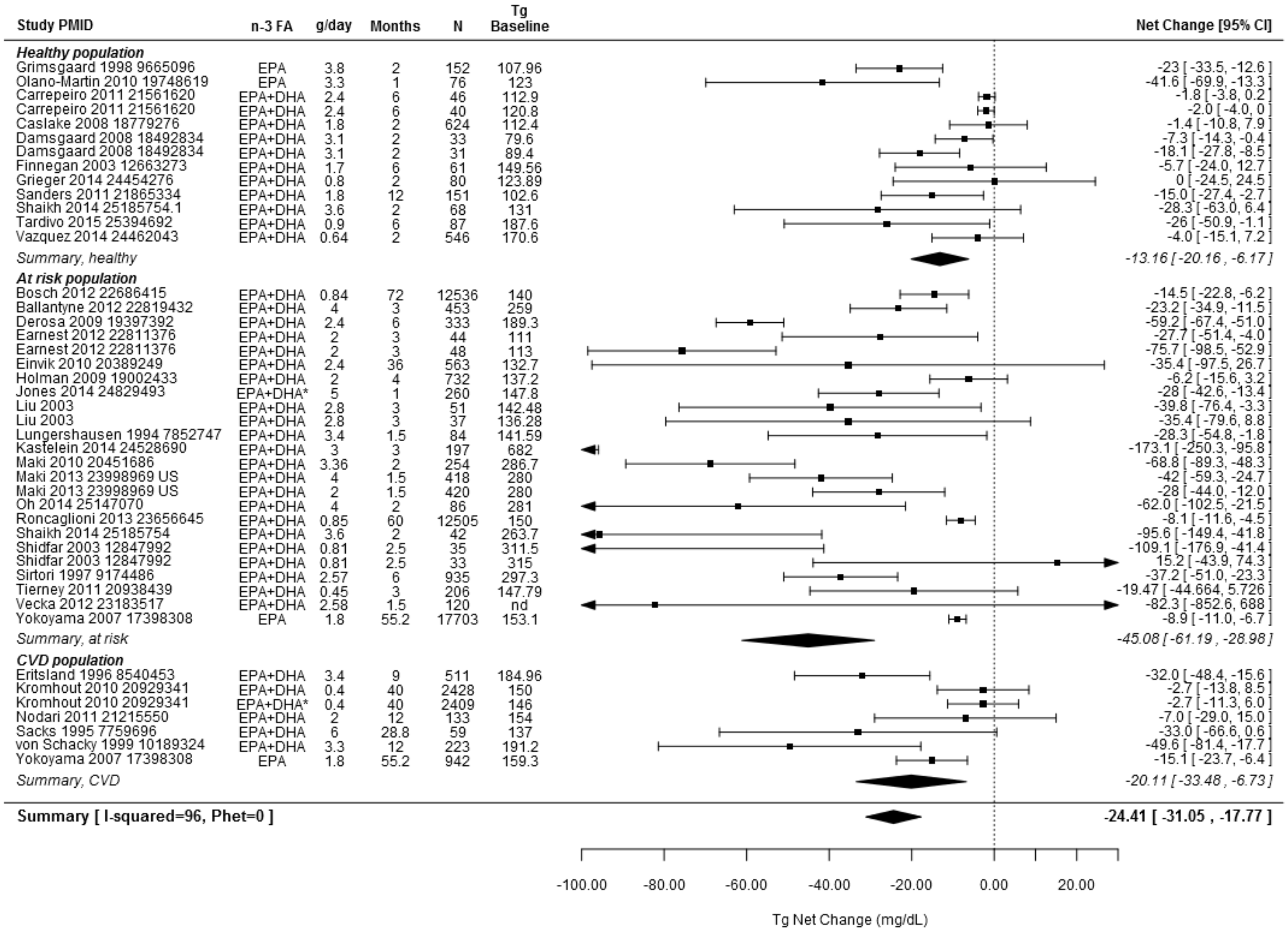
Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline, mg/dL	Ctrl N	Ctrl Baseline, mg/dL	Net Chg, mg/dL (95% CI)	Reported P value
Jones 2014 24829493 Canada	At risk	ALA	5.9 g/d (canola)	Placebo	0.2 g/d (CornSaff)	4 wk	Assessed by coordinators	130	147.8	130	147.8	5.4 (−9.6, 20.3)	NS
			1.4 g/d (canolaOleic)	Placebo	0.2 g/d (CornSaff)	4 wk	Assessed by coordinators	130	147.8	130	147.8	5.5 (−9.4, 20.4)	NS
Rodriguez-Leyva 2013 24126178 Canada	At risk	ALA	5.9 g/d (flaxseed)	Placebo	0	1 y	Plasma ALA and enterolignan levels	43	141.6	41	150.4	26.5 (−4.4, 57.5)	0.07
Kromhout 2010 20929341 Netherlands	CVD	ALA	2 g/d (plant oil)	Placebo	0	40 mo	Audit of unused margarine tubs returned	1197	146	1236	150	−5.3 (−15.1, 4.5)	
		ALA (+EPA+DHA)	2 g/d (plant oil)	(EPA+DHA)	0			1212	145	1192	144	−5.3 (−15.4, 4.8)	
ALA vs ALA (doses)													
Jones 2014 24829493 Canada	At risk	ALA	5.9 g/d (canola)	ALA	1.4 g/d (canolaOleic)	4 wk	Assessed by coordinators	130	147.8	130	147.8	−0.1 (−14.7, 14.5)	NS
EPA+DHA vs ALA													
Finnegan 2003 12663273 UK	Healthy	EPA+DHA	1.7 g/d (marine oil capsule and marine oil margarine)	ALA	4.5 g/d (rapeseed oil margarine)	6 mo	Pill count	31	141.59	30	146.90	−27.7 (−48.7, −6.6)	nd
		EPA+DHA	0.8 g/d (marine oil margarine)	ALA	4.5 g/d (ALA margarine)	6 mo	Pill count	30	146.02	30	146.90	−14.3 (−33.3, 4.8)	nd

Table 43. Triglycerides: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline, mg/dL	Ctrl N	Ctrl Baseline, mg/dL	Net Chg, mg/dL (95% CI)	Reported P value
Kromhout 2010 20929341 Netherlands	CVD	EPA+DHA	0.4 g/d (Marine oil) [E:D 3:2]	ALA	2 g/d (plant oil)	40 mo	Audit of unused margarine tubs returned	1192	144	1197	146	2.7 (−8.5, 13.8)	
SDA vs Placebo													
Pieters 2015 25226826 Netherlands	At risk	SDA	1.2 g/d (suppl)	Placebo	0	1.5 mo	nd	32	120.35	32	110.53	9.73 (−4.73, 24.19)	0.21
SDA vs Marine oil													
Kuhnt 2014 24553695 Germany	Healthy	SDA	2.0 g/d (suppl)	EPA+DHA+DPA	1.9 g/d (suppl: marine oil)	2 mo	nd	20	78.76	10	68.14	−1.75 (−17.59, 14.08)	
Kuhnt 2014 24553695 Germany	Healthy	SDA	2.0 g/d (suppl)	EPA+DHA+DPA	1.9 g/d (suppl: marine oil)	2 mo	nd	20	100.89	9	79.65	13.16 (−10.11, 36.42)	

Abbreviations: ALA = alphalinolenic acid, Ctrl = control, CVD = cardiovascular disease, DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, E:D = EPA to DHA ratio, EPA = eicosapentaenoic acid, F/up = followup, FA = fatty acid(s), FFQ = food frequency questionnaire, Int = intervention, n/N = number with outcome/number analyzed, n6:3 = omega-6 to omega-3 fatty acid ratio, n-3 FA = omega-3 fatty acids, ND = no data, NS = not significant, PMID = PubMed Identification number, RCT = randomized controlled trial, SDA = stearidonic acid.

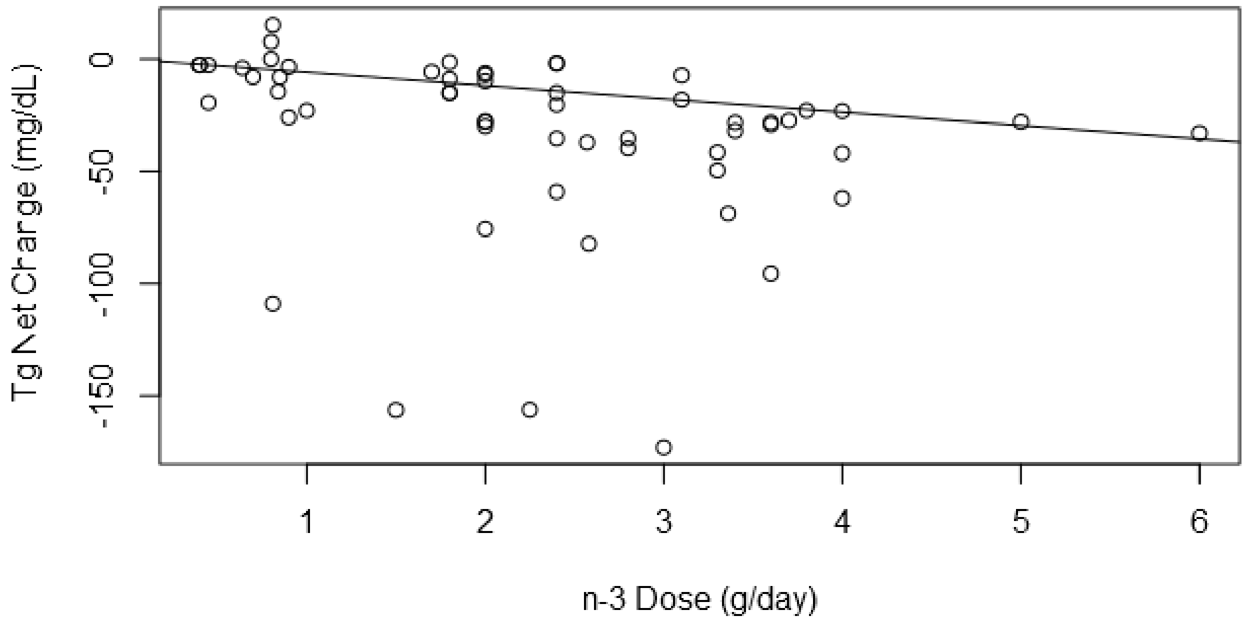
Figure 39. Triglycerides: Randomized trials of marine oils



Random effects model meta-analysis of n-3 FA versus placebo (or no n-3 FA), with subgroup analyses by population. In all meta-analyses, only studies that reported sufficient results data are included.

Abbreviations: CI = confidence interval, CVD = cardiovascular disease, DHA = docosahexaenoic acid

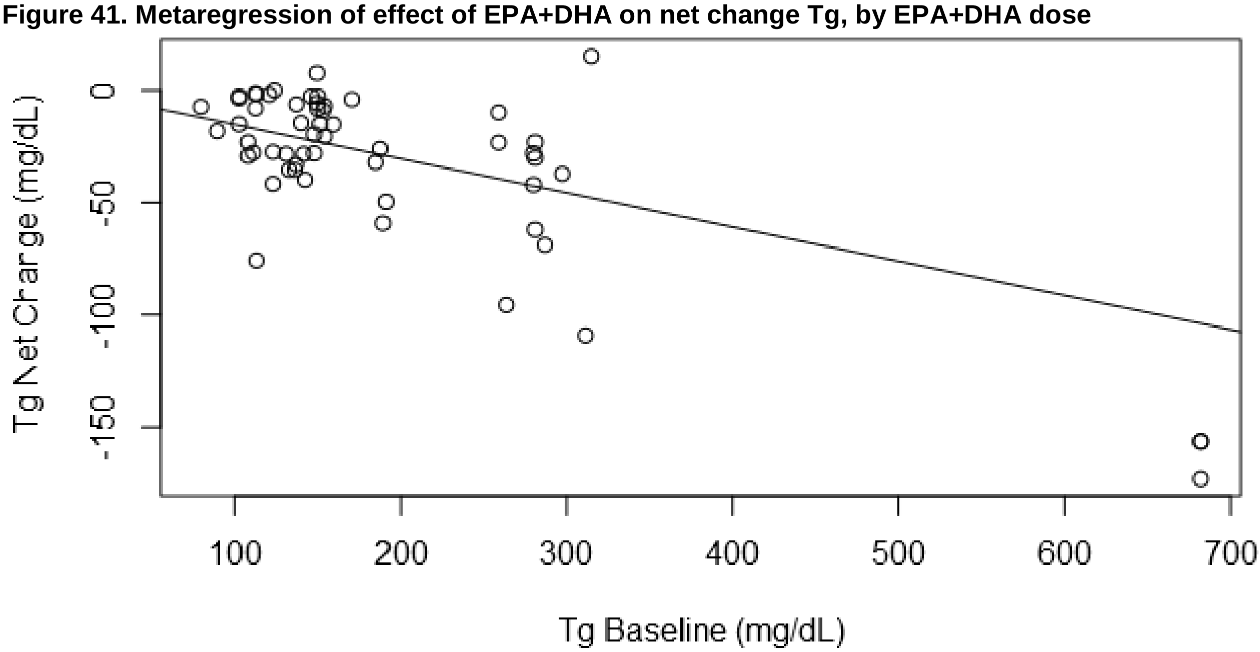
Figure 40. Metaregression of effect of EPA+DHA on net change Tg, by mean baseline Tg



Association of mean baseline Tg (tgbaseline) in mg/dL on net change Tg (tgnetdiff) in mg/dL.

Abbreviations: DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid, n-3 = omega-3 fatty acids, Tg = triglycerides.

Figure 41. Metaregression of effect of EPA+DHA on net change Tg, by EPA+DHA dose



Association of EPA+DHA dose (nd_dose) in g/d on net change Tg (tgnetdiff) in mg/dL.

Abbreviations: DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid, Tg = triglycerides.

Total Cholesterol to HDL-c Ratio

Randomized Controlled Trials

Eleven RCTs provided data on effect of n-3 FA on the ratio of total cholesterol to HDL-c (Total:HDL-c) (Table 44),[61, 115, 116, 119, 136, 166, 167, 169, 177, 180, 188] one in a healthy population, eight in people at increased risk for CVD, and one in patients with CVD. Two of the trial reported Total:HDL-c among their primary outcomes (Grimsgaard 1998, Rodriguez-Leyva 2013).[61, 167]

Total n-3 FA Versus Placebo

Two trials compared total n-3 FA (ALA+EPA+DHA) versus placebo, following 2708 patients for 1 and 40 months; one in people at increased risk for CVD,[180] one in people with CVD.[119] Doses of ALA+EPA+DHA included ALA 1.2 g/d and EPA+DHA+DPA 5 g/d, and ALA 2 g/d and EPA+DHA 0.4 g/d. Baseline Total:HDL-c ratio was 4.0 in one trial and not reported in the other. Compliance was measured in both studies, but not reported. The estimates of the net differences were not significant, one with a wide confidence interval.

Marine Oil Versus Placebo

Eight trials compared marine oil supplementation to placebo.[61, 115, 116, 119, 136, 166, 177, 180] Six of eight trials found statistically significant reductions in Total:HDL-c ratios. Across populations, by meta-analysis, the summary net difference in Total:HDL-c ratio with EPA+DHA versus placebo was a statistically significant −0.17 (95% CI −0.26 to −0.09) (Figure 42). Across studies, by metaregression, effect sizes did not statistically differ by population (at risk P=0.57, CVD P=0.61), marine oil dose (P=0.67), or baseline ratio (P=0.16).

Healthy Population

Two trials compared both EPA, DHA, and EPA+DHA separately to a placebo in 536 healthy participants, total.[61, 136] Compliance was assessed with pill count and plasma checks. The baseline Total:HDL-c ratio in the placebo group ranged from 3.53 to 4.43 and followup ranged from 2 months to 1 year. The Grimsgaard trial found significant reductions with both ethyl ester marine oils compared to placebo (−0.2 and −0.3). While the Sanders trial found nonsignificant net change results between interventions and placebo. The two trials yielded a subgroup meta-analysis summary effect of −0.16 (95% CI −0.32 to −0.01).

At-Risk-for-CVD Population

Six trials compared EPA+DHA to placebo in 1185 people at increased risk for CVD.[115 , 116, 119, 166, 177, 180] Compliance was assessed by pill count or meal consumption in two trials. EPA+DHA dosages ranged from 1.5 to 5 g/d and followup ranged from 1 month to 3 years. Baseline Total:HDL-c ratios ranged from 4.29 to 4.7 in four trials and was 8.8 in one trial of patients (Kastelein 2014) with severe hypertriglyceridemia (≥500 mg/dL) at baseline.[177] All but one trial found a significant reduction in Total:HDL-c ratio. Net change Total:HDL-c ratio varied between −1.2 and −0.1. The pooled effect size was a statistically nonsignificant −0.24 (95% CI −0.35 to −0.14). Exclusion of Kastelein 2014 did not substantially affect the pooled estimate.

CVD Population

One trial compared 3 months of 0.4 g/d EPA+DHA in patients with CVD and found a net change of −0.03 (95% CI −0.17 to 0.10).[119] Separate analyses were reported for patient taking statins or not. The study did not report compliance information. Baseline Total:HDL-c ratio data were also not reported. In both subgroups, no significant change in Total:HDL-c ratio was found, but there was a net increase in the ratio (0.09) in patients not taking statins and a net decrease in the ratio (−0.07) in those on statins.

RCT Subgroup Analyses

In the trial of patients with CVD, there was no apparent difference in effect on Total:HDL-c ratio based on cointervention with statins.[119] In a trial of people at increased risk of CVD, there was no interaction between EPA+DHA and general diet counseling.

By meta-regression, across studies there were no significant differences in effect (interactions) followup duration (P=0.17). However, the at risk for CVD population, mean baseline Total:HDL-c ratio level and EPA+DHA dose across studies were significantly associated with net change Total:HDL-c ratio. Controlling for these three variables, each increase in mean baseline Total:HDL-c level by 1 was associated with a greater net change Total:HDL-c of −0.16 (95% CI −0.25 to −0.07; P=0.0008). Each increase of EPA+DHA dose by 1 g/d was also associated with a greater net change Total:HDL-c of −0.07 (95% CI −0.11 to −0.02; P=0.003). The at risk for CVD population was associated with a greater net change Total:HDL-c of 0.77 (95% CI 0.29 to 1.25; P=0.002).

Marine Oil, Comparison of Different Doses

As noted, the trial of people with severe hypertriglyceridemia compared three doses of EPA+DHA (3, 2.25, and 1.5 g/d).[177] At 3 month followup, the net differences among the three doses were not significantly different from each other. A second trial, comparing 2 and 4 g/d of total oil (of EPA+DHA) also found no significant differences in effect between the two doses at 1.5 months.[166] A third trial, comparing 3.36 g/d 1.68 g/d of EPA+DHA also found no significant differences in effect between the two doses at 1 year.

ALA Versus Placebo

Three trials evaluated ALA versus placebo.[119, 167, 180] In a trial of people at increased risk for CVD, no significant effects of ALA (both 1.4 and 5.9 g/d) were found on Total:HDL-c ratios at 1 month in 390 participants.[180] No difference in effect between the two doses was found in this trial. Similarly no significant effects were found in a trial of 2 g/d ALA in 2,088 people with CVD at 3.4 years.[119] or in a trial of 5.9 g/d ALA in 48 people at 1 year.[167]

Comparison of Different Specific n-3 FA

Grimsgaard 1998 compared EPA 3.8 g/d and DHA 3.6 g/d ethyl esters in 157 healthy people for 2 months. No difference in net change Total:HDL-c ratio was found.[61] Tatsuno 2013 compared two doses of EPA+DHA (3.36 and 1.68 g/d) to EPA 1.8 g/d alone (all ethyl esters).[169] Again, no differences in effect on Total:HDL-c ratio were found. Jones 2014 compared 5.9 g/d and 1.4 g/d of ALA. Again, no difference in effect on Total:HDL-c ratio were found.[180]

SDA Versus Placebo

Pieters 2015 compared 1.2 g/d SDA to placebo in 32 patients at risk for CVD. At 1.5 month followup, no significant differences in change Total:HDL-c ratio were found.[188]

Observational Studies

Observational studies did not evaluate Total:HDL-c ratio.

Table 44. Total cholesterol to HDL-c ratio: RCTs

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline	Ctrl N	Ctrl Baseline	Net Chg	Reported P value
Total n-3 FA vs Placebo													
Jones 2014 24829493 Canada	At risk	ALA+EPA+DHA	3.5 g/d (suppl)	Placebo	ALA 0.2 g/d (Canola oil)	1 mo	Meal consumption	130	4.01	130	4.24	−0.1 (−0.3, 0.04)	<0.05
Kromhout 2010 20929341 Netherlands	CVD	ALA+EPA+DHA no statin	2.4 g/d (Marine, Plant oil)	Placebo, no statin	0	3.4 y	nd	96	nd	113	nd	0.14 (−0.11, 0.39)	
		ALA+EPA+DHA + Statin	2.4 g/d (Marine, Plant oil)	Placebo + Statin	0	3.4 y	nd	947	nd	943	nd	−0.04 (−0.11, 0.04)	
Marine oil vs Placebo													
Grimsgaard 1998 9665096 Scandinavia	Healthy	EPA	3.8 g/d (Ethyl ester)	Placebo	0	2 mo	Pill count	75	4.70	77	4.43	−0.2 (−0.4, −0.1)	0.007
	Healthy	DHA	3.6 g/d (Ethyl ester)	Placebo	0	2 mo	Pill count	72	4.62	77	4.43	−0.3 (−0.5, −0.1)	0.0006
Sanders 2011 21865334 UK	Healthy	EPA+DHA	1.8 g/d (suppl=marine oil)	Placebo	0	1 y	Pill Count, Plasma Check	80	3.34	71	3.53	−0.07 (−0.35, 0.21)	nd
		EPA+DHA	0.9 g/d (suppl=marine oil)	Placebo	0	1 y	Pill Count, Plasma Check	81	3.34	71	3.53	−0.03 (−0.31, 0.25)	nd
		EPA+DHA	0.45 g/d (suppl=marine oil)	Placebo	0	1 y	Pill Count, Plasma Check	80	3.49	71	3.53	−0.01 (−0.29, 0.27)	nd
Einvik 2010 20389249 Scandinavia	At risk	EPA+DHA	2.4 g/d (Marine oil) [E:D 1.4]	Placebo	0	3 y	Pill count	70	4.8	68	4.7	−0.3 (−0.8, 0.2)	
		EPA+DHA + diet intervention	2.4 g/d (Marine oil) [E:D 1.4]	Placebo + diet intervention	0	3 y	Pill count	69	4.8	71	4.6	−0.3 (−0.7, 0.1)	

Table 44. Total cholesterol to HDL-c ratio: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline	Ctrl N	Ctrl Baseline	Net Chg	Reported P value
Kastelein 2014 24528690 World	At risk	EPA+DHA	3 g/d (Marine oil) [E:D 2.75]	Placebo	0	3 mo	nd	99	9.0	98	8.8	−1.2 (−1.9, −0.4)	<0.01
		EPA+DHA	2.25 g/d (Marine oil) [E:D 2.75]	Placebo	0	3 mo	nd	97	8.9	98	8.8	−0.7 (−1.5, 0)	<0.05
		EPA+DHA	1.5 g/d (Marine oil) [E:D 2.75]	Placebo	0	3 mo	nd	99	8.8	98	8.8	−1.0 (−1.8, −0.3)	<0.05
Maki 2010 20451686 U.S.	At risk	EPA+DHA (+simvastatin)	3.36 g/d (Marine oil) [E:D 1.24]	Placebo (+simvastatin)	0	2 mo	nd	122	4.0	132	4.3	−0.3 (−0.5, −0.1)	<0.001
Maki 2013 23998969 U.S.	At risk	EPA+DHA	4 g/d total oil (free FA oil) [nd]	Placebo	0	1.5 mo	nd	207	4.9	211	4.7	−0.2 (−0.3, −0.1)	<0.001
		EPA+DHA	2 g/d total oil (free FA oil) [nd]	Placebo	0	1.5 mo	nd	209	4.8	211	4.7	−0.1 (−0.2, 0.05)	NS
Jones 2014 24829493 Canada	At risk	EPA+DHA (+ALA)	EPA: 0.1 g/d, DHA: 3.5 g/d, DPA: 1.4 g/d (canola+DHA)	(ALA)	0	1 mo	Meal consumption	130	4.01	130	4.29	−0.3 (−0.4, −0.1)	<0.05
Kromhout 2010 20929341 Netherlands	CVD	EPA+DHA	0.4 g/d (Marine oil) [E:D 1.5]	Placebo	0	3.4 y	nd	102	nd	113	nd	0.09 (−0.15, 0.33)	
		EPA+DHA + Statin	0.4 g/d (Marine oil) [E:D 1.5]	Placebo + Statin	0	3.4 y	nd	920	nd	943	nd	−0.07 (−0.14, 0.01)	

Table 44. Total cholesterol to HDL-c ratio: RCTs (continued)

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline	Ctrl N	Ctrl Baseline	Net Chg	Reported P value
Marine oil vs marine oil (doses)													
Sanders 2011 21865334 UK	Healthy	EPA+DHA	1.8 g/d(suppl=marine oil)	EPA+DHA	0.9 g/d (marine oil)	1 y	Pill Count, Plasma Check	80	3.34	81	3.34	−0.04 (−0.30, 0.22)	nd
		EPA+DHA	1.8 g/d (marine oil)	EPA+DHA	0.45 g/d (marine oil)	1 y	Pill Count, Plasma Check	80	3.34	80	3.49	−0.06 (−0.33, 0.21)	nd
		EPA+DHA	0.9 g/d (marine oil)	EPA+DHA	0.45 g/d (marine oil)	1 y	Pill Count, Plasma Check	81	3.34	80	3.49	−0.02 (−0.28, 0.24)	nd
Kastelein 2014 24528690 World	At risk	EPA+DHA	3 g/d (Marine oil) [E:D 2.75]	EPA+DHA	2.25 g/d (Marine oil) [E:D 2.75]	3 mo	nd	99	9.0	97	8.9	−0.4 (−1.1, 0.3)	
		EPA+DHA	3 g/d (Marine oil) [E:D 2.75]	EPA+DHA	1.5 g/d (Marine oil) [E:D 2.75]	3 mo	nd	99	9.0	99	8.8	−0.1 (−0.9, 0.6)	
		EPA+DHA	2.25 g/d (Marine oil) [E:D 2.75]	EPA+DHA	1.5 g/d (Marine oil) [E:D 2.75]	3 mo	nd	97	8.9	99	8.8	0.3 (−0.5, 1.0)	
Maki 2013 23998969 U.S.	At risk	EPA+DHA	4 g/d total oil (free FA oil) [nd]	EPA+DHA	2 g/d total oil (free FA oil) [nd]	1.5 mo	nd	207	4.9	209	4.8	−0.1 (−0.2, 0.05)	
Tatsuno 2013 24314359 Japan	At risk	EPA+DHA	3.36 g/d (Ethyl esters) E:D 1.24	EPA +DHA	1.68 g/d (Ethyl esters) E:D 1.24	1 y	nd	170	nd	165	nd	−0.5% (−3.9, 2.9)	

Table 44. Total cholesterol to HDL-c ratio: RCTs (continued)

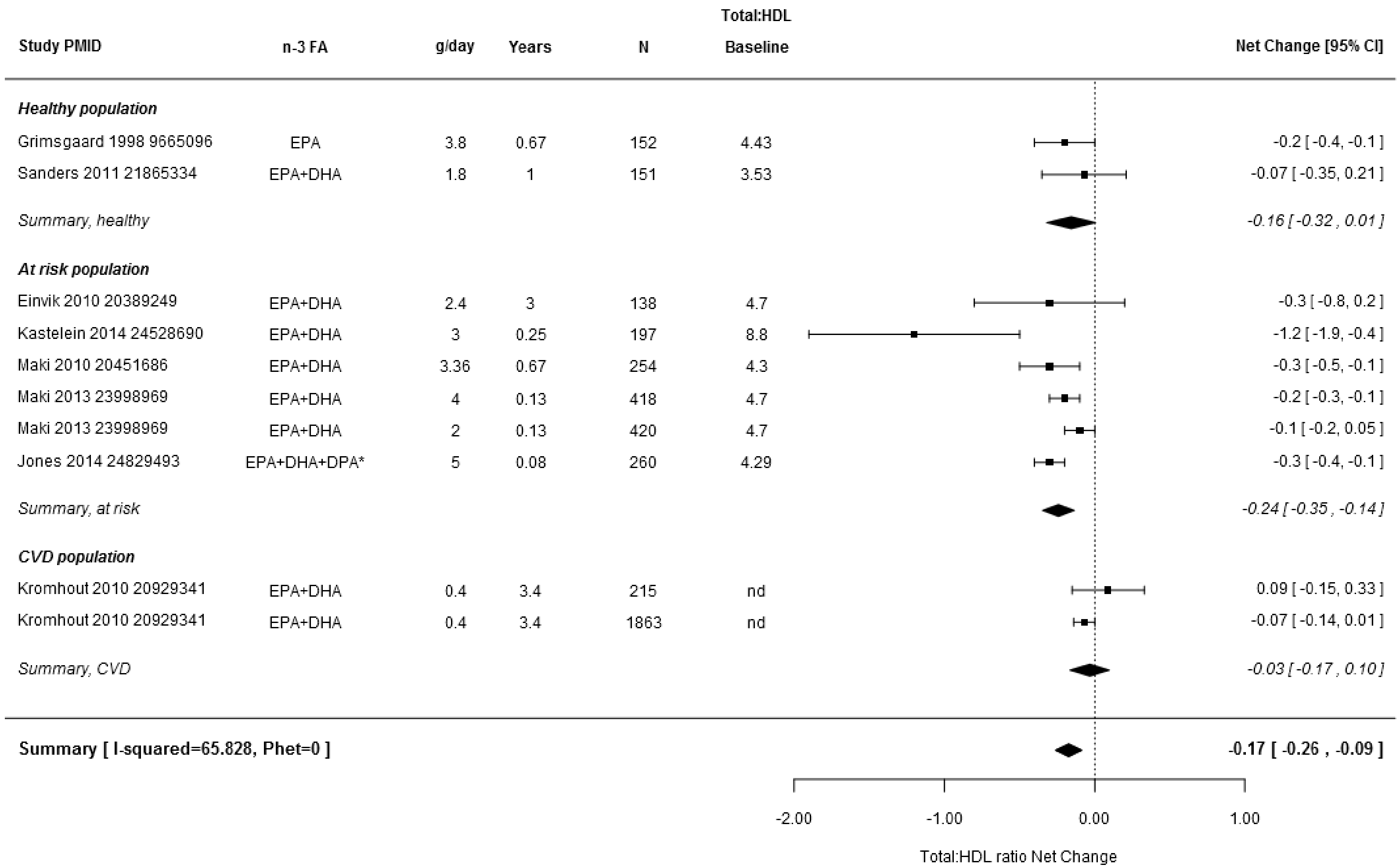
Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline	Ctrl N	Ctrl Baseline	Net Chg	Reported P value
Marine oil vs Marine oil (miscellaneous)													
Grimsgaard 1998 9665096 Scandinavia	Healthy	EPA	3.8 g/d (Ethyl ester)	DHA	3.6 g/d (Ethyl ester)	2 mo	Pill count	72	4.62	75	4.70	0.1 (−0.1, 0.2)	0.4
Tatsuno 2013 24314359 Japan	At risk	EPA+DHA	3.36 g/d (Ethyl esters) E:D 1.24	EPA	1.8 g/d (Ethyl ester)	1 y	nd	170	nd	165	nd	−1.4% (−4.9, 2.1)	
		EPA+DHA	1.68 g/d (Ethyl esters) E:D 1.24	EPA	1.8 g/d (Ethyl ester)	1 y	nd	170	nd	165	nd	−0.9% (−3.9, 2.2)	
ALA vs Placebo													
Jones 2014 24829493 Canada	At risk	ALA	5.9 g/d (Canola oil)	Placebo	ALA 0.2 g/d (Canola oil)	1 mo	Meal consumption	130	4.29	130	4.24	0.2 (0.001, 0.3)	
		ALA	1.4 g/d (Canola Oleic oil)	Placebo	ALA 0.2 g/d (Canola oil)	1 mo	Meal consumption	130	4.29	130	4.24	0.1 (−0.001, 0.3)	
Rodriguez-Leyva 2013 24126178 Canada	At risk	ALA	5.9 g/d (flaxseed)	Placebo	0	1 y	Plasma ALA and enterolignan levels	43	3.8	41	4.0	0.2 (−0.3, 0.7)	0.62
Kromhout 2010 20929341 Netherlands	CVD	ALA	2 g/d (Plant oil)	Placebo	0	3.4 y	nd	102	nd	113	nd	0.07 (−0.17, 0.31)	
		ALA + Statin	2 g/d (Plant oil)	Placebo + Statin	0	3.4 y	nd	930	nd	943	nd	0.06 (−0.02, 0.13)	

Table 44. Total cholesterol to HDL-c ratio: RCTs (continued)

ALA vs ALA (doses)													
Jones 2014 24829493 Canada	At risk	ALA	5.9 g/d (Canola oil)	ALA	1.4 g/d (Canola Oleic oil)	1 mo	Meal consumption	130	4.29	130	4.29	0.02 (−0.1, 0.2)	NS
SDA vs Placebo													
Pieters 2015 25226826 Netherlands	At risk	SDA	1.2 g/d (suppl)	Placebo	0	1.5 mo	nd	32	4.32	32	4.37	−0.06 (−0.21, 0.10)	0.48

Abbreviations: ALA = alphalinolenic acid, Ctrl = control, CVD = cardiovascular disease, DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, E:D = EPA to DHA ratio, EPA = eicosapentaenoic acid, F/up = followup, FA = fatty acid(s), HDL-c = high density lipoprotein cholesterol, Int = intervention, n/N = number with outcome/number analyzed, n6:3 = omega-6 to omega-3 fatty acid ratio, ND = no data, NS = not significant, PMID = PubMed Identification number, RCT = randomized controlled trial, SDA = stearidonic acid.

Figure 42. Total cholesterol to HDL-c ratio: Randomized trials of marine oils



Random effects model meta-analysis of n-3 FA versus placebo (or no n-3 FA), with subgroup analyses by population. In all meta-analyses, only studies that reported sufficient results data are included.

Abbreviations: CI = confidence interval, CVD = cardiovascular disease, DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, EPA = eicosapentaenoic acid, HDL-c = high density lipoprotein cholesterol, n-3 FA = omega-3 fatty acid, Phet = P value of chi-squared test of heterogeneity across studies, PMID = PubMed Identification number.

LDL-c to HDL-c Ratio

Randomized Controlled Trials

Five RCTs provided data on effect of n-3 FA on the ratio of LDL-c to HDL-c (LDL:HDL-c) (Table 45),[46, 76, 167, 169, 178] one studied a healthy population, while four looked at people at increased risk for CVD. Two of the trials reported LDL:HDL-c among their primary outcomes (Rodriguez-Leyva 2013, Shidfar 2003).[76, 167]

Marine Oil Versus Placebo

Liu 2003 compared 2.8 g/d of EPA+DHA to placebo in 88 people at increased risk for CVD.[46] Baseline LDL:HDL-c ratio was about 3.1. Analyses were reported separately for a factorial analysis with simvastatin. At 3 month followup, no effect of LDL:HDL-c ratio was found with EPA+DHA supplementation in either subgroup, with no difference in effect regardless of simvastatin cotreatment.

Shidfar 2003 compared 0.81 g/d of EPA+DHA to placebo in 68 people at increased risk for CVD.[76] Baseline LDL:HDL-c ratio was about 4.2. Analyses were reported separately for a factorial analysis with vitamin C. At 2.5 month followup, no effect of LDL:HDL-c ratio was found with total n-3 FA supplementation in either subgroup, with no difference in effect regardless of vitamin C cosupplementation.

Tatsuno 2013 (in a trial without a placebo arm) compared 3.36 and 1.68 g/d EPA+DHA ethyl esters in 335 people at increased risk for CVD.[169] At 3 month followup, no significant difference in change in LDL:HDL-c ratio was found.

ALA Versus Placebo

One trial evaluated ALA versus placebo.[167] In 84 people at increased risk for CVD, no significant effects of ALA (5.9 g/d) were found on LDL:HDL-c ratios at 1 year.

Comparison of Different Specific n-3 FA

Tatsuno 2013 compared 3.36 and 1.68 g/d EPA+DHA and 1.8 g/d EPA (all ethyl esters) in 502 people at increased risk for CVD.[169] At 3 month followup, no significant differences in change in LDL:HDL-c ratios were found.

SDA Versus Marine Oil

Kuhnt 2014 compared 2.0 g/d SDA and 1.9 g/d EPA+DHA+DPA in 59 healthy people (broken into cohorts based on body mass index and age). At 2 month followup, no significant differences in change in LDL:HDL-c ratios were found.[178]

Observational Studies

Observational studies did not evaluate Total:HDL-c ratio.

Table 45. LDL-c to HDL-c ratio: RCTs

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline	Ctrl N	Ctrl Baseline	Net Chg	Reported P value
Marine oil vs Placebo													
Liu 2003 Sweden	At risk	EPA+DHA	2.8 g/d (Marine oil) [E:D 1.55]	Placebo	0	3 mo	Pill count	29	3.20	22	3.11	−0.02 (−0.45, 0.41)	NS
		EPA+DHA + simvastatin	2.8 g/d (Marine oil) [E:D 1.55]	Placebo + simvastatin	0	3 mo	Pill count	19	3.28	18	3.02	−0.1 (−0.7, 0.5)	NS
Shidfar 2003 12847992 Iran	At risk	EPA+DHA	EPA 0.5 g/d, DHA 0.31 g/d (suppl) [E:D 1.6]	Placebo	0	2.5 mo	nd	16	4.42	19	4.2	−0.3 (−1.5, 0.9)	
		EPA+DHA + vitamin C	EPA 0.5 g/d, DHA 0.31 g/d (suppl) [E:D 1.6]	Placebo + vitamin C	0	2.5 mo	nd	16	4.4	17	4.3	0.2 (−1.1, 1.5)	
Marine oil vs Marine oil (doses)													
Tatsuno 2013 24314359 Japan	At risk	EPA+DHA	3.36 g/d (Ethyl esters) E:D 1.24	EPA+DHA	1.68 g/d (Ethyl esters) E:D 1.24	1 y	nd	170	nd	165	nd	2.6% (−1.5, 6.7)	
Marine oil vs Marine oil (miscellaneous)													
Tatsuno 2013 24314359 Japan	At risk	EPA+DHA	3.36 g/d (Ethyl esters) E:D 1.24	EPA	1.8 g/d (Ethyl ester)	1 y	nd	170	nd	165	nd	1.8% (−2.4, 5.9)	
	At risk	EPA+DHA	1.68 g/d (Ethyl esters) E:D 1.24	EPA	1.8 g/d (Ethyl ester)	1 y	nd	170	nd	165	nd	−0.9% (−4.5, 2.8)	

Table 45. LDL-c to HDL-c ratio: RCTs

Study Year PMID Region	Population	Int (n3 FA)	Int n3 Dose (Source) [E:D; n6:3]	Control	Ctrl n3 Dose (Source) [E:D; n6:3]	F/up Time	Compliance Verification	Int N	Int Baseline	Ctrl N	Ctrl Baseline	Net Chg	Reported P value
ALA vs Placebo													
Rodriguez-Leyva 2013 24126178 Canada	At risk	ALA	5.9 g/d (flaxseed)	Placebo	0	1 y	Plasma ALA and enterolignan levels	43	2.2	41	2.2	0.1 (−0.3, 0.5)	0.57
SDA vs Marine oil													
Kuhnt 2014 24553695 Germany	Healthy	SDA	2.0 g/d (suppl)	EPA+DHA+DPA	1.9 g/d (suppl: marine oil)	2 mo	nd	20	1.87	10	1.58	0.02 (−0.45, 0.49)	
Kuhnt 2014 24553695 Germany	Healthy	SDA	2.0 g/d (suppl)	EPA+DHA+DPA	1.9 g/d (suppl: marine oil)	2 mo	nd	20	2.36	9	1.81	0.03 (−0.59, 0.65)	

Abbreviations: ALA = alphalinolenic acid, Ctrl = control, CVD = cardiovascular disease, DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, E:D = EPA to DHA ratio, EPA = eicosapentaenoic acid, F/up = followup, HDL-c = high density lipoprotein cholesterol, Int = intervention, LDL-c = low density lipoprotein cholesterol, n/N = number with outcome/number analyzed, n6:3 = omega-6 to omega-3 fatty acid ratio, n-3 FA = omega-3 fatty acids, ND = no data, NS = not significant, PMID = PubMed Identification number, RCT = randomized controlled trial, SDA = stearidonic acid.

Adverse Events

Of 61 RCTs included in this systematic review, only 4 RCTs of EPA/DHA ethyl ester, 19 RCTs of marine oils (EPA+DHA), 1 RCT of ALA, and 1 RCT comparing total n-3 FA, marine oil, ALA, and placebo reported information on adverse events that may or may not be associated with the interventions (Table 46).[53, 58, 61, 62, 70, 81, 87, 90, 96, 99, 115, 116, 119, 123, 133, 147, 151, 157, 166, 167, 169, 174, 177, 184, 187] There were no serious adverse events that were considered related to the study interventions in these 25 RCTs. Four of the 20 marine oil RCTs and one of the two ALA trials reported no adverse events. Most of the reported adverse events were mild and transient, such as gastrointestinal discomforts, nausea, skin abnormalities, eczema, pain, allergic reactions, fishy taste, headache, and infection. The most common adverse events related to n-3 FA supplements (that occurred more frequently among those taking supplements) were mild gastrointestinal effects such as belching (0.4-58% [marine oil] vs. 1.7-4% [placebo]; 2 studies), nausea (3.6-8.9% vs. 1.0-5.6%, 2 studies), diarrhea (5.1-8.9% vs. 2.0%, 1 study), or fishy taste (5.3-67% vs. 0-3%, 2 studies), or combined gastrointestinal symptoms (e.g., nausea, diarrhea, or epigastric discomfort) (marine oil: 1.5.0-6% vs. 0.8-4.5%, 7 studies; total n-3 FA: 1.3% vs. 0.8%, 1 study; ALA: 0.8% vs. 0.8%). Only one study explicitly reported on bleeding (hemorrhages such as cerebral and fundal bleedings, epistaxis, and subcutaneous bleeding), finding a higher rate with EPA ethyl ester and statin (1.1%) versus statin alone (0.6%, $P<0.0001$) (Yokoyama 2007). This study was one of only two trials that reported statistically significantly more adverse events with marine oils than placebo (Yokoyama 2007, Kastelein 2014 [total adverse events only]; see Table 42). No study reported statistically significant higher rates of serious or severe adverse events between study arms, and no serious or severe adverse event was attributed to n-3 FA. Six of the marine oil trials explicit stated that most or all adverse events were mild (Einvik 2010, Grimsgaard 1998, Ras 2014, Shaikh 2014, Tatsuno 2013, Yokoyama 2007). Three studies reported on the rate of adverse events leading to discontinuation, none of which were reported as statistically significantly different between groups (1.4-17% vs. 0.9-26%).

Table 46. Adverse events

Study Year PMID Region (Population)	F/up Time	n-3 FA (N)	Dose	AE n-3 FA	Control (N)	AE Control	P-Value	Note
EPA or DHA ethyl ester								
Ballantyne 2012 22819432 U.S. (High CVD risk)	3 mo	EPA+DHA (233)	4 g/d	Total: 45.5% Eructations: 0.9% Serious AEs§: 3.0%	Placebo (233)	Total: 48.1% Eructations: 1.7% Serious AEs: 2.1%		"No serious AEs were considered related to study drug."
(High CVD risk)		EPA+DHA (236)	2 g/d	Total: 44.9% Eructations: 0.4% Serious AEs: 2.5%				
Grimsgaard 1998 9280188 Norway (Healthy)	2 mo	EPA (75)	3.8 g/d	Belching: 57% Fishy taste: 65%	Placebo (77)	Belching: 4% Fishy taste: 3%		"Adverse effects were mild and transient"
		DHA (72)	3.6 g/d	Belching: 58% Fishy taste: 67%				
Tatsuno 2013 24314359 Japan (Dyslipidemia)	1 y	EPA+DHA (167)	3.36 g/d	Total: 9.9% Gastritis: 3.5% Constipation: 3.5% Eczema: 4.1%				"Most AEs were mild or moderate in severity."
		EPA+DHA (171)	1.68 g/d	Total: 13.3% Gastritis: 3.6% Constipation: 1.8% Eczema: 3.0%				
		EPA (165)	1.8 g/d	Total: 12.6% Gastritis: 2.4% Constipation: 0.0% Eczema: 1.2%				
Yokoyama 2007 17398308 Japan (Dyslipidemia)	5 y	EPA + statin (9326)	1.8 g/d	Total: 25.3% Abnl lab data: 4.1% GI*: 3.8% Skin†: 1.7% Hemorrhage‡: 1.1%	Statin (9319)	Total 21.7% Abnl lab data: 3.5% GI: 1.7% Skin: 0.7% Hemorrhage: 0.6%	Total <0.0001 Abnl lab data: 0.04 GI: <0.0001 Skin: <0.0001 Hemorrhage: <0.0001	"Most adverse effects attributable to EPA allocation were regarded as mild."
Marine oils (EPA+DHA)								
Brouwer 2006 16772624 N. Europe (CVD)	1 y	EPA+DHA (273)	0.96 g/d	GI*: 6%	Placebo (273)	GI*: 4%	NS (implied)	
Carter 2012 22707560 U.S. (Healthy)	2 mo	EPA+DHA (19)	2.7 g/d	0%	Placebo (19)	0%		No AEs reported

Table 46. Adverse events (continued)

Study Year PMID Region (Population)	F/up Time	n-3 FA (N)	Dose	AE n-3 FA	Control (N)	AE Control	P-Value	Note
Einvik 2010 20389249 Norway (Dyslipidemia)	3 y	EPA+DHA (282)	2.4 g/d	Regurgitation: 4%	Placebo (281)	Regurgitation: 0%		"Side effects were mild and without consequence"
Galan 2010 21115589 France (CVD)	4.7 y	EPA+DHA (633)	0.6 g/d	Side effects††: 2.6%	Placebo (626)	Side effects: 1.6%		
Holman 2009 19002433 UK (Diabetes)	4 mo	EPA+DHA (197)	2 g/d	Serious AEs§: 10%	Placebo (202)	Serious AEs: 9%	0.082	"There were no significant differences in nonserious AE between groups."
		EPA + DHA +atorvastatin (200)	2 g/d	Serious AEs: 17%	Placebo + atorvastatin (201)	Serious AEs: 7%		
Kastelein 2014 24528690 Europe (Dyslipidemia)	12 wk	EPA+DHA (99)	3.0 g/d	Total: 44.4% AEs related to treatment: 25.3% Severe AEs‡‡: 1.0% Diarrhea: 10.1% Nausea: 5.1% Vomiting: 0% Abdominal pain: 1.0%	Placebo (99)	Total: 26.3% AEs related to treatment: 3.0% Severe AEs§§: 5.1% Diarrhea: 2.0% Nausea: 1.0% Vomiting: 1.0% Abdominal pain: 1.0%	Total: 0.036	
		EPA+DHA (101)	EPA: 2.25 g/d	Total: 42.6% AEs related to treatment: 16.8% Severe AEs||||: 3.0% Diarrhea: 5.9% Nausea: 8.9% Vomiting: 4.0% Abdominal pain: 1.0%				
		EPA+DHA (100)	EPA: 1.50 g/d	Total: 40.0% AEs related to treatment: 18.0% Severe AEs¶¶: 2.0% Diarrhea: 10.0% Nausea: 6.0% Vomiting: 2.0% Abdominal pain: 4.0%				

Table 46. Adverse events (continued)

Study Year PMID Region (Population)	F/up Time	n-3 FA (N)	Dose	AE n-3 FA	Control (N)	AE Control	P-Value	Note
Lungershausen 1994 7852747 Australia (Hypertension)	1.5 mo	EPA+DHA (42)	3.4 g/d	0%	Placebo (42)	0%		No AEs reported
Macchia 2013 23265344 Argentina and Italy (CVD)	12 mo	EPA+DHA (289)	0.85−0.882	GI*: 2.0%	Placebo (297)	GI*: 2.7%		
Maki 2010 20451686 U.S. (Dyslipidemia)	8 wk	EPA+DHA + simvastatin (122)	3.36 g/d		Placebo + simvastatin (132)			"There was no significant difference in the frequency of AEs between groups. No serious AEs were considered treatment related."
Maki 2013 23998969 U.S. (Dyslipidemia)	1.5 mo	EPA+DHA (216)	4 g/d	Total: 41.7% Serious AEs‖: 0.5% AEs related to treatment: 20.4% AEs leading to discontinuation: 3.2%	Placebo (216)	Total: 27.9% Serious AEs¶: 1.4% AEs related to treatment: 6.0% AEs leading to discontinuation: 0.9%		
		EPA+DHA (215)	2 g/d	Total: 33.0% Serious AEs**: 1.4% AEs related to treatment: 9.8% AEs leading to discontinuation: 1.4%				
Marchioli 2002 11997274 Italy (CVD)	3.5 y	EPA+DHA (5666)	0.850-0.882 g/d	0%	No intervention (5668)	0%		No AEs reported.
Nodari 2011 21844082 Italy (CVD)	1 y	EPA+DHA (94)	0.850−0.882 g/d	Total: 2.1%	Placebo (94)	Total: 3.2%		

Table 46. Adverse events (continued)

Study Year PMID Region (Population)	F/up Time	n-3 FA (N)	Dose	AE n-3 FA	Control (N)	AE Control	P-Value	Note
Raitt 2005 15956633 U.S. (CVD)	2 y	EPA+DHA (100)	1.3 g/d	AEs leading to discontinuation: 17%	Placebo (100)	AEs leading to discontinuation: 26%	NS	"No significant differences in serious AEs… possible exception of an excess of hospitalizations for neurologic events inpatients assigned to placebo."
Ras 2014 25122648 Scandinavia (Healthy)	1 mo	EPA+DHA (62)	1.8 g/d		Placebo (64)		NS (implied)	"Overall, AEs were mild... There was no remarkable difference in the number of subjects experiencing AEs or in the nature and frequency of AEs between the 5 treatment groups."
		EPA+DHA (62)	1.3 g/d					
		EPA+DHA (64)	0.9 g/d					
Shaikh 2014 25185754 U.S. (Healthy)	2 mo	EPA+DHA (56)	3.6 g/d	Fishy belching: 5.3% Flatulence: 3.6% Nausea: 3.6%	Placebo (54)	Fishy belching: 0% Flatulence: 0% Nausea: 5.6%		"No serious adverse events related to the study treatment were observed."
Sirtori 1997 9174486 Italy (Dyslipidemia)	6 mo	EPA+DHA	2.57 g/d (470)	GI*: 3.8%	Placebo (465)	GI*: 4.5%		
Tavazzi 2008 18757090 Italy (CVD)	3.9 y	EPA+DHA (3494)	0.850−0.882 g/d]	AEs leading to discontinuation: 3% GI*: 2.7% Allergic reaction: 0.09%	Placebo (3481)	AEs leading to discontinuation: 3% GI*: 2.6% Allergic reaction: 0.3%	Discontinuation: 0.87	
Vazquez 2014 24462043 Spain (Healthy)	2 mo	EPA+DHA (273)	0.64 g/d	0%	Placebo (273)	0%		No AEs reported
von Schacky 1999 10189324 Canada (CVD)	2 y	EPA+DHA (112)	EPA+DHA 3.3 g/d (3 mo), 1.65 g/d (21 mo)	GI*: 3.6%	Placebo (111)	GI*: 2.7%		
ALA								
Rodriguez-Leyva 2013 24126178 Canada (CVD)	1 y	ALA (59)	5.9 g/d	0%	Placebo (52)	0%		No AEs reported

Table 46. Adverse events (continued)

Study Year PMID Region (Population)	F/up Time	n-3 FA (N)	Dose	AE n-3 FA	Control (N)	AE Control	P-Value	Note
Multiple n-3 FA								
Kromhout 2010 20929341 Netherlands (CVD)	40 mo	ALA+EPA+DHA (1212)	2.4 g/d	GI*: 1.3%	Placebo (1236)	GI*: 0.8%	NS (implied)	
		EPA+DHA (1192)	0.4 g/d	GI*: 1.5%				
		ALA (1197)	2.0 g/d	GI*: 0.8%				

* Such as nausea, diarrhea, or epigastric discomfort.
† Such as eruption, itching, exanthema, or eczema
‡ Such as cerebral and fundal bleedings, epistaxis, and subcutaneous bleeding
§ Not defined.
||Coronary artery disease (this “adverse event” was included here only because it was grouped within “serious adverse events” and was compared with other events; otherwise it would only be evaluated as a cardiovascular outcome)
¶ Such as intestinal obstruction, bronchitis, and hyperglycemia
** Such as diverticular perforation, musculoskeletal chest pain, and osteoarthritis
†† Gastrointestinal disturbances, nausea, and cutaneous reactions
‡‡ Diarrhea
§§ Myocarditis, abdominal pain, acute sinusitis, ear infection, increased blood triglycerides
|||| Coronary artery disease, pulmonary embolism, implantable defibrillator insertion (these “adverse events” were included here only because they was grouped within “severe adverse events” and were compared with other events; otherwise it would only have been evaluated as cardiovascular outcomes)
¶¶ Microalbuminuria, urticaria.

Abbreviations: Abnl = abnormal, AE = adverse event, ALA = alphalinolenic acid, CVD = cardiovascular disease, DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid, F/up = followup, GI = gastrointestinal, n-3 FA = omega-3 fatty acids, NS = not significant, PMID = PubMed Identification number.

Summary by n-3 FA

The trials of clinical outcomes were almost all conducted in populations at increased risk of CVD, largely related to dyslipidemia, or with CVD. The trials that reported intermediate outcomes (BP and lipoproteins), were conducted in generally healthy, at-risk, and CVD populations. The observational studies, in contrast, were almost all conducted in general (unrestricted by CVD or risk factors) or healthy populations. One observational study evaluated BP; none evaluated lipids.

Total n-3 FA (ALA+EPA+DHA)

Overall, there is insufficient evidence regarding the effect of or association between total n-3 FA (combined ALA and marine oils) and clinical or intermediate outcomes (Table 47). There is low strength of evidence of no association between total n-3 FA intake and stroke death, and total (fatal and nonfatal) MI (each association based on longitudinal observational studies of dietary intake). For both outcomes, the strength of evidence was rated low because of a lack of confirmatory RCT data.

Clinical Event Outcomes, RCTs

No RCTs reported clinical event outcomes for comparisons of total n-3 FA versus placebo.

Intermediate Outcomes, RCTs

Two RCTs that evaluated BP compared combined ALA and marine oil (ALA 1.2 g/d [canola oil] or 2 g ["plant oil"], and 3.6 or 0.4 g EPA+DHA) versus placebo reported on intermediate outcomes. Neither trial found significant effects on BP, LDL-c, HDL-c, Tg, or Total:HDL-c ratio.

Observational Studies, Intake

Seven studies evaluated total n-3 FA intake. For each outcome there was no consistent (and replicated) significant association between total n-3 FA intake and risk reduction. One of three studies found a significant association between higher total n-3 FA intake and *higher* risk of MACE. In contrast, one of three studies found an association with reduced risk of CVD death; one of two studies found a significant association with MI death; one study each found significant associations with lower risk of ischemic stroke death and CHF death. No studies found significant associations with all-cause death (1 study), CHD death (2 studies), total (ischemic and hemorrhagic) stroke death (3 studies), MI (1 study), total (fatal and nonfatal) stroke (1 study), SCD (1 study), or incident hypertension (1 study).

One study found no significant difference in association of total n-3 FA with total CVD death between men and women or by amount of fish consumption. Another study found no significant difference in association with MI death, total stroke death, or ischemic stroke death by baseline Total:HDL-c ratio.

Observational Studies, Biomarkers

Three studies evaluated biomarkers for total n-3 FA (combined; plasma, blood, or erythrocyte). One study evaluated numerous outcomes and found significant associations between higher biomarker level and reduced risk of most outcomes (CVD death, CHD death, all-cause death, CHD, ischemic stroke, SCD, AFib, and CHF), but not stroke death, total stroke, or hemorrhagic stroke. In contrast, a second study found no significant association with CHD. The third study found no significant association overall with incident hypertension, but did find a significant association in between higher total n-3 FA and hypertension in younger women (<55 years old) but not in older women.

Table 47. Evidence profile for the effect and association of total n-3 FA with CVD outcomes*

Outcome	SoE Grade	Design No. Studies	Study Limitations	Consistency	Precision	Other Issues	Finding
Major adverse cardiovascular events (MACE)	Insufficient	RCT: 0 Obs intake: 3 Obs biomarkers: 0	Low	RCT: NA Obs intake: Inconsistent Obs biomarkers: NA All: NA	RCT: NA Obs intake: Imprecise Obs biomarker: NA	No RCT	RCT: NA Obs intake: Unclear Obs biomarkers: NA
CVD death (including stroke)	Insufficient	RCT: 0 Obs intake: 4 Obs biomarkers: 1	Low	RCT: NA Obs intake: Inconsistent Obs biomarkers: NA All: Inconsistent	RCT: NA Obs intake: Precise Obs biomarker: Precise	No RCT	RCT: NA Obs intake: Unclear Obs biomarkers: Lower risk
Cardiac death	Insufficient	RCT: 0 Obs intake: 0 Obs biomarkers: 0	Low	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	NA	No data	RCT: NA Obs intake: NA Obs biomarkers: NA
Coronary heart disease death	Insufficient	RCT: 0 Obs intake: 2 Obs biomarkers: 1	Moderate	RCT: NA Obs intake: Consistent Obs biomarkers: NA All: inconsistent	RCT: NA Obs intake: Imprecise Obs biomarker: Precise	Sparse	RCT: NA Obs intake: No association Obs biomarkers: Lower risk
Myocardial infarction death	Insufficient	RCT: 0 Obs intake: 2 Obs biomarkers: 0	Moderate	RCT: Obs intake: Inconsistent Obs biomarkers All: NA	RCT: NA Obs intake: Imprecise Obs biomarker: Imprecise	Sparse	RCT: NA Obs intake: Unclear Obs biomarkers: NA
Heart failure death	Insufficient	RCT: 0 Obs intake: 1 Obs biomarkers: 0	Moderate	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: Imprecise Obs biomarker: Unclear	Sparse	RCT: NA Obs intake: Lower risk Obs biomarkers: NA
Stroke death	Low	RCT: 0 Obs intake: 4 Obs biomarkers: 1	Low	RCT: NA Obs intake: Consistent Obs biomarkers: NA All: Consistent	RCT: NA Obs intake: Imprecise Obs biomarker: Imprecise	No RCT	RCT: NA Obs intake: No association Obs biomarkers: No association
Ischemic stroke death	Insufficient	RCT: 0 Obs intake: 2 Obs biomarkers: 0	Moderate	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: Unclear Obs biomarker: NA	Sparse	RCT: NA Obs intake: Lower risk Obs biomarkers: NA
Hemorrhagic stroke death	Insufficient	RCT: 0 Obs intake: 0 Obs biomarkers: 0	NA	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	NA	No data	RCT: NA Obs intake: NA Obs biomarkers: NA
Death, all-cause	Insufficient	RCT: 0 Obs intake: 1 Obs biomarkers: 1	Moderate	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: Precise Obs biomarker: Precise	Sparse	RCT: NA Obs intake: No association Obs biomarkers: Lower risk

Table 47. Evidence profile for the effect and association of total n-3 FA with CVD outcomes (continued)

Outcome	SoE Grade	Design No. Studies	Study Limitations	Consistency	Precision	Other Issues	Finding
Coronary heart disease	Insufficient	RCT: 0 Obs intake: 0 Obs biomarkers: 2	Low	RCT: NA Obs: NA Obs biomarkers: Inconsistent All: Consistent	RCT: NA Obs intake: NA Obs biomarker: Precise	Sparse	RCT: NA Obs intake: NA Obs biomarkers: Unclear
Myocardial infarction	Low	RCT: 0 Obs intake: 3 Obs biomarkers: 0	Low	RCT: NA Obs intake: Consistent Obs biomarkers: NA All: NA	RCT: NA Obs intake: Imprecise Obs biomarker: NA	No RCT	RCT: NA Obs intake: No association Obs biomarkers: NA
Acute coronary syndrome	Insufficient	RCT: 0 Obs intake: 1 Obs biomarkers: 0	Low	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: Unclear Obs biomarkers: NA	Sparse	RCT: NA Obs intake: No association Obs biomarkers: NA
Angina pectoris	Insufficient	RCT: 0 Obs intake: 0 Obs biomarkers: 0	NA	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	NA	No data	RCT: NA Obs intake: NA Obs biomarkers: NA
Atrial fibrillation	Insufficient	RCT: 0 Obs intake: 0 Obs biomarkers: 1	Low	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarkers: Unclear	Sparse	RCT: NA Obs intake: NA Obs biomarkers: Lower risk
Congestive heart failure	Insufficient	RCT: 0 Obs intake: 0 Obs biomarkers: 1	Low	RCT: NA Obs: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarkers: Unclear	Sparse	RCT: NA Obs intake: NA Obs biomarkers: No association
Stroke, total	Insufficient	RCT: 0 Obs: 1 Obs biomarkers: 1	Low	RCT: NA Obs intake: NA Obs biomarkers: NA All: Consistent	RCT: NA Obs intake: Imprecise Obs biomarkers: Imprecise	Sparse	RCT: NA Obs intake: No association Obs biomarkers: No association
Stroke, ischemic	Insufficient	RCT: 0 Obs intake: 0 Obs biomarkers: 1	Low	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarkers: Imprecise	Sparse	RCT: NA Obs intake: NA Obs biomarkers: Lower risk
Stroke, hemorrhagic	Insufficient	RCT: 0 Obs intake: 0 Obs biomarkers: 1	Low	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarkers: Imprecise	Sparse	RCT: NA Obs intake: NA Obs biomarkers: No association

Table 47. Evidence profile for the effect and association of total n-3 FA with CVD outcomes (continued)

Outcome	SoE Grade	Design No. Studies	Study Limitations	Consistency	Precision	Other Issues	Finding
Sudden cardiac death	Insufficient	RCT: 0 Obs intake: 1 Obs biomarkers: 1	Low	RCT: NA Obs intake: NA Obs biomarkers: NA All: Consistent	RCT: NA Obs intake: Imprecise Obs biomarkers: Imprecise	Sparse	RCT: NA Obs intake: No association Obs biomarkers: No association
Revascularization	Insufficient	RCT: 0 Obs intake: 0 Obs biomarkers: 0	NA	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	NA	No data	RCT: NA Obs intake: NA Obs biomarkers: NA
Hypertension	Insufficient	RCT: 0 Obs intake: 2 Obs biomarkers: 0	Low	RCT: NA Obs intake: Inconsistent Obs biomarkers: NA All: NA	RCT: NA Obs intake: Precise Obs biomarker: NA	Sparse	RCT: NA Obs intake: Unclear Obs biomarkers: NA
Blood pressure (SBP, DBP, MAP combined)	Insufficient	RCT: 2 Obs intake: 0 Obs biomarkers: 0	Low	RCT: Consistent Obs intake: NA Obs biomarkers: NA All: NA	RCT: Imprecise Obs intake: NA Obs biomarker: NA	Sparse	RCT: No effect Obs intake: NA Obs biomarkers: NA
LDL-c	Insufficient	RCT: 2 Obs intake: 0 Obs biomarkers: 0	Low	RCT: Consistent Obs intake: NA Obs biomarkers: NA All: NA	RCT: Imprecise Obs intake: NA Obs biomarker: NA	No Obs	RCT: No effect Obs intake: NA Obs biomarkers: NA
HDL-c	Insufficient	RCT: 2 Obs intake: 0 Obs biomarkers: 0	Low	RCT: Consistent Obs intake: NA Obs biomarkers: NA All: NA	RCT: Imprecise Obs intake: NA Obs biomarker: NA	No Obs	RCT: No effect Obs intake: NA Obs biomarkers: NA
Triglycerides	Insufficient	RCT: 2 Obs intake: 0 Obs biomarkers: 0	Low	RCT: Inconsistent Obs intake: NA Obs biomarkers: NA All: NA	RCT: Imprecise Obs intake: NA Obs biomarker: NA	No Obs	RCT: Unclear Obs intake: NA Obs biomarkers: NA
HDL-c/Total cholesterol to LDL-c ratios	Insufficient	RCT: 2 Obs intake: 0 Obs biomarkers: 0	Low	RCT: Consistent Obs intake: NA Obs biomarkers: NA All: NA	RCT: Precise Obs intake: NA Obs biomarker: NA	No Obs	RCT: No effect Obs intake: NA Obs biomarkers: NA

* No reporting bias was detected for any outcome. All studies that measured n-3 FA intake were assessed to be direct, while all biomarker studies were assessed to be indirect.

Abbreviations: CVD = cardiovascular disease, DBP = diastolic blood pressure, HDL-c = high density lipoprotein cholesterol, LDL-c = low density lipoprotein cholesterol, MACE = major adverse cardiovascular event (including cardiac and stroke events and death; variously defined by studies), MAP = mean arterial blood pressure, n-3 FA = omega-3 fatty acids, NA = not applicable, Obs = observational study, RCT = randomized controlled trial, SBP = systolic blood pressure, SoE = strength of evidence.

Marine Oil, Total: EPA+DHA±DPA

Overall, there is low, moderate, or high strength of evidence of no effect (or association) of marine oils and most clinical CVD outcomes and BP, and high strength of evidence of significant effects of higher marine oil intake on lipoproteins and Tg. (Table 48). There is insufficient evidence for many outcomes of interest. Specifically, there is high strength of evidence of that marine oils statistically significantly lower Tg—possibly with greater effects with higher doses and in people with higher baseline Tg—and statistically significantly raise HDL-c and LDL-c by similar amounts. There is also high strength of evidence that marine oil significantly lowers Total:HDL-c ratio and low strength of evidence that marine oil significantly lowers risk of ischemic stroke (for which no RCTs confirmed the observational study finding). There is a high strength of evidence of no effect of marine oil on risk of MACE, all-cause death, SCD, revascularization, and BP, moderate strength of evidence of no effect of marine oil on risk of AFib, and low strength of evidence of no effect of marine oil on risk of CVD death, CHD death, total CHD, MI, CHF, total stroke, and hemorrhagic stroke. Strength of evidence was rated as low for CHD and hemorrhagic stroke due to a lack of confirmatory RCT data; and for CVD death, CHF, and total stroke because RCTs and observational studies yielded conflicting conclusions (RCTs found no effect, observational studies found statistically significant associations). Strength of evidence was rated low for CHD death primarily because RCTs and observational studies both yielded imprecise estimates suggesting no effect/association. For MI, the strength of evidence was rated low primarily because the summary effect size estimate was relatively strong (HR = 0.88), but the 95% CI only minimally crossed the significance threshold (95% CI 0.77 to 1.02); this scenario yielded low confidence that the conclusion would remain stable with future RCTs and subsequent greater statistical power. This issue was also pertinent for CVD death where summary HR = 0.92 (95% CI 0.82 to 1.02).There is insufficient evidence for other outcomes.

Four RCTs explicitly evaluated (purified) EPA and/or DHA ethyl esters;[61, 90, 96, 161, 169] all other trials explicitly or implicitly evaluated marine oil preparations. No study directly compared formulations. The effects on clinical and intermediate outcomes found among the ethyl ester trials were all statistically or qualitatively similar to the effects found in other studies.

Clinical Event Outcomes, RCTs

Regarding clinical event outcomes, 19 trials in populations at increased risk for CVD (3 RCTs) and CVD populations (17 RCTs) mostly found no significant effects of marine oil (EPA+DHA±DPA) versus placebo on specific clinical event outcomes. Across RCTs, EPA+DHA doses ranged from 0.34 to 6 g/d (median 0.866 g/d). Followup ranged from 1 to over 10 years (median 3.9 years).

Two of 17 trials found significantly lower risk of all-cause death with EPA+DHA (both 0.866 g/d; HR = 0.79 and 0.91), however, the meta-analyzed HR was nonsignificant at 0.97 (95% CI 0.92 to 1.03) with no differences across trials by marine oil dose, followup time, or population (CVD, at risk, healthy). Four trials also found no within-study subgroup differences in effect on death for multiple subgroup comparisons.

Ten RCTs reported on MACE, only two of which found significant reductions in outcome with 0.866 g/d EPA+DHA at 3.9 year followup and with 1.8 g/d EPA at 5 year followup (in an at-risk population, but not in a parallel CVD population). Meta-analysis of MACE found a no effect (HR=0.96; 95% CI 0.91 to 1.02) with no significant differences across studies by marine oil dose (range 0.4−2 g/d), followup time (range 1−5 y), or population category. Within-study subgroup analyses found a significant effect in women but not men in one trial, but no significant difference in effect between sexes in a second trial, and no differences between multiple subgroups in three trials.

None of the 11 trials that reported on total MI found a significant effect. Meta-analysis, however, found a nonsignificant effect size (HR=0.88; 95% CI 0.77 to 1.02), with no significant differences across studies by marine oil dose, followup time, or population category. In one trial, no significant difference in effect was found based on cointervention with B vitamins.

Two of seven RCTs found significant effects of 0.866 g/d marine oil (EPA+DHA) on risk of CVD death in populations of people with existing CVD. Meta-analysis found a nonsignificant effect size (HR=0.92; 95% CI 0.82 to 1.02), with no significant differences across studies by marine oil dose, followup time, or population.

Nine RCTs all found no significant effect of EPA+DHA with SCD; by meta-analysis (with the EPA trial), summary HR=1.04 (95% CI 0.92 to 1.17). Seven RCTs also found no significant effect of marine oils with total stroke; by meta-analysis, summary HR=0.98 (95% CI 0.88 to 1.09).

Six RCTs evaluated angina pectoris, three stable angina, one hospitalization for angina, and three unstable angina. One trial found that 1.8 g/d of purified EPA ethyl ester had an additive effect on statin to reduce unstable angina incidence after 5 years in people with dyslipidemia; however the five trials in people with existing CVD found no significant effects of 0.84 to 6 g/d marine oils. The six RCTs evaluating CHF had a similar pattern. The one trial of 0.85 g/d marine oil in people with multiple risk factors for CHF found a significant risk reduction in CHF hospitalization with n-3 FA supplementation, but the five studies in people with existing CVD found no significant effects of 0.84 to 6 g/d marine oils.

All EPA+DHA RCTs that evaluated revascularization (6 trials), CHD death (4 trials), total stroke death (3 trials), AFib (3 trials), and CHF death (1 trial) found no significant effect of marine oils. One trial found an effect in participants with diabetes that was not seen in those without diabetes, but no test of interaction was reported. Two trials compared effect of marine oils on AFib in multiple subgroups, finding no significant differences.

Four EPA+DHA RCTs found inconsistent effects on cardiac death, with effect sizes ranging from 0.45 to 1.45. One trial found a statistically significant *reduction* in cardiac death with 0.866 g/d EPA+DHA at 3.5 years (RR=0.65; 95% CI 0.51 to 0.82); one trial found a statistically significant *increase* in cardiac death with a fish diet with EPA+DHA supplements (0.855 g/d EPA+DHA; HR=1.45; 95% CI 1.05 to 1.99), but no significant effect on cardiac death among people only given advice to increase fish intake (by 0.45 g/d EPA+DHA) or in two other trials of 0.96 and 2.6 g/d EPA+DHA. The trial that found increased risk with combined fish diet and EPA+DHA supplementation found no significant difference in effect between multiple sets of subgroups based on drug cointervention.

Intermediate Outcomes, RCTs

Twenty-nine RCTs that compared EPA+DHA to placebo evaluated systolic BP, of which 28 also reported on diastolic BP. Ten RCTs were in healthy populations, 13 in those at risk for CVD, and six in those with CVD. All trials found no significant difference in BP across EPA+DHA doses of 0.30 to 6 g/d and followup durations of 1 month to 6 years. By meta-analysis, no significant effects on systolic (summary net difference = 0.10 mmHg; 95% CI −0.20 to 0.40) or diastolic (summary net difference = −0.19 mmHg; 95% CI −0.43 to 0.05) BP were found. Four of the trials also found no effect on MAP. By meta-regression, no differences in effect across studies were found by marine oil dose, followup duration or population. Three trials directly compared different EPA+DHA doses and found no differences in effect (1.7 vs. 0.8 g/d; 1.8 vs. 0.9 or 0.45 g/d; 3.4 vs. 1.7 g/d). One trial found no difference in effect between people with normal BP or prehypertension.

Numerous included RCTs compared the effect of marine oils and placebo (or equivalent) on blood lipids. Thirty-nine RCTs evaluated LDL-c and 34 evaluated HDL-c. Marine oil doses ranged from 0.3 to 6 g/d (median 2.4 g/d) and study followup times ranged from 1 month to 6 years (median 3 months). Meta-analysis of the effect of marine oils on LDL-c found a statistically significant, but small effect *increasing* LDL-c (1.98 mg/dL; 95% CI 0.38 to 3.58). Marine oils increased HDL-c also by a statistically significant, but small effect (0.92 mg/dL; 95% CI 0.18 to 1.66). For both lipoprotein fractions, no significant differences in effect across studies were found by marine oil dose, followup duration or population. Seven studies found no significant differences in effect within study by EPA+DHA dose. For HDL-c, three trials found no significant difference in effect between people using statins or not; one or two trials, each, found no significant differences between subgroups based on sex or age. One trial found a larger HDL-c effect in a subgroup also randomized to an exercise regimen; one of two trials found a larger HDL-c effect in people with impaired glucose tolerance compared to those with normoglycemia. Eight trials mostly found no significant effects of marine oil (0.4−5 g/d for 1 month to 3 years) on Total:HDL-c ratio, but with a statistically significant summary effect of −0.17 (95% CI −0.26 to −0.09). One trial of 2.8 g/d EPA+DHA found no significant effect on LDL:HDL-c ratio; another trial found no significant difference in change in ratio between 3.4 and 1.7 g/d EPA+DHA.

Forty-one included RCTs mostly found significant effects of marine oils (0.3−6 g/d; median 2.4 g/d for 1 month to 6 years; median 3 months) on Tg levels. Meta-analysis found a summary net change of −24 mg/dL (95% CI −31 to−18), with no significant difference in effect based on population or followup time across studies. By metaregression, each increase in mean baseline Tg concentration by 1 mg/dL was associated with a greater net decrease in Tg concentration of −0.15 mg/dL (95% CI −0.22 to−0.08; P<0.0001); each increase of EPA+DHA dose by 1 g/d was also associated with a greater net decrease in Tg concentration of −5.9 mg/dL (95% CI −9.9 to−2.0; P=0.003). No clear inflection point was found at any dose. Five of six trials found no significant difference in Tg change by EPA+DHA dose, but across trials all doses of 3.4 and 4 g/d lowered Tg concentration by at least 30 mg/dL more than lower doses (1−2 g/d), while all pairwise comparisons of lower doses (1.7−3 g/d) to even lower doses (0.7−2.25 g/d) found much smaller differences between doses (−17 to 6 mg/dL). Two trials both found significantly larger Tg concentration lowering effects of EPA (3.6 or 3.3 g/d) than DHA (3.8 or 3.7 g/d). No significant differences were found based on statin use (4 trials), vitamin C use (1 trial), concurrent high or low linoleic acid diet (1 trial), concurrent general dietary advice (1 trial), or age (1 trial). One trial found a significantly larger effect on Tg among people also taking a multivitamin. One trial found a larger effect of higher dose EPA+DHA (1.8 g/d) in men than women, but no significant difference between sexes at 0.8 g/d. One trial found no significant difference in effect between people with impaired glucose tolerance and those with noninsulin dependent diabetes, but among those with diabetes, a larger effect was found in those with baseline HDL-c ≤35 mg/dL compared to higher levels.

Observational Studies, Intake

Twenty-one observational studies evaluated associations between total EPA+DHA±DPA intake (regardless of source) and numerous clinical outcomes. Only eight (38%) of these found significant associations with any clinical outcome.

By meta-analysis, overall there is a statistically significant association between marine oil intake and CVD death across a median dose range of 0.066 to 1.58 g/d (effect size per g/d = 0.88; 95% CI 0.82 to 0.95). Meta-analyses with the addition of a spline knot point at different dose thresholds (from 0.1 to 1.2 g/d) consistently found a stronger association (of higher dose being associated with lower risk) at *lower* doses than at higher doses (ES below knot less than 1; ES above knot closer to 1). This implies the possibility of a ceiling effect (where intake above a certain level adds no further benefit). However, at no dose threshold was there a statistically significant difference between the ES below the dose threshold (knot) and above the threshold. The best fit curve was found with a knot at 0.3 g/d. The lowest P value between lower-dose and higher-dose ES estimates was found at 0.2 g/d (P=0.26).

By meta-analysis, overall there no significant association between marine oil intake and CHD death across a median dose range of 0.04 to 2.1 g/d (effect size per g/d = 1.09; 95% CI 0.76 to 1.57). Meta-analyses with the addition of a spline knot point at different dose thresholds (from 0.1 to 1.2 g/d) found stronger associations (of higher dose being associated with lower risk) at lower doses than at higher doses (ES below knot less than 1; ES above knot closer to 1) for knots below 0.7 g/d, but stronger associations at higher doses above 0.7 g/d. However, the differences in effect size between lower and higher doses were always highly nonsignificant, implying no difference in association. The best fit curve was found with a knot at 0.5 g/d. The lowest P value between lower-dose and higher-dose ES estimates was found at the lowest tested threshold, 0.1 g/d (P=0.46).

By meta-analysis, overall there no significant association between marine oil intake and all-cause death across a median dose range of 0.066 to 1.58 g/d (effect size per g/d = 0.62; 95% CI 0.31 to 1.25). However, meta-analyses with the addition of a spline knot point at different dose thresholds (from 0.1 to 1.2 g/d) consistently found stronger associations (of higher dose being associated with lower risk) at *lower* doses than at higher doses (ES below knot less than 1; ES above knot closer to 1). This implies the possibility of a ceiling effect (where intake above a certain level adds no further benefit). For thresholds ≤0.4 g/d the associations are statistically significant at lower doses, but not statistically significant at higher doses. The difference between low- and high-dose associations is statistically significantly different at a threshold of 0.2 g/d (P=0.047). The best fit curve was found with a knot at 0.3 g/d. This analysis may suggest that marine oil intake above about 0.2 to 0.4 g/d may not further strengthen any association between higher marine oil intake and lower rate of all-cause death.

By meta-analysis, overall there no significant association between marine oil intake and CHD across a median dose range of 0.038 to 3.47 g/d (effect size per g/d = 0.94; 95% CI 0.81 to 1.10]). Meta-analyses with the addition of a spline knot point at different dose thresholds (from 0.1 to 1.4 g/d) consistently found a stronger association (of higher dose being associated with lower risk) at *lower* doses than at higher doses (ES below knot less than 1, ES above know about 1). At all knot points the differences were nonsignificant. This weakly suggests the possibility of a ceiling effect (where intake above a certain level adds no further benefit). The best fit curve was found with a knot at 0.4 g/d. The P values for differences between lower- and higher-dose knots were between 0.12 and 0.14 at all knots ≥0.3 g/d.

By meta-analysis, overall there is a statistically significant association between marine oil intake and total stroke across a median dosage range of 0.025 to 0.6 g/d (effect size per g/d = 0.68; 95% CI 0.53 to 0.87). Meta-analyses with the addition of a spline knot point at different dose thresholds (from 0.1 to 0.5 g/d) consistently found a much stronger association (of higher dose being associated with lower risk) at *lower* doses than at higher doses (ES below know less than 1; ES above know greater than 1); although, the difference in effect sizes above and below the knots were never statistically significant This implies a possible ceiling effect ceiling effect (where intake above a certain level adds no further benefit). However, given that the differences between lower and higher dose ES remained large across the range of testable dose thresholds, the actual ceiling dose threshold may be above the analyzable range (i.e., >0.5 g/d). The best fit curve was found with the lowest knot at 0.1 g/d. The P values for differences between lower- and higher-dose effect sizes ranged from 0.14 to 0.20.

By meta-analysis, overall there is a statistically significant association between higher marine oil intake and *lower* risk of ischemic stroke across a median dosage range of 0.025 to 0.6 g/d (effect size per g/d = 0.51; 95% CI 0.29 to 0.89). Meta-analyses with the addition of a spline knot point at different dose thresholds (from 0.1 to 0.5 g/d) consistently found a much stronger association (of higher dose being associated with lower risk) at *lower* doses than at higher doses (ES below knot less than 1; ES above knot near or greater than 1). All effect sizes below the knots were statistically significant and all above the knots were nonsignificant. The differences between lower- and higher-dose effect sizes were all statistically significant (P=0.03-0.049). This implies a ceiling effect (where intake above a certain level adds no further benefit). However, it is unclear what the threshold may be, as it may be greater than the highest threshold tested (0.4 g/d). The best fit curve was found with a knot at either 0.3 or 0.4 g/d. The difference between lower-dose and higher-dose ES estimates was statistically significant with a knot at 0.1 g/d.

By meta-analysis, overall there is no significant association between marine oil intake and hemorrhagic stroke across a median dosage range of 0.025 to 0.6 g/d (effect size per g/d = 0.61; 95% CI 0.34 to 1.11). Meta-analyses with the addition of a spline knot point at different dose thresholds (from 0.1 to 0.5 g/d) consistently found similar associations above and below the knots. At no threshold was the difference in effect sizes statistically significant. The best fit curve was found with a knot at 0.1 g/d. The lowest P value between lower-dose and higher-dose ES estimates was found at 0.5 g/d (P=0.78).

By meta-analysis, overall there is a just-significant association between higher marine oil intake and decreased risk of CHF across a median dosage range of 0.014 to 0.71 g/d (effect size per g/d = 0.76; 95% CI 0.58 to 1.00). Meta-analyses with the addition of a spline knot point at different dose thresholds (from 0.1 to 0.5 g/d) consistently found a stronger association (of higher dose being associated with lower risk) at *lower* doses than at higher doses (ES below knot less than 1; ES above knot closer to 1). This implies the possibility of a ceiling effect (where intake above a certain level adds no further benefit). However, given that the differences between lower and higher dose ES remained large across the range of testable dose thresholds, the actual ceiling dose threshold may be above the analyzable range (i.e., >0.5 g/d). At thresholds of 0.1 and 0.2 g/d, the difference in effect size at lower and higher doses were statistically significant (P values 0.04 and 0.03, respectively). But the most significant difference was found at the highest threshold tested, 0.5 g/d (P=0.02). The best fit curve was found with the lowest knot tested, 0.1 g/d.

A minority of studies found significant associations of decreased risk of other outcomes with increasing intake of EPA+DHA±DPA: MACE (1 of 2 studies), all-cause death (1 of 3 studies), CVD death (1 of 4 studies), CHD death (3 of 7 studies), MI (1 of 2 studies), incident CHF (1 of 5 studies), and AFib (1 of 3 studies). No studies found significant associations with cardiac death (1 study), total stroke death (1 study), ischemic stroke death (1 study), coronary revascularization (1 study), ventricular arrhythmia (1 study), SCD (2 studies), and incident hypertension (1 study). One study each analyzed MI death and ischemic stroke death and found a significant association.

Observational Studies, Biomarkers

Five studies evaluated combined EPA+DHA±DPA biomarkers, including adipose tissue, cholesteryl ester, erythrocyte, phospholipid, and plasma n-3 FA levels. Of the outcomes evaluated, none was analyzed by more than two studies. One study each found no significant association between various biomarker levels and MI, hemorrhagic stroke, total stroke (with a P value of 0.07), or cardiac death. One study found a significant association between higher phospholipid EPA+DHA+DPA and incident CHD. Another found a significant association between higher adipose EPA+DHA+DPA and acute coronary syndrome in men, but not in women. Two studies each evaluated CHF, ischemic stroke, and MACE. For each outcome only one of the studies found significant associations with EPA+DHA±DPA biomarker levels. In one of the studies of CHF, phospholipid EPA+DHA+DPA level was associated with the outcome in women only but cholesteryl ester EPA+DHA+DPA levels were not associated in either sex.

Table 48. Evidence profile for the effect and association of marine oil (EPA+DHA± DPA) with CVD outcomes*

Outcome	SoE Grade	Design No. Studies	Study Limitations	Consistency	Precision	Other Issues	Finding
Major adverse cardiovascular events (MACE)	High	RCT: 10 Obs intake: 3 Obs biomarkers: 2	Low	RCT: Consistent Obs intake: Consistent Obs biomarkers: Inconsistent All: Inconsistent	RCT: Precise Obs intake: Precise Obs biomarker: Precise	None	RCT: No effect 0.96 (0.91, 1.02) Obs intake: No association Obs biomarkers: Unclear
CVD death (including stroke)	Low	RCT: 7 Obs intake: 6 Obs biomarkers: 0	Low	RCT: Consistent Obs intake: Inconsistent Obs biomarkers: NA All: Inconsistent	RCT: Imprecise Obs intake: Imprecise Obs biomarker: NA	None	RCT: No effect 0.92 (0.82, 1.02) Obs intake: Lower risk 0.88 (0.82, 0.95) per g/d Obs biomarkers: NA
Cardiac death	Insufficient	RCT: 5 Obs intake: 1 Obs biomarkers: 1	Low	RCT: Inconsistent Obs intake: NA Obs biomarkers: NA All: Inconsistent	RCT: Precise Obs intake: Imprecise Obs biomarker: Imprecise	Sparse Obs	RCT: Unclear Obs intake: No association Obs biomarkers: No association
Coronary heart disease death	Low	RCT: 4 Obs intake: 7 Obs biomarkers: 0	Moderate	RCT: Consistent Obs intake: Inconsistent Obs biomarker: NA All: Inconsistent	RCT: Imprecise Obs intake: Imprecise Obs biomarker: NA	None	RCT: No effect Obs intake: No association 1.09 (0.76, 1.57) per g/d Obs biomarkers: NA
Myocardial infarction death	Insufficient	RCT: 0 Obs intake: 1 Obs biomarkers: 0	Low	RCT: NA Obs: NA Obs intake: NA All: NA	RCT: NA Obs intake: Imprecise Obs biomarker: NA	Sparse	RCT: NA Obs intake: Lower risk Obs biomarkers: NA
Heart failure death	Insufficient	RCT: 1 Obs intake: 0 Obs biomarkers: 0	Low	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: Imprecise Obs intake: NA Obs biomarker: NA	Sparse	RCT: No effect Obs intake: NA Obs biomarkers: NA
Stroke death	Insufficient	RCT: 2 Obs intake: 1 Obs biomarkers: 0	Low	RCT: Consistent Obs intake: NA Obs biomarkers: NA All: Consistent	RCT: Imprecise Obs intake: Imprecise Obs biomarker: NA	Sparse	RCT: No effect Obs intake: No association Obs biomarkers: NA
Ischemic stroke death	Insufficient	RCT: 0 Obs intake: 1 Obs biomarkers: 0	Moderate	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: Unclear Obs biomarker: NA	Sparse	RCT: NA Obs intake: Lower risk Obs biomarkers: NA
Hemorrhagic stroke death	Insufficient	RCT: 0 Obs intake: 1 Obs biomarkers: 0	Moderate	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: Unclear Obs biomarker: NA	Sparse	RCT: NA Obs intake: No association Obs biomarkers: NA

Table 48. Evidence profile for the effect and association of marine oil (EPA+DHA± DPA) with CVD outcomes (continued)

Outcome	SoE Grade	Design No. Studies	Study Limitations	Consistency	Precision	Other Issues	Finding
Death, all-cause	High	RCT: 17 Obs intake: 3 Obs biomarkers: 0	Low	RCT: Consistent Obs intake: Consistent Obs biomarkers: NA All: Inconsistent	RCT: Precise Obs intake: Precise Obs biomarker: NA	None	RCT: No effect 0.97 (0.92, 1.03) Obs intake: No association 0.62 (0.31, 1.25) per g/d Obs biomarkers: NA
Coronary heart disease	Low	RCT: 0 Obs intake: 7 Obs biomarkers: 1	Low	RCT: NA Obs intake: Consistent Obs biomarkers: NA All: Consistent	RCT: NA Obs intake: Precise Obs biomarker: Precise	No RCT	RCT: NA Obs intake: No association 0.94 (0.81, 1.10) per g/d Obs biomarkers: Lower risk
Myocardial infarction	Low	RCT: 11 Obs intake: 1 Obs biomarkers: 0	Low	RCT: Consistent Obs intake: NA Obs biomarkers: NA All: Consistent	RCT: Imprecise Obs intake: Precise Obs biomarker: NA	Sparse Obs	RCT: No effect 0.88 (0.77, 1.02) Obs intake: No association Obs biomarkers: NA
Acute coronary syndrome	Insufficient	RCT: 0 Obs intake: 1 Obs biomarkers: 1	Low	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: Imprecise Obs biomarker: Imprecise	Sparse	RCT: NA Obs intake: No association Obs biomarkers: No association
Angina pectoris	Low	RCT: 6 Obs intake: 0 Obs biomarkers: 0	Low	RCT: Inconsistent Obs intake: NA Obs biomarkers: NA All: NA	RCT: Imprecise Obs intake: NA Obs biomarker: NA	Heterogeneous outcomes	RCT: No effect Obs intake: NA Obs biomarkers: NA
Atrial fibrillation	Moderate	RCT: 3 Obs intake: 3 Obs biomarkers: 0	Low	RCT: Consistent Obs intake: Inconsistent Obs biomarkers: NA All: Consistent	RCT: Precise Obs intake: Imprecise Obs biomarker: NA	Few studies	RCT: No effect Obs intake: Unclear Obs biomarkers: NA
Ventricular Arrhythmia	Insufficient	RCT: 1 Obs intake: 0 Obs biomarkers: 0	Low	RCT: NA Obs intake: NA Obs biomarkers: NA	RCT: Precise Obs intake: NA Obs biomarkers: NA	Sparse	RCT: No effect Obs intake: NA Obs biomarkers: NA
Congestive heart failure	Low	RCT: 6 Obs intake: 5 Obs biomarkers: 2	Low	RCT: Consistent Obs intake: Consistent Obs biomarkers: Consistent All: Inconsistent	RCT: Imprecise Obs intake: Precise Obs biomarker: Imprecise	Few RCTs	RCT: No effect Obs intake: Lower risk 0.76 (0.58, 1.00) per g/d Obs biomarkers: No association
Stroke, total	Low	RCT: 7 Obs intake: 4 Obs biomarkers: 2	Low	RCT: Consistent Obs intake: Consistent Obs biomarkers: Inconsistent All: Consistent	RCT: Precise Obs intake: Imprecise Obs biomarker: Imprecise	None	RCT: No effect 0.97 (0.83, 1.13) Obs intake: Lower risk 0.68 (0.53, 0.87) per g/d Obs biomarkers: Unclear

Table 48. Evidence profile for the effect and association of marine oil (EPA+DHA± DPA) with CVD outcomes (continued)

Outcome	SoE Grade	Design No. Studies	Study Limitations	Consistency	Precision	Other Issues	Finding
Stroke, ischemic	Low	RCT: 2 Obs intake: 5 Obs biomarkers: 2	Low	RCT: Consistent Obs intake: Consistent Obs biomarkers: Inconsistent All: Inconsistent	RCT: Precise Obs intake: Imprecise Obs biomarker: Imprecise	Sparse RCT	RCT: No effect Obs intake: Lower risk 0.51 (0.29, 0.89) per g/d Obs biomarkers: Unclear
Stroke, hemorrhagic	Low	RCT: 2 Obs intake: 5 Obs biomarkers: 1	Low	RCT: Consistent Obs intake: Consistent Obs biomarkers: NA All: Consistent	RCT: Precise Obs intake: Imprecise Obs biomarker: Imprecise	Sparse RCT	RCT: NA Obs intake: No association 0.61 (0.34, 1.11) per g/d Obs biomarkers: No association
Sudden cardiac death	High	RCT: 9 Obs intake: 1 Obs biomarkers: 0	Low	RCT: Consistent Obs intake: NA Obs biomarkers: NA All: Consistent	RCT: Precise Obs intake: Imprecise Obs biomarkers: NA	None	RCT: No effect 1.04 (0.92, 1.17) Obs intake: No association Obs biomarkers: NA
Revascularization	High	RCT: 6 Obs intake: 1 Obs biomarkers: 0	Low	RCT: Consistent Obs intake: NA Obs biomarkers: NA All: NA	RCT: Precise Obs intake: Obs biomarker:	Sparse Obs	RCT: No effect Obs intake: No association Obs biomarkers: NA
Hypertension	Insufficient	RCT: 0 Obs intake: 1 Obs biomarkers: 0	Low	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: Precise Obs biomarker: NA	Sparse	RCT: NA Obs intake: No association Obs biomarkers: NA
Blood pressure (SBP, DBP, MAP combined)	High	RCT: 29 Obs intake: 0 Obs biomarkers: 0	Low	RCT: Consistent Obs intake: NA Obs biomarkers: NA All: NA	RCT: Precise Obs intake: NA Obs biomarker: NA	No Obs	RCT: No effect SBP: 0.1 mmHg (−0.2, 0.4) DBP: −0.2 mmHg (−0.4, 0.05) Obs intake: NA Obs biomarkers: NA
LDL-c	High	RCT: 39 Obs intake: 0 Obs biomarkers: 0	Low	RCT: Consistent Obs intake: NA Obs biomarkers: NA All: NA	RCT: Precise Obs intake: NA Obs biomarker: NA	No Obs	RCT: Higher risk (raise LDL-c) 1.98 mg/dL (0.38, 3.58) Obs intake: NA Obs biomarkers: NA
HDL-c	High	RCT: 34 Obs intake: 0 Obs biomarkers: 0	Low	RCT: Consistent Obs intake: NA Obs biomarkers: NA All: NA	RCT: Precise Obs intake: NA Obs biomarker: NA	No Obs	RCT: Lower risk (raise HDL-c) 0.88 mg/dL (0.20, 1.57) Obs intake: NA Obs biomarkers: NA

Table 48. Evidence profile for the effect and association of marine oil (EPA+DHA± DPA) with CVD outcomes (continued)

Outcome	SoE Grade	Design No. Studies	Study Limitations	Consistency	Precision	Other Issues	Finding
Triglycerides	High	RCT: 41 Obs intake: 0 Obs biomarkers: 0	Low	RCT: Consistent Obs intake: NA Obs biomarkers: NA All: NA	RCT: Precise Obs intake: NA Obs biomarker: NA	No Obs	RCT: Lower risk (lower triglycerides) −24 mg/dL (−31, −18) Obs intake: NA Obs biomarkers: NA
HDL-c/Total cholesterol to LDL-c ratios	High	RCT: 11 Obs intake: 0 Obs biomarkers: 0	Low	RCT: Consistent Obs intake: NA Obs biomarkers: NA All: NA	RCT: Precise Obs intake: NA Obs biomarker: NA	No Obs	RCT: Lower risk −0.17 (−0.26, −0.09) Obs intake: NA Obs biomarkers: NA

* No reporting bias was detected for any outcome. All studies that measured n-3 FA intake were assessed to be direct, while all biomarker studies were assessed to be indirect.

Abbreviations: CVD = cardiovascular disease, DBP = diastolic blood pressure, DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, EPA = eicosapentaenoic acid, HDL-c = high density lipoprotein cholesterol, LDL-c = low density lipoprotein cholesterol, MAP = mean arterial blood pressure, n-3 FA = omega-3 fatty acids, NA = not applicable, Obs = observational study, RCT = randomized controlled trial, SBP = systolic blood pressure, SoE = strength of evidence.

EPA

For the most part, there is insufficient evidence regarding the effect of or association with EPA (specifically) and CVD clinical and intermediate outcomes (Table 49). There is low strength of evidence of no association between EPA intake and CHD and between EPA biomarkers and AFib; no RCTs evaluated these outcomes.

Clinical Event Outcomes, RCTs

Regarding clinical event outcomes, one trial in an at risk population (dyslipidemia), found that after 5 years, compared with placebo, people taking purified EPA 1.8 g/d had significantly lower risk of MACE and angina, but no significant difference in all-cause death, CHD death, coronary revascularization, SCD, or MI (also in the subgroup of people with prior CVD). Subgroup analysis for CHD death found no clear difference between those who also had CVD versus those without CVD.

Intermediate Outcomes, RCTs

One trial of purified EPA 3.8 g/d versus placebo found no significant effect on systolic BP, diastolic BP, or MAP. This trial and another of EPA 3.3 g/d found no significant effect of EPA on LDL-c or HDL-c. Both trials, however, found significant net reductions in Tg concentration (−42 and −23 mg/dL). The trial of EPA 3.8 g/d also found a significant reduction in Total:HDL-c ratio (−0.2).

Observational Studies, Intake

Eight studies evaluated associations between estimated total EPA intake (specifically) and clinical outcomes. No outcome was evaluated by more than two studies. One study each found no significant association between EPA intake and acute coronary syndrome, ischemic stroke, or total stroke death. One study found a significant association between higher EPA intake and lower ischemic stroke death in healthy adults (in quantiles with median EPA intake >0.07 g/d in men and >0.06 g/d in women), but no association with hemorrhagic stroke death. One study found a significant association between higher EPA intake and lower risk of all-cause death (>0.01 g/d) in healthy adults. Another study found a significant association with MACE in healthy adults (>0.09 g/d). Two studies, each, found no significant associations between EPA intake and incident CHD (although P=0.06 in one) or CHD death. For both incident hypertension and CVD death, one of two studies found significant associations between higher EPA (0.02 g/d for hypertension and 0.01 g/d for CVD death) intake and lower risk of outcomes; the other studies found no such associations.

Observational Studies, Biomarkers

Ten studies evaluated associations between various EPA biomarkers and clinical outcomes. For three clinical outcomes, two of three studies found significant associations between higher EPA biomarker level and reduced risk of outcome. Three studies of healthy adults evaluated CHD, two of which found increased plasma or phospholipid EPA levels were associated with reduced CHD risk; the third study evaluated blood EPA levels. Three studies, two in healthy adults, one in people with hypercholesterolemia, evaluated MACE; the study of people with hypercholesterolemia found an association of reduced MACE risk with higher plasma EPA, as did one study of phospholipid EPA in healthy adults. The third study found no significant association between erythrocyte EPA and MACE in healthy adults. Three studies, two in healthy adults, one in adults with a history of MI, evaluated CHF; in one study of healthy adults higher plasma EPA was associated with reduced CHF risk, but the other study of healthy adults found no association with phospholipid or cholesteryl ester EPA. The study in people with a history of MI also found an association with higher blood EPA. In this latter study, significant interactions were found for sex (no association was seen in women, in contrast with a significant association in men), statin use (those on statins had no association, in contrast with those on statins), and baseline HDL-c level (those with higher HDL-c had no association, in contrast with those with HDL-c <40 mg/dL). No interactions were found for age, use of angiotensin receptor blocker drugs, use of beta blocker drugs, diabetes, dyslipidemia, baseline LDL-c, hypertension, glomerular filtration function, or hypertriglyceridemia.

One of three studies found a significant association between higher EPA biomarkers (plasma EPA) and lower risk of death in healthy adults, but a second study of plasma EPA in healthy adults found no such association; nor did a study of blood EPA in people with a history of MI. One of two studies of plasma EPA in healthy adults found a significant association with CVD death. Two studies found no significant association between EPA biomarkers and ischemic stroke. One study found a significant association between erythrocyte EPA and incident hypertension. One study each found no associations between EPA biomarker levels and acute coronary syndrome, AFib, SCD, MI, hemorrhagic stroke, total stroke, cardiac death, CHD death, or total stroke death.

Table 49. Evidence profile for the effect and association of EPA, specifically, with CVD outcomes*

Outcome	SoE Grade	Design No. Studies	Study Limitations	Consistency	Precision	Other Issues	Finding
Major adverse cardiovascular events (MACE)	Insufficient	RCT: 1 Obs intake: 1 Obs biomarker: 3	Low	RCT: NA Obs intake: NA Obs biomarker: Inconsistent All: Inconsistent	RCT: Precise Obs intake: Imprecise Obs biomarker: Imprecise	Sparse RCT	RCT: Lower risk Obs intake: Lower risk Obs biomarker: Unclear
CVD death (including stroke)	Insufficient	RCT: 0 Obs intake: 2 Obs biomarker: 1	Low	RCT: NA Obs intake: Inconsistent Obs biomarker: NA All: NA	RCT: NA Obs intake: Precise Obs biomarker: Precise	No RCT	RCT: NA Obs intake: Unclear Obs biomarker: Lower risk
Cardiac death	Insufficient	RCT: 0 Obs intake: 0 Obs biomarker: 1	Low	RCT: NA Obs intake: NA Obs biomarker: NA All: NA	RCT: NA Obs intake: NA Obs biomarker: Unclear	Sparse	RCT: NA Obs intake: NA Obs biomarker: No association
Coronary heart disease death	Insufficient	RCT: 1 Obs intake: 2 Obs biomarker: 1	Low	RCT: NA Obs intake: Consistent Obs biomarker: NA All: Consistent	RCT: Imprecise Obs intake: Imprecise Obs biomarker: Imprecise	None	RCT: No effect Obs intake: No association Obs biomarker: No association
Myocardial infarction death	Insufficient	RCT: 0 Obs intake: 0 Obs biomarker: 0	NA	RCT: NA Obs intake: NA Obs biomarker: NA All: NA	NA	No data	RCT: NA Obs intake: NA Obs biomarker: NA
Heart failure death	Insufficient	RCT: 0 Obs intake: 0 Obs biomarker: 0	NA	RCT: NA Obs intake: NA Obs biomarker: NA All: NA	NA	No data	RCT: NA Obs intake: NA Obs biomarker: NA
Stroke death	Insufficient	RCT: 1 Obs intake: 1 Obs biomarker: 1	Low	RCT: NA Obs intake: Obs biomarker: All: Consistent	RCT: Imprecise Obs intake: Imprecise Obs biomarker: Imprecise	Sparse	RCT: No effect Obs intake: No association Obs biomarker: No association
Ischemic stroke death	Insufficient	RCT: 0 Obs intake: 1 Obs biomarker: 0	Moderate	RCT: NA Obs intake: NA Obs biomarker: NA All: NA	RCT: NA Obs intake: Precise Obs biomarker: NA	Sparse	RCT: NA Obs intake: Lower risk Obs biomarker: NA
Hemorrhagic stroke death	Insufficient	RCT: 0 Obs intake: 1 Obs biomarker: 0	Moderate	RCT: NA Obs intake: NA Obs biomarker: NA All: NA	RCT: NA Obs intake: Imprecise Obs biomarker: NA	Sparse	RCT: NA Obs intake: No association Obs biomarker: NA

Table 49. Evidence profile for the effect and association of EPA, specifically, with CVD outcomes (continued)

Outcome	SoE Grade	Design No. Studies	Study Limitations	Consistency	Precision	Other Issues	Finding
Death, all-cause	Insufficient	RCT: 1 Obs intake: 0 Obs biomarker: 3	Low	RCT: NA Obs intake: NA Obs biomarker: Inconsistent All: NA	RCT: Precise Obs intake: NA Obs biomarker: Precise	No RCT	RCT: No effect Obs intake: NA Obs biomarker: Unclear
Coronary heart disease	Low	RCT: 0 Obs intake: 2 Obs biomarker: 3	Low	RCT: NA Obs intake: Yes Obs biomarker: NA All: NA	RCT: NA Obs intake: Imprecise Obs biomarker: Imprecise	No RCT	RCT: NA Obs intake: No association Obs biomarker: Unclear
Myocardial infarction	Insufficient	RCT: 1 Obs intake: 0 Obs biomarker: 1	Low	RCT: NA Obs intake: NA Obs biomarker: NA All: NA	RCT: Imprecise Obs intake: NA Obs biomarker: Precise	Sparse	RCT: No effect Obs intake: NA Obs biomarker: No association
Acute coronary syndrome	Insufficient	RCT: 0 Obs intake: 1 Obs biomarker: 1	Low	RCT: NA Obs intake: NA Obs biomarker: NA All: NA	RCT: NA Obs intake: Imprecise Obs biomarker: Imprecise	Sparse	RCT: NA Obs intake: No association Obs biomarker: No association
Angina pectoris	Insufficient	RCT: 1 Obs intake: 0 Obs biomarker: 0	Low	RCT: NA Obs intake: NA Obs biomarker: NA All: NA	RCT: Precise Obs intake: NA Obs biomarker: NA	Sparse	RCT: Lower risk Obs intake: NA Obs biomarker: NA
Atrial fibrillation	Low	RCT: 0 Obs intake: 0 Obs biomarker: 3	Low	RCT: NA Obs intake: NA Obs biomarker: NA All: NA	RCT: NA Obs intake: NA Obs biomarker: Imprecise	No RCT	RCT: NA Obs intake: NA Obs biomarker: No association
Ventricular Arrhythmia	Insufficient	RCT: 0 Obs intake: 0 Obs biomarkers: 0	NA	RCT: NA Obs intake: NA Obs biomarkers: NA	RCT: NA Obs intake: NA Obs biomarkers: NA	No data	RCT: NA Obs intake: NA Obs biomarkers: NA
Congestive heart failure	Insufficient	RCT: 0 Obs intake: 0 Obs biomarker: 3	Low	RCT: NA Obs intake: NA Obs biomarker: Consistent All: NA	RCT: NA Obs intake: NA Obs biomarker: Precise	No RCT	RCT: NA Obs intake: NA Obs biomarker: Unclear
Stroke, total	Insufficient	RCT: 0 Obs intake: 0 Obs biomarker: 1	Low	RCT: NA Obs intake: NA Obs biomarker: NA All: NA	RCT: NA Obs intake: NA Obs biomarker: Imprecise	Sparse	RCT: NA Obs intake: NA Obs biomarker: No association
Stroke, ischemic	Insufficient	RCT: 1 Obs intake: 1 Obs biomarkers: 2	Low	RCT: NA Obs intake: NA Obs biomarkers: Consistent All: Consistent	RCT: Precise Obs intake: Imprecise Obs biomarker: Imprecise	Sparse	RCT: No effect Obs intake: No association Obs biomarkers: No association

Table 49. Evidence profile for the effect and association of EPA, specifically, with CVD outcomes (continued)

Outcome	SoE Grade	Design No. Studies	Study Limitations	Consistency	Precision	Other Issues	Finding
Stroke, hemorrhagic	Insufficient	RCT: 1 Obs intake: 0 Obs biomarkers: 1	Low	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: Precise Obs intake: NA Obs biomarker: NA	Sparse	RCT: No effect Obs intake: NA Obs biomarkers: No association
Sudden cardiac death	Insufficient	RCT: 1 Obs intake: 0 Obs biomarkers: 1	Low	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: Imprecise Obs intake: NA Obs biomarkers: NA	No RCT	RCT: No effect Obs intake: NA Obs biomarkers: No association
Revascularization	Insufficient	RCT: 1 Obs intake: 0 Obs biomarker: 0	Low	RCT: NA Obs intake: NA Obs biomarker: NA All: NA	RCT: Precise Obs intake: NA Obs biomarker: NA	Sparse	RCT: No effect Obs intake: NA Obs biomarker: NA
Hypertension	Insufficient	RCT: 0 Obs intake: 0 Obs biomarker: 0	NA	RCT: NA Obs intake: NA Obs biomarker: NA All: NA	NA	No data	RCT: NA Obs intake: NA Obs biomarker: NA
Blood pressure (SBP, DBP, MAP combined)	Insufficient	RCT: 2 Obs intake: 0 Obs biomarker: 1	NA	RCT: Inconsistent Obs intake: NA Obs biomarker: NA All: NA	RCT: Imprecise Obs intake: NA Obs biomarker: Imprecise	Sparse	RCT: No effect Obs intake: NA Obs biomarker: Lower risk
LDL-c	Insufficient	RCT: 2 Obs intake: 0 Obs biomarker: 0	NA	RCT: NA Obs intake: NA Obs biomarker: NA All: NA	RCT: Imprecise Obs intake: NA Obs biomarker: NA	Sparse	RCT: No effect Obs intake: NA Obs biomarker: NA
HDL-c	Insufficient	RCT: 2 Obs intake: 0 Obs biomarker: 0	NA	RCT: NA Obs intake: NA Obs biomarker: NA All: NA	RCT: Imprecise Obs intake: NA Obs biomarker: NA	Sparse	RCT: No effect Obs intake: NA Obs biomarker: NA
Triglycerides	Insufficient	RCT: 2 Obs intake: 0 Obs biomarker: 0	Low	RCT: Consistent Obs intake: NA Obs biomarker: NA All: NA	RCT: Precise Obs intake: NA Obs biomarker: NA	Sparse	RCT: Lower risk (lower triglycerides) Obs intake: NA Obs biomarker: NA
HDL-c/Total cholesterol to LDL-c ratios	Insufficient	RCT: 1 Obs intake: 0 Obs biomarker: 0	Low	RCT: NA Obs intake: NA Obs biomarker: NA All: NA	RCT: Precise Obs intake: NA Obs biomarker: NA	Sparse	RCT: Lower risk Obs intake: NA Obs biomarker: NA

* No reporting bias was detected for any outcome. All studies that measured n-3 FA intake were assessed to be direct, while all biomarker studies were assessed to be indirect.

Abbreviations: CVD = cardiovascular disease, DBP = diastolic blood pressure, EPA = eicosapentaenoic acid, HDL-c = high density lipoprotein cholesterol, LDL-c = low density lipoprotein cholesterol, MACE = major adverse cardiovascular events, MAP = mean arterial blood pressure, n-3 FA = omega-3 fatty acids, NA = not applicable, Obs = observational study, RCT = randomized controlled trial, SBP = systolic blood pressure, SoE = strength of evidence.

DHA

For the most part, there is insufficient evidence regarding the effect of or association with EPA (specifically) and CVD clinical and intermediate outcomes (Table 50). There is moderate strength of evidence of no effect of purified DHA supplementation on BP or LDL-c and low strength of evidence of no association between DHA intake and incident CHD (from observational studies only).

Clinical Event Outcomes, RCTs

No trial that reported clinical event outcomes evaluated DHA alone.

Intermediate Outcomes, RCTs

Two trials compared purified DHA (3.6 and 2 g/d) to placebo and found no significant effects on systolic or diastolic BP. One of the trials also found no significant effect on MAP. Three trials of DHA (3.7, 3.6, or 2 g/d) also found no significant effect compared to placebo on LDL-c or HDL-c. Two of the trials (3.7 and 3.6 g/d) reported on Tg concentration changes and both found significant net reductions compared to placebo with DHA supplementation (−27 and −29 mg/dL) . The trial of DHA 3.6 g/d also found a significant reduction in Total:HDL-c ratio (−0.3).

Observational Studies, Intake

Eight studies evaluated the association between estimated total DHA intake (specifically) and risk of clinical outcomes. No study evaluated any outcome in more than two studies. Two studies found significant associations between higher DHA intake and lower risk of incident hypertension in healthy young adults (18−30 years old in one study; 39−54 year old women in a subgroup of one study), but not in an older subgroup in one study (55−89 years old). In the study of young adults, a significant association was found in quartiles with DHA intake >0.06 g/d. One of two studies of healthy adults found an association of lower CVD death with DHA intake >0.15 g/d. Two studies each found no association with CHD death or incident CHD (in populations with a broad range of ages, from 20−69 to 45−84 years old). One study each found significant associations of higher DHA intake with MACE (>0.15 g/d DHA), ischemic stroke death (>0.15 g/d), and all-cause death (>0.02 g/d). In one study each, no associations were found with acute coronary syndrome, ischemic stroke, hemorrhagic stroke death, or total stroke death.

Observational Studies, Biomarkers

Eleven studies evaluated various DHA biomarkers and their associations with clinical outcomes. A high proportion of association analyses were statistically significant favoring higher DHA biomarker levels. Four studies evaluated MACE (with various definitions); two found significant associations between higher DHA biomarker levels (phospholipid and adipose DHA) and lower risk of MACE in healthy adults. The other two studies found no association, one in hypercholesterolemic adults on statins (plasma DHA) and one in healthy adults (erythrocyte DHA). Two of three studies in healthy adults found significant associations between lower CHD risk and higher plasma or phospholipid DHA; the third study, also in healthy adults found no association with blood DHA. Three studies evaluated CHF. One found associations between higher cholesteryl ester and phospholipid DHA and lower risk of incident CHF in healthy women, but not healthy men (whether the associations were significantly different between women and men was not reported). One study found that overall, there was no significant association with blood DHA in adults with a history of MI, but that there were significant associations in subgroups of people (where the difference in association between subgroups was at least nearly significant [$P<0.10$]), such that significant association were found in people (after MI) not taking a statin (P interaction with statin use = 0.003), ≥65 years old (P interaction = 0.051), with LDL-c ≥100 mg/dL (P interaction = 0.068), and with HDL-c ≤40 mg/dL (P interaction = 0.096). Three studies also evaluated all-cause death, two of which found significantly lower risk of death with higher plasma DHA (healthy adults) and blood DHA (in people with a history of MI who were not taking statins); another study of healthy adults found no association with plasma DHA.

Two studies found nonsignificant associations between higher cholesteryl ester DHA (P=0.07), phospholipid DHA (P=0.08), and plasma DHA (P=0.052) and lower risk of ischemic stroke in healthy adults. One study of healthy adults found an association between higher plasma DHA and lower risk of CVD death (both studies evaluated plasma DHA). One study each found significant associations between higher DHA biomarker levels and lower incidence of AFib, SCD, and CHD death (all plasma DHA in healthy adults). One study found a significant association between higher adipose DHA and lower risk of acute coronary syndrome in healthy men, but not healthy women. Another study found a significant association between higher erythrocyte DHA and lower risk of incident hypertension in healthy women aged 39 to 54 years, but not in women older than 54 years. One study found no significant associations between plasma DHA and both total stroke and total stroke death in healthy adults. One study, each, found no significant associations with MI, hemorrhagic stroke, or cardiac death.

Table 50. Evidence profile for the effect and association of DHA, specifically, with CVD outcomes*

Outcome	SoE Grade	Design No. Studies	Study Limitations	Consistency	Precision	Other Issues	Finding
Major adverse cardiovascular events (MACE)	Insufficient	RCT: 0 Obs intake: 1 Obs biomarker: 4	Low	RCT: NA Obs intake: NA Obs biomarker: Inconsistent All: NA	RCT: NA Obs intake: Imprecise Obs biomarker: Imprecise	No RCT	RCT: NA Obs intake: Unclear Obs biomarker: Unclear
CVD death (including stroke)	Insufficient	RCT: 0 Obs intake: 2 Obs biomarker: 1	Low	RCT: NA Obs intake: Consistent Obs biomarker: NA All: NA	RCT: NA Obs intake: Precise Obs biomarker: Precise	No RCT	RCT: NA Obs: Unclear Obs biomarker: Lower risk
Cardiac death	Insufficient	RCT: 0 Obs intake: 0 Obs biomarker: 1	Low	RCT: NA Obs intake: NA Obs biomarker: NA All: NA	RCT: NA Obs intake: NA Obs biomarker: Unclear	Sparse	RCT: NA Obs intake: NA Obs biomarker: No association
Coronary heart disease death	Insufficient	RCT: 0 Obs intake: 2 Obs biomarker: 1	Low	RCT: NA Obs intake: Consistent Obs biomarker: NA All: NA	RCT: NA Obs intake: Imprecise Obs biomarker: Precise	No RCT	RCT: NA Obs intake: No association Obs biomarker: Lower risk
Myocardial infarction death	Insufficient	RCT: 0 Obs intake: 0 Obs biomarker: 0	NA	RCT: NA Obs intake: NA Obs biomarker: NA All: NA	NA	No data	RCT: NA Obs intake: NA Obs biomarker: NA
Heart failure death	Insufficient	RCT: 0 Obs intake: 0 Obs biomarker: 0	NA	RCT: NA Obs intake: NA Obs biomarker: NA All: NA	NA	No data	RCT: NA Obs intake: NA Obs biomarker: NA
Stroke death	Insufficient	RCT: 0 Obs intake: 1 Obs biomarker: 1	Low	RCT: NA Obs intake: NA Obs biomarker: NA All: NA	RCT: NA Obs intake: Imprecise Obs biomarker: Imprecise	Sparse	RCT: NA Obs intake: No association Obs biomarker: Unclear
Ischemic stroke death	Insufficient	RCT: 0 Obs intake: 1 Obs biomarker: 0	Moderate	RCT: NA Obs intake: NA Obs biomarker: NA All: NA	RCT: NA Obs intake: Precise Obs biomarker: NA	Sparse	RCT: NA Obs intake: Lower risk Obs biomarker: NA
Hemorrhagic stroke death	Insufficient	RCT: 0 Obs intake: 1 Obs biomarker: 0	Moderate	RCT: NA Obs intake: NA Obs biomarker: All:	RCT: NA Obs intake: Imprecise Obs biomarker: NA	Sparse	RCT: NA Obs intake: No association Obs biomarker: NA
Death, all-cause	Insufficient	RCT: 0 Obs intake: 0 Obs biomarker: 3	Low	RCT: NA Obs intake: NA Obs biomarker: NA All: NA	RCT: NA Obs intake: NA Obs biomarker: Precise	No RCT	RCT: NA Obs intake: NA Obs biomarker: Unclear

Table 50. Evidence profile for the effect and association of DHA, specifically, with CVD outcomes (continued)

Outcome	SoE Grade	Design No. Studies	Study Limitations	Consistency	Precision	Other Issues	Finding
Coronary heart disease	Low	RCT: 0 Obs intake: 2 Obs biomarker: 3	Low	RCT: NA Obs intake: Yes Obs biomarker: Inconsistent All: NA	RCT: NA Obs intake: Imprecise Obs biomarker: Imprecise	No RCT	RCT: NA Obs intake: No association Obs biomarker: Unclear
Myocardial infarction	Insufficient	RCT: 0 Obs intake: 1 Obs biomarker: 0	Low	RCT: NA Obs intake: NA Obs biomarker: NA All: NA	RCT: NA Obs intake: Unclear Obs biomarker: NA	Sparse	RCT: NA Obs intake: No association Obs biomarker: NA
Acute coronary syndrome	Insufficient	RCT: 0 Obs intake: 1 Obs biomarker: 1	Low	RCT: NA Obs intake: NA Obs biomarker: NA All: NA	RCT: NA Obs intake: Imprecise Obs biomarker: Imprecise	Sparse	RCT: NA Obs intake: No association Obs biomarker: NA
Angina pectoris	Insufficient	RCT: 0 Obs intake: 0 Obs biomarker: 0	NA	RCT: NA Obs intake: NA Obs biomarker: NA All: NA	NA	No data	RCT: NA Obs intake: NA Obs biomarker: NA
Atrial fibrillation	Insufficient	RCT: 0 Obs intake: 0 Obs biomarker: 1	NA	RCT: NA Obs intake: NA Obs biomarker: NA All: NA	RCT: NA Obs intake: NA Obs biomarker: Precise	Sparse	RCT: NA Obs intake: NA Obs biomarker: Lower risk
Ventricular Arrhythmia	Insufficient	RCT: 0 Obs intake: 0 Obs biomarkers: 0	NA	RCT: NA Obs intake: NA Obs biomarkers: NA	RCT: NA Obs intake: NA Obs biomarkers: NA	No data	RCT: NA Obs intake: NA Obs biomarkers: NA
Congestive heart failure	Insufficient	RCT: 0 Obs intake: 0 Obs biomarker: 3	NA	RCT: NA Obs intake: NA Obs biomarker: Consistent All: NA	RCT: NA Obs intake: NA Obs biomarker: Imprecise	No RCT	RCT: NA Obs intake: NA Obs biomarker: Unclear
Stroke incidence and death	Insufficient	RCT: 0 Obs intake: 0 Obs biomarker: 1	NA	RCT: NA Obs intake: NA Obs biomarker: NA All: NA	RCT: NA Obs intake: NA Obs biomarker: Imprecise	Sparse	RCT: NA Obs intake: NA Obs biomarker: No association
Ventricular arrhythmia	Insufficient	RCT: 0 Obs intake: 0 Obs biomarker: 0	NA	RCT: NA Obs intake: NA Obs biomarker: NA All: NA	NA	No data	RCT: NA Obs intake: NA Obs biomarker: NA
Revascularization	Insufficient	RCT: 0 Obs intake: 0 Obs biomarker: 0	NA	RCT: NA Obs intake: NA Obs biomarker: NA All: NA	NA	No data	RCT: NA Obs intake: NA Obs biomarker: NA

Table 50. Evidence profile for the effect and association of DHA, specifically, with CVD outcomes (continued)

Outcome	SoE Grade	Design No. Studies	Study Limitations	Consistency	Precision	Other Issues	Finding
Hypertension	Insufficient	RCT: 0 Obs intake: 0 Obs biomarker: 0	NA	RCT: NA Obs intake: NA Obs biomarker: NA All: NA	NA	No data	RCT: NA Obs intake: NA Obs biomarker: NA
Blood pressure (SBP, DBP, MAP combined)	Moderate	RCT: 3 Obs intake: 0 Obs biomarker: 1	NA	RCT: Consistent Obs intake: NA Obs biomarker: NA All: NA	RCT: Precise Obs intake: NA Obs biomarker: Imprecise	Few studies	RCT: No effect Obs intake: NA Obs biomarker: Lower risk
LDL-c	Moderate	RCT: 3 Obs intake: 0 Obs biomarker: 0	Low	RCT: Consistent Obs intake: NA Obs biomarker: NA All: NA	RCT: Precise Obs intake: NA Obs biomarker: NA	Few studies	RCT: No effect Obs intake: NA Obs biomarker: NA
HDL-c	Insufficient	RCT: 3 Obs intake: 0 Obs biomarker: 0	Low	RCT: Inconsistent Obs intake: NA Obs biomarker: NA All: NA	RCT: Precise Obs intake: NA Obs biomarker: NA	Few studies	RCT: Unclear Obs intake: NA Obs biomarker: NA
Triglycerides	Insufficient	RCT: 2 Obs intake: 0 Obs biomarker: 0	Low	RCT: Consistent Obs intake: NA Obs biomarker: NA All: NA	RCT: Precise Obs intake: NA Obs biomarker: NA	Sparse	RCT: Lower risk (lower triglycerides) Obs intake: NA Obs biomarker: NA
HDL-c/Total cholesterol to LDL-c ratios	Insufficient	RCT: 0 Obs intake: 0 Obs biomarker: 0	NA	RCT: NA Obs intake: NA Obs biomarker: NA All: NA	NA	No data	RCT: NA Obs intake: NA Obs biomarker: NA

* No reporting bias was detected for any outcome. All studies that measured n-3 FA intake were assessed to be direct, while all biomarker studies were assessed to be indirect.

Abbreviations: CVD = cardiovascular disease, DBP = diastolic blood pressure, DHA = docosahexaenoic acid, HDL-c = high density lipoprotein cholesterol, LDL-c = low density lipoprotein cholesterol, MAP = mean arterial blood pressure, n-3 FA = omega-3 fatty acids, NA = not applicable, Obs = observational study, RCT = randomized controlled trial, SBP = systolic blood pressure, SoE = strength of evidence.

DPA

Overall, there is insufficient evidence regarding effect of or association between DPA (specifically) and CVD clinical and intermediate outcomes (Table 51). There is low strength of evidence of no association between DPA biomarker levels and risk of AFib (from observational studies only).

RCTs

No eligible RCTs compared purified DPA formulations versus placebo.

Observational Studies, Intake

Two observational studies evaluated estimated total DPA intake (specifically). One study found no significant association between DPA intake and acute coronary syndrome in either healthy men or women. The other found significant associations between higher DPA intake and both incident CHD and MACE in healthy adults, in both instances with a significant association in the quartile with DPA intake >0.04 g/d.

Observational Studies, Biomarkers

Seven studies evaluated the association of various DPA biomarkers with clinical outcomes, all in healthy adults. No outcome was evaluated by more than three studies. One study in adults age ≥65 years was the only study that evaluated several clinical outcomes. It found significant associations between higher plasma DPA and lower risks of all-cause and CVD death, nonsignificant associations with incident CHF (P=0.057) and total stroke death (P=0.056), but no significant associations with AFib, SCD, hemorrhagic, ischemic, or total stroke, or CHD death. For two outcomes, one of three studies found significant associations; one study found a significant association between blood DPA and incident CHD, but two found no associations with plasma or phospholipid DPA; one study found a significant association between adipose tissue DPA and MACE, but two found no associations with phospholipid or erythrocyte DPA. One study evaluated acute coronary syndrome and found a significant association in men with adipose tissue DPA, but not in women. One study evaluated incident hypertension and found a significant association of erythrocyte DPA in younger women (39−54 years old), but not older women (55−89 years old). One study found no significant association with cardiac death.

Table 51. Evidence profile for the effect and association of DPA biomarkers, specifically, with CVD outcomes (observational studies only)*

Outcome	SoE Grade	Biomarker Studies No. Studies	Study Limitations	Consistency	Precision	Other Issues	Finding
MACE	Insufficient	3	Low	Inconsistent	Imprecise	None	Unclear
CVD death (including stroke)	Insufficient	1	Low		Imprecise	None	Lower risk
Cardiac death	Insufficient	1	Low		Unclear	None	No association
Coronary heart disease death	Insufficient	1	Low		Imprecise	None	No association
Myocardial infarction death	Insufficient	0	NA		NA	None	NA
Heart failure death	Insufficient	0	NA		NA	None	NA
Stroke death	Insufficient	1	Low		Imprecise	None	Lower risk
Ischemic stroke death	Insufficient	0	NA		NA	None	NA
Hemorrhagic stroke death	Insufficient	0	NA		NA	None	NA
Death, all-cause	Insufficient	1	Low		Precise	None	Lower risk
Coronary heart disease	Insufficient	3	Low	Inconsistent	Imprecise	None	Unclear
Myocardial infarction	Insufficient	0	NA		NA	None	NA
Acute coronary syndrome	Insufficient	1	Low	NA	Imprecise	Sparse	No association
Angina pectoris	Insufficient	0	NA	NA	NA	NA	NA
Atrial fibrillation	Low	3	Low	Consistent	Imprecise	None	No association
Congestive heart failure	Insufficient	1	Low	NA	Imprecise	Sparse	Lower risk
Stroke incidence and death	Insufficient	1	Low	NA	Precise	Sparse	No association
Ventricular arrhythmia	Insufficient	0	NA	NA	NA	NA	NA
Revascularization	Insufficient	0	NA	NA	NA	None	NA
Hypertension	Insufficient	0	NA	NA	NA	None	NA
Blood pressure (SBP, DBP, MAP combined)	Insufficient	1	Low	NA	Imprecise	Sparse	Lower risk
LDL-c	Insufficient	0	NA	NA	NA	None	NA
HDL-c	Insufficient	0	NA	NA	NA	None	NA
Triglycerides	Insufficient	0	NA	NA	NA	None	NA
HDL-c/Total cholesterol to LDL-c ratios	Insufficient	0	NA	NA	NA	None	NA

* No reporting bias was detected for any outcome. All studies that measured n-3 FA intake were assessed to be direct, while all biomarker studies were assessed to be indirect.

Abbreviations: CVD = cardiovascular disease, DBP = diastolic blood pressure, DPA = docosapentaenoic acid, HDL-c = high density lipoprotein cholesterol, LDL-c = low density lipoprotein cholesterol, MACE = major adverse cardiovascular events, MAP = mean arterial blood pressure, n-3 FA = omega-3 fatty acids, NA = not applicable, Obs = observational study, RCT = randomized controlled trial, SBP = systolic blood pressure, SoE = strength of evidence.

SDA

Overall, there is insufficient evidence regarding effect of or association between SDA (specifically) and CVD clinical and intermediate outcomes (Table 52).

RCTs

A single study compared 1.2 g/d SDA to placebo in patients at risk for CVD and found no significant differences in change in systolic or diastolic BP, or LDL-c, HDL-c, or Tg at 6 weeks.

Observational Studies

A single eligible observational study in healthy men evaluated baseline erythrocyte SDA and clinical outcomes. Erythrocyte SDA was not significantly associated with either MACE or cardiac death.

Marine Oil FA Comparisons

There is insufficient evidence regarding comparisons of specific marine oil FA.

Clinical Event Outcomes, RCTs

No trial that reported clinical event outcomes compared marine oil FA.

Intermediate Outcomes, RCTs

Two trials that compared marine oil FA (EPA 3.8 g/d vs. DHA 3.6 g/d; EPA+DHA 3.4 and 1.7 g/d vs. EPA 1.8 g/d) found no significant differences in effect on BP, LDL-c, HDL-c, Tg, or Total:HDL-c ratio.

One trial compared 2.0 g/d SDA and 1.9 g/d EPA+DHA+DPA in healthy people. At 2 month followup, no significant differences in change in systolic or diastolic BP, or LDL-c, HDL-c, Tg, Total:HDL-c, or LDL:HDL-c ratios were found.

Table 52. Evidence profile for the effect and association of SDA biomarkers, specifically, with CVD outcomes (observational studies only)*

Outcome	SoE Grade	Design No. Studies	Study Limitations	Consistency	Precision	Other Issues	Finding
MACE	Insufficient	1	Low	NA	Obs biomarker: Unclear	Sparse	No association
CVD death (including stroke)	Insufficient	0	NA	NA	NA	No data	NA
Cardiac death	Insufficient	1	Low	NA	Obs biomarker: Unclear	Sparse	No association
Coronary heart disease death	Insufficient	0	NA	NA	NA	No data	NA
Myocardial infarction death	Insufficient	0	NA	NA	NA	No data	NA
Heart failure death	Insufficient	0	NA	NA	NA	No data	NA
Stroke death	Insufficient	0	NA	NA	NA	No data	NA
Ischemic stroke death	Insufficient	0	NA	NA	NA	No data	NA
Hemorrhagic stroke death	Insufficient	0	NA	NA	NA	No data	NA
Death, all-cause	Insufficient	0	NA	NA	NA	No data	NA
Coronary heart disease	Insufficient	0	NA	NA	NA	No data	NA
Myocardial infarction	Insufficient	0	NA	NA	NA	No data	NA
Acute coronary syndrome	Insufficient	0	NA	NA	NA	No data	NA
Angina pectoris	Insufficient	0	NA	NA	NA	No data	NA
Atrial fibrillation	Insufficient	0	NA	NA	NA	No data	NA
Ventricular Arrhythmia	Insufficient	0	NA	NA	NA	No data	NA
Congestive heart failure	Insufficient	0	NA	NA	NA	No data	NA
Stroke incidence and death	Insufficient	0	NA	NA	NA	No data	NA
Ventricular arrhythmia	Insufficient	0	NA	NA	NA	No data	NA
Revascularization	Insufficient	0	NA	NA	NA	No data	NA
Hypertension	Insufficient	0	NA	NA	NA	No data	NA
Blood pressure (SBP, DBP, MAP combined)	Insufficient	1	Low	NA	Precise	Sparse	No effect
LDL-c	Insufficient	1	Low	NA	Precise	Sparse	No effect
HDL-c	Insufficient	1	Low	NA	Precise	Sparse	No effect
Triglycerides	Insufficient	1	Low	NA	Precise	Sparse	No effect
HDL-c/Total cholesterol to LDL-c ratios	Insufficient	1	Low	NA	Precise	Sparse	No effect

* No reporting bias was detected for any outcome. All studies that measured n-3 FA intake were assessed to be direct, while all biomarker studies were assessed to be indirect.

Abbreviations: CVD = cardiovascular disease, DBP = diastolic blood pressure, HDL-c = high density lipoprotein cholesterol, LDL-c = low density lipoprotein cholesterol, MACE = major adverse cardiovascular events, MAP = mean arterial blood pressure, n-3 FA = omega-3 fatty acids, NA = not applicable, Obs = observational study, RCT = randomized controlled trial, SBP = systolic blood pressure, SDA = stearidonic acid, SoE = strength of evidence.

ALA

There is moderate strength of evidence of no significant effect of ALA intake on BP, LDL-c, HDL-c, or Tg (Table 53). There is low strength of evidence of no association between ALA intake or biomarker level and CHD or CHD death, AFib, and CHF, each based primarily on observational studies; there was only a single or no RCTs evaluating these outcomes. There is insufficient evidence regarding other outcomes.

Clinical Event Outcomes, RCTs

Two RCTs that evaluated ALA supplementation versus placebo reported clinical event outcomes, one in participants with CVD and one in healthy participants. All analyses were nonsignificant, for all-cause death (2 trials) and from one trial each, MACE, CVD death, cardiac death, CHD death, CHF death, total MI, incident angina, total stroke, ventricular arrhythmia, and SCD. Within-study subgroup analyses revealed no significant differences in effect for various subgroups for MACE (1 trial) or with or without diabetes for CHD death (1 trial).

Intermediate Outcomes, RCTs

Five ALA RCTs evaluated BP, with doses ranging from 1.4 to 5.9 g/d for 1 to 3.4 years. All found no significant effect on systolic or diastolic BP, mostly with wide confidence intervals. One of the trials found no significant difference in effect on BP between those with hypertension and the study population as a whole. Another trial found no significant difference in effect between 1.4 and 5.9 g/d ALA. No trial reported on MAP.

Five trials reported no significant effects of ALA on LDL-c, HDL-c, Tg, or Total:HDL-c ratio (3 trials). No differences in effect were found in the one trial that compared 1.4 and 5.9 g/d ALA. No trial reported on LDL:HDL-c ratio.

Observational Studies, Intake

Thirteen observational studies evaluated ALA intake. One of these was a pooling of 11 prior studies (the pooled studies were not included in duplicate for the outcomes evaluated by the pooling study). The large majority of analyses found no significant associations; only two studies found any significant associations between higher ALA intake and clinical outcomes.

By meta-analysis, overall there is no statistically significant association between ALA intake and CHD death across a median dose range of 0.59 to 2.5 g/d (effect size per g/d = 0.95 [95% CI 0.87 to 1.04]). Meta-analyses with the addition of a spline knot point at different dose thresholds (from 0.1 to 1.2 g/d) consistently found a stronger association (of higher dose being associated with lower risk at *higher* doses than at lower doses (ES above knot < ES below know), but at several knot points this difference was marginal. This implies the possibility of a floor effect (where intake above a certain minimum amount is needed before any benefit accrues). However, at no dose threshold was there a statistically significant difference between the ES above the dose threshold (knot) and below the threshold. The best fit curve was found with a knot at 0.9 g/d. The lowest P value between lower-dose and higher-dose ES estimates was found at 1.2 g/d (P=0.41), the highest dose threshold that could be tested.

By meta-analysis, overall there is no association between ALA intake and CHD across a median dosage range of 0.2 to 2.5 g/d (effect size per g/d = 0.98 [95% CI 0.93 to 1.04]). Meta-analyses with the addition of a spline knot point at different dose thresholds (from 0.5 to 1.4 g/d) consistently found marginally smaller ES at lower doses than at higher doses. At no dose threshold was there a statistically significant difference between the ES below the dose threshold (knot) and above the threshold. The best fit curve was found with a knot at 0.6 g/d. The lowest P value between lower-dose and higher-dose ES estimates was found at 0.5 g/d (P=0.28).

Two studies both found significant associations between higher ALA intake and reduced all-cause death (>2.2 g/d in healthy adults; also in healthy men but insufficient data were reported regarding a dose threshold). One of two studies found a significant association between higher ALA intake (>0.6 g/d) and lower risk of SCD in healthy women but not in a subset of women with CVD; the second study found no significant association in healthy adults. One of two studies found a significant association between higher ALA intake (unclear threshold) and lower risk of CVD death in younger men (35−57 years old), but another study found no association in older men (≥65 years old). For all other analyzed clinical outcomes, no significant associations were found with ALA intake, including CHF (4 studies), CVD (3 studies), MACE (2 studies), hemorrhagic and ischemic stroke (2 studies each), AFib (1 study), and hypertension (1 study).

Observational Studies, Biomarkers

Eight studies evaluated various ALA biomarkers. Almost all analyses found no significant associations between ALA biomarkers and clinical outcomes. No outcome was evaluated by more than three studies. For CHF, one of three studies found a significant association between higher plasma ALA in healthy men, but two other studies found no significant associations in healthy adults with plasma, cholesteryl ester, or phospholipid ALA. One of two studies found a significant association between higher plasma ALA and lower risk of CVD death, but the other study found no significant association also with plasma ALA in healthy adults. No significant associations were found for ischemic stroke (3 studies), incident CHD, hemorrhagic and total stroke (2 studies each), MACE (2 studies), all-cause death (2 studies), or AFib, SCD, incident hypertension, cardiac death, or CHD death (1 study each).

Table 53. Evidence profile for the effect and association of ALA with CVD outcomes*

Outcome	SoE Grade	Design No. Studies	Study Limitations	Consistency	Precision	Other Issues	Finding
Major adverse cardiovascular events (MACE)	Insufficient	RCT: 1 Obs intake: 2 Obs biomarker: 0	Low	RCT: NA Obs intake: Consistent Obs biomarker: All: NA	RCT: Precise Obs intake: Imprecise Obs biomarker: NA	Sparse	RCT: NA Obs intake: 0 Obs biomarker: NA
CVD death (including stroke)	Insufficient	RCT: 1 Obs intake: 3 Obs biomarker: 2	Low	RCT: NA Obs intake: Inconsistent Obs biomarker: Consistent All: NA	RCT: Imprecise Obs intake: Imprecise Obs biomarker: Imprecise	Sparse RCT	RCT: No effect Obs intake: Unclear Obs biomarker: No association
Cardiac death	Insufficient	RCT: 0 Obs intake: 0 Obs biomarker: 1	Low	RCT: NA Obs intake: NA Obs biomarker: NA All: NA	RCT: NA Obs intake: NA Obs biomarker: Unclear	Sparse	RCT: NA Obs intake: NA Obs biomarker: No association
Coronary heart disease death	Low	RCT: 1 Obs intake: 4 Obs biomarker: 1	Low	RCT: NA Obs intake: Consistent Obs biomarker: NA All: NA	RCT: Imprecise Obs intake: Imprecise Obs biomarker: Imprecise	Sparse RCT	RCT: No effect Obs intake: No association 0.94 (0.85, 1.03) per g/d Obs biomarker: No association
Myocardial infarction death	Insufficient	RCT: 0 Obs intake: 0 Obs biomarker: 0	NA	RCT: NA Obs intake: NA Obs biomarker: NA All: NA	NA	No data	RCT: NA Obs intake: NA Obs biomarker: NA
Heart failure death	Insufficient	RCT: 0 Obs intake: 0 Obs biomarker: 0	NA	RCT: NA Obs intake: NA Obs biomarker: NA All: NA	NA	No data	RCT: NA Obs intake: NA Obs biomarker: NA
Stroke death	Insufficient	RCT: 0 Obs intake: 0 Obs biomarker: 0	NA	RCT: NA Obs intake: NA Obs biomarker: NA All: NA	NA	No data	RCT: NA Obs intake: NA Obs biomarker: NA
Ischemic stroke death	Insufficient	RCT: 0 Obs intake: 0 Obs biomarker: 0	NA	RCT: NA Obs intake: NA Obs biomarker: NA All: NA	NA	No data	RCT: NA Obs intake: NA Obs biomarker: NA
Hemorrhagic stroke death	Insufficient	RCT: 0 Obs intake: 0 Obs biomarker: 0	NA	RCT: NA Obs intake: NA Obs biomarker: NA All: NA	NA	No data	RCT: NA Obs intake: NA Obs biomarker: NA

Table 53. Evidence profile for the effect and association of ALA with CVD outcomes (continued)

Outcome	SoE Grade	Design No. Studies	Study Limitations	Consistency	Precision	Other Issues	Finding
Death, all-cause	Insufficient	RCT: 1 Obs intake: 0 Obs biomarker: 2	Low	RCT: NA Obs intake: NA Obs biomarker: NA All: NA	RCT: Imprecise Obs intake: NA Obs biomarker: Precise	Sparse	RCT: No effect Obs intake: NA Obs biomarker: No association
Coronary heart disease	Low	RCT: 0 Obs intake: 6 Obs biomarker: 0	Low	RCT: NA Obs intake: Yes Obs biomarker: NA All: NA	RCT: NA Obs intake: Imprecise Obs biomarker: NA	No RCT	RCT: NA Obs intake: No association 0.97 (0.92, 1.03) per g/d Obs biomarker: NA
Myocardial infarction	Insufficient	RCT: 1 Obs intake: 0 Obs biomarker: 0	Low	RCT: NA Obs intake: NA Obs biomarker: NA All: NA	RCT: Imprecise Obs intake: NA Obs biomarker: NA	Sparse	RCT: Unclear Obs intake: NA Obs biomarker: NA
Acute coronary syndrome	Insufficient	RCT: 0 Obs intake: 0 Obs biomarker: 0	NA	RCT: NA Obs intake: NA Obs biomarker: NA All:	NA	No data	RCT: NA Obs intake: NA Obs biomarker: NA
Angina pectoris	Insufficient	RCT: 1 Obs intake: 0 Obs biomarker: 0	Low	RCT: NA Obs intake: NA Obs biomarker: NA All: NA	RCT: Imprecise Obs intake: NA Obs biomarker: NA	Sparse	RCT: No effect Obs intake: NA Obs biomarker: NA
Atrial fibrillation	Low	RCT: 0 Obs intake: 3 Obs biomarker: 3	Low	RCT: NA Obs intake: Consistent Obs biomarker: NA All: NA	RCT: NA Obs intake: Imprecise Obs biomarker: Imprecise	No RCT	RCT: NA Obs intake: No association Obs biomarker: No association
Ventricular Arrhythmia	Insufficient	RCT: 1 Obs intake: 0 Obs biomarkers: 0	Low	RCT: NA Obs intake: NA Obs biomarkers: NA	RCT: Precise Obs intake: NA Obs biomarkers: NA	Sparse	RCT: No effect Obs intake: NA Obs biomarkers: NA
Congestive heart failure	Low	RCT: 1 Obs intake: 4 Obs biomarker: 3	Low	RCT: NA Obs intake: Consistent Obs biomarker: Consistent All: Consistent	RCT: Imprecise Obs intake: Precise Obs biomarker: Precise	Sparse RCT	RCT: No effect Obs: No association Obs biomarker: Unclear
Stroke incidence and death	Insufficient	RCT: 1 Obs intake: 3 Obs biomarker: 2	Low	RCT: NA Obs intake: Consistent Obs biomarker: Consistent All: Consistent	RCT: Imprecise Obs intake: Imprecise Obs biomarker: Imprecise	Sparse RCT	RCT: No effect Obs intake: Unclear Obs biomarker: No association

Table 53. Evidence profile for the effect and association of ALA with CVD outcomes (continued)

Outcome	SoE Grade	Design No. Studies	Study Limitations	Consistency	Precision	Other Issues	Finding
Ventricular arrhythmia	Insufficient	RCT: 1 Obs intake: 0 Obs biomarker: 0	Low	RCT: NA Obs intake: NA Obs biomarker: NA All: NA	RCT: Imprecise Obs intake: NA Obs biomarker: NA	Sparse	RCT: No effect Obs intake: NA Obs biomarker: NA
Revascularization	Insufficient	RCT: 0 Obs intake: 0 Obs biomarker: 0	NA	RCT: NA Obs intake: NA Obs biomarker: NA All: NA	NA	No data	RCT: NA Obs intake: NA Obs biomarker: NA
Hypertension	Insufficient	RCT: 0 Obs intake: 0 Obs biomarker: 0	NA	RCT: NA Obs intake: NA Obs biomarker: NA All: NA	NA	No data	RCT: NA Obs intake: NA Obs biomarker: NA
Blood pressure (SBP, DBP, MAP combined)	Moderate	RCT: 5 Obs intake: 0 Obs biomarker: 1	Low	RCT: Consistent Obs intake: NA Obs biomarker: NA All: NA	RCT: Precise Obs intake: NA Obs biomarker: Imprecise	Few studies	RCT: No effect Obs intake: NA Obs biomarker: No association
LDL-c	Moderate	RCT: 5 Obs intake: 0 Obs biomarker: 0	Low	RCT: Consistent Obs intake: NA Obs biomarker: NA All: NA	RCT: Imprecise Obs intake: NA Obs biomarker: NA	Sparse	RCT: No effect Obs intake: NA Obs biomarker: NA
HDL-c	Moderate	RCT: 5 Obs intake: 0 Obs biomarker: 0	Low	RCT: Consistent Obs intake: NA Obs biomarker: NA All: NA	RCT: Precise Obs intake: NA Obs biomarker: NA	Few studies	RCT: No effect Obs intake: NA Obs biomarker: NA
Triglycerides	Moderate	RCT: 5 Obs intake: 0 Obs biomarker: 0	Low	RCT: Consistent Obs intake: NA Obs biomarker: NA All: NA	RCT: Imprecise Obs intake: NA Obs biomarker: NA	No data	RCT: No effect Obs intake: NA Obs biomarker: NA
HDL-c/Total cholesterol to LDL-c ratios	Insufficient	RCT: 3 Obs intake: 0 Obs biomarker: 0	Low	RCT: Consistent Obs intake: NA Obs biomarker: NA All: NA	RCT: Precise Obs intake: NA Obs biomarker: NA	Sparse	RCT: No effect Obs intake: NA Obs biomarker: NA

* No reporting bias was detected for any outcome. All studies that measured n-3 FA intake were assessed to be direct, while all biomarker studies were assessed to be indirect.

Abbreviations: ALA = alphalinolenic acid, CVD = cardiovascular disease, DBP = diastolic blood pressure, HDL-c = high density lipoprotein cholesterol, LDL-c = low density lipoprotein cholesterol, MAP = mean arterial blood pressure, n-3 FA = omega-3 fatty acids, NA = not applicable, Obs = observational study, RCT = randomized controlled trial, SBP = systolic blood pressure, SoE = strength of evidence.

Marine Oil Versus ALA

There is insufficient evidence of direct comparisons between marine oil and ALA intake on CVD outcomes. Across studies, the comparison between marine oil and ALA is unclear, largely because of insufficient evidence regarding ALA; however, where there is high strength of evidence of significant effects of marine oil on improving Tg and HDL-c, there is moderate strength of evidence of no effect of ALA intake on these intermediate outcomes.

Clinical Event Outcomes, RCTs

No trial that reported clinical event outcomes directly compared marine oils and ALA.

Intermediate Outcomes, RCTs

One trial that compared two doses of EPA+DHA (1.7 and 0.8 g/d) with ALA 4.5 g/d found no differences in systolic or diastolic BP at 4 months. Across trials, regardless of n-3 FA type, there was no evidence of an effect of BP; no difference in effect was apparent between marine oil and ALA trials.

Two trials that compared EPA+DHA (0.8 and 1.7 g/d in one trial, 0.4 g/d in the other) to ALA (4.5 [rapeseed oil margarine] and 2 g/d ["plant oil" margarine], respectively) for 6 months and 3.4 years found no differences between n-3 FA types for LDL-c, HDL-c, or Tg. Neither trial reported on lipid ratios. No evident differences were found across trials between marine oils and ALA for their (nonsignificant) effects on LDL-c and HDL-c. In contrast with the two trials that directly compared EPA+DHA and ALA, 32 marine oil (versus placebo) trials fairly consistently found significant effect on Tg reduction in contrast with the four ALA (versus placebo) trials, which mostly had imprecise estimates of effects on Tg.

Subgroup Analyses Summary

Overall, 24 RCTs[46, 58, 70, 76, 85, 89, 90, 94, 96, 97, 99, 115, 119, 123, 128, 146, 147, 150, 156, 157, 160, 166, 167, 179, 195] and 9 observational studies[72, 83, 102, 148, 154, 159, 162, 171, 181] reported on subgroup (or factorial) analyses. For most outcomes, there is insufficient evidence regarding differential effects (or associations) in different subgroups of study participants evaluated within studies. Metaregression results across studies are summarized in the summary by n-3 FA, above. (In brief, only for the effect of marine oil on Tg was there an indication across studies of interactions by dose and baseline Tg, with larger effects with higher dose and higher baseline Tg.) Among outcomes with sufficient RCT data to allow meta-analysis, no discernable difference in effect was found across trials based on publication year.

Twenty-two subgroup analyses by sex were reported (10 with ALA, 11 with marine oil, 1 with total n-3 FA). One of three RCTs of marine oil on MACE found a greater beneficial effect of n-3 FA in women (HR [supplement vs. placebo] =0.82 in women vs. 1.04 in men; P interaction = 0.04). One of three observational studies of CHF found a stronger association with between higher blood EPA and lower risk of CHF in men than women (HR [lower intake vs. higher intake] = 5.82 in men vs. 0.69 in women; P interaction = 0.008), but no interaction with blood DHA. One RCT found a stronger effect on lowering Tg of supplementation with higher-dose marine oil (1.8 g/d) in men than in women (difference not reported; P interaction = 0.038), but this interaction was not found with lower-dose marine oil (0.7 g/d). All 19 other analyses were not statistically significant (or no statistical difference was reported).

Twenty subgroup analyses by statin use were reported (1 with ALA, 19 with marine oil). All but one study found difference in effect or association based on statin use. One study found a stronger association between higher blood DHA and, separately, higher blood EPA, and lower risk of CHF in those not using statins; DHA: HR [lower intake vs. higher intake] = 6.65 (without statins) vs. 0.74 (with statins), P interaction = 0.003; EPA: HR [lower intake vs. higher intake] = 6.40 (without statins) vs. 1.45 (with statins), P interaction = 0.048. A relatively small number of RCTs of lipoproteins (LDL-c and HDL-c) and Tg analyzed interactions between n-3 FA and statins and found no interaction between statin use and the effect of marine oil supplementation on lipids (LDL-c 5 RCTs, Tg 4 RCTs, HDL-c 3 RCTs). No studies explicitly compared the interaction of n-3 FA intake (or biomarker level) with aspirin intake on outcomes.

Sixteen subgroup analyses comparing those with and without diabetes were reported (6 with ALA, 10 with marine oil). Two RCT analyses reported only that a statistically significant effect of n-3 FA was found among participants with diabetes but no significant effect was found those without diabetes (marine oil and CHD death, ALA and ventricular arrhythmia). All other analyses reported no difference in effect or association based on diabetes status.

Summary by Key Question

Key Question 1

What is the efficacy or association of n-3 FA (EPA, DHA, EPA+DHA, DPA, SDA, ALA, or total n-3 FA) exposures in reducing CVD outcomes (incident CVD events, including all-cause death, CVD death, nonfatal CVD events, new diagnosis of CVD, peripheral vascular disease, CHF, major arrhythmias, and hypertension diagnosis) and specific CVD risk factors (BP, key plasma lipids)?

- Total n-3 FA
    - Overall, there is insufficient evidence regarding the effect of or association between total n-3 FA (combined ALA and marine oils) and clinical or intermediate outcomes. There is low strength of evidence of no association between total n-3 FA intake and stroke death, and total (fatal and nonfatal) MI (each association based on longitudinal observational studies of dietary intake).
    - For each outcome there was no consistent (and replicated) significant association between total n-3 FA intake and risk reduction.
- Marine oils
    - There is high strength of evidence from RCTs that marine oils clinically and statistically significantly lower Tg. There is also evidence that they statistically, but arguably not clinically, significantly raise HDL-c, but lower LDL-c. Finally, there is high strength of evidence that marine oil supplementation significantly lowers Total:HDL-c ratio.
    - There is high strength of evidence of that marine oils statistically significantly lower Tg—possibly with greater effects with higher doses and in people with higher baseline Tg—and statistically significantly raise HDL-c and LDL-c by similar amounts. There is also high strength of evidence that marine oil significantly lowers Total:HDL-c ratio
    - There is low strength of evidence that marine oil significantly lowers risk of ischemic stroke.

- There is a high strength of evidence of no effect of marine oil on risk of MACE, all-cause death, SCD, revascularization, and BP; moderate strength of evidence of no effect of marine oil on risk of AFib; and low strength of evidence of no effect of marine oil on risk of CVD death, CHD death, total CHD, MI, angina pectoris, CHF, total stroke, and hemorrhagic stroke. There is insufficient evidence for other outcomes.

- Marine oils, EPA
  - There is insufficient evidence regarding the effect of or association with EPA (specifically) and most CVD clinical and intermediate outcomes. There is low strength of evidence of no association between EPA intake and CHD and between EPA biomarkers and AFib.
- Marine oils, DHA
  - For the most part, there is insufficient evidence regarding the effect of or association with DHA and CVD clinical and intermediate outcomes. There is moderate strength of evidence of no effect of purified DHA supplementation on BP or LDL-c and low strength of evidence of no association between DHA intake and incident CHD (from observational studies).
- Marine oils, DPA
  - Overall, there is insufficient evidence regarding effect of or association between DPA (specifically) and most CVD clinical and intermediate outcomes. There is low strength of evidence of no association between DPA biomarker levels and risk of AFib.
- SDA
  - Overall, there is insufficient evidence regarding effect of or association between SDA (specifically) and CVD clinical and intermediate outcomes.
- ALA
  - There is moderate strength of evidence of no significant effect of ALA intake on BP, LDL-c, HDL-c, or Tg. There is low strength of evidence of no association between ALA intake or biomarker level and CHD or CHD death, AFib, and CHF, each based on observational studies. There is insufficient evidence regarding other outcomes.

Key Question 1, Subquestions

1.1.1. What is the efficacy or association of n-3 FA in preventing CVD outcomes in people without known CVD (primary prevention)?

- There was insufficient evidence for cardiac death, CHF death, ischemic stroke death, hemorrhagic stroke death, revascularization, acute coronary syndrome, angina pectoris, ventricular arrhythmia, incident hypertension, TC/HDL-c ratio, and LDL-c/HDL-c ratio.
- There was insufficient RCT evidence and inconsistent observational evidence for CHD death, MI death, all-cause death, total MI, and SCD.
- There was insufficient RCT evidence but observational evidence of no association for MACE, CVD death, total stroke death, incident CHD, total stroke, ischemic stroke, hemorrhagic stroke, AFib, and CHF.
- There was strong RCT evidence for no effect for BP (systolic and diastolic), MAP (only 3 trials), LDL-c, and HDL-c.
- There was strong RCT evidence for a significant protective effect for Tg.

1.1.2. What is the efficacy or association of n-3 FA in preventing CVD outcomes in people at high risk for CVD (primary prevention)?

- There was insufficient evidence for CVD death, cardiac death, CHD death, MI death, CHF death, total stroke death, ischemic stroke death, hemorrhagic stroke death, incident CHD, revascularization, acute coronary syndrome, angina pectoris, total stroke, ischemic stroke, hemorrhagic stroke, SCD, AFib, ventricular arrhythmia, CHF, incident hypertension, and MAP.
- There was inconsistent RCT evidence for total MI.
- There was strong RCT evidence for no effect for MACE, all-cause death, BP (systolic and diastolic), LDL-c, HDL-c, TC/HDL-c ratio, and LDL-c/HDL-c ratio.
- There was strong RCT evidence for a significant protective effect for Tg.

1.1.3. What is the efficacy or association of n-3 FA in preventing CVD outcomes in people with known CVD (secondary prevention)?

- There was insufficient evidence for MI death, CHF death, total stroke death, ischemic stroke death, hemorrhagic stroke death, CHD, acute coronary syndrome, angina pectoris, ischemic stroke, hemorrhagic stroke, ventricular arrhythmia, incident hypertension, MAP, TC/HDL-c ratio, and LDL-c/HDL-c ratio.
- There was inconsistent RCT evidence for CVD death and cardiac death. There was RCT evidence of no effect for MACE, CHD death, all-cause death, total MI, revascularization, total stroke, SCD, AFib, and CHF.
- There was strong RCT evidence of no effect for BP (systolic and diastolic) and LDL-c.
- There was strong RCT evidence of a protective effect for HDL-c and Tg.

1.2. What is the relative efficacy of different n-3 FA on CVD outcomes and risk factors?

- There is low strength of evidence of no difference between EPA+DHA and its individual components.
- There is low strength of evidence of greater efficacy of marine oils over ALA.

1.3. Can the CVD outcomes be ordered by strength of intervention effect of n-3 FA ?

- Based on the summary effect sizes of meta-analyzed RCTs, marine oils had no significant effect on CVD outcomes. The order of effect sizes of CVD outcomes with sufficient data to allow meta-analysis, was MI (ES=0.88), CVD death (ES=0.92), MACE (ES=0.96), all-cause death (ES=0.97), total stroke (ES=0.98), and SCD (ES=1.04).

Key Question 2

n-3 FA variables and modifiers

2.1. How does the efficacy or association of n-3 FA in preventing CVD outcomes and with CVD risk factors differ in subpopulations, including men, premenopausal women, postmenopausal women, and different age or race/ethnicity groups?

- There was insufficient evidence to assess the efficacy or association of n-3 FA in preventing CVD outcomes and with CVD risk factors in subgroups based on race/ethnicity and whether women were pre- or postmenopausal.
- 5 studies (mostly observational) found no significant differences in association based on age, with cutoffs for subgroups ranging between 60 and 70 years of age.

- Two studies found no interaction with age as a continuous variable. One trial found a significant difference in favor of women, two observational studies found a significant difference in favor of men, and 9 studies (mix of RCT and observational) found no difference between men and women.

2.2 What are the effects of potential confounders or interacting factors—such as plasma lipids, body mass index, BP, diabetes, kidney disease, other nutrients or supplements, and drugs (e.g., statins, aspirin, diabetes drugs, hormone replacement therapy)?

- There was insufficient evidence to assess the following potential confounders or interacting factors: beta-blocker use, baseline HDL-c, glargine use, nitrate use, digoxin use, diuretic use, eGFR, ACEi use, anticoagulant use, total cholesterol levels, or use of fish oil supplements.
- There was inconsistent evidence for the following potential confounders or interacting factors: triglyceride levels, statin use, b-vitamin use, and baseline LDL-c.
- There was evidence of no interactions with body mass index, hypertension status, diabetes status, and baseline TC/HDL-c ratio.

2.3 What is the efficacy or association of different ratios of n-3 FA components in dietary supplements or biomarkers on CVD outcomes and risk factors?

- No study directly compared efficacy or association of different ratios of n-3 FA components on outcomes. Across studies, there were insufficient data to make these assessments.

2.4 How does the efficacy or association of n-3 FA on CVD outcomes and risk factors differ by ratios of different n-3 FA—DHA, EPA, and ALA, or other n-3 FA?

- No study directly compared efficacy or association of different ratios of n-3 FA components on outcomes. Across studies, there were insufficient data to make these assessments.

2.5 How does the efficacy or association of n-3 FA on CVD outcomes and risk factors differ by source (e.g., fish and vs. seafood, common plant oils (e.g., soybean vs,, canola), fish oil supplements, fungal-algal supplements, flaxseed oil supplements)?

- No study directly compared efficacy or association of different sources of n-3 FA on outcomes. Across studies, there were insufficient data to make these assessments.

2.6 How does the ratio of n-6 FA to n-3 FA intakes or biomarker concentrations affect the efficacy or association of n-3 FA on CVD outcomes and risk factors?

- No trial or observational studies evaluated n-6 FA to n-3 FA intake concentrations and no differences across studies by this ratio was evident.

2.7 Is there a threshold or dose-response relationship between n-3 FA exposures and CVD outcomes and risk factors? Does the study type affect these relationships?

- Among trials, for all clinical CVD outcomes there is insufficient evidence regarding a dose-response relationship within or between trials.
- For BP, LDL-c, and HDL-c, trials do not find significant differences in effect by marine oil dose either within or between trials.

- Trials comparing marine oil doses mostly found no significant difference between higher and lower dose marine oils. However, a possible pattern could be discerned such that higher doses of 3.4 or 4 g/d reduced Tg by at least 30 mg/dL more than lower doses of 1 to 2 g/d. Higher doses ≤3 g/d (1.7−3 g/d) yielded much smaller relative differences in Tg change compared to lower doses (0.7−2.25 g/d). By metaregression, each increase of EPA+DHA dose by 1 g/d was associated with a greater net change Tg of −5.9 mg/dL (95% CI −9.9 to−2.0; P=0.003); no inflection point was found above which the association plateaued.
- Metaregressions of observational studies yielded the following conclusions:
    - For all-cause death, there may be a ceiling effect at about 0.2 g/d, such that increasing marine oil intake up to this level may be associated with lower all-cause death, but increasing intake above this level may not be associated with further decreased risk.
    - For total stroke, ischemic stroke, and CHF, at lower ranges of intake there were statistically significant associations between higher marine oil intake level and lower risk of outcome, in contrast to associations found at higher ranges of intake. However, the associations at lower and higher doses were not statistically significant from each other. For ischemic stroke, associations between higher doses and risk of stroke were stronger and statistically significant across lower doses than at higher doses (with thresholds between lower and higher doses from 0.1 and 0.4 g/d) and the differences in associations between lower and higher doses were statistically significant. Any dose inflection point that may exist is likely to be beyond the range of testable thresholds (i.e., >0.4 g/d). Similarly, for CHF significant associations were found at lower doses, in contrast to at higher doses, with thresholds ranging from 0.1 to 0.5 g/d, and the differences were statistically significant at most thresholds. Any dose inflection point that may exist is likely to be beyond the range of testable thresholds (i.e., >0.5 g/d).
    - For CVD death, CHD death, total CHD, and hemorrhagic stroke, there were no apparent differences in association between marine oil intake dose and outcome at lower or higher dose ranges.
    - For CHD death and CHD, there were no apparent differences in association between ALA intake dose and outcome at lower or higher dose ranges.

2.8 How does the duration of intervention or exposure influence the effect of n-3 FA on CVD outcomes and risk factors?

- None of the meta-regressions found a significant interaction for follow-up time. No difference in effect was found within studies at different durations of intervention. Observational studies did not evaluate differences in duration of exposure.

2.9 What is the effect of baseline n-3 FA status (intake or biomarkers) on the efficacy of n-3 FA intake or supplementation on CVD outcomes and risk factors?

- No study found a significant difference in subgroups based on baseline fish or n-3 FA intake.

Key Question 3

Adverse events

3.1 What adverse effects are related to n-3 FA intake (in studies of CVD outcomes and risk factors)?

- No serious or severe adverse events were related to n-3 FA intake (supplementation). Most reported adverse events were mild and gastrointestinal in nature; however, only 2 of 25 trials reported statistically significant differences in adverse events between n-3 FA supplements and placebo.

3.2 What adverse events are reported specifically among people with CVD or diabetes (in studies of CVD outcomes and risk factors)?

- Among 10 trials of patients with CVD (9 with marine oil, 1 with total n-3 FA, 2 with ALA), either no adverse events or no significant difference between n-3 FA and placebo were reported.
- A single study reported adverse events from a trial of people with diabetes, finding no significant differences in serious or nonserious adverse events between marine oil and placebo.

Discussion

Overall Summary of Key Findings

In this systematic review we identified 61 eligible randomized controlled trials (RCT)s (in 82 publications) and 37 eligible prospective longitudinal and nested case-control studies (in 65 publications) for inclusion based on prespecified eligibility criteria. Most of the 19 RCTs that evaluated the effects of marine oil supplements (eicosapentaenoic acid [EPA] + docosahexaenoic acid [DHA]) compared with placebo on clinical cardiovascular disease (CVD) outcomes in populations at risk for CVD or with CVD, while most of the observational studies examined the associations between intake of various individual omega-3 fatty acids (n-3 FA) and in combination with each other in relationship to long-term CVD events in generally healthy populations. The RCTs of intermediate CVD outcomes (blood pressure [BP] and lipids) were conducted in all three populations of interest (generally healthy, at risk for CVD—primarily due to dyslipidemia, or with CVD). Only a single observational study evaluated BP; none evaluated lipids.

The main findings of the studies, regarding effect or association of higher n-3 FA intake or biomarker level and outcomes are summarized in the following tables. Table 54 includes analyses of n-3 FA and outcome pairs for which there is evidence to support an effect or association of higher n-3 FA intake and risk of a CVD outcome or on a CV risk factor. These include high strength of evidence that higher marine oil intake statistically significantly raises high density lipoprotein cholesterol (HDL-c), lowers triglycerides (Tg) concentration and Total:HDL-c ratio, but also raises low density lipoprotein cholesterol (LDL-c). There is low strength of evidence that higher marine oil intake is associated with lower risk of ischemic stroke.

Table 55 includes analyses of n-3 FA and outcome pairs for which there is evidence supporting no effect or association of n-3 FA intake (or biomarker level) and outcomes. These include high strength of evidence for no effect of or association between marine oil intake and major adverse cardiac events (MACE), all-cause mortality, sudden cardiac death (SCD), coronary revascularization, or BP; moderate strength of evidence of no association between marine oil intake and atrial fibrillation (AFib), and between DHA intake and BP or LDL-c, and between alphalinolenic acid (ALA) and BP, LDL-c, HDL-c, or Tg; and low strength of evidence of no association between total n-3 FA intake and stroke death or myocardial infarction (MI); between marine oil intake and CVD death, coronary heart disease (CHD) death, total CHD, MI, angina pectoris, CHF, total stroke or hemorrhagic stroke; between EPA intake and CHD; between EPA biomarkers and AFib; between DHA intake and CHD; between docosapentaenoic acid (DPA) biomarkers and AFib; and between ALA intake and CHD, CHD death, AFib, or CHF. Analyses of n-3 FA and outcome pairs not included in the table provided insufficient evidence.

Table 54. Main findings of high, moderate, or low strength of evidence of significant effects or associations between omega-3 fatty acids and outcomes

There is **high** strength of evidence for the following effects or associations of *higher* n-3 FA intake or biomarker levels and *lower* cardiovascular disease (CVD) risks or events:

- Marine oil* supplementation (or increased intake) and an increase in HDL-c
  - RCTs (of mostly supplements)
  - Summary net change in HDL-c: 0.9 mg/dL (95% CI 0.2, 1.6)
- Marine oil* supplementation (or increased intake) and a decrease in Tg
  - RCTs (of mostly supplements)
  - Summary net change in Tg: −24 mg/dL (95% CI −31, −18)
- Marine oil* supplementation (or increased intake) and a decrease in total cholesterol to HDL-c ratio
  - RCTs (of mostly supplements)
  - Summary net change in Total:HDL-c ratio: −0.17 (95% CI −0.26, −0.09)

There is **high** strength of evidence for the following effects or associations of *higher* n-3 FA intake or biomarker levels and *higher* CVD risk:

- Marine oil* supplementation (or increased intake) and an increase in LDL-c
  - RCTs (of mostly supplements)
  - Summary net change in LDL-c: 2.0 mg/dL (95% CI 0.4, 3.6)

There is **low** strength of evidence for the following effects or associations of *higher* n-3 FA intake and *lower* CVD risks or events:

- Marine oil* higher dietary intake and a lower risk of ischemic stroke
  - Observational studies (of total dietary intake), significant by metaregression: 0.51 (95% CI 0.29, 0.89) per g/d

* Statements about "marine oil" are based on all evidence of analyses of EPA+DHA+DPA, EPA+DHA, EPA, DHA, and DPA as supplements (e.g., fish oil) or as components of dietary intake (e.g., from fatty fish).

Abbreviations: CHD = coronary heart disease (also known as coronary artery disease), CHF = congestive heart failure, CI = confidence interval, CVD = cardiovascular disease, DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, EPA = eicosapentaenoic acid, HDL-c = high density lipoprotein cholesterol, HR = hazard ratio, LDL-c = low density lipoprotein cholesterol, n-3 FA = omega-3 fatty acids, RCT = randomized controlled trial, Tg = triglycerides.

Table 55. Main findings of high, moderate, or low strength of evidence of no significant effects or associations between omega-3 fatty acids and outcomes

There is **high** strength of evidence of *no effect or association* of n-3 FA intake or biomarker level and the following outcomes:

- Marine oil* supplementation (or increased dietary intake) and risk of major adverse cardiovascular event (MACE)
    - RCTs (of mostly supplements); observational studies (of total dietary intake) also found no significant associations
    - Summary effect size (RCTs): 0.96 (95% CI 0.91, 1.02)
- Marine oil* supplementation (or increased dietary intake) and all-cause death
    - RCTs (of mostly supplements) supported by observational studies (of total dietary intake)
    - Summary effect size (RCTs): 0.97 (95% CI 0.92, 1.03)
    - Observational studies (of total dietary intake): 0.62 (95% CI 0.31, 1.25) per g/d
- Marine oil* supplementation (or increased dietary intake) and sudden cardiac death (SCD)
    - RCTs (of mostly supplements) supported by an observational study (of total dietary intake)
    - Summary effect size (RCTs): 1.04 (95% CI 0.92, 1.17)
- Marine oil* supplementation (or increased dietary intake) and coronary revascularization
    - RCTs (of mostly supplements) supported by an observational study (of total dietary intake)
- Marine oil* supplementation (or increased dietary intake) and systolic or diastolic blood pressure
    - RCTs (of mostly supplements)
    - Summary net change in systolic blood pressure: 0.1 mg/dL (95% CI −0.2, 0.4)
    - Summary net change in diastolic blood pressure: −0.2 mg/dL (95% CI −0.4, 0.5)

There is **moderate** strength of evidence of *no effect or association* of n-3 FA intake or biomarker level and the following outcomes:

- Marine oil* supplementation (or increased dietary intake) and atrial fibrillation
    - RCTs (of mostly supplements); observational studies of intake were inconsistent
- Purified DHA supplementation and systolic or diastolic blood pressure
    - RCTs (of supplements only)
- Purified DHA supplementation and LDL-c
    - RCTs (of supplements only)
- ALA supplementation (or increased dietary intake) and systolic or diastolic blood pressure
    - RCTs (of mostly supplements)
- ALA supplementation (or increased dietary intake) intake and LDL-c, HDL-c, and Tg
    - RCTs (of mostly supplements)

Table 55. Main findings of high, moderate, or low strength of evidence of no significant effects or associations between omega-3 fatty acids and outcomes, continued

There is **low** strength of evidence of *no effect or association* of n-3 FA intake or biomarker level and the following outcomes:

- Total n-3 FA higher dietary intake and stroke death
  - Observational studies (of total dietary intake and biomarkers)
- Total n-3 FA higher dietary intake and myocardial infarction
  - Observational studies (of total dietary intake)
- Marine oil* supplementation (or increased dietary intake) and cadiovascular disease (CVD) death
  - Summary effect size (RCTs): 0.92 (95% CI 0.82, 1.02)†
  - Observational studies (of total dietary intake): 0.88 (95% CI 0.82, 0.95) per g/d
- Marine oil* supplementation (or increased dietary intake) and coronary heart disease (CHD) death
  - RCTs (of mostly supplements) imprecise
  - Observational studies (of total dietary intake): 1.09 (95% CI 0.76, 1.57) per g/d
- Marine oil* higher dietary intake and coronary heart disease (CHD)
  - Observational studies (of total dietary intake), supported by a single study of n-3 FA biomarkers
  - Observational studies (of total dietary intake): 0.94 (95% CI 0.81, 1.10) per g/d
- Marine oil* supplementation (or increased dietary intake) and myocardial infarction
  - Summary effect size (RCTs): 0.88 (95% CI 0.77, 1.02)†
- Marine oil* supplementation and angina pectoris
  - RCTs (of supplements) with heterogeneous outcomes (definitions of angina pectoris)
- Marine oil* supplementation (or increased dietary intake) and congestive heart failure (CHF)
  - RCTs (of mostly supplements) imprecise and could not be meta-analyzed, all nonsignificant
  - Observational studies (of total dietary intake) significant by metaregression: 0.76 (95% CI 0.58, 1.00) per g/d ($P<0.05$)
- Marine oil* supplementation (or increased dietary intake) and total stroke (fatal and nonfatal ischemic and hemorrhagic stroke)
  - Summary effect size (RCTs): 0.97 (95% CI 0.83, 1.13)
  - Observational studies (of total dietary intake): 0.68 (95% CI 0.53, 0.87) per g/d
- Marine oil* higher dietary intake and hemorrhagic stroke
  - Observational studies (of total dietary intake): 0.61 (95% CI 0.34, 1.11) per g/d
- EPA higher dietary intake and CHD
  - Observational studies (of total dietary intake)
- EPA higher biomarker levels and atrial fibrillation
  - Observational studies (of biomarkers)
- DHA higher dietary intake and CHD
  - Observational studies (of total dietary intake and biomarkers)
- DPA higher biomarker levels and atrial fibrillation
  - Observational studies (of biomarkers)
- ALA higher dietary intake and CHD death and, separately, total CHD
  - Observational studies (of total dietary intake); CHD death finding supported by one RCT (of supplementation) and one observational study of biomarkers
  - Observational studies (of total dietary intake): CHD death 0.94 (95% CI 0.85, 1.03) per g/d
  - Observational studies (of total dietary intake): CHD 0.97 (95% CI 0.92, 1.03) per g/d
- ALA higher dietary intake and atrial fibrillation
  - Observational studies (of total dietary intake and biomarkers)
- ALA supplementation (or increased dietary intake) and congestive heart failure (CHF)
  - Observational studies (of total dietary intake and biomarkers), supported by one RCT (of supplementation)

* Statements about “marine oil” are based on all evidence of analyses of EPA+DHA+DPA, EPA+DHA, EPA, DHA, and DPA as supplements (e.g., fish oil) or as components of dietary intake (e.g., from fatty fish).
† There is low confidence that this summary estimate would remain suggestive of no effect with the addition of future trial data (and greater statistical power).

Abbreviations: ALA = alphalinolenic acid, CHD = coronary heart disease, CHF = congestive heart failure, DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, EPA = eicosapentaenoic acid, HDL-c = high density lipoprotein cholesterol, LDL-c = low density lipoprotein cholesterol, MACE = major adverse cardiovascular event (including cardiac and stroke events and death; variously defined by studies), n-3 FA = omega-3 fatty acids, RCT = randomized controlled trial, SCD = sudden cardiac death, Tg = triglycerides.

Studies within each category of analysis (by study design and by n-3 FA) were diverse, due to differences in outcomes evaluated, definitions of specific outcomes, as well as the n-3 FA intervention doses or compositions (for RCTs) or the dietary/biomarker n-3 FA exposure assessments and quantifications (for observational studies). Overall we found a lack of conclusive or consistent findings for CVD events within RCTs, mostly due to sparse data and underpowered trials as indicated by wide confidence intervals. The majority of the individual RCTs did not find statistically significant effects of marine oil supplements (EPA+DHA, various doses) on CVD outcomes. Pooled meta-analyses suggest that people with CVD or at risk for CVD who received marine oil supplements may have a small risk reduction in CVD death (pooled HR 0.92; 95% CI 0.82 to 1.02) compared with those who received placebo. Across outcomes, the effects of marine oil supplements were often larger in earlier RCTs than in more recent RCTs. These data may be confounded by shifts over time in concomitant therapy to reduce CVD risk (e.g., statins, aspirin), decreasing smoking rates, and overall declining rates of CVD events. No meta-regression across studies found significant changes in effect sizes by publication year; however, it is likely that all such meta-regressions of clinical outcomes were underpowered due to relatively small numbers of trials.

Observational studies were mixed regarding the associations between n-3 FA intake or biomarkers and risk of MACE (where each study used its own combination of specific CVD outcomes). The strength of associations between higher levels of n-3 FA and lower risk of CVD outcomes, when found, were often larger than those in RCTs. While all observational studies adjusted associations for potentially confounding variables, the specific variables included in models varied greatly across observational studies. Furthermore, all observational studies compared higher intake levels of n-3 FA with lowest intake level, which included people who may have other nutrition deficiencies that may affect chronic disease risks but often cannot be "controlled for" in the analyses (resulting in residual, uncontrolled confounding).

The overall findings for the effects of marine oil supplements on intermediate CVD outcomes remain largely unchanged since the original report. In this update, there were no significant effects found in 29 RCTs that compared marine oils (0.3−6 g/d) on systolic or diastolic BP compared with placebo. Thirty-three RCTs evaluated LDL-c and HDL-c. Meta-analyses of the effect of marine oils on HDL-c and LDL-c found small, but statistically significant amounts (summary net change HDL-c = 1.2 mg/dL [95% CI 0.6 to 1.8]; LDL-c = 2.0 mg/dL [95% CI 0.4 to 3.6]). The clinical significance of these small increases in both HDL-c and LDL-c on CVD outcomes, particularly in combination, is unclear. For both lipids, no differences in effect across studies were found by marine oil dose, followup duration or population. The strongest effect of marine oils (0.3−6 g/d) was found among the 40 RCTs of Tg. Meta-analysis found a summary net change of −23 mg/dL (95% CI −29 to −18), with no significant difference in effect based on population or followup time across studies. However, across trials, the effect was dose-dependent and also dependent on the studies' mean baseline Tg values. By metaregression, each increase of EPA+DHA dose by 1 g/d was also associated with a greater net change Tg of −6.8 mg/dL (95% CI −11.4 to −2.2) and each increase in mean baseline Tg level by 1 mg/dL was associated with a greater net change Tg of −0.12 mg/dL (95% CI −0.22 to −0.03). However, the few trials that directly compared marine oil doses did not consistently find a dose effect; although, marine oil doses ≥3 g/d all resulted in larger reductions in Tg compared to lower doses, in contrast to doses <3 g/d which had smaller reductions in Tg compared to even lower doses. There were no observational studies evaluating these intermediate CVD outcomes.

In the original report, there was only one RCT of ALA (linseed oil) versus control oil (sunflower seed oil),[49] conducted in the 1960s, that evaluated clinical event outcomes. In this update we identified only one additional RCT of ALA (plant source not reported) versus placebo (oleic acid) in participants with a history of MI that reported clinical outcomes.[119] Given the sparseness of trials of the effect on clinical CVD outcomes of higher ALA intake and the differences between the two trials, no conclusion can be drawn regarding effect of ALA on CVD outcomes. For intermediate outcomes, five ALA RCTs (with doses ranging from 1.4 to 5.9 g/d) evaluated BP outcomes, and four of the five RCTs also evaluated LDL-c, HDL-c, Tg, or Total:HDL-c ratio (2 trials) outcomes. All found no significant differences in these outcomes between ALA and placebo. Thirteen observational studies evaluated ALA intake. The large majority of analyses found no significant associations; only two studies found any significant associations between higher ALA intake and clinical outcomes (reduced all-cause death, SCD, and CHD death risks).

The potential threshold-effects of n-3 FA on CVD events could not be determined from the RCTs because there were limited number of RCTs for many outcomes and most RCTs did not find significant effects. Only for Tg is there evidence among trials of a dose effect, such that higher dose marine oils result in greater reductions in Tg. Using data from observational studies, the linear dose-response and potential threshold effects of n-3 FA on several CVD events were tested by meta-analytical techniques. There was a near-significant association between EPA and DHA intake and CHD across a median dose range of 0.04 to 3.47 g/d (effect size per g/d = 0.90 [95% CI 0.80 to 1.01]), and a just-significant association between EPA and DHA intake and *higher* risk of ischemic stroke across a median dosage range of 0.025 to 0.6 g/d (effect size per g/d = 1.03 [95% CI 1.00 to 1.07]), but no dose-response relationships found between EPA and DHA intake and hemorrhagic stroke. The interpretations of the threshold-effects were limited because differences in associations at lower doses (statistically significant associations between higher intake and lower risk) and associations at higher doses (no significant associations between intake and outcome) were generally similar regardless of the cut point chosen between lower and higher dose analyses.

No differences in effects or associations were found between different populations (healthy or general population, at increased risk for CVD—largely due to dyslipidemia, or with CVD). However, this conclusion is weak given that few studies compared populations, few RCTs were conducted in healthy populations and few observational studies were conducted in at risk or CVD populations.

Limitations

Overall, both RCTs and observational studies (i.e., longitudinal observational and nested case-control studies) included in this systematic review generally had few risk of bias concerns. Across RCTs, the most common risk of bias limitation was a lack of intention-to-treat analyses (25% of the included RCTs). Of included RCTs, 18 percent could not blind study participants because the intervention was dietary (increased fish intake, not n-3 FA supplements), and 15 percent of RCTs were at risk of attrition bias primarily due to overall dropout rates greater than 20 percent. Most studies reported similar dropout rates between groups. Although more than 90 percent of the included RCTs reported similar baseline demographic characteristics between groups, about 40 percent did not report baseline n-3 FA intake or status. This is a critical point because baseline n-3 FA status likely affects response to changes in n-3 FA intake (diet or supplements). Across observational studies, the most common risk of bias limitation was reporting inadequacy related to the ranges and distribution of n-3 FA exposures (45% did not fully report such data). Of included observational studies, 12 percent did not report the dietary assessment instrument, and most of the n-3 FA dietary intake assessment included only dietary sources (not n-3 FA supplements). At best, studies reported that they used a food frequency questionnaire to estimate n-3 FA intake, without complete details. Of those studies that reported biomarker data, this is not an issue of concern. However, a variety of different n-3 FA biomarkers were investigated across studies, making comparisons and meta-analysis difficult.

For clinical CVD outcomes, all but one of the RCTs was conducted in either high risk individuals or people with existing CVD. In contrast, most observational studies examining the associations between dietary n-3 FA intake or biomarkers of n-3 FA intake and clinical outcomes were conducted in generally healthy populations. The definitions of most clinical outcomes were heterogeneous across studies regardless of the study designs. For most clinical outcomes, there were few or no RCTs. Few trials compared n-3 FA dose, formulation, or source. No trial compared different n-3 to n-6 FA ratios of supplements or intake. None of the observational studies attempted to determine a threshold effect of any associations between n-3 FA and the outcome of interest.

Other study-reporting issues that precluded analyses from being included in meta-analyses were that studies of n-3 FA intake used a variety of methods to measure intake (g/d, percent Kcal, percent fat or fatty acid intake); several studies failed to report median or range data of n-3 FA levels within quantiles, confidence intervals (or equivalent) of association hazard ratios, or conducted only linear analyses across a full range of n-3 FA values. In addition, studies varied in the range of n-3 FA status (e.g., intake level) within each study, often with n-3 FA ranges that did not or hardly overlapped. All of the observational studies measured dietary n-3 FA intake or biomarkers of n-3 FA intake at a single time point, baseline, and related these data to the long-term (mostly >10 years) clinical outcomes (CVD events). These analyses rely on the assumption that baseline intake reflects long-term intake, both prior to the beginning of the study and during the course of the observational period. In adults, the relative stability of dietary patterns may minimize the bias due to changing dietary patterns. However, study participants may have changed their dietary or supplement intake of n-3 FA due to concerns about CVD, due to advancing age or new CVD risk factors (e.g., new diagnoses of hypertension, diabetes, or dyslipidemia). These potential dietary changes are unlikely to have occurred at random and may, therefore, introduce bias due to the differential misclassifications of exposure status. This review included neither weight-loss intervention studies nor did we evaluate weight change as an outcome. We also did not include *post hoc* subgroup analyses (with subgroups defined by status at study end; e.g., by weight loss). Very few, if any, eligible studies evaluated weight change or its interaction with CV-related outcomes. Therefore, this review cannot comment on any potential interactions between weight change and n-3 FA status on CV outcomes.

There are numerous differences between RCTs and observational studies, making the comparisons across the two study designs difficult to make. Of note, the doses of marine oil supplements (EPA+DHA) in RCTs were often much higher than the highest intake reported for observational studies. Furthermore, not all observational studies explicitly included n-3 FA supplements in their assessment of intake and very few of the RCTs attempted to account for background fish or n-3 FA intake as an effect modifier.

Due to significant clinical heterogeneity across studies, the interpretation of overall meta-analysis results is limited. Dose-response meta-analysis of observational studies should be interpreted with caution as many factors many invalidate the results such as heterogeneity in the covariate adjustments across studies and errors or biases in dietary assessments.

While this report represents a complete systematic review, it does not encompass all trials or longitudinal observational studies that report on CVD and intermediate outcomes. Particularly, if one includes small studies (trials with <30 participants per study group or observational studies with <100 participants, several hundred more studies could potentially have met eligibility criteria. Due to time and resource limitations, we restricted the review to the approximately 100 studies that are most likely to have adequately addressed the primary research questions of interest.

Future Research Recommendations

Future RCTs should characterize the preparations of n-3 FA and placebo used for the intervention in terms of the FA composition and molecular form of the FA (e.g., ethyl esters, Tg), as well as indicating their sources. Of potential interest in future studies is whether effects differ based on these factors. The placebo foods and oils should have the same caloric density and to the extent possible similar food or oil types as the source of n-3 FA. The composition of the background diet should also be reported, as should FA composition, macronutrient content and whether the participants were weight-stable. Researchers are encouraged to use standard, common CVD outcomes to allow comparison across studies. Assessment of n-3 FA status and intake should be evaluated at study entry and post-intervention in all study participants using to better understand potential changes in n-3 FA intake in populations with different background diets (e.g., whether the effect of supplementation differs in people with high- or low-fish diets). If trials include participants with a broad range of n-3 FA status or intake (e.g., with both high- and low-fish diets), subgroup analyses should be conducted to evaluate possible differential effects based on these variables. The effects (or lack thereof) of marine oils (EPA+DHA) on BP, LDL-c, HDL-c, and Tg are well established so additional RCTs on these intermediate outcomes alone are unlikely to add any new knowledge, and therefore are not recommended.

There is an ongoing need to improve self-reported dietary assessment methods and food databases for all nutrients including n-3 FA. As national dietary patterns shift and new processed foods are introduced into the marketplace, food composition tables used to analyze food frequency questionnaire data need to be updated to ensure accurate estimation of n-3 FA (and other nutrient) intake. Similar to trial registries, a data repository for raw observational study data would greatly improve the transparency of data analyses (potentially reduce both reporting and publication biases) and the appropriateness and methodology of meta-analytical techniques for pooling observational studies. An individual participant-level meta-analysis of observational studies of marine oils could address limitations of the study-level meta-analyses that are currently feasible.

Conclusions

Results from the RCTs of clinical event outcomes are applicable only to at risk of CVD and CVD populations. Results from the RCTs of intermediate outcomes are applicable to all populations. In contrast, results from observational studies (which did not evaluate intermediate outcomes) are applicable only to generally healthy populations. We graded the strength of the body of evidence for each intervention/exposure and comparison of intervention, and for each outcome by assessing the number of studies, their study designs, the study limitations (i.e., risk of bias and overall methodological quality), the directness of the evidence to the Key Questions, the consistency of study results, the precision of any estimates of effect, the likelihood of reporting bias, and the overall findings across studies. We concluded that there is insufficient evidence regarding the effect of or association between total n-3 FA (ALA + marine oils [EPA+DHA+DPA) and clinical or intermediate outcomes. There is low strength of evidence of no association between total n-3 FA intake and stroke death, and total (fatal and nonfatal) MI (each association based on longitudinal observational studies). For marine oil (EPA+DHA±DPA), there is insufficient evidence for most outcomes of interest but there is low to high strength of evidence of a beneficial effect of higher marine oil intake for selected CVD and intermediate outcomes. Specifically, there is high strength of evidence of that marine oils clinically and statistically significantly lower Tg—possibly with greater effects with higher doses and in people with higher baseline Tg. There is also high strength of evidence that marine oils statistically, but arguably not clinically, significantly raise both HDL-c and LDL-c. There is also high strength of evidence that marine oil significantly lowers Total:HDL-c ratio. There is low strength of evidence that marine oil supplementation lowers risk of ischemic stroke. There is a high strength of evidence of no effect of marine oil on risk of MACE, all-cause death, sudden cardiac death, coronary revascularization, and blood pressure; moderate strength of evidence of no effect of marine oil on risk of atrial fibrillation; and low strength of evidence of no associations of marine oil intake and cardiovascular death, CHD death, CHD, myocardial infarction, angina pectoris, CHF, total stroke, or hemorrhagic stroke.

For individual n-3 FA, there is insufficient evidence regarding the effect of or association with EPA, DHA, DPA, stearidonic acid (SDA), or ALA (specifically) and most CVD clinical outcomes. For EPA, there is low strength of evidence of no association between EPA intake and CHD and between EPA biomarkers and AFib. For DHA, there is moderate strength of evidence of no effect of purified DHA supplementation on BP or LDL-c and low strength of evidence of no association between DHA intake and incident CHD (from observational studies). For DPA, there is low strength of evidence of an association between higher DPA biomarker levels and lower risk of AFib. For ALA, there is moderate strength of evidence of no significant effect of ALA intake on BP, LDL-c, HDL-c, or Tg. There is low strength of evidence of no association between ALA intake or biomarker level and CHD or CHD death, AFib, or CHF, based on observational studies.

There is insufficient evidence of direct comparisons between marine oil and ALA intake on CVD outcomes. Across studies, the comparison between marine oil and ALA is unclear, largely because of insufficient evidence regarding ALA; however, where there is high strength of evidence of significant effects of marine oil on improving Tg and HDL-c, there is moderate strength of evidence of no effect of ALA intake on these intermediate outcomes. No RCTs examined the additive effects of n-3 FA versus the effects of individual n-3 FA.

In the scientific community, there is a perception of “conflicting evidence” for the role of n-3 FA in prevention or treatment of CVD between RCT and observational study data.[196, 197] This perception may in part stem from inconsistent scientific conclusions among several of the expert panels or may relate to whether the potential beneficial effects of n-3 FA were from fish (or other marine foods) intake or from dietary supplements.[5-8] Our qualitative comparisons between RCTs and observational studies (i.e., longitudinal observational and nested case-control studies) included in this systematic review showed that the evidence base from the two study designs relating n-3 FA to CVD outcomes often are not comparable as they address different research questions. It is important to note that observational studies of fish consumption without quantifications of n-3 FA were not included in this systematic review. Our findings highlight the importance of including both observational studies and RCTs to assess the strength of body of evidence because the two study designs each have their own strengths and weakness and often provide complementary pieces of information for causal inferences. Nutrition observational studies typically measure and compare people with different dietary behaviors (thus different levels of nutrient exposure) in relationship to the disease risks, while nutrition RCTs are typically designed to compare a specific (usually narrowly defined) nutrition intervention to a control) in a relatively homogenous and well-defined study population. By design, nutrition observational studies and RCTs address different research questions. The observed relationships between higher or lower levels of intake and disease risks are important to describe potential behavioral target for interventions for prevention or treatment of a disease but will never be sufficient to pin point the specific mechanism or doses for the interventions. Therefore it is unlikely that a RCT can be designed to "verify" or "validate" nutrition observational results. On the other hand, RCTs are the most valid design for comparative effectiveness research questions. Long-term nutrition RCTs, however, often suffer compliance or contamination issues that can void the advantages of initial randomization. No single study can provide a "definitive answer" due to the unique challenges in nutrition RCTs and observational studies. It is necessary to carefully review the totality of evidence while considering the strengths and limitations of the individual studies.

References

1. Bang HO, Dyerberg J, Hjoorne N. The composition of food consumed by Greenland Eskimos. Acta medica Scandinavica. 1976;200(1-2):69-73. PMID: 961471.
2. Burdge GC, Calder PC. Dietary alphalinolenic acid and health-related outcomes: a metabolic perspective. Nutr Res Rev. 2006 Jun;19(1):26-52. PMID: 19079874.
3. Balk E, Chung M, Lichtenstein A, et al. Effects of omega-3 fatty acids on cardiovascular risk factors and intermediate markers of cardiovascular disease. Evid Rep Technol Assess (Summ). 2004 Mar(93):1-6. PMID: 15133887.
4. Wang C, Chung M, Lichtenstein A, et al. Effects of omega-3 fatty acids on cardiovascular disease. Evid Rep Technol Assess (Summ). 2004 Mar(94):1-8. PMID: 15133888.
5. Report of the Joint FAO/WHO Expert Consultation on the Risks and Benefits of Fish Consumption. Food and Agriculture Organization of the United Nations; Geneva: World Health Organization Rome; 2011.
6. Institute of Medicine, Panel on Micronutrients. Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein and Amino Acids. Panel on Macronutrients Panel on the Definition of Dietary Fiber, Subcommittee on Upper Reference Levels of Nutrients, Subcommittee on Interpretation and Uses of Dietary Reference Intakes, and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board: National Academies Press; 2005.
7. McGuire S. US Department of Agriculture and US Department of Health and Human Services, Dietary Guidelines for Americans, 2010. Washington, DC: US Government Printing Office, January 2011. Adv Nutr. 2011;2(3):293-4.
8. Institute of Medicine. Seafood Choices: Balancing Benefits and Risks. Nesheim MC, Yaktine AL, editors. Washington, DC: The National Academies Press; 2007.
9. Harika RK, Eilander A, Alssema M, et al. Intake of fatty acids in general populations worldwide does not meet dietary recommendations to prevent coronary heart disease: a systematic review of data from 40 countries. Ann Nutr Metab. 2013;63(3):229-38. PMID: 24192557.
10. Balk EM, Horsley TA, Newberry SJ, et al. A collaborative effort to apply the evidence-based review process to the field of nutrition: challenges, benefits, and lessons learned. Am J Clin Nutr. 2007 Jun;85(6):1448-56. PMID: 17556679.
11. Chung M, Balk EM, Ip S, et al. Systematic review to support the development of nutrient reference intake values: challenges and solutions. Am J Clin Nutr. 2010 Aug;92(2):273-6. PMID: 20504974.
12. Chung M, Balk EM, Ip S, et al. Reporting of Systematic Reviews of Micronutrients and Health: A Critical Appraisal: Nutrition Research Series, Vol 3. Rockville (MD)2009.
13. Chung M, Balk EM, Ip S, et al. Reporting of systematic reviews of micronutrients and health: a critical appraisal. Am J Clin Nutr. 2009 Apr;89(4):1099-113. PMID: 19244363.
14. Chung M, Newberry SJ, Ansari MT, et al. Two methods provide similar signals for the need to update systematic reviews. J Clin Epidemiol. 2012 Jun;65(6):660-8. PMID: 22464414.
15. Lichtenstein AH, Yetley EA, Lau J. Application of systematic review methodology to the field of nutrition. J Nutr. 2008 Dec;138(12):2297-306. PMID: 19022948.
16. Lichtenstein AH, Yetley EA, Lau J. Application of Systematic Review Methodology to the Field of Nutrition: Nutritional Research Series, Vol 1. Rockville (MD)2009.
17. Moorthy D, Chung M, Lee J, et al. Concordance Between the Findings of Epidemiological Studies and Randomized Trials in Nutrition: An Empirical Evaluation and Citation Analysis: Nutritional Research Series, Vol 6. Rockville (MD)2013.

18. Russell R, Chung M, Balk EM, et al. Opportunities and challenges in conducting systematic reviews to support the development of nutrient reference values: vitamin A as an example. Am J Clin Nutr. 2009 Mar;89(3):728-33. PMID: 19176732.

19. Russell R, Chung M, Balk EM, et al. Issues and Challenges in Conducting Systematic Reviews to Support Development of Nutrient Reference Values: Workshop Summary: Nutrition Research Series, Vol 2. Rockville (MD)2009.

20. Shekelle PG, Newberry SJ, Wu H, et al. Identifying Signals for Updating Systematic Reviews: A Comparison of Two Methods. Rockville (MD) 2011.

21. Trikalinos TA, Lee J, Moorthy D, et al. Effects of Eicosapentanoic Acid and Docosahexanoic Acid on Mortality Across Diverse Settings: Systematic Review and Meta-Analysis of Randomized Trials and Prospective Cohorts: Nutritional Research Series, Vol 4. Rockville (MD)2012.

22. Trikalinos TA, Moorthy D, Chung M, et al. Comparison of Translational Patterns in Two Nutrient-Disease Associations: Nutritional Research Series, Vol 5. Rockville (MD)2011.

23. Trikalinos TA, Moorthy D, Chung M, et al. Concordance of randomized and nonrandomized studies was unrelated to translational patterns of two nutrient-disease associations. J Clin Epidemiol. 2012 Jan;65(1):16-29. PMID: 22047889.

24. Freedman LS, Commins JM, Moler JE, et al. Pooled results from 5 validation studies of dietary self-report instruments using recovery biomarkers for energy and protein intake. Am J Epidemiol. 2014 Jul 15;180(2):172-88. PMID: 24918187.

25. Archer E, Hand GA, Blair SN. Validity of U.S. nutritional surveillance: National Health and Nutrition Examination Survey caloric energy intake data, 1971-2010. PloS One. 2013;8(10):e76632. PMID: 24130784.

26. Schoeller DA, Thomas D, Archer E, et al. Self-report-based estimates of energy intake offer an inadequate basis for scientific conclusions. Am J Clin Nutr. 2013 Jun;97(6):1413-5. PMID: 23689494.

27. Hodson L, Skeaff CM, Fielding BA. Fatty acid composition of adipose tissue and blood in humans and its use as a biomarker of dietary intake. Progress in lipid research. 2008 Sep;47(5):348-80. PMID: 18435934.

28. Serra-Majem L, Nissensohn M, Overby NC, et al. Dietary methods and biomarkers of omega 3 fatty acids: a systematic review. Br J Nutr. 2012 Jun;107 Suppl 2:S64-76. PMID: 22591904.

29. Fekete K, Marosvolgyi T, Jakobik V, et al. Methods of assessment of n-3 long-chain polyunsaturated fatty acid status in humans: a systematic review. Am J Clin Nutr. 2009 Jun;89(6):2070S-84S. PMID: 19420097.

30. Khoueiry G, Abi Rafeh N, Sullivan E, et al. Do omega-3 polyunsaturated fatty acids reduce risk of sudden cardiac death and ventricular arrhythmias? A meta-analysis of randomized trials. Heart Lung. 2013 Jul-Aug;42(4):251-6. PMID: 23714269.

31. Kotwal S, Jun M, Sullivan D, et al. Omega 3 Fatty acids and cardiovascular outcomes: systematic review and meta-analysis. Circ Cardiovasc Qual Outcomes. 2012 Nov;5(6):808-18. PMID: 23110790.

32. Rizos EC, Ntzani EE, Bika E, et al. Association between omega-3 fatty acid supplementation and risk of major cardiovascular disease events: a systematic review and meta-analysis. JAMA. 2012 Sep 12;308(10):1024-33. PMID: 22968891.

33. Delgado-Lista J, Perez-Martinez P, Lopez-Miranda J, et al. Long chain omega-3 fatty acids and cardiovascular disease: a systematic review. Br J Nutr. 2012 Jun;107 Suppl 2:S201-13. PMID: 22591894.

34. Kwak SM, Myung SK, Lee YJ, et al. Efficacy of omega-3 fatty acid supplements (eicosapentaenoic acid and docosahexaenoic acid) in the secondary prevention of cardiovascular disease: a meta-analysis of randomized, double-blind, placebo-controlled trials. Arch. Intern Med. 2012 May 14;172(9):686-94. PMID: 22493407.

35. Chen Q, Cheng LQ, Xiao TH, et al. Effects of omega-3 fatty acid for sudden cardiac death prevention in patients with cardiovascular disease: a contemporary meta-analysis of randomized, controlled trials. Cardiovascular drugs and therapy / sponsored by the International Society of Cardiovascular Pharmacotherapy. 2011 Jun;25(3):259-65. PMID: 21626218.

36. Zhao YT, Chen Q, Sun YX, et al. Prevention of sudden cardiac death with omega-3 fatty acids in patients with coronary heart disease: a meta-analysis of randomized controlled trials. Ann Med. 2009;41(4):301-10. PMID: 19148838.

37. Kramer BS, Wilentz J, Alexander D, et al. Getting it right: being smarter about clinical trials. PLoS Med. 2006 Apr;3(6):e144. PMID: 16608383.

38. Geleijnse JM, Giltay EJ, Grobbee DE, et al. Blood pressure response to fish oil supplementation: metaregression analysis of randomized trials. J Hypertens. 2002 Aug;20(8):1493-9. PMID: 12172309.

39. Methods guide for effectiveness and comparative effectiveness reviews: Agency for Healthcare Research and Quality; 2011.

40. Hill AB. The environment and disease: association or causation? Proceedings of the Royal Society of Medicine. 1965;58(5):295.

41. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ (Clinical research ed). 2011;343:d5928. PMID: 22008217.

42. Wells GA SB, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. . The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses [9/25/2014]; Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

43. Chung M, Balk EM, Brendel M, et al. Vitamin D and calcium: a systematic review of health outcomes. Evidence report/technology assessment. 2009 Aug(183):1-420. PMID: 20629479.

44. Yu WW, Schmid CH, Lichtenstein AH, et al. Empirical evaluation of meta-analytic approaches for nutrient and health outcome dose-response data. Res Synth Methods.. 2013 Sep;4(3):256-68. PMID: 25379059.

45. Berkman ND, Lohr KN, Ansari MT, et al. Grading the strength of a body of evidence when assessing health care interventions: an EPC update. J Clin Epidemiol. 2014 Dec 20. PMID: 25721570.

46. Liu M, Wallmon A, Wallin R, Saldeen T. Effects of stable fish oil and simvastatin on plasma lipoproteins in patients with hyperlipidemia. Nutrition research.23(8):1027-34.

47. Dolecek TA. Epidemiological evidence of relationships between dietary polyunsaturated fatty acids and mortality in the multiple risk factor intervention trial. Proceedings of the Society for Experimental Biology and Medicine Society for Experimental Biology and Medicine (New York, NY). 1992 Jun;200(2):177-82. PMID: 1579579.

48. Burr ML, Fehily AM, Gilbert JF, et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). Lancet. 1989 Sep 30;2(8666):757-61. PMID: 2571009.

49. Natvig H, Borchgrevink CF, Dedichen J, et al. A controlled trial of the effect of linolenic acid on incidence of coronary heart disease. The Norwegian vegetable oil experiment of 1965-66. Scand J Clin Lab Invest Suppl. 1968;105:1-20. PMID: 5756076.

50. Morris MC, Manson JE, Rosner B, et al. Fish consumption and cardiovascular disease in the physicians' health study: a prospective study. Am J Epidemiol. 1995 Jul 15;142(2):166-75. PMID: 7598116.

51. Sacks FM, Stone PH, Gibson CM et al. Controlled trial of fish oil for regression of human coronary atherosclerosis. HARP Research Group. J Am Coll Cardiol. 1995 Jun;25(7):1492-8. PMID: 7759696.

52. Guallar E, Hennekens CH, Sacks FM, et al. A prospective study of plasma fish oil levels and incidence of myocardial infarction in U.S. male physicians. J Am Coll Cardiol. 1995 Feb;25(2):387-94. PMID: 7829792.

53. Lungershausen YK, Abbey M, Nestel PJ, Howe PR. Reduction of blood pressure and plasma triglycerides by omega-3 fatty acids in treated hypertensives. J Hypertens. 1994 Sep;12(9):1041-5. PMID: 7852747.

54. Ascherio A, Rimm EB, Stampfer MJ. Dietary intake of marine n-3 fatty acids, fish intake, and the risk of coronary disease among men. N Engl J Med. 1995 Apr 13;332(15):977-82. PMID: 7885425.

55. Sacks FM, Hebert P, Appel LJ, et al. Short report: the effect of fish oil on blood pressure and high-density lipoprotein-cholesterol levels in phase I of the Trials of Hypertension Prevention. J Hypertens. 1994 Feb;12(2):209-13. PMID: 8021472.

56. Eritsland JA, H.; Gronseth, K.; Fjeld, N. B.; Abdelnoor, M. Effect of dietary supplementation with n-3 fatty acids on coronary artery bypass graft patency. The American journal of cardiology. 1996 Jan 1;77(1):31-6. PMID: 8540453.

57. Pietinen P, Ascherio A, Korhonen P, et al. Intake of fatty acids and risk of coronary heart disease in a cohort of Finnish men. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. Am J Epidemiol. 1997 May 15;145(10):876-87. PMID: 9149659.

58. Sirtori CR, Paoletti R, Mancini M, et al. N-3 fatty acids do not lead to an increased diabetic risk in patients with hyperlipidemia and abnormal glucose tolerance. Italian Fish Oil Multicenter Study. Am J Clin Nutr. 1997 Jun;65(6):1874-81. PMID: 9174486.

59. Grimsgaard S, Bonaa KH, Hansen JB, Nordoy A. Highly purified eicosapentaenoic acid and docosahexaenoic acid in humans have similar triacylglycerol-lowering effects but divergent effects on serum fatty acids. Am J Clin Nutr. 1997 Sep;66(3):649-59. PMID: 9280188.

60. Albert CM, Hennekens CH, O'Donnell CJ, et al. Fish consumption and risk of sudden cardiac death. JAMA. 1998 Jan 7;279(1):23-8. PMID: 9424039.

61. Grimsgaard S, Bonaa KH, Hansen JB, Myhre ES. Effects of highly purified eicosapentaenoic acid and docosahexaenoic acid on hemodynamics in humans. Am J Clin Nutr. 1998 Jul;68(1):52-9. PMID: 9665096.

62. von Schacky C, Angerer P, Kothny W, et al. The effect of dietary omega-3 fatty acids on coronary atherosclerosis. A randomized, double-blind, placebo-controlled trial. Ann Intern Med. 1999 Apr 6;130(7):554-62. PMID: 10189324.

63. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. Lancet. 1999 Aug 7;354(9177):447-55. PMID: 10465168.

64. Ness AR, Whitley E, Burr ML, et al. The long-term effect of advice to eat more fish on blood pressure in men with coronary disease: results from the diet and reinfarction trial. J Hum Hypertens. 1999 Nov;13(11):729-33. PMID: 10578215.

65. Iso H, Rexrode KM, Stampfer MJ, et al. Intake of fish and omega-3 fatty acids and risk of stroke in women. JAMA. 2001 Jan 17;285(3):304-12. PMID: 11176840.

66. Vessby B, Uusitupa M, Hermansen K, et al. Substituting dietary saturated for monounsaturated fat impairs insulin sensitivity in healthy men and women: The KANWU Study. Diabetologia. 2001 Mar;44(3):312-9. PMID: 11317662.

67. Nilsen DW, Albrektsen G, Landmark K, el al. Effects of a high-dose concentrate of n-3 fatty acids or corn oil introduced early after an acute myocardial infarction on serum triacylglycerol and HDL cholesterol. Am J Clin Nutr. 2001 Jul;74(1):50-6. PMID: 11451717.

68. Yuan JM, Ross RK, Gao YT, Yu MC. Fish and shellfish consumption in relation to death from myocardial infarction among men in Shanghai, China. Am J Epidemiol. 2001 Nov 1;154(9):809-16. PMID: 11682363.

69. Hu FB, Bronner L, Willett WC, et al. Fish and omega-3 fatty acid intake and risk of coronary heart disease in women. JAMA. 2002 Apr 10;287(14):1815-21. PMID: 11939867.

70. Marchioli R, Barzi F, Bomba E, et al. Early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction: time-course analysis of the results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione. Circulation. 2002 Apr 23;105(16):1897-903. PMID: 11997274.

71. Ness AR, Hughes J, Elwood PC, et al. The long-term effect of dietary advice in men with coronary disease: follow-up of the Diet and Reinfarction trial (DART). Eur J Clin Nutr. 2002 Jun;56(6):512-8. PMID: 12032650.

72. Nagata C, Takatsuka N, Shimizu H. Soy and fish oil intake and mortality in a Japanese community. Am J Epidemiol. 2002 Nov 1;156(9):824-31. PMID: 12397000.

73. He K, Rimm EB, Merchant A, et al. Fish consumption and risk of stroke in men. JAMA. 2002 Dec 25;288(24):3130-6. PMID: 12495393.

74. Burr ML, Ashfield-Watt PA, Dunstan FD, et al. Lack of benefit of dietary advice to men with angina: results of a controlled trial. Eur J Clin Nutr. 2003 Feb;57(2):193-200. PMID: 12571649.

75. Finnegan YE, Minihane AM, Leigh-Firbank EC, et al. Plant- and marine-derived n-3 polyunsaturated fatty acids have differential effects on fasting and postprandial blood lipid concentrations and on the susceptibility of LDL to oxidative modification in moderately hyperlipidemic subjects. Am J Clin Nutr. 2003 Apr;77(4):783-95. PMID: 12663273.

76. Shidfar F, Keshavarz A, Jallali M, et al. Comparison of the effects of simultaneous administration of vitamin C and omega-3 fatty acids on lipoproteins, apo A-I, apo B, and malondialdehyde in hyperlipidemic patients. Int J Vitam Nutr Res. 2003 May;73(3):163-70. PMID: 12847992.

77. Grundt H, Nilsen DW, Hetland O, Mansoor MA. Clinical outcome and atherothrombogenic risk profile after prolonged wash-out following long-term treatment with high doses of n-3 PUFAs in patients with an acute myocardial infarction. Clin Nutr. 2004 Aug;23(4):491-500. PMID: 15297084.

78. Mozaffarian D, Ascherio A, Hu FB, et al. Interplay between different polyunsaturated fatty acids and risk of coronary heart disease in men. Circulation. 2005 Jan 18;111(2):157-64. PMID: 15630029.

79. Frost L and Vestergaard P. n-3 Fatty acids consumed from fish and risk of atrial fibrillation or flutter: the Danish Diet, Cancer, and Health Study. Am J Clin Nutr. 2005 Jan;81(1):50-4. PMID: 15640459.

80. Harrison RA, Sagara M, Rajpura A, et al. Can foods with added soya-protein or fish-oil reduce risk factors for coronary disease? A factorial randomised controlled trial. Nutrition, metabolism, and cardiovascular diseases: NMCD. 2004 Dec;14(6):344-50. PMID: 15853118.

81. Raitt MH, Connor WE, Morris C, et al. Fish oil supplementation and risk of ventricular tachycardia and ventricular fibrillation in patients with implantable defibrillators: a randomized controlled trial. JAMA. 2005 Jun 15;293(23):2884-91. PMID: 15956633.

82. Leaf A, Albert CM, Josephson M, et al. Prevention of fatal arrhythmias in high-risk subjects by fish oil n-3 fatty acid intake. Circulation. 2005 Nov 1;112(18):2762-8. PMID: 16267249.

83. Albert CM, Oh K, Whang W, et al. Dietary alphalinolenic acid intake and risk of sudden cardiac death and coronary heart disease. Circulation. 2005 Nov 22;112(21):3232-8. PMID: 16301356.

84. Iso H, Kobayashi M, Ishihara J, et al. Intake of fish and n3 fatty acids and risk of coronary heart disease among Japanese: the Japan Public Health Center-Based (JPHC) Study Cohort I. Circulation. 2006 Jan 17;113(2):195-202. PMID: 16401768.

85. Rasmussen BM, Vessby B, Uusitupa M, et al. Effects of dietary saturated, monounsaturated, and n-3 fatty acids on blood pressure in healthy subjects. Am J Clin Nutr. 2006 Feb;83(2):221-6. PMID: 16469978.

86. Brouwer IA, Heeringa J, Geleijnse JM, et al. Intake of very long-chain n-3 fatty acids from fish and incidence of atrial fibrillation. The Rotterdam Study. Am Heart J. 2006 Apr;151(4):857-62. PMID: 16569549.

87. Brouwer IA, Zock PL, Camm AJ, et al. Effect of fish oil on ventricular tachyarrhythmia and death in patients with implantable cardioverter defibrillators: the Study on Omega-3 Fatty Acids and Ventricular Arrhythmia (SOFA) randomized trial. JAMA. 2006 Jun 14;295(22):2613-9. PMID: 16772624.

88. Hjerkinn EM, Abdelnoor M, Breivik L, et al. Effect of diet or very long chain omega-3 fatty acids on progression of atherosclerosis, evaluated by carotid plaques, intima-media thickness and by pulse wave propagation in elderly men with hypercholesterolaemia. Eur J Cardiovasc Prev Rehabil. 2006 Jun;13(3):325-33. PMID: 16926660.

89. Burr ML. Secondary prevention of CHD in UK men: the Diet and Reinfarction Trial and its sequel. Proc Nutr Soc. 2007 Feb;66(1):9-15. PMID: 17343767.

90. Yokoyama M, Origasa H, Matsuzaki M, et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. Lancet. 2007 Mar 31;369(9567):1090-8. PMID: 17398308.

91. Davidson MH, Stein EA, Bays H, et al. Efficacy and tolerability of adding prescription omega-3 fatty acids 4 g/d to simvastatin 40 mg/d in hypertriglyceridemic patients: an 8-week, randomized, double-blind, placebo-controlled study. Clin Ther. 2007 Jul;29(7):1354-67. PMID: 17825687.

92. Marchioli R, Marfisi RM, Borrelli G, et al. Efficacy of n-3 polyunsaturated fatty acids according to clinical characteristics of patients with recent myocardial infarction: insights from the GISSI-Prevenzione trial. J Cardiovascular Med (Hagerstown). 2007 Sep;8 Suppl 1:S34-7. PMID: 17876196.

93. Tanaka K, Ishikawa Y, Yokoyama M, et al. Reduction in the recurrence of stroke by eicosapentaenoic acid for hypercholesterolemic patients: subanalysis of the JELIS trial. Stroke; a journal of cerebral circulation. 2008 Jul;39(7):2052-8. PMID: 18451347.

94. Damsgaard CT, Frokiaer H, Andersen AD, Lauritzen L. Fish oil in combination with high or low intakes of linoleic acid lowers plasma triacylglycerols but does not affect other cardiovascular risk markers in healthy men. J Nutr. 2008 Jun;138(6):1061-6. PMID: 18492834.

95. Warensjo E, Sundstrom J, Vessby B, et al. Markers of dietary fat quality and fatty acid desaturation as predictors of total and cardiovascular mortality: a population-based prospective study. Am J Clin Nutr. 2008 Jul;88(1):203-9. PMID: 18614742.

96. Tavazzi L, Maggioni AP, Marchioli R, et al. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet. 2008 Oct 4;372(9645):1223-30. PMID: 18757090.

97. Caslake MJ, Miles EA, Kofler BM, et al. Effect of sex and genotype on cardiovascular biomarker response to fish oils: the FINGEN Study. Am J Clin Nutr. 2008 Sep;88(3):618-29. PMID: 18779276.

98. Yamagishi K, Iso H, Date C, et al. Fish, omega-3 polyunsaturated fatty acids, and mortality from cardiovascular diseases in a nationwide community-based cohort of Japanese men and women the JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk) Study. J Am Coll Cardiol. 2008 Sep 16;52(12):988-96. PMID: 18786479.

99. Holman RR, Paul S, Farmer A, Tucker L, Stratton IM, Neil HA. Atorvastatin in Factorial with Omega-3 EE90 Risk Reduction in Diabetes (AFORRD): a randomised controlled trial. Diabetologia. 2009 Jan;52(1):50-9. PMID: 19002433.

100. Yamagishi K, Nettleton JA, Folsom AR. Plasma fatty acid composition and incident heart failure in middle-aged adults: the Atherosclerosis Risk in Communities (ARIC) Study. Am Heart J. 2008 Nov;156(5):965-74. PMID: 19061714.

101. Virtanen JK, Mozaffarian D, Chiuve SE, Rimm EB. Fish consumption and risk of major chronic disease in men. Am J Clin Nutr. 2008 Dec;88(6):1618-25. PMID: 19064523.

102. Levitan EB, Wolk A, Mittleman MA. Fish consumption, marine omega-3 fatty acids, and incidence of heart failure: a population-based prospective study of middle-aged and elderly men. Eur Heart J. 2009 Jun;30(12):1495-500. PMID: 19383731.

103. Derosa G, Maffioli P, D'Angelo A. Effects of long chain omega-3 fatty acids on metalloproteinases and their inhibitors in combined dyslipidemia patients. Expert Opin Pharmacother. 2009 Jun;10(8):1239-47. PMID: 19397392.

104. Marchioli R, Levantesi G, Silletta MG. Effect of n-3 polyunsaturated fatty acids and rosuvastatin in patients with heart failure: results of the GISSI-HF trial. Expert Rev Cardiovasc Ther. 2009 Jul;7(7):735-48. PMID: 19589110.

105. Ebrahimi M, Ghayour-Mobarhan M, Rezaiean S, et al. Omega-3 fatty acid supplements improve the cardiovascular risk profile of subjects with metabolic syndrome, including markers of inflammation and auto-immunity. Acta cardiologica. 2009 Jun;64(3):321-7. PMID: 19593941.

106. Troseid M, Arnesen H, Hjerkinn EM, Seljeflot I. Serum levels of interleukin-18 are reduced by diet and n-3 fatty acid intervention in elderly high-risk men. Metabolism: clinical and experimental. 2009 Nov;58(11):1543-9. PMID: 19595382.

107. Olano-Martin E, Anil E, Caslake M. Contribution of apolipoprotein E genotype and docosahexaenoic acid to the LDL-cholesterol response to fish oil. Atherosclerosis. 2010 Mar;209(1):104-10. PMID: 19748619.

108. Dijkstra SC, Brouwer IA, van Rooij FJ, et al. Intake of very long chain n-3 fatty acids from fish and the incidence of heart failure: the Rotterdam Study. Eur J Heart Failure. 2009 Oct;11(10):922-8. PMID: 19789394.

109. Joensen AM, Schmidt EB, Dethlefsen C, et al. Dietary intake of total marine n-3 polyunsaturated fatty acids, eicosapentaenoic acid, docosahexaenoic acid and docosapentaenoic acid and the risk of acute coronary syndrome - a cohort study. Br J Nutr. 2010 Feb;103(4):602-7. PMID: 19825219.

110. Virtanen JK, Mursu J, Voutilainen S, Tuomainen TP. Serum long-chain n-3 polyunsaturated fatty acids and risk of hospital diagnosis of atrial fibrillation in men. Circulation. 2009 Dec 8;120(23):2315-21. PMID: 19933935.

111. Berry JD, Prineas RJ, van Horn L, et al. Dietary fish intake and incident atrial fibrillation (from the Women's Health Initiative). Am J Cardiol. 2010 Mar 15;105(6):844-8. PMID: 20211329.

112. Levitan EB, Wolk A, Mittleman MA. Fatty fish, marine omega-3 fatty acids and incidence of heart failure. Eur J Clin Nutr. 2010 Jun;64(6):587-94. PMID: 20332801.

113. de Goede J, Geleijnse JM, Boer JM, et al. Marine (n-3) fatty acids, fish consumption, and the 10-year risk of fatal and nonfatal coronary heart disease in a large population of Dutch adults with low fish intake. J Nutr. 2010 May;140(5):1023-8. PMID: 20335635.

114. Geleijnse JM, Giltay EJ, Schouten EG, et al. Effect of low doses of n-3 fatty acids on cardiovascular diseases in 4,837 post-myocardial infarction patients: design and baseline characteristics of the Alpha Omega Trial. Am Heart J. 2010 Apr;159(4):539-46 e2. PMID: 20362710.

115. Einvik K, Klemsdal TO, Sandvik L, Hjerkinn EM. A randomized clinical trial on n-3 polyunsaturated fatty acids supplementation and all-cause mortality in elderly men at high cardiovascular risk. Eur J Cardiovasc Prev Rehabil 2010 Oct;17(5):588-92. PMID: 20389249.

116. Maki KC, Dicklin MR, Davidson MH, et al. Baseline lipoprotein lipids and low-density lipoprotein cholesterol response to prescription omega-3 acid ethyl ester added to Simvastatin therapy. Am J Cardiol. 2010 May 15;105(10):1409-12. PMID: 20451686.

117. Ishikawa Y, Yokoyama M, Saito Y, et al. Preventive effects of eicosapentaenoic acid on coronary artery disease in patients with peripheral artery disease. Circ J. 2010 Jul;74(7):1451-7. PMID: 20484828.

118. Wang L, Manson JE, Forman JP, et al. Dietary fatty acids and the risk of hypertension in middle-aged and older women. Hypertension. 2010 Oct;56(4):598-604. PMID: 20713915.

119. Kromhout D, Giltay EJ, Geleijnse JM. n-3 fatty acids and cardiovascular events after myocardial infarction. N Engl J Med. 2010 Nov 18;363(21):2015-26. PMID: 20929341.

120. Tierney AC, McMonagle J, Shaw DI, et al. Effects of dietary fat modification on insulin sensitivity and on other risk factors of the metabolic syndrome--LIPGENE: a European randomized dietary intervention study. Int J Obes (Lond). 2011 Jun;35(6):800-9. PMID: 20938439.

121. Rauch B, Schiele R, Schneider S, et al. OMEGA, a randomized, placebo-controlled trial to test the effect of highly purified omega-3 fatty acids on top of modern guideline-adjusted therapy after myocardial infarction. Circulation. 2010 Nov 23;122(21):2152-9. PMID: 21060071.

122. Itakura H, Yokoyama M, Matsuzaki M, et al. Relationships between plasma fatty acid composition and coronary artery disease. J Atheroscler Thromb. 2011;18(2):99-107. PMID: 21099130.

123. Galan P, Kesse-Guyot E, Czernichow S, et al. Effects of B vitamins and omega 3 fatty acids on cardiovascular diseases: a randomised placebo controlled trial. BMJ (Clinical research ed). 2010;341:c6273. PMID: 21115589.

124. Xun P, Hou N, Daviglus M, et al Fish oil, selenium and mercury in relation to incidence of hypertension: a 20-year follow-up study. J Intern Med. 2011 Aug;270(2):175-86. PMID: 21205024.

125. Nodari S, Triggiani M, Campia U, et al. Effects of n-3 polyunsaturated fatty acids on left ventricular function and functional capacity in patients with dilated cardiomyopathy. J Am Coll Cardiol. 2011 Feb 15;57(7):870-9. PMID: 21215550.

126. Woodward M, Tunstall-Pedoe H, Batty GD, et al. The prognostic value of adipose tissue fatty acids for incident cardiovascular disease: results from 3944 subjects in the Scottish Heart Health Extended Cohort Study. Eur Heart J. 2011 Jun;32(11):1416-23. PMID: 21345851.

127. de Goede J, Verschuren WM, Boer JM, et al. Alphalinolenic acid intake and 10-year incidence of coronary heart disease and stroke in 20,000 middle-aged men and women in the Netherlands. PloS One. 2011;6(3):e17967. PMID: 21464993.

128. Carrepeiro MM, Rogero MM, Bertolami MC, et al. Effect of n-3 fatty acids and statins on oxidative stress in statin-treated hypercholestorelemic and normocholesterolemic women. Atherosclerosis. 2011 Jul;217(1):171-8. PMID: 21561620.

129. Belin RJ, Greenland P, Martin L, et al. Fish intake and the risk of incident heart failure: the Women's Health Initiative. Circ Heart Fail. 2011 Jul;4(4):404-13. PMID: 21610249.

130. Wang L, Tsai M, Manson JE, et al. Erythrocyte fatty acid composition is associated with the risk of hypertension in middle-aged and older women. J Nutr. 2011 Sep;141(9):1691-7. PMID: 21734059.

131. Szabo de Edelenyi F, Vergnaud AC, Ahluwalia N, et al. Effect of B-vitamins and n-3 PUFA supplementation for 5 years on blood pressure in patients with CVD. Br J Nutr. 2012 Mar;107(6):921-7. PMID: 21801476.

132. Mozaffarian D, Lemaitre RN, King IB, et al. Circulating long-chain omega-3 fatty acids and incidence of congestive heart failure in older adults: the cardiovascular health study: a cohort study. Ann Intern Med. 2011 Aug 2;155(3):160-70. PMID: 21810709.

133. Nodari S, Triggiani M, Campia U, et al. n-3 polyunsaturated fatty acids in the prevention of atrial fibrillation recurrences after electrical cardioversion: a prospective, randomized study. Circulation. 2011 Sep 6;124(10):1100-6. PMID: 21844082.

134. Joensen AM, Overvad K, Dethlefsen C, et al. Marine n-3 polyunsaturated fatty acids in adipose tissue and the risk of acute coronary syndrome. Circulation. 2011 Sep 13;124(11):1232-8. PMID: 21859970.

135. Vedtofte MS, Jakobsen MU, Lauritzen L, Heitmann BL. Dietary alphalinolenic acid, linoleic acid, and n-3 long-chain PUFA and risk of ischemic heart disease. Am J Clin Nutr. 2011 Oct;94(4):1097-103. PMID: 21865326.

136. Sanders TA, Hall WL, Maniou Z. Effect of low doses of long-chain n-3 PUFAs on endothelial function and arterial stiffness: a randomized controlled trial. Am J Clin Nutr. 2011 Oct;94(4):973-80. PMID: 21865334.

137. Strom M, Halldorsson TI, Mortensen EL, Torp-Pedersen C, Olsen SF. Fish, n-3 fatty acids, and cardiovascular diseases in women of reproductive age: a prospective study in a large national cohort. Hypertension. 2012 Jan;59(1):36-43. PMID: 22146511.

138. Levitan EB, Wolk A, Hakansson N, Mittleman MA. Alphalinolenic acid, linoleic acid and heart failure in women. Br J Nutr. 2012 Oct;108(7):1300-6. PMID: 22172525.

139. Larsson SC, Virtamo J, Wolk A. Dietary fats and dietary cholesterol and risk of stroke in women. Atherosclerosis. 2012 Mar;221(1):282-6. PMID: 22265275.

140. Wu JH, Lemaitre RN, King IB, et al. Association of plasma phospholipid long-chain omega-3 fatty acids with incident atrial fibrillation in older adults: the cardiovascular health study. Circulation. 2012 Mar 6;125(9):1084-93. PMID: 22282329.

141. Eussen SR, Geleijnse JM, Giltay EJ, et al. Effects of n-3 fatty acids on major cardiovascular events in statin users and non-users with a history of myocardial infarction. Eur Heart J. 2012 Jul;33(13):1582-8. PMID: 22301766.

142. Blacher J, Czernichow S, Paillard F, Ducimetiere P, Hercberg S, Galan P. Cardiovascular effects of B-vitamins and/or N-3 fatty acids: the SU.FOL.OM3 trial. Int J Cardiol. 2013 Jul 31;167(2):508-13. PMID: 22365647.

143. de Goede J, Verschuren WM, Boer JM, Kromhout D, Geleijnse JM. Gender-specific associations of marine n-3 fatty acids and fish consumption with 10-year incidence of stroke. PloS One. 2012;7(4):e33866. PMID: 22496770.

144. Gronroos NN, Chamberlain AM, Folsom AR, et al. Fish, fish-derived n-3 fatty acids, and risk of incident atrial fibrillation in the Atherosclerosis Risk in Communities (ARIC) study. PloS One. 2012;7(5):e36686. PMID: 22570739.

145. De Goede J, Verschuren WM, Boer JM, et al. N-6 and n-3 fatty acid cholesteryl esters in relation to incident stroke in a Dutch adult population: a nested case-control study. Nutr Metab Cardiovasc Dis. 2013 Aug;23(8):737-43. PMID: 22633188.

146. Bosch J, Gerstein HC, Dagenais G, et al. n-3 fatty acids and cardiovascular outcomes in patients with dysglycemia. N Engl J Med. 2012 Jul 26;367(4):309-18. PMID: 22686415.

147. Carter JR, Schwartz CE, Yang H, Joyner MJ. Fish oil and neurovascular control in humans. Am J Physiol Heart Circ Physiol. 2012 Aug 15;303(4):H450-6. PMID: 22707560.

148. Lemaitre RN, Sitlani C, Song X, et al. Circulating and dietary alphalinolenic acid and incidence of congestive heart failure in older adults: the Cardiovascular Health Study. Am J Clin Nutr. 2012 Aug;96(2):269-74. PMID: 22743310.

149. Khaw KT, Friesen MD, Riboli E, Luben R, Wareham N. Plasma phospholipid fatty acid concentration and incident coronary heart disease in men and women: the EPIC-Norfolk prospective study. PLoS Med. 2012;9(7):e1001255. PMID: 22802735.

150. Earnest CP, Kupper JS, Thompson AM, Guo W, Church T. Complementary effects of multivitamin and omega-3 fatty acid supplementation on indices of cardiovascular health in individuals with elevated homocysteine. Int J Vitam Nutr Res. 2012 Feb;82(1):41-52. PMID: 22811376.

151. Ballantyne CM, Bays HE, Kastelein JJ, et al. Efficacy and safety of eicosapentaenoic acid ethyl ester (AMR101) therapy in statin-treated patients with persistent high triglycerides (from the ANCHOR study). Am J Cardiol. 2012 Oct 1;110(7):984-92. PMID: 22819432.

152. Baxheinrich A, Stratmann B, Lee-Barkey YH, et al. Effects of a rapeseed oil-enriched hypoenergetic diet with a high content of alphalinolenic acid on body weight and cardiovascular risk profile in patients with the metabolic syndrome. Br J Nutr. 2012 Aug;108(4):682-91. PMID: 22894911.

153. Wilk JB, Tsai MY, Hanson NQ, Gaziano JM, Djousse L. Plasma and dietary omega-3 fatty acids, fish intake, and heart failure risk in the Physicians' Health Study. Am J Clin Nutr. 2012 Oct;96(4):882-8. PMID: 22952185.

154. Hara M, Sakata Y, Nakatani D, et al. Low levels of serum n-3 polyunsaturated fatty acids are associated with worse heart failure-free survival in patients after acute myocardial infarction. Circ J. 2013;77(1):153-62. PMID: 23047296.

155. Matsumoto C, Matthan NR, Wilk JB, et al. Erythrocyte stearidonic acid and other n-3 fatty acids and CHD in the Physicians' Health Study. Br J Nutr. 2013 Jun;109(11):2044-9. PMID: 23098619.

156. Vecka M, Dusejovska M, Stankova B, et al. N-3 polyunsaturated fatty acids in the treatment of atherogenic dyslipidemia. Neuro Endocrinol Lett. 2012;33 Suppl 2:87-92. PMID: 23183517.

157. Macchia A, Grancelli H, Varini S, et al. Omega-3 fatty acids for the prevention of recurrent symptomatic atrial fibrillation: results of the FORWARD (Randomized Trial to Assess Efficacy of PUFA for the Maintenance of Sinus Rhythm in Persistent Atrial Fibrillation) trial. J Am Coll Cardiol. 2013 Jan 29;61(4):463-8. PMID: 23265344.

158. Fretts AM, Mozaffarian D, Siscovick DS, et al. Associations of plasma phospholipid and dietary alphalinolenic acid with incident atrial fibrillation in older adults: the Cardiovascular Health Study. J Am Heart Assoc. 2013 Feb;2(1):e003814. PMID: 23525429.

159. Mozaffarian D, Lemaitre RN, King IB, et al. Plasma phospholipid long-chain omega-3 fatty acids and total and cause-specific mortality in older adults: a cohort study. Ann Intern Med. 2013 Apr 2;158(7):515-25. PMID: 23546563.

160. Roncaglioni MC, Tombesi M, Avanzini F, et al. n-3 fatty acids in patients with multiple cardiovascular risk factors. N Engl J Med. 2013 May 9;368(19):1800-8. PMID: 23656645.

161. Tatsuno I, Saito Y, Kudou K, Ootake J. Efficacy and safety of TAK-085 compared with eicosapentaenoic acid in Japanese subjects with hypertriglyceridemia undergoing lifestyle modification: the omega-3 fatty acids randomized double-blind (ORD) study. J Clin Lipidol. 2013 May-Jun;7(3):199-207. PMID: 23725919.

162. Takata Y, Zhang X, Li H, et al. Fish intake and risks of total and cause-specific mortality in 2 population-based cohort studies of 134,296 men and women. Am J Epidemiol. 2013 Jul 1;178(1):46-57. PMID: 23788668.

163. Aleksova A, Masson S, Maggioni AP, et al. n-3 polyunsaturated fatty acids and atrial fibrillation in patients with chronic heart failure: the GISSI-HF trial. Eur J Heart Failure. 2013 Nov;15(11):1289-95. PMID: 23839902.

164. Yamagishi KF, A. R.; Steffen, L. M. Plasma fatty acid composition and incident ischemic stroke in middle-aged adults: the Atherosclerosis Risk in Communities (ARIC) Study. Cerebrovascular diseases (Basel, Switzerland). 2013;36(1):38-46. PMID: 23920478.

165. Rix TA, Joensen AM, Riahi S, et al. Marine n-3 fatty acids in adipose tissue and development of atrial fibrillation: a Danish cohort study. Heart (British Cardiac Society). 2013 Oct;99(20):1519-24. PMID: 23945170.

166. Maki KC, Orloff DG, Nicholls SJ, et al. A highly bioavailable omega-3 free fatty acid formulation improves the cardiovascular risk profile in high-risk, statin-treated patients with residual hypertriglyceridemia (the ESPRIT trial). Clin Ther. 2013 Sep;35(9):1400-11 e1-3. PMID: 23998969.

167. Rodriguez-Leyva D, Weighell W, Edel A, et al. Potent antihypertensive action of dietary flaxseed in hypertensive patients. Hypertension. 2013 Dec;62(6):1081-9. PMID: 24126178.

168. Ninomiya T, Nagata M, Hata J, et al. Association between ratio of serum eicosapentaenoic acid to arachidonic acid and risk of cardiovascular disease: the Hisayama Study. Atherosclerosis. 2013 Dec;231(2):261-7. PMID: 24267237.

169. Tatsuno I, Saito Y, Kudou K, Ootake J. Long-term safety and efficacy of TAK-085 in Japanese subjects with hypertriglyceridemia undergoing lifestyle modification: the omega-3 fatty acids randomized long-term (ORL) study. J Clin Lipidol. 2013 Nov-Dec;7(6):615-25. PMID: 24314359.

170. Koh AS, Pan A, Wang R, et al. The association between dietary omega-3 fatty acids and cardiovascular death: the Singapore Chinese Health Study. Eur J Prev Cardiol. 2015 Mar;22(3):364-72. PMID: 24343844.

171. de Oliveira Otto MC, Wu JH, Baylin A, et al. Circulating and dietary omega-3 and omega-6 polyunsaturated fatty acids and incidence of CVD in the Multi-Ethnic Study of Atherosclerosis. J Am Heart Assoc. 2013 Dec;2(6):e000506. PMID: 24351702.

172. Amiano P, Machon M, Dorronsoro M, et al. Intake of total omega-3 fatty acids, eicosapentaenoic acid and docosahexaenoic acid and risk of coronary heart disease in the Spanish EPIC cohort study. Nutr Metab Cardiovasc Dis. 2014 Mar;24(3):321-7. PMID: 24360762.

173. Grieger JA, Miller MD, Cobiac L. Investigation of the effects of a high fish diet on inflammatory cytokines, blood pressure, and lipids in healthy older Australians. Food Nutr Res. 2014 Jan 15;58. PMID: 24454276.

174. Vazquez C, Botella-Carretero JI, Corella D, et al. White fish reduces cardiovascular risk factors in patients with metabolic syndrome: the WISH-CARE study, a multicenter randomized clinical trial. Nutr Metab Cardiovasc Dis. 2014 Mar;24(3):328-35. PMID: 24462043.

175. Miyagawa N, Miura K, Okuda N, et al. Long-chain n-3 polyunsaturated fatty acids intake and cardiovascular disease mortality risk in Japanese: a 24-year follow-up of NIPPON DATA80. Atherosclerosis. 2014 Feb;232(2):384-9. PMID: 24468152.

176. Bell GA, Kantor ED, Lampe JW, et al. Intake of long-chain omega-3 fatty acids from diet and supplements in relation to mortality. Am J Epidemiol. 2014 Mar 15;179(6):710-20. PMID: 24496442.

177. Kastelein JJ, Maki KC, Susekov A, et al. Omega-3 free fatty acids for the treatment of severe hypertriglyceridemia: the EpanoVa fOr Lowering Very high triglyceridEs (EVOLVE) trial. J Clin Lipidol. 2014 Jan-Feb;8(1):94-106. PMID: 24528690.

178. Kuhnt K, Fuhrmann C, Kohler M, et al. Dietary echium oil increases long-chain n-3 PUFAs, including docosapentaenoic acid, in blood fractions and alters biochemical markers for cardiovascular disease independently of age, sex, and metabolic syndrome. J Nutr. 2014 Apr;144(4):447-60. PMID: 24553695.

179. Soares TS, Piovesan CH, Gustavo Ada S, et al. Alimentary habits, physical activity, and Framingham global risk score in metabolic syndrome. Arq Bras Cardiol. 2014 Apr;102(4):374-82. PMID: 24652053.

180. Jones PJ, Senanayake VK, Pu S, et al. DHA-enriched high-oleic acid canola oil improves lipid profile and lowers predicted cardiovascular disease risk in the canola oil multicenter randomized controlled trial. Am J Clin Nutr. 2014 Jul;100(1):88-97. PMID: 24829493.

181. Vedtofte MS, Jakobsen MU, Lauritzen L, et al. Association between the intake of alphalinolenic acid and the risk of CHD. Br J Nutr. 2014 Sep 14;112(5):735-43. PMID: 24964401.

182. Zeng FF, Sun LL, Liu YH, et al. Higher erythrocyte n-3 PUFAs are associated with decreased blood pressure in middle-aged and elderly Chinese adults. J Nutr. 2014 Aug;144(8):1240-6. PMID: 24966412.

183. Hellstrand S, Ericson U, Gullberg B, et al. Genetic variation in FADS1 has little effect on the association between dietary PUFA intake and cardiovascular disease. J Nutr. 2014 Sep;144(9):1356-63. PMID: 25008580.

184. Ras RT, Demonty I, Zebregs YE, et al. Low doses of eicosapentaenoic acid and docosahexaenoic acid from fish oil dose-dependently decrease serum triglyceride concentrations in the presence of plant sterols in hypercholesterolemic men and women. J Nutr. 2014 Oct;144(10):1564-70. PMID: 25122648.

185. Oh PC, Koh KK, Sakuma I, et al. Omega-3 fatty acid therapy dose-dependently and significantly decreased triglycerides and improved flow-mediated dilation, however, did not significantly improve insulin sensitivity in patients with hypertriglyceridemia. Int J Cardiol. 2014 Oct 20;176(3):696-702. PMID: 25147070.

186. Fretts AM, Mozaffarian D, Siscovick DS, et al. Plasma phospholipid and dietary alphalinolenic acid, mortality, CHD and stroke: the Cardiovascular Health Study. Br J Nutr. 2014 Oct 14;112(7):1206-13. PMID: 25159901.

187. Shaikh NA, Yantha J, Shaikh S, et al. Efficacy of a unique omega-3 formulation on the correction of nutritional deficiency and its effects on cardiovascular disease risk factors in a randomized controlled VASCAZEN((R)) REVEAL Trial. Molecular and cellular biochemistry. 2014 Nov;396(1-2):9-22. PMID: 25185754.

188. Pieters DJ, Mensink RP. Effects of stearidonic acid on serum triacylglycerol concentrations in overweight and obese subjects: a randomized controlled trial. Eur J Clin Nutr. 2015 Jan;69(1):121-6. PMID: 25226826.

189. Tardivo AP, Nahas-Neto J, Orsatti CL, et al. Effects of omega-3 on metabolic markers in postmenopausal women with metabolic syndrome. Climacteric. 2015 Apr;18(2):290-8. PMID: 25394692.

190. Pase MP, Grima N, Cockerell R, et al. The effects of long-chain omega-3 fish oils and multivitamins on cognitive and cardiovascular function: a randomized, controlled clinical trial. J Am Coll Nutr. 2015;34(1):21-31. PMID: 25565485.

191. Bergkvist C, Berglund M, Glynn A, et al. Dietary exposure to polychlorinated biphenyls and risk of myocardial infarction - a population-based prospective cohort study. Int J Cardiol. 2015 Mar 15;183:242-8. PMID: 25679993.

192. Edel AL, Rodriguez-Leyva D, Maddaford TG, et al. Dietary flaxseed independently lowers circulating cholesterol and lowers it beyond the effects of cholesterol-lowering medications alone in patients with peripheral artery disease. J Nutr. 2015 Apr;145(4):749-57. PMID: 25694068.

193. Kromhout D, Geleijnse JM, de Goede J, et al. n-3 fatty acids, ventricular arrhythmia-related events, and fatal myocardial infarction in postmyocardial infarction patients with diabetes. Diabetes care. 2011 Dec;34(12):2515-20. PMID: 22110169.

194. Oh R. Practical applications of fish oil (Omega-3 fatty acids) in primary care. J Am Board Fam Pract. 2005 Jan-Feb;18(1):28-36. PMID: 15709061.

195. Brinton EA, Ballantyne CM, Bays HE, et al. Effects of icosapent ethyl on lipid and inflammatory parameters in patients with diabetes mellitus-2, residual elevated triglycerides (200-500 mg/dL), and on statin therapy at LDL-C goal: the ANCHOR study. Cardiovasc Diabetol. 2013;12:100. PMID: 23835245.

196. Mozaffarian D, Wu JH. Omega-3 fatty acids and cardiovascular disease: effects on risk factors, molecular pathways, and clinical events. J Am Coll Cardiol. 2011 Nov 8;58(20):2047-67. PMID: 22051327.

197. Yakoot M. Vitamin e and omega-3: what to believe: observational studies or randomized controlled trials? Heart views. 2012 Apr;13(2):66-8. PMID: 22919450.

Abbreviations

AA	arachidonic acid
AE	adverse event
Abnl	abnormal
ACEi	angiotensin-converting enzyme inhibitor
ACS	acute coronary syndrome
AFib	atrial fibrillation
AHRQ	Agency for Healthcare Research and Quality
AIC	Akaike information criterion (estimation of fit of regression with spline)
ALA	alphalinolenic acid
ARB	angiotensin receptor blocker
BP	blood pressure
CABG	coronary artery bypass grafting
CHD	coronary heart disease
CHF	congestive heart failure
CI	confidence interval
CKD	chronic kidney disease
CMS	cardiometabolic syndrome
Ctrl	control
CVA	cerebrovascular accident (stroke)
CV	cardiovascular
CVD	cardiovascular disease
DBP	diastolic blood pressure
DHA	docosahexaenoic acid
DM	diabetes mellitus
DPA	docosapentaenoic acid
eGFR	epidermal growth factor receptor
EPA	eicosapentaenoic acid
E:D	EPA to DHA ratio
EPC	Evidence-based Practice Centers
ES	effect size
FA	fatty acid(s)
F/up	followup
FFQ	food frequency questionnaire
GI	gastrointestinal
HDL-c	high density lipoprotein cholesterol
HR	hazard ratio
HTN	hypertension
Int	intervention
LA	linoleic acid
LDL-c	low density lipoprotein cholesterol
LVEF	left ventricular ejection fraction
MACE	major adverse cardiovascular events
MAP	mean arterial blood pressure
MI	myocardial infarction
MUFA	monounsaturated fatty acid
n-3 FA	omega−3 fatty acid(s)
n6:3	omega-6 to omega-3 fatty acid ratio
n-6 FA	omega−6 fatty acid(s)

n/N	number with outcome/number analyzed
NA	not applicable
ND	no data
NYHA	New York Heart Association class
Obs	observational study
ODS	Office of Dietary Supplements
OR	odds ratio
PAD	peripheral artery disease
PCI	percutaneous coronary intervention
PCTA	percutaneous transluminal coronary angioplasty
PPFA	plasma polyunsaturated fatty acids
PUFA	polyunsaturated fatty acids
RBC	red blood cell
RCT	randomized controlled trial
RD	risk difference
RR	relative risk
SBP	systolic blood pressure
SCD	sudden cardiac death
SDA	stearidonic acid
SFA	saturated fatty acid
SoE	Strength of Evidence
TEP	Technical Expert Panel
Tg	triglycerides
TOO	task order officer

Appendix A. Search Strategy

Table A-1. Primary update of omega-3 fatty acid and CVD search in Ovid

For outcomes included in original omega-3 fatty acid and CVD report
Limited to 2002-2015. Search run on June 8, 2015.
Databases: MEDLINE®, Cochrane Central Trials Registry® and Cochrane Database of Systematic Reviews®, CAB Abstracts®. All in Ovid.

#	Search	
1.	exp fatty acids, omega-3/	Omega 3 terms
2.	((omega-3 or omega 3 or omega3) and fatty acid$).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
3.	fatty acids, essential/	
4.	linolenic acids/	
5.	exp fish oils/	
6.	((n 3 or n3 or n-3) and (oil$ or pufa or fatty acid$ or omega 3)).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
7.	Docosahexaenoic Acids/	
8.	docosahexa?noic.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc] or docosapenta?noic.mp.	
9.	Eicosapentaenoic Acid/	
10.	eicosapenta?noic.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
11.	icosapent?enoic.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
12.	(alpha linolenic or alphalinolenic or alpha-linolenic).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
13.	(linolenate or cervonic or timnodonic or stearidonic).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
14.	menhaden oil$.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
15.	((flax or flaxseed or flax seed or linseed or rape seed or rapeseed or canola or soy or soybean or walnut or mustard seed or perilla or shiso) adj2 oil$).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
16.	(walnut$ or butternut$ or soybean$ or pumpkin seed$).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
17.	(fish adj2 oil$).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
18.	(cod liver oil$ or codliver oil$ or marine oil$ or marine fat$).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
19.	(salmon or mackerel or herring or tuna or halibut or seaweed or anchov$ or sardine$).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
20.	(Ropufa or MaxEPA or Omacor or Efamed or ResQ or Epagis or Almarin or Coromega or Lovaza or Vascepa or icosapent ethyl).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
21.	(fish consumption or fish intake or (fish adj2 diet$)).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
22.	(mediterranean adj diet$).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
23.	((red blood cell or phospholipid or plasma fatty acid or plasma or phospholipid or triacylglycerol or cholesteryl or ester or adipos$ or fatty acid or erythrocyte or ghost or platelet or granulocyte or neutrophil or mononuclear or LDL or HDL) and (DHA or docosahexa?noic or docosapenta?noic or EPA or eicosapenta?noic or SDA or linolenic or stearidonic or omega)).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	n-3 Biomarkers
24.	or/1-23	n-3
25.	exp cardiovascular diseases/	Cardiovascular diseases, risk factors, adverse events
26.	atherosclero$.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
27.	Arteriosclero$.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
28.	cardioprotect$.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
29.	Coronary.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
30.	heart disease$.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
31.	Myocardial infarct$.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
32.	exp Cerebrovascular Accident/	
33.	stroke.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
34.	(Transient Ischemic Attack or TIA).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
35.	exp lipids/	
36.	lipid$.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
37.	exp cholesterol/	
38.	cholesterol.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	

#	Search	
39.	exp Lipoproteins, LDL/	
40.	exp Lipoproteins, HDL/	
41.	exp triglycerides/	
42.	triglycerides.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
43.	exp Hyperlipidemias/	
44.	hypertriglyceridem$.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
45.	hyperlipidemia$.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
46.	exp dyslipidemias/	
47.	dyslipidemia$.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
48.	exp blood pressure/	
49.	blood pressure.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
50.	(diastol$ or systol$ or mean arterial).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
51.	exp hypertension/	
52.	hypertension.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
53.	exp Hemorrhage/	
54.	hemorrhag$.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
55.	bleeding.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
56.	or/25-55	
57.	24 and 56	n-3 & CVD
58.	(random$ or rct$).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	Study designs
59.	exp randomized controlled trials/	
60.	exp Randomized Controlled Trials as Topic/	
61.	exp random allocation/	
62.	exp double-blind method/	
63.	exp single-blind method/	
64.	randomized controlled trial.pt.	
65.	clinical trial.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
66.	(clin$ adj trial$).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
67.	((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
68.	exp placebos/	
69.	placebo$.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
70.	randomly allocated.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
71.	(allocated adj2 random$).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
72.	comparative study.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
73.	follow-up studies/	
74.	(follow up or followup).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
75.	exp case-control studies/	
76.	(case adj20 control).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
77.	exp longitudinal studies/	
78.	longitudinal.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
79.	exp cohort studies/	
80.	cohort.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
81.	exp prospective studies/	
82.	exp evaluation studies/	
83.	(observational adj (study or studies)).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
84.	Cross-Sectional Studies/	
85.	(cross section$ or cross-section$).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
86.	food frequency questionnaire$.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
87.	or/58-86	
88.	57 and 87	n-3, CVD, Designs
89.	limit 88 to (addresses or autobiography or bibliography or biography or case reports or comment or congresses or dictionary or directory or editorial or festschrift or government publications or historical article or interview or lectures or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index)	Not non-studies
90.	88 not 89	
91.	limit 90 to english language	Limits
92.	limit 91 to humans	

#	Search	
93.	(guidelines or practice guideline or meta analysis or systematic review).pt.	SRs, GLs
94.	(systematic$ adj3 review$).tw.	
95.	93 or 94	
96.	57 and 95	
97.	limit 96 to yr="2002 - 2015"	Non-SRs
98.	92 not 96	SRs
99.	limit 98 to yr="2002 - 2015"	

Table A-2. New search of omega-3 fatty acid and CVD for new outcomes in Ovid

For outcomes included in original omega-3 fatty acid and CVD report
Dates: 2000 to June 8, 2015.
Databases: MEDLINE®, Cochrane Central Trials Registry® and Cochrane Database of Systematic Reviews®, CAB Abstracts®. All in Ovid.

#	Search	
1.	exp fatty acids, omega-3/	
2.	((omega-3 or omega 3 or omega3) and fatty acid$).mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
3.	fatty acids, essential/	
4.	linolenic acids/	
5.	exp fish oils/	
6.	((n 3 or n3 or n-3) and (oil$ or pufa or fatty acid$ or omega 3)).mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
7.	Docosahexaenoic Acids/	
8.	docosahexa?noic.mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc] or docosapenta?noic.mp.	
9.	Eicosapentaenoic Acid/	
10.	eicosapenta?noic.mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
11.	icosapent?enoic.mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
12.	(alpha linolenic or alphalinolenic or alpha-linolenic).mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
13.	(linolenate or cervonic or timnodonic or stearidonic).mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
14.	menhaden oil$.mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
15.	((flax or flaxseed or flax seed or linseed or rape seed or rapeseed or canola or soy or soybean or walnut or mustard seed or perilla or shiso) adj2 oil$).mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
16.	(walnut$ or butternut$ or soybean$ or pumpkin seed$).mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
17.	(fish adj2 oil$).mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
18.	(cod liver oil$ or codliver oil$ or marine oil$ or marine fat$).mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
19.	(salmon or mackerel or herring or tuna or halibut or seaweed or anchov$ or sardine$).mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
20.	(Ropufa or MaxEPA or Omacor or Efamed or ResQ or Epagis or Almarin or Coromega or Lovaza or Vascepa or icosapent ethyl).mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
21.	(fish consumption or fish intake or (fish adj2 diet$)).mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
22.	(mediterranean adj diet$).mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
23.	((red blood cell or phospholipid or plasma fatty acid or plasma or phospholipid or triacylglycerol or cholesteryl or ester or adipos$ or fatty acid or erythrocyte or ghost or platelet or granulocyte or neutrophil or mononuclear or LDL or HDL) and (DHA or docosahexa?noic or Docosapenta?noic or EPA or eicosapenta?noic or SDA or linolenic or stearidonic or omega)).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
24.	or/1-23	
25.	(random$ or rct$).mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
26.	exp randomized controlled trials/	
27.	exp Randomized Controlled Trials as Topic/	
28.	exp random allocation/	
29.	exp double-blind method/	
30.	exp single-blind method/	
31.	randomized controlled trial.pt.	
32.	clinical trial.mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
33.	(clin$ adj trial$).mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
34.	((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
35.	exp placebos/	
36.	placebo$.mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
37.	randomly allocated.mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
38.	(allocated adj2 random$).mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
39.	comparative study.mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
40.	follow-up studies/	
41.	(follow up or followup).mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
42.	exp case-control studies/	
43.	(case adj20 control).mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
44.	exp longitudinal studies/	

45.	longitudinal.mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
46.	exp cohort studies/	
47.	cohort.mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
48.	exp prospective studies/	
49.	exp evaluation studies/	
50.	(observational adj (study or studies)).mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
51.	Cross-Sectional Studies/	
52.	(cross section$ or cross-section$).mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
53.	food frequency questionnaire$.mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
54.	or/25-53	
55.	24 and 54	
56.	exp heart failure/	
57.	Heart failure$.mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
58.	exp pulmonary edema/	
59.	pulmonary edema.mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
60.	pulmonary oedema.mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
61.	(ejection adj2 fraction).mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
62.	exp peripheral vascular diseases/	
63.	(peripheral and vascular and disease$).mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
64.	claudication.mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
65.	exp arrhythmias, cardiac/	
66.	(arrhythmi$ or Antiarrhythmi$).mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
67.	Fibrillation.mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
68.	Flutter.mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
69.	exp tachycardia/	
70.	tachycardia.mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
71.	tachyarrhythmia.mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
72.	exp bradycardia/	
73.	bradycardia.mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
74.	exp death, sudden/	
75.	(sudden adj death).mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
76.	or/56-75	
77.	24 and 54 and 76	
78.	limit 77 to (addresses or autobiography or bibliography or biography or case reports or comment or congresses or dictionary or directory or editorial or festschrift or government publications or historical article or interview or lectures or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index)	
79.	77 not 78	
80.	limit 79 to english language	
81.	limit 80 to humans	
82.	(guidelines or practice guideline or meta analysis or systematic review).pt.	
83.	(systematic$ adj3 review$).tw.	
84.	82 or 83	
85.	24 and 76 and 84	
86.	81 not 85	

Table A-3. Searches run in EMBASE®

All outcomes
Dates: 2000 to June 8, 2015.
EMBASE®

Search 1
fatty AND acids, AND essential OR essential AND fatty AND ('acids'/exp OR acids) OR (n AND 3 OR n3 OR 'n 3' AND (oil* OR pufa OR fatty AND acid* OR omega AND 3 OR omega3 OR 'omega 3')) OR docosahexa*noic OR docosapenta*noic OR eicosapenta*noic OR icosapent*enoic OR (alpha AND linolenic OR alphalinolenic OR 'alpha linolenic' OR linolenic AND acids) OR (linoleic AND acid) OR cervonic OR timnodonic OR stearidonic OR (flaxseed OR flax AND seed OR linseed OR rape AND seed OR rapeseed OR canola OR soy OR soybean OR walnut OR mustard AND seed OR perilla OR shiso OR menhaden OR fish AND oil*) OR (walnut* OR butternut* OR soybean* OR pumpkin AND seed*) OR (cod AND liver AND oil* OR codliver AND oil* OR marine AND oil* OR marine AND fat*) OR salmon OR mackerel OR herring OR tuna OR halibut OR seaweed OR anchov* OR sardine* OR (ropufa OR maxepa OR omacor OR efamed OR resq OR epagis OR almarin OR coromega OR lovaza OR vascepa OR icosapent AND ethyl) OR (fish AND consumption OR fish AND intake) OR fish NEAR/2 diet* OR Mediterranean NEAR/2 diet* OR (red AND blood AND cell OR phospholipid OR plasma AND fatty AND acid OR plasma OR phospholipid OR triacylglycerol OR cholesteryl OR ester OR adipos* OR fatty AND acid OR erythrocyte OR ghost OR platelet OR granulocyte OR neutrophil OR mononuclear OR ldl OR hdl AND (dha OR docosahexa?noic OR docosapenta?noic OR epa OR eicosapenta?noic OR sda OR linolenic OR stearidonic OR omega))
AND ('cardiovascular disease' OR atherosclero* OR arteriosclero* OR cardioprotect* OR (coronary OR heart AND disease* OR myocardial AND infarct*) OR (cerebrovascular AND accident) OR stroke.mp OR (transient AND ischemic AND attack) OR tia OR lipid* OR cholesterol OR 'low density lipoprotein' OR 'high density lipoprotein' OR hyperlipidemia* OR hypertriglyceridem* OR dyslipidemia* OR (blood AND pressure) OR (diastol* OR systol* OR mean AND arterial) OR hypertension OR hemorrhag* OR 'bleeding')
AND (randomized AND controlled AND trial OR 'randomization' OR 'single blind procedure' OR 'double blind procedure' OR 'crossover procedure' OR 'placebo' OR rct OR (random* AND allocat*) OR (single AND blind*) OR (double AND blind*) OR (treble OR triple) NEAR/2 blind* OR (prospective AND study) OR 'clinical study' OR 'case control study' OR 'longitudinal study' OR 'retrospective study' OR 'prospective study' OR 'cohort analysis' OR cohort NEAR/2 (study OR studies) OR (case AND control NEAR/2 (study OR studies)) OR (follow AND up NEAR/2 (study OR studies)) OR observational NEAR/2 (study OR studies) OR (food AND frequency AND questionnaire*)) NOT ('abstract report' OR 'case study' OR 'case report') AND [humans]/lim AND [english]/lim AND [2000-2014]/py

Search2
fatty AND acids, AND essential OR essential AND fatty AND ('acids'/exp OR acids) OR (n AND 3 OR n3 OR 'n 3' AND (oil* OR pufa OR fatty AND acid* OR omega AND 3 OR omega3 OR 'omega 3')) OR docosahexa*noic OR docosapenta*noic OR eicosapenta*noic OR icosapent*enoic OR (alpha AND linolenic OR alphalinolenic OR 'alpha linolenic' OR linolenic AND acids) OR (linoleic AND acid) OR cervonic OR timnodonic OR stearidonic OR (flaxseed OR flax AND seed OR linseed OR rape AND seed OR rapeseed OR canola OR soy OR soybean OR walnut OR mustard AND seed OR perilla OR shiso OR menhaden OR fish AND oil*) OR (walnut* OR butternut* OR soybean* OR pumpkin AND seed*) OR (cod AND liver AND oil* OR codliver AND oil* OR marine AND oil* OR marine AND fat*) OR salmon OR mackerel OR herring OR tuna OR halibut OR seaweed OR anchov* OR sardine* OR (ropufa OR maxepa OR omacor OR efamed OR resq OR epagis OR almarin OR coromega OR lovaza OR vascepa OR icosapent AND ethyl) OR (fish AND consumption OR fish AND intake) OR fish NEAR/2 diet* OR mediterranean NEAR/2 diet* OR (red AND blood AND cell OR phospholipid OR plasma AND fatty AND acid OR plasma OR phospholipid OR triacylglycerol OR cholesteryl OR ester OR adipos* OR fatty AND acid OR erythrocyte OR ghost OR platelet OR granulocyte OR neutrophil OR mononuclear OR ldl OR hdl AND (dha OR docosahexa?noic OR docosapenta?noic OR epa OR eicosapenta?noic OR sda OR linolenic OR stearidonic OR omega))

AND ('cardiovascular disease' OR atherosclero* OR arteriosclero* OR cardioprotect* OR (coronary OR heart AND disease* OR myocardial AND infarct*) OR (cerebrovascular AND accident) OR stroke.mp OR (transient AND ischemic AND attack) OR tia OR lipid* OR cholesterol OR 'low density lipoprotein' OR 'high density lipoprotein' OR hyperlipidemia* OR hypertriglyceridem* OR dyslipidemia* OR (blood AND pressure) OR (diastol* OR systol* OR mean AND arterial) OR hypertension OR hemorrhag* OR 'bleeding')
AND (randomized AND controlled AND trial OR 'randomization' OR 'single blind procedure' OR 'double blind procedure' OR 'crossover procedure' OR 'placebo' OR rct OR (random* AND allocat*) OR (single AND blind*) OR (double AND blind*) OR (treble OR triple) NEAR/2 blind* OR (prospective AND study) OR 'clinical study' OR 'case control study' OR 'longitudinal study' OR 'retrospective study' OR 'prospective study' OR 'cohort analysis' OR cohort NEAR/2 (study OR studies) OR (case AND control NEAR/2 (study OR studies)) OR (follow AND up NEAR/2 (study OR studies)) OR observational NEAR/2 (study OR studies) OR (food AND frequency AND questionnaire*)) NOT ('abstract report' OR 'case study' OR 'case report') AND [humans]/lim AND [english]/lim

Appendix B. Excluded Studies

Table B-1. Excluded studies

PMID	Authors	Title	Journal	Rejection Reason
none	L. F. Darghosian et al.	Effect of omega-three polyunsaturated fatty acids on inflammation, oxidative stress, and recurrence of atrial fibrillation	American Journal of Cardiology	<1 yr CVD
none	V. V. E. Lomivorotov and S. M.; Pokushalov and E. A.; Romanov and A. B.; Ponomarev and D. N.; Cherniavsky and A. M.; Shilova and A. N.; Karaskov and A. M.; Lomivorotov and V. N.	Randomized trial of fish oil infusion to prevent atrial fibrillation after cardiac surgery: data from an implantable continuous cardiac monitor		<1 yr CVD
23890856	Kumar S and Sutherland F and Stevenson I and Lee JM and Garg ML and Sparks PB	Effects of long-term omega-3 polyunsaturated fatty acid supplementation on paroxysmal atrial tachyarrhythmia burden in patients with implanted pacemakers: results from a prospective randomised study.	International Journal of Cardiology	<1 yr CVD
22128614	Sorice M1, Tritto FP, Sordelli C, Gregorio R, Piazza L.	N-3 polyunsaturated fatty acids reduces post-operative atrial fibrillation incidence in patients undergoing "on-pump" coronary artery bypass graft surgery.	Monaldi Arch Chest Dis.	<1 yr CVD
22120130	Kumar S and Sutherland F and Morton JB and Lee G and Morgan J and Wong J and Eccleston DE and Voukelatos J and Garg ML and Sparks PB	Long-term omega-3 polyunsaturated fatty acid supplementation reduces the recurrence of persistent atrial fibrillation after electrical cardioversion.	Heart Rhythm : The Official Journal of the Heart Rhythm Society	<1 yr CVD
21762871	Farquharson AL1, Metcalf RG, Sanders P, Stuklis R, Edwards JR, Gibson RA, Cleland LG, Sullivan TR, James MJ, Young GD.	Effect of dietary fish oil on atrial fibrillation after cardiac surgery.	Am J Cardiol.	<1 yr CVD
21078810	Kowey PR1, Reiffel JA, Ellenbogen KA, Naccarelli GV, Pratt CM.	Efficacy and safety of prescription omega-3 fatty acids for the prevention of recurrent symptomatic atrial fibrillation: a randomized controlled trial.	JAMA.	<1 yr CVD
21059740	Bianconi L1, Cal˜ L, Mennuni M, Santini L, Morosetti P, Azzolini P, Barbato G, Biscione F, Romano P, Santini M.	n-3 polyunsaturated fatty acids for the prevention of arrhythmia recurrence after electrical cardioversion of chronic persistent atrial fibrillation: a randomized, double-blind, multicentre study.	Europace.	<1 yr CVD
20061328	Heidarsdottir R1, Arnar DO, Skuladottir GV, Torfason B, Edvardsson V, Gottskalksson G, Palsson R, Indridason OS.	Does treatment with n-3 polyunsaturated fatty acids prevent atrial fibrillation after open heart surgery?	Europace.	<1 yr CVD
20042769	Saravanan P1, Bridgewater B, West AL, O'Neill SC, Calder PC, Davidson NC.	Omega-3 fatty acid supplementation does not reduce risk of atrial fibrillation after coronary artery bypass surgery: a randomized, double-blind, placebo-controlled clinical trial.		<1 yr CVD
19629889	Heidt MC1, Vician M, Stracke SK, Stadlbauer T, Grebe MT, Boening A, Vogt PR, Erdogan A.	Beneficial effects of intravenously administered N-3 fatty acids for the prevention of atrial fibrillation after coronary artery bypass surgery: a prospective randomized study.	Thorac Cardiovasc Surg.	<1 yr CVD
15253884	Singer P and Wirth M	Can n-3 PUFA reduce cardiac arrhythmias? Results of a clinical trial.	Prostaglandins, Leukotrienes, and Essential Fatty Acids	<1 yr CVD
12891211	Geelen A and Zock PL and Swenne CA and Brouwer IA and Schouten EG and Katan MB	Effect of n-3 fatty acids on heart rate variability and baroreflex sensitivity in middle-aged subjects.	American Heart Journal	<1 yr CVD

PMID	Authors	Title	Journal	Rejection Reason
11303007	Durrington PN1, Bhatnagar D, Mackness MI, Morgan J, Julier K, Khan MA, France M.	An omega-3 polyunsaturated fatty acid concentrate administered for one year decreased triglycerides in simvastatin treated patients with coronary heart disease and persisting hypertriglyceridaemia.	Heart.	<1 yr CVD
10334433	Johansen O, Brekke M, Seljeflot I, et al.	N-3 fatty acids do not prevent restenosis after coronary angioplasty: results from the CART study. Coronary Angioplasty Restenosis Trial.	J Am Coll Cardiol.	<1 yr CVD
8840843	Cairns JA., Gill J., Morton B., Roberts R., Gent M., Hirsh J., Holder D., Finnie K., Marquis JF., Naqvi S., Cohen E.	Fish oils and low-molecular-weight heparin for the reduction of restenosis after percutaneous transluminal coronary angioplasty. The EMPAR Study.	Circulation. 1996 Oct 1;94(7):1553-60.	<1 yr CVD
4161161	Borchgrevink, 1966	Absence of prophylactic effect of linolenic acid in patients with coronary heart-disease.	Lancet. 1966 Jul 23;2(7456):187-9.	<1 yr CVD
2568519	Reis GJ, Boucher TM, Sipperly ME, et al.	Randomised trial of fish oil for prevention of restenosis after coronary angioplasty	Lancet	<1 yr CVD
2537349	Grigg LE1, Kay TW, Valentine PA, Larkins R, Flower DJ, Manolas EG, O'Dea K, Sinclair AJ, Hopper JL, Hunt D.	Determinants of restenosis and lack of effect of dietary supplementation with eicosapentaenoic acid on the incidence of coronary artery restenosis after angioplasty.	J Am Coll Cardiol.	<1 yr CVD
21466598	Iggman D and Gustafsson IB and Berglund L and Vessby B and Marckmann P and Riserus U	Replacing dairy fat with rapeseed oil causes rapid improvement of hyperlipidaemia: a randomized controlled study.	Journal of Internal Medicine	<4 wk
15893193	Calo L and Bianconi L and Colivicchi F and Lamberti F and Loricchio ML and de Ruvo E and Meo A and Pandozi C and Staibano M and Santini M	N-3 Fatty acids for the prevention of atrial fibrillation after coronary artery bypass surgery: a randomized, controlled trial.	Journal of the American College of Cardiology	<4 wk
15591305	Turvey EA and Heigenhauser GJ and Parolin M and Peters SJ	Elevated n-3 fatty acids in a high-fat diet attenuate the increase in PDH kinase activity but not PDH activity in human skeletal muscle.	Journal of Applied Physiology (Bethesda, Md. : 1985)	<4 wk
14506493	Roberts WG and Gordon MH and Walker AF	Effects of enhanced consumption of fruit and vegetables on plasma antioxidant status and oxidative resistance of LDL in smokers supplemented with fish oil.	European Journal of Clinical Nutrition	<4 wk; No outcome of interest
none	Nygard OS and E. Pedersen and E. R. Ebbing and M. Svingen and G. Schartum-Hansen and H. Bjorndal and B. Seifert and R. Mayer and K. Nilsen and D. W. Nordrehaug and J. E.	Dietary intake of N-3 long-chain polyunsaturated fatty acids, diabetes mellitus and risk of myocardial infarction in patients with suspected coronary artery disease	Circulation	Abstract only
none	T. A. B. Mori and V. Barden and A. E. Puddey and I. B. Irish and A. B. Cowpland and C. A. Watts and G. F. Beilin and L. J.	20-Hete contributes to the blood pressure reduction following omega-3 fatty acid supplementation in patients with chronic kidney disease	Journal of Hypertension	Abstract only
none	Y. K. Sun and W. P.; Yuan and J. M.; Choi and H.; Ong and C. N.; Van Dam and R. M.	Circulating omega-3 fatty acids and risk of acute myocardial infarction in Singapore Chinese	Circulation	Abstract only
ABSTRACT	Davidson M, Liebson P, Bagdade J, Messer J, Schoenberger J.	Marine lipid concentrate reduces coronary risk factors: double blind comparison with olive oil	J Am Coll Cardiol 1986;7:247A.	Abstract only
ABSTRACT	M. N. D. Aldin and N. R. T. Carioca and A. A. F. Cartolano and F. D. C.	Omega-3 fatty acid changes size and concentration of lipoproteins of Brazilian subjects included in Cardionutri study	Global Heart	Abstract only

PMID	Authors	Title	Journal	Rejection Reason
ABSTRACT	R. M. Braeckman and M. S. Ballantyne and C. M. Stirtan and W. G. Soni and P. N.	Effects of AMR101, a pure eicosapentaenoic omega-3 fatty acid, on the fatty acid profile in plasma and red blood cells in statin-treated patients with persistent high triglycerides (results from the anchor study)	Circulation	Abstract only
ABSTRACT	Wilt T, Lofgren R, Nichol K, Schorer A, Crespin L, Eckfeldt J.	Fish oil ingestion does not lower blood pressure in normotensive or hypertensive men	Clin Res 1989;3:916A.	Abstract only
19421317	Shearer GC1, Pottala JV, Spertus JA, Harris WS.	Red blood cell fatty acid patterns and acute coronary syndrome.	PLoS One.	Case control study
19303975	Lemaitre RN1, King IB, Sotoodehnia N, Rea TD, Raghunathan TE, Rice KM, Lumley TS, Knopp RH, Cobb LA, Copass MK, Siscovick DS.	Red blood cell membrane alpha-linolenic acid and the risk of sudden cardiac arrest.	Metabolism.	Case control study
18606916	Campos H1, Baylin A, Willett WC.	Alpha-linolenic acid and risk of nonfatal acute myocardial infarction.	Circulation.	Case control study
17258965	Lopes C1, Aro A, Azevedo A, Ramos E, Barros H.	Intake and adipose tissue composition of fatty acids and risk of myocardial infarction in a male Portuguesecommunity sample.	J Am Diet Assoc.	Case control study
17223410	Harris WS1, Reid KJ, Sands SA, Spertus JA.	Blood omega-3 and trans fatty acids in middle-aged acute coronary syndrome patients.	Am J Cardiol.	Case control study
12668490	Baylin A1, Kabagambe EK, Ascherio A, Spiegelman D, Campos H.	Adipose tissue alpha-linolenic acid and nonfatal acute myocardial infarction in Costa Rica.	Circulation.	Case control study
12530773	Tavani A, Bertuzzi M, Negri E, Sorbara L, La Vecchia C.	Alcohol, smoking, coffee and risk of non-fatal acute myocardial infarction in Italy.	Eur J Epidemiol. 2001;17(12):1131-7.	Case control study
11839624	Lemaitre RN1, King IB, Raghunathan TE, Pearce RM, Weinmann S, Knopp RH, Copass MK, Cobb LA, Siscovick DS.	Cell membrane trans-fatty acids and the risk of primary cardiac arrest.	Circulation.	Case control study
11266195	Sasazuki 2001 Japan	Case-control study of nonfatal myocardial infarction in relation to selected foods in Japanese men and women.	Jpn Circ J. 2001 Mar;65(3):200-6.	Case control study
10195943	Guallar E1, Aro A, Jiménez FJ, Martín-Moreno JM, Salminen I, van't Veer P, Kardinaal AF, Gómez-Aracena J, Martin BC, Kohlmeier L, Kark JD, Mazaev VP,Ringstad J, Guillén J, Riemersma RA, Huttunen JK, Thamm M, Kok FJ.	Omega-3 fatty acids in adipose tissue and risk of myocardial infarction: the EURAMIC study.	Arterioscler Thromb Vasc Biol.	Case control study
8503947	Luostarinen R1, Boberg M, Saldeen T.	Fatty acid composition in total phospholipids of human coronary arteries in sudden cardiac death.	Atherosclerosis.	Case control study
7563561	Siscovick 1995 US	Dietary intake and cell membrane levels of long-chain n-3 polyunsaturated fatty acids and the risk of primary cardiac arrest.	JAMA. 1995 Nov 1;274(17):1363-7.	Case control study
6279124	Lea EJ, Jones SP, Hamilton DV.	The fatty acids of erythrocytes of myocardial infarction patients.	Atherosclerosis.	Case control study
4050552	Skuladottir G, Hardarson T, Sigfusson N, Oddsson G, Gudbjarnason S.	Arachidonic acid levels in serum phospholipids of patients with angina pectoris or fatal myocardial infarction.	Acta Med Scand.	Case control study
2880015	Wood DA, Riemersma RA, Butler S, Thomson M, Macintyre C, Elton RA, Oliver MF.	Linoleic and eicosapentaenoic acids in adipose tissue and platelets and risk of coronary heart disease.	Lancet.	Case control study

PMID	Authors	Title	Journal	Rejection Reason
none	S. A. F. H. W. J. T. M. D. P. M. H. K. J. J. P. Van Dam M	Efficacy of concentrated n-3 fatty acids in hypertriglyceridaemia: A comparison with gemfibrozil	Clinical Drug Investigation	Comparator not different or no n-3
none	D. G. J. W. M. E. B. S. J. H. D. P. N. M. K. J. J. P. Stalenhoef Afh	The effect of concentrated n-3 fatty acids versus gemfibrozil on plasma lipoproteins, low density lipoprotein heterogeneity and oxidizability in patients with hypertrygliceridemia	Atherosclerosis	Comparator not different or no n-3
12499320	Laidlaw M and Holub BJ	Effects of supplementation with fish oil-derived n-3 fatty acids and gamma-linolenic acid on circulating plasma lipids and fatty acid profiles in women.	The American Journal of Clinical Nutrition	Comparator not different or no n-3
none	P. J. H. S. Jones and V. K.; Pu and S.; Jenkins and D. J. A.; Connelly and P. W.; Lamarche and B.; Couture and P.; Charest and A.; Baril-Gravel and L.; West and S. G.; Liu and X.; Fleming and J. A.; McCrea and C. E.; Kris-Etherton and P. M.	Dha-enriched high-oleic acid canola oil improves lipid profile and lowers predicted cardiovascular disease risk in the canola oil multicenter randomized controlled trial	American Journal of Clinical Nutrition	Duplicate publication, no additional data
none	S. S. Tsugane and N.	The JPHC study: Design and some findings on the typical Japanese diet	Japanese Journal of Clinical Oncology	Duplicate publication, no additional data
none	N. T. Eliana and A.; Dias and F.; Orsatti and C.; Rodrigues and M.; Nahas-Neto and J.	Effect of diet and omega 3 supplementation on the metabolic and inflammatory markers in postmenopausal women with metabolic syndrome: A randomized controlled trial	Climacteric	Duplicate publication, no additional data
24777981	Caligiuri SP and Aukema HM and Ravandi A and Guzman R and Dibrov E and Pierce GN	Flaxseed consumption reduces blood pressure in patients with hypertension by altering circulating oxylipins via an alpha-linolenic acid-induced inhibition of soluble epoxide hydrolase.	Hypertension	Duplicate publication, no additional data
24529505	T. M. Hisamatsu and K. Ohkubo and T. Yamamoto and T. Fujiyoshi and A. Miyagawa and N. Kadota and A. Takashima and N. Okuda and N. Yoshita and K. Kita and Y. Murakami and Y. Nakamura and Y. Okamura and T. Horie and M. Okayama and A. Ueshima and H.	High long-chain n-3 fatty acid intake attenuates the effect of high resting heart rate on cardiovascular mortality risk: A 24-year follow-up of Japanese general population	Journal of Cardiology	Duplicate publication, no additional data
23835245	Brinton EA	Effects of icosapent ethyl on lipid and inflammatory parameters in patients with diabetes mellitus-2, residual elevated triglycerides (200-500 mg/dL), and on statin therapy at LDL-C goal: The ANCHOR study		Duplicate publication, no additional data
23351824	Masson S and Marchioli R and Mozaffarian D and Bernasconi R and Milani V and Dragani L and Tacconi M and Marfisi RM and Borgese L and Cirrincione V and Febo O and Nicolis E and Maggioni AP and Tognoni G and Tavazzi L and Latini R	Plasma n-3 polyunsaturated fatty acids in chronic heart failure in the GISSI-Heart Failure Trial: relation with fish intake, circulating biomarkers, and mortality.	American Heart Journal	Duplicate publication, no additional data
23312051	Derosa G and Cicero AF and Fogari E and D'Angelo A and Bonaventura A and Romano D and Maffioli P	Effects of n-3 PUFAs on postprandial variation of metalloproteinases, and inflammatory and insulin resistance parameters in dyslipidemic patients: evaluation with euglycemic clamp and oral fat load.	Journal of Clinical Lipidology	Duplicate publication, no additional data

PMID	Authors	Title	Journal	Rejection Reason
22653220	Itakura H and Yokoyama M and Matsuzaki M and Saito Y and Origasa H and Ishikawa Y and Oikawa S and Sasaki J and Hishida H and Kita T and Kitabatake A and Nakaya N and Sakata T and Shimada K and Shirato K and Matsuzawa Y	The change in low-density lipoprotein cholesterol concentration is positively related to plasma docosahexaenoic acid but not eicosapentaenoic acid.	Journal of Atherosclerosis and Thrombosis	Duplicate publication, no additional data
22186099	Sasaki J and Yokoyama M and Matsuzaki M and Saito Y and Origasa H and Ishikawa Y and Oikawa S and Itakura H and Hishida H and Kita T and Kitabatake A and Nakaya N and Sakata T and Shimada K and Shirato K and Matsuzawa Y	Relationship between coronary artery disease and non-HDL-C, and effect of highly purified EPA on the risk of coronary artery disease in hypercholesterolemic patients treated with statins: sub-analysis of the Japan EPA Lipid Intervention Study (JELIS).	Journal of Atherosclerosis and Thrombosis	Duplicate publication, no additional data
22110169	Kromhout D and Geleijnse JM and de Goede J and Oude Griep LM and Mulder BJ and de Boer MJ and Deckers JW and Boersma E and Zock PL and Giltay EJ	n-3 fatty acids, ventricular arrhythmia-related events, and fatal myocardial infarction in postmyocardial infarction patients with diabetes.	Diabetes Care	Duplicate publication, no additional data
21839455	Paniagua JA and Perez-Martinez P and Gjelstad IM and Tierney AC and Delgado-Lista J and Defoort C and Blaak EE and Riserus U and Drevon CA and Kiec-Wilk B and Lovegrove JA and Roche HM and Lopez-Miranda J	A low-fat high-carbohydrate diet supplemented with long-chain n-3 PUFA reduces the risk of the metabolic syndrome.	Atherosclerosis	Duplicate publication, no additional data
21315217	Finzi AA and Latini R and Barlera S and Rossi MG and Ruggeri A and Mezzani A and Favero C and Franzosi MG and Serra D and Lucci D and Bianchini F and Bernasconi R and Maggioni AP and Nicolosi G and Porcu M and Tognoni G and Tavazzi L and Marchioli R	Effects of n-3 polyunsaturated fatty acids on malignant ventricular arrhythmias in patients with chronic heart failure and implantable cardioverter-defibrillators: A substudy of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca (GISSI-HF) trial.	American Heart Journal	Duplicate publication, no additional data
21036355	Neil HA and Ceglarek U and Thiery J and Paul S and Farmer A and Holman RR	Impact of atorvastatin and omega-3 ethyl esters 90 on plasma plant sterol concentrations and cholesterol synthesis in type 2 diabetes: a randomised placebo controlled factorial trial.	Atherosclerosis	Duplicate publication, no additional data
20631323	Jimenez-Gomez Y and Marin C and Peerez-Martinez P and Hartwich J and Malczewska-Malec M and Golabek I and Kiec-Wilk B and Cruz-Teno C and Rodriguez F and Gomez P and Gomez-Luna MJ and Defoort C and Gibney MJ and Perez-Jimenez F and Roche HM and Lopez-Miranda J	A low-fat, high-complex carbohydrate diet supplemented with long-chain (n-3) fatty acids alters the postprandial lipoprotein profile in patients with metabolic syndrome.	The Journal of Nutrition	Duplicate publication, no additional data
20233037	Hartwich J and Leszczynska-Golabek I and Kiec-Wilk B and Siedlecka D and Perez-Martinez P and Marin C and Lopez-Miranda J and Tierney A and Monagle JM and Roche HM and Defoort C and Wolkow P and Dembinska-Kiec A	Lipoprotein profile, plasma ischemia modified albumin and LDL density change in the course of postprandial lipemia. Insights from the LIPGENE study.	Scandinavian Journal of Clinical and Laboratory Investigation	Duplicate publication, no additional data
20202290	Gulseth HL and Gjelstad IM and Tierney AC and Shaw DI and Helal O and Hees AM and Delgado-Lista J and Leszczynska-Golabek I and Karlstrom B and Lovegrove J and Defoort C and Blaak EE and Lopez-Miranda J and Dembinska-Kiec A and Riserus U and Roche HM and Birkeland KI and Drevon CA	Dietary fat modifications and blood pressure in subjects with the metabolic syndrome in the LIPGENE dietary intervention study.	The British Journal of Nutrition	Duplicate publication, no additional data

PMID	Authors	Title	Journal	Rejection Reason
20145342	Origasa H and Yokoyama M and Matsuzaki M and Saito Y and Matsuzawa Y	Clinical importance of adherence to treatment with eicosapentaenoic acid by patients with hypercholesterolemia.	Circulation Journal : Official Journal of the Japanese Circulation Society	Duplicate publication, no additional data
19481310	Hartwich J and Malec MM and Partyka L and Perez-Martinez P and Marin C and Lopez-Miranda J and Tierney AC and Mc Monagle J and Roche HM and Defoort C and Wolkow P and Dembinska-Kiec A	The effect of the plasma n-3/n-6 polyunsaturated fatty acid ratio on the dietary LDL phenotype transformation - insights from the LIPGENE study.	Clinical Nutrition (Edinburgh, Scotland)	Duplicate publication, no additional data
19447387	Oikawa S and Yokoyama M and Origasa H and Matsuzaki M and Matsuzawa Y and Saito Y and Ishikawa Y and Sasaki J and Hishida H and Itakura H and Kita T and Kitabatake A and Nakaya N and Sakata T and Shimada K and Shirato K	Suppressive effect of EPA on the incidence of coronary events in hypercholesterolemia with impaired glucose metabolism: Sub-analysis of the Japan EPA Lipid Intervention Study (JELIS).	Atherosclerosis	Duplicate publication, no additional data
19423946	Matsuzaki M and Yokoyama M and Saito Y and Origasa H and Ishikawa Y and Oikawa S and Sasaki J and Hishida H and Itakura H and Kita T and Kitabatake A and Nakaya N and Sakata T and Shimada K and Shirato K and Matsuzawa Y	Incremental effects of eicosapentaenoic acid on cardiovascular events in statin-treated patients with coronary artery disease.	Circulation Journal : Official Journal of the Japanese Circulation Society	Duplicate publication, no additional data
18667204	Saito Y and Yokoyama M and Origasa H and Matsuzaki M and Matsuzawa Y and Ishikawa Y and Oikawa S and Sasaki J and Hishida H and Itakura H and Kita T and Kitabatake A and Nakaya N and Sakata T and Shimada K and Shirato K	Effects of EPA on coronary artery disease in hypercholesterolemic patients with multiple risk factors: sub-analysis of primary prevention cases from the Japan EPA Lipid Intervention Study (JELIS).	Atherosclerosis	Duplicate publication, no additional data
18544171	P. B. Galan and S. Blacher and J. Czernichow and S. Hercberg and S.	The SU.FOL.OM3 Study: A secondary prevention trial testing the impact of supplementation with folate and B-vitamins and/or Omega-3 PUFA on fatal and non fatal cardiovascular events, design, methods and participants characteristics	Trials	Duplicate publication, no additional data
17934973	Furenes EB and Seljeflot I and Solheim S and Hjerkinn EM and Arnesen H	Long-term influence of diet and/or omega-3 fatty acids on matrix metalloproteinase-9 and pregnancy-associated plasma protein-A in men at high risk of coronary heart disease.	Scandinavian Journal of Clinical and Laboratory Investigation	Duplicate publication, no additional data
17327141	Lindi V and Schwab U and Louheranta A and Vessby B and Hermansen K and Tapsell L and Riccardi G and Rivellese AA and Laakso M and Uusitupa MI	The G-250A polymorphism in the hepatic lipase gene promoter is associated with changes in hepatic lipase activity and LDL cholesterol: The KANWU Study.	Nutrition, Metabolism, and Cardiovascular Diseases : NMCD	Duplicate publication, no additional data
16087142	A. L. Macchia and G. Franzosi and M. G. Geraci and E. Maggioni and A. P. Marfisi and R. Nicolosi and G. L. Schweiger and C. Tavazzi and L. Tognoni and G. Valagussa and F. Marchioli and R.	Left ventricular systolic dysfunction, total mortality, and sudden death in patients with myocardial infarction treated with n-3 polyunsaturated fatty acids	European Journal of Heart Failure	Duplicate publication, no additional data
15175795	Lindman AS and Pedersen JI and Hjerkinn EM and Arnesen H and Veierod MB and Ellingsen I and Seljeflot I	The effects of long-term diet and omega-3 fatty acid supplementation on coagulation factor VII and serum phospholipids with special emphasis on the R353Q polymorphism of the FVII gene.	Thrombosis and Haemostasis	Duplicate publication, no additional data
12618280	Rivellese AA and Maffettone A and Vessby B and Uusitupa M and Hermansen K and Berglund L and Louheranta A and Meyer BJ and Riccardi G	Effects of dietary saturated, monounsaturated and n-3 fatty acids on fasting lipoproteins, LDL size and post-prandial lipid metabolism in healthy subjects.	Atherosclerosis	Duplicate publication, no additional data

PMID	Authors	Title	Journal	Rejection Reason
11317662	Vessby B and Uusitupa M and Hermansen K and Riccardi G and Rivellese AA and Tapsell LC and Nalsen C and Berglund L and Louheranta A and Rasmussen BM and Calvert GD and Maffetone A and Pedersen E and Gustafsson IB and Storlien LH	Substituting dietary saturated for monounsaturated fat impairs insulin sensitivity in healthy men and women: The KANWU Study.	Diabetologia	Duplicate publication, no additional data
10232627	Hu FB1, Stampfer MJ, Manson JE, Rimm EB, Wolk A, Colditz GA, Hennekens CH, Willett WC.	Dietary intake of alpha-linolenic acid and risk of fatal ischemic heart disease among women.	Am J Clin Nutr.	Duplicate publication, no additional data
9022561	Whelton PK, Kumanyika SK, Cook NR, Cutler JA, Borhani NO, Hennekens CH, Kuller LH, Langford H, Jones DW, Satterfield S, Lasser NL, Cohen JD.	Efficacy of nonpharmacologic interventions in adults with high-normal blood pressure: results from phase 1 of the Trials of Hypertension Prevention. Trials of Hypertension Prevention Collaborative Research Group.	Am J Clin Nutr. 1997 Feb;65(2 Suppl):652S-660S.	Duplicate publication, no additional data
7702027	Eritsland J., Arnesen H., Seljeflot I., Høstmark AT.	Long-term metabolic effects of n-3 polyunsaturated fatty acids in patients with coronary artery disease.	The American Journal of Clinical Nutrition, 1995;61- 4	Duplicate publication, no additional data
20181806	Chan DC and Nguyen MN and Watts GF and Ooi EM and Barrett PH	Effects of atorvastatin and n-3 fatty acid supplementation on VLDL apolipoprotein C-III kinetics in men with abdominal obesity.	The American Journal of Clinical Nutrition	Factorial N<30 n-3 arms
16825679	Chan DC and Watts GF and Nguyen MN and Barrett PH	Factorial study of the effect of n-3 fatty acid supplementation and atorvastatin on the kinetics of HDL apolipoproteins A-I and A-II in men with abdominal obesity.	The American Journal of Clinical Nutrition	Factorial N<30 n-3 arms
12059988	Chan DC and Watts GF and Mori TA and Barrett PH and Beilin LJ and Redgrave TG	Factorial study of the effects of atorvastatin and fish oil on dyslipidaemia in visceral obesity.	European Journal of Clinical Investigation	Factorial N<30 n-3 arms
18403189	Yusof HM and Miles EA and Calder P	Influence of very long-chain n-3 fatty acids on plasma markers of inflammation in middle-aged men.	Prostaglandins, Leukotrienes, and Essential Fatty Acids	N<10
8349330	Vandongen R1, Mori TA, Burke V, Beilin LJ, Morris J, Ritchie J.	Effects on blood pressure of omega 3 fats in subjects at increased risk of cardiovascular disease.	Hypertension.	N<30/arm
24710321	L. K. Fezeu and Laporte and F. and Kesse-Guyot and E. and Andreeva and V. A. and Blacher and J. and Hercberg and S. and Galan and P.	Baseline plasma fatty acids profile and incident cardiovascular events in the SU.FOL.OM3 trial: the evidence revisited		No analysis/comparison of interest
24401815	AlSaleh A and Maniou Z and Lewis FJ and Hall WL and Sanders TA and O'Dell SD	Interaction between a CSK gene variant and fish oil intake influences blood pressure in healthy adults.	The Journal of Nutrition	No analysis/comparison of interest
20410091	G. Pocobelli and Kristal and A. R. and Patterson and R. E. and Potter and J. D. and Lampe and J. W. and Kolar and A. and Evans and I. and White and E.	Total mortality risk in relation to use of less-common dietary supplements		No n-3 dose data
17027436	Moore CS and Bryant SP and Mishra GD and Krebs JD and Browning LM and Miller GJ and Jebb SA	Oily fish reduces plasma triacylglycerols: a primary prevention study in overweight men and women.	Nutrition (Burbank, Los Angeles County, Calif.)	No n-3 dose data
11507963	Egeland GM, Meyer HE, Selmer R, Tverdal A, Vollset SE.	Cod liver oil consumption, smoking, and coronary heart disease mortality: three counties, Norway.	Int J Circumpolar Health. 2001 Apr;60(2):143-9.	No n-3 dose data
11507963	G. M. M. Egeland and H. E. Selmer and R. Tverdal and A. Vollset and S. E.	Cod liver oil consumption, smoking, and coronary heart disease mortality: three counties, Norway	International Journal of Circumpolar Health	No n-3 dose data

PMID	Authors	Title	Journal	Rejection Reason
none	C. M. B. Ballantyne and H.; Braeckman and R.; Philip and S.; Stirtan and W.; Doyle and R.; Soni and P. N.; Juliano and R. A.	Icosapent ethyl (eicosapentaenoic acid ethyl ester): Effects on remnant-like particle cholesterol from the marine and anchor studies	Circulation	No outcome of interest
none	A. B. Anullkesson and C.; Bergkvist and M.; Glynn and A.; Julin and B.; Wolk and A.	Dietary exposure to polychlorinated biphenyls and incidence of myocardial infarction in men-a population-based prospective cohort study	Circulation	No outcome of interest
25733777	K. S. Laake and I.; Fagerland and M. W.; Njerve and I. U.; Arnesen and H.; Solheim and S.	Effects on serum fractalkine by diet and omega-3 fatty acid intervention: Relation to clinical outcome	Mediators of Inflammation	No outcome of interest
24952576	M. Laidlaw and Cockerline and C. A. and Rowe and W. J.	A randomized clinical trial to determine the efficacy of manufacturers' recommended doses of omega-3 fatty acids from different sources in facilitating cardiovascular disease risk reduction		No outcome of interest
24378016	L. L. M. H. W. S. S. G. C. B. R. C. Augustine Ah	Treatment with omega-3 fatty acid ethyl-ester alters fatty acid composition of lipoproteins in overweight or obese adults with insulin resistance	Prostaglandins, Leukotrienes, and Essential Fatty Acids	No outcome of interest
24063767	Walker CG and Browning LM and Mander AP and Madden J and West AL and Calder PC and Jebb SA	Age and sex differences in the incorporation of EPA and DHA into plasma fractions, cells and adipose tissue in humans.	The British Journal of Nutrition	No outcome of interest
23885702	Lemke SL and Maki KC and Hughes G and Taylor ML and Krul ES and Goldstein DA and Su H and Rains TM and Mukherjea R	Consumption of stearidonic acid-rich oil in foods increases red blood cell eicosapentaenoic acid.	Journal of the Academy of Nutrition and Dietetics	No outcome of interest
23756586	Katz DL and Davidhi A and Ma Y and Kavak Y and Bifulco L and Njike VY	Effects of walnuts on endothelial function in overweight adults with visceral obesity: a randomized, controlled, crossover trial.	Journal of the American College of Nutrition	No outcome of interest
23325450	Bays HE and Ballantyne CM and Braeckman RA and Stirtan WG and Soni PN	Icosapent ethyl, a pure ethyl ester of eicosapentaenoic acid: effects on circulating markers of inflammation from the MARINE and ANCHOR studies.	American Journal of Cardiovascular Drugs : Drugs, Devices, and other Interventions	No outcome of interest
23179200	Zong G and Demark-Wahnefried W and Wu H and Lin X	Effects of flaxseed supplementation on erythrocyte fatty acids and multiple cardiometabolic biomarkers among Chinese with risk factors of metabolic syndrome.	European Journal of Nutrition	No outcome of interest
22661243	Crochemore IC and Souza AF and de Souza AC and Rosado EL	omega-3 polyunsaturated fatty acid supplementation does not influence body composition, insulin resistance, and lipemia in women with type 2 diabetes and obesity.	Nutrition in Clinical Practice : Official Publication of the American Society for Parenteral and Enteral Nutrition	No outcome of interest
22108152	Maki KC and Bays HE and Dicklin MR and Johnson SL and Shabbout M	Effects of prescription omega-3-acid ethyl esters, coadministered with atorvastatin, on circulating levels of lipoprotein particles, apolipoprotein CIII, and lipoprotein-associated phospholipase A2 mass in men and women with mixed dyslipidemia.	Journal of Clinical Lipidology	No outcome of interest
21624541	Kumar S and Sutherland F and Teh AW and Heck PM and Lee G and Garg ML and Sparks PB	Effects of chronic omega-3 polyunsaturated fatty acid supplementation on human pulmonary vein and left atrial electrophysiology in paroxysmal atrial fibrillation.	The American Journal of Cardiology	No outcome of interest

PMID	Authors	Title	Journal	Rejection Reason
20394870	Gajos G1, Rostoff P, Undas A, Piwowarska W.	Effects of polyunsaturated omega-3 fatty acids on responsiveness to dual antiplatelet therapy in patients undergoing percutaneous coronary intervention: the OMEGA-PCI (OMEGA-3 fatty acids after pci to modify responsiveness to dual antiplatelet therapy) study.	J Am Coll Cardiol.	No outcome of interest
19843899	Carney RM1, Freedland KE, Rubin EH, Rich MW, Steinmeyer BC, Harris WS.	Omega-3 augmentation of sertraline in treatment of depression in patients with coronary heart disease: a randomized controlled trial.	JAMA	No outcome of interest
19158225	Kelley DS and Siegel D and Fedor DM and Adkins Y and Mackey BE	DHA supplementation decreases serum C-reactive protein and other markers of inflammation in hypertriglyceridemic men.	The Journal of Nutrition	No outcome of interest
19133114	Valdivielso P and Rioja J and Garcia-Arias C and Sanchez-Chaparro MA and Gonzalez-Santos P	Omega 3 fatty acids induce a marked reduction of apolipoprotein B48 when added to fluvastatin in patients with type 2 diabetes and mixed hyperlipidemia: a preliminary report.	Cardiovascular Diabetology	No outcome of interest
18689552	Austria JA and Richard MN and Chahine MN and Edel AL and Malcolmson LJ and Dupasquier CM and Pierce GN	Bioavailability of alpha-linolenic acid in subjects after ingestion of three different forms of flaxseed.	Journal of the American College of Nutrition	No outcome of interest
18156400	Kelley DS and Siegel D and Vemuri M and Chung GH and Mackey BE	Docosahexaenoic acid supplementation decreases remnant-like particle-cholesterol and increases the (n-3) index in hypertriglyceridemic men.	The Journal of Nutrition	No outcome of interest
17179018	Steffen LM1, Folsom AR, Cushman M, Jacobs DR Jr, Rosamond WD.	Greater fish, fruit, and vegetable intakes are related to lower incidence of venous thromboembolism: the Longitudinal Investigation of Thromboembolism Etiology.	Circulation.	No outcome of interest
15262190	Mesa MD and Buckley R and Minihane AM and Yaqoob P	Effects of oils rich in eicosapentaenoic and docosahexaenoic acids on the oxidizability and thrombogenicity of low-density lipoprotein.	Atherosclerosis	No outcome of interest
15208005	Harris WS and Von Schacky C	The Omega-3 Index: a new risk factor for death from coronary heart disease?	Preventive Medicine	No outcome of interest
12771973	Pedersen H and Petersen M and Major-Pedersen A and Jensen T and Nielsen NS and Lauridsen ST and Marckmann P	Influence of fish oil supplementation on in vivo and in vitro oxidation resistance of low-density lipoprotein in type 2 diabetes.	European Journal of Clinical Nutrition	No outcome of interest
12075272	Maresta A., Balduccelli M., Varani E., Marzilli M., Galli C., Heiman F., Lavezzari M., Stragliotto E., De Caterina R.	Prevention of postcoronary angioplasty restenosis by omega-3 fatty acids: main results of the Esapent for Prevention of Restenosis ITalian Study (ESPRIT).	American Heart Journal; 2002, 143-6	No outcome of interest
12062374	Angerer P., Kothny W., Störk S., von Schacky C.	Effect of dietary supplementation with omega-3 fatty acids on progression of atherosclerosis in carotid arteries.	Cardiovascular Research, 2002, 54-1	No outcome of interest
8688759	Ascherio A1, Rimm EB, Giovannucci EL, Spiegelman D, Stampfer M, Willett WC.	Dietary fat and risk of coronary heart disease in men: cohort follow up study in the United States.	BMJ.	No outcome of interest
8540453	Eritsland J1, Arnesen H, Gr¿nseth K, Fjeld NB, Abdelnoor M.	Effect of dietary supplementation with n-3 fatty acids on coronary artery bypass graft patency.	Am J Cardiol.	No outcome of interest
8462079	Franzen, 1993	A prospective, randomized, and double-blind trial on the effect of fish oil on the incidence of restenosis following PTCA.	Cathet Cardiovasc Diagn. 1993 Apr;28(4):301-10.	No outcome of interest
7955181	Leaf A1, Jorgensen MB, Jacobs AK, Cote G, Schoenfeld DA, Scheer J, Weiner BH, Slack JD, Kellett MA, Raizner AE, et al.	Do fish oils prevent restenosis after coronary angioplasty?	Circulation.	No outcome of interest

PMID	Authors	Title	Journal	Rejection Reason
6320945	Woodcock BE, Smith E, Lambert WH, Jones WM, Galloway JH, Greaves M, Preston FE.	Beneficial effect of fish oil on blood viscosity in peripheral vascular disease.	Br Med J (Clin Res Ed).	No outcome of interest
2842680	Dehmer GJ1, Popma JJ, van den Berg EK, Eichhorn EJ, Prewitt JB, Campbell WB, Jennings L, Willerson JT, Schmitz JM.	Reduction in the rate of early restenosis after coronary angioplasty by a diet supplemented with n-3 fatty acids	N Engl J Med.	No outcome of interest
2842680	Dehmer GJ1, Popma JJ, van den Berg EK, Eichhorn EJ, Prewitt JB, Campbell WB, Jennings L, Willerson JT, Schmitz JM.	Reduction in the rate of early restenosis after coronary angioplasty by a diet supplemented with n-3 fatty acids.	N Engl J Med.	No outcome of interest
2568519	Reis GJ1, Boucher TM, Sipperly ME, Silverman DI, McCabe CH, Baim DS, Sacks FM, Grossman W, Pasternak RC.	Randomised trial of fish oil for prevention of restenosis after coronary angioplasty.	Lancet.	No outcome of interest
2526993	Milner MR1, Gallino RA, Leffingwell A, Pichard AD, Brooks-Robinson S, Rosenberg J, Little T, Lindsay J Jr.	Usefulness of fish oil supplements in preventing clinical evidence of restenosis after percutaneous transluminal coronary angioplasty.	Am J Cardiol.	No outcome of interest
1902298	Singer P., Wirth M., Kretschmer H.	Different changes of n-6 fatty acids in lipoproteins from hyperlipemic subjects after diets supplemented with n-3 fatty acids.	Prostaglandins Leukot Essent Fatty Acids. 1991 Feb;42(2):107-11.	No outcome of interest
1537131	Bairati I1, Roy L, Meyer F.	Double-blind, randomized, controlled trial of fish oil supplements in prevention of recurrence of stenosis after coronary angioplasty.	Circulation.	No outcome of interest
1289091	Bellamy CM1, Schofield PM, Faragher EB, Ramsdale DR.	Can supplementation of diet with omega-3 polyunsaturated fatty acids reduce coronary angioplasty restenosis rate?	Eur Heart J.	No outcome of interest
none	G. Colussi and Catena and C. and Dialti and V. and Pezzutto and F. and Mos and L. and Sechi and L. A.	Fish meal supplementation and ambulatory blood pressure in patients with hypertension: relevance of baseline membrane fatty acid composition		Non-comparative
20156032	Bays HE and Maki KC and McKenney J and Snipes R and Meadowcroft A and Schroyer R and Doyle RT and Stein E	Long-term up to 24-month efficacy and safety of concomitant prescription omega-3-acid ethyl esters and simvastatin in hypertriglyceridemic patients.	Current Medical Research and Opinion	Non-comparative
19584895	Patenaude A and Rodriguez-Leyva D and Edel AL and Dibrov E and Dupasquier CM and Austria JA and Richard MN and Chahine MN and Malcolmson LJ and Pierce GN	Bioavailability of alpha-linolenic acid from flaxseed diets as a function of the age of the subject.	European Journal of Clinical Nutrition	Non-comparative
19364085	De Luis DA and Conde R and Aller R and Izaola O and Gonzalez Sagrado M and Perez Castrillon JL and Duenas A and Romero E	Effect of omega-3 fatty acids on cardiovascular risk factors in patients with type 2 diabetes mellitus and hypertriglyceridemia: an open study.	European Review for Medical and Pharmacological Sciences	Non-comparative
18525453	Vega GL and Chandalia M and Szczepaniak LS and Grundy SM	Effects of N-3 fatty acids on hepatic triglyceride content in humans.	Journal of Investigative Medicine : The Official Publication of the American Federation for Clinical Research	Non-comparative
18242615	Elvevoll EO and Eilertsen KE and Brox J and Dragnes BT and Falkenberg P and Olsen JO and Kirkhus B and Lamglait A and Osterud B	Seafood diets: hypolipidemic and antiatherogenic effects of taurine and n-3 fatty acids.	Atherosclerosis	Non-comparative
17461697	Burns T and Maciejewski SR and Hamilton WR and Zheng M and Mooss AN and Hilleman DE	Effect of omega-3 fatty acid supplementation on the arachidonic acid:eicosapentaenoic acid ratio.	Pharmacotherapy	Non-comparative

PMID	Authors	Title	Journal	Rejection Reason
15173404	Surette ME and Edens M and Chilton FH and Tramposch KM	Dietary echium oil increases plasma and neutrophil long-chain (n-3) fatty acids and lowers serum triacylglycerols in hypertriglyceridemic humans.	The Journal of Nutrition	Non-comparative
14639803	Nestares T and Lopez-Jurado M and Urbano G and Seiquer I and Ramirez-Tortosa MC and Ros E and Mataix J and Gil A	Effects of lifestyle modification and lipid intake variations on patients with peripheral vascular disease.	International Journal for Vitamin and Nutrition Research. Internationale Zeitschrift fur Vitamin- und Ernahrungsforschung. Journal International de Vitaminologie et de Nutrition	Non-comparative
11938024	Kesavulu MM and Kameswararao B and Apparao Ch and Kumar EG and Harinarayan CV	Effect of omega-3 fatty acids on lipid peroxidation and antioxidant enzyme status in type 2 diabetic patients.	Diabetes & Metabolism	Non-comparative
none	J. M. Yuan	Seafood and myocardial infarction in China		Not available
11494668	Meshcheriakova VA, Plotnikova OA, Sharafetdinov KhKh, Alekseeva RI, Mal'tsev GIu, Kulakova SN.	Comparative study of effects of diet therapy including eiconol or linseed oil on several parameters of lipid metabolism in patients with type 2 diabetes mellitus.	Vopr Pitan.	Not in English
11247166	Alekseeva RI, Sharafetdinov KhKh, Plotnikova OA, Meshcheriakova VA, Mal'tsev GIu, Kulakova SN.	Effects of diet therapy including eiconol on clinical and metabolic parameters in patients with type 2 diabetes mellitus.	Vopr Pitan.	Not in English
none	M. I. Gautam and A.; Shiba and Y.; Motoki and H.; Takeuchi and T.; Okada and A.; Tomita and T.; Miyashita and Y.; Koyama and J.; Ikeda and U.	Importance of fatty acid compositions in patients with peripheral arterial disease	PLoS ONE	Not longitudinal
none	K. M. B. Smith and L. M. Kantor and M. Sahyoun and N. R.	Relationship between fish intake, n-3 fatty acids, mercury and risk markers of CHD (National Health and Nutrition Examination Survey 1999-2002)	Public Health Nutrition	Not longitudinal
18579573	Turunen AW and Verkasalo PK and Kiviranta H and Pukkala E and Jula A and Mannisto S and Rasanen R and Marniemi J and Vartiainen T	Mortality in a cohort with high fish consumption.	International Journal of Epidemiology	Not longitudinal
11684529	Djoussé L, Pankow JS, Eckfeldt JH, Folsom AR, Hopkins PN, Province MA, Hong Y, Ellison RC.	Relation between dietary linolenic acid and coronary artery disease in the National Heart, Lung, and Blood Institute Family Heart Study.	Am J Clin Nutr. 2001 Nov;74(5):612-9.	Not longitudinal
1350705	Bonaa, 1992	Habitual fish consumption, plasma phospholipid fatty acids, and serum lipids: the Tromsø study	Am J Clin Nutr. 1992 Jun;55(6):1126-34.	Not longitudinal
none	P. H. Wurtz and A. S.; Soininen and P.; Tynkkynen and T.; Prieto-Merino and D.; Tillin and T.; Ghorbani and A.; Artati and A.; Wang and Q.; Tiainen and M.; Kangas and A. J.; Kettunen and J.; Kaikkonen and J.; Mikkila and V.; Jula and A.; Kahonen and M.; Lehtimaki and T.; Lawlor and D. A.; Gaunt and T. R.; Hughes and A. D.; Sattar and N.; Illig and T.; Adamski and J.; Wang and T. J.; Perola and M.; Ripatti and S.; Vasan and R. S.; Raitakari and O. T.; Gerszten and R. E.; Casas and J. P.; Chaturvedi and N.; Ala-Korpela and M.; Salomaa and V.	Metabolite profiling and cardiovascular event risk: A prospective study of 3 population-based cohorts	Circulation	Not primary study

PMID	Authors	Title	Journal	Rejection Reason
none	A. M. Farmer and V. Dinneen and S. Clar and C.	Fish oil in people with type 2 diabetes mellitus	Cochrane Database of Systematic Reviews (Online)	Not primary study
none	F. D. Campbell and H. O. Critchley and J. A. Ford and G. A. Bradburn and M.	A systematic review of fish-oil supplements for the prevention and treatment of hypertension	European Journal of Preventive Cardiology	Not primary study
none	H. S. Leon and M. C. Sivakumaran and S. Dorgan and M. Chatterley and T. Tsuyuki and R. T.	Effect of fish oil on arrhythmias and mortality: systematic review	BMJ (Clinical research ed.)	Not primary study
none	Y. Li and Zhou and ChengHui and Pei and HanJun and Zhou and XianLiang and Li and LiHuan and Wu and YongJian and Hui and RuTai	Fish consumption and incidence of heart failure: a meta-analysis of prospective cohort studies		Not primary study
none	Y. Momiyama	Association between serum omega-3 to omega-6 polyunsaturated fatty acid ratio and cardiovascular events in a general Japanese population	Atherosclerosis	Not primary study
none	D. d. G. Kromhout and J.; Kromhout and Daan; de Goede and Janette	Update on cardiometabolic health effects of omega-3 fatty acids	Current Opinion in Lipidology	Not primary study
none	L. Gao and Cao and Jian and Mao and QunXia and Lu and XueChun and Zhou and XianLiang and Fan and Li	Influence of omega-3 polyunsaturated fatty acid-supplementation on platelet aggregation in humans: a meta-analysis of randomized controlled trials		Not primary study
none	W. Xin and Wei and Wei and Lin and ZhiQin and Zhang and XiaoXia and Yang and HongXia and Zhang and Tao and Li and Bin and Mi and ShuHua	Fish oil and atrial fibrillation after cardiac surgery: a meta-analysis of randomized controlled trials		Not primary study
none	E. C. N. Rizos and E. E.	(omega)-3 fatty acids and lutein+zeaxanthin supplementation for the prevention of cardiovascular disease	JAMA Internal Medicine	Not primary study
none	S. I. Khalesi and C.; Schubert and M.	Flaxseed consumption may reduce blood pressure: A systematic review and meta-analysis of controlled trials	Journal of Nutrition	Not primary study
none	L. H. Schwingshackl and G.	Dietary fatty acids in the secondary prevention of coronary heart disease: A systematic review, meta-analysis and meta-regression	BMJ Open	Not primary study
none	X. Y. Y. Guo and X. L.; Chen and Y. W.; Tang and R. B.; Du and X.; Dong and J. Z.; Ma and C. S.; Guo and Xue-Yuan; Yan and Xian-Liang; Chen and Ying-Wei; Tang and Ri-Bo; Du and Xin; Dong and Jian-Zeng; Ma and Chang-Sheng	Omega-3 fatty acids for postoperative atrial fibrillation: alone or in combination with antioxidant vitamins?	Heart, Lung & Circulation	Not primary study
none	J. E. Y. Enns and A.; Zarychanski and R.; Abou-Setta and A. M.; Friesen and C.; Zahradka and P.; Taylor and C. G.; Enns and Jennifer E.; Yeganeh and Azadeh; Zarychanski and Ryan; Abou-Setta and Ahmed M.; Friesen and Carol; Zahradka and Peter; Taylor and Carla G.	The impact of omega-3 polyunsaturated fatty acid supplementation on the incidence of cardiovascular events and complications in peripheral arterial disease: a systematic review and meta-analysis	BMC Cardiovascular Disorders	Not primary study
none	T. Z. Zheng and J.; Wang and Y.; Liu and W.; Wang and Z.; Shang and Y.; Zhang and W.; Zhang and Y.; Zhong and M.	The limited effect of omega-3 polyunsaturated fatty acids on cardiovascular risk in patients with impaired glucose metabolism: A meta-analysis	Clinical Biochemistry	Not primary study
none	P. Calder	Limited impact of omega-3 fatty acids in patients with multiple cardiovascular risk factors	Evidence-Based Medicine	Not primary study

PMID	Authors	Title	Journal	Rejection Reason
none	Z. Kmietowicz	Omega 3 supplements do not reduce cardiovascular risk in elderly	BMJ (Online)	Not primary study
none	P. E. V. E. Miller and M.; Alexander and D. D.	Long-chain Omega-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid and blood pressure: A meta-analysis of randomized controlled trials	American Journal of Hypertension	Not primary study
none	R. W. Chowdhury and S.; Kunutsor and S.; Crowe and F.; Ward and H. A.; Johnson and L.; Franco and O. H.; Butterworth and A. S.; Forouhi and N. G.; Thompson and S. G.; Khaw and K. T.; Mozaffarian and D.; Danesh and J.; Di Angelantonio and E.	Association of dietary, circulating, and supplement fatty acids with coronary risk: A systematic review and meta-analysis	Annals of Internal Medicine	Not primary study
none	Y. T. D. Wen and J. H.; Gao and Q.	Effects of Omega-3 fatty acid on major cardiovascular events and mortality in patients with coronary heart disease: a meta-analysis of randomized controlled trials	Nutrition Metabolism & Cardiovascular Diseases	Not primary study
22011460	Danthiir V and Burns NR and Nettelbeck T and Wilson C and Wittert G	The older people, omega-3, and cognitive health (EPOCH) trial design and methodology: a randomised, double-blind, controlled trial investigating the effect of long-chain omega-3 fatty acids on cognitive ageing and wellbeing in cognitively healthy older adults.	Nutrition JJournal	Not primary study
18082485	Gerstein H and Yusuf S and Riddle MC and Ryden L and Bosch J	Rationale, design, and baseline characteristics for a large international trial of cardiovascular disease prevention in people with dysglycemia: the ORIGIN Trial (Outcome Reduction with an Initial Glargine Intervention).	American HHeart JJournal	Not primary study
17124558	Rauch B and Schiele R and Schneider S and Gohlke H and Diller F and Gottwik M and Steinbeck G and Heer T and Katus H and Zimmer R and Erdogan A and Pfafferott C and Senges J	Highly purified omega-3 fatty acids for secondary prevention of sudden cardiac death after myocardial infarction-aims and methods of the OMEGA-study.	Cardiovascular Drugs and Therapy / Sponsored by the International Society of Cardiovascular Pharmacotherapy	Not primary study
11837985	Marchioli R and Schweiger C and Tavazzi L and Valagussa F	Efficacy of n-3 polyunsaturated fatty acids after myocardial infarction: results of GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico.	Lipids	Not primary study
2053348	Singer P, Hueve J.	Blood pressure-lowering effect of fish oil, propranolol and the combination of both in mildly hypertensive patients	World Rev Diet 1991;66:522-3.	Not primary study
none	T. K. Teramoto and R.; Miyazaki and S.; Teramukai and S.; Sato and Y.; Okuda and Y.; Shirayama and M.	Lipid and Blood Pressure Control for the Prevention of Cardiovascular Disease in Hypertensive Patients: A Subanalysis of the OMEGA Study	Journal of Atherosclerosis and Thrombosis	Not specifically n-3 intervention/ exposure
none	M. R. K. Mahmoodi and M.; Mehrabi and Y.	The effects of omega-3 plus vitamin E and zinc plus vitamin C supplementation on cardiovascular risk markers in postmenopausal women with type 2 diabetes	Therapeutic Advances in Endocrinology and Metabolism	Not specifically n-3 intervention/ exposure

PMID	Authors	Title	Journal	Rejection Reason
none	K. R. Tuttle and Shuler and L. A. and Packard and D. P. and Milton and J. E. and Daratha and K. B. and Bibus and D. M. and Short and R. A.	Comparison of low-fat versus Mediterranean-style dietary intervention after first myocardial infarction (from the Heart Institute of Spokane Diet Intervention and Evaluation Trial)		Not specifically n-3 intervention/ exposure
none	C. d. Natale and Minerva and V. and Patti and L. and Mazzarella and R. and Ciano and O. and Maione and S. and Luongo and D. and Naviglio and D. and Marotta and G. and Turco and S. and Ciati and R. and Melegari and C. and Rivellese and A. A. and Riccardi and G.	Effects of baked products enriched with n-3 fatty acids, folates, beta -glucans, and tocopherol in patients with mild mixed hyperlipidemia		Not specifically n-3 intervention/ exposure
none	E. R. S.-S. J. M.-G. M. A. A. F. V. J. C. D. D. O. S. G. D. L. T. R. M. Fito M	Effect of the Mediterranean diet on heart failure biomarkers: A randomized sample from the PREDIMED trial	European Journal of Heart Failure	Not specifically n-3 intervention/ exposure
none	F. Tsofliou and Fyfe and C. L. and Matheson and I. and Jackson and D. M. and Horgan and G. W. and Wahle and K. W. J. and Ahren and B. and Williams and L. M. and Sneddon and A. A.	Modulation of fasted and postprandial plasma lipids in healthy volunteers by a dietary mixture of omega-3 fatty acids and conjugated linoleic acid		Not specifically n-3 intervention/ exposure
none	F. Y. Moloney and T. P. Mullen and A. Nolan and J. J. Roche and H. M.	Conjugated linoleic acid supplementation, insulin sensitivity, and lipoprotein metabolism in patients with type 2 diabetes mellitus	American Journal of Clinical Nutrition	Not specifically n-3 intervention/ exposure
none	Avellone G. and Guarnotta and V. and Garbo and V. di and Abruzzese and G. and Campisi and D. and Pinto and A. and Pizzo and G. and Licata and G.	Impact of atorvastatin plus n-3 PUFA on metabolic, inflammatory and coagulative parameters in metabolic syndrome without and with type 2 diabetes mellitus	International Journal of Medicine	Not specifically n-3 intervention/ exposure
none	J. Tovar and Nilsson and A. and Johansson and M. and Ekesbo and R. and Aberg and A. M. and Johansson and U. and Bjorck and I.	A diet based on multiple functional concepts improves cardiometabolic risk parameters in healthy subjects		Not specifically n-3 intervention/ exposure
none	O. A. P. Tokede and A. B. Hanson and N. Q. Tsai and M. Y. Weir and N. A. Glynn and R. J. Gaziano and J. M. Djousse and L.	Plasma phospholipid trans fatty acids and risk of heart failure	American Journal of Clinical Nutrition	Not specifically n-3 intervention/ exposure
none	R. Casas and Sacanella and E. and Urpi-Sarda and M. and Chiva-Blanch and G. and Ros and E. and Martinez-Gonzalez and M. A. and Covas and M. I. and Lamuela-Raventos and R. M. and Salas-Salvado and J. and Fiol and M. and Aros and F. and Estruch and R.	The effects of the Mediterranean diet on biomarkers of vascular wall inflammation and plaque vulnerability in subjects with high risk for cardiovascular disease. A randomized trial		Not specifically n-3 intervention/ exposure
none	R. N. K. Lemaitre and I. B. Mozaffarian and D. Sotoodehnia and N. Rea and T. D. Kuller and L. H. Tracy and R. P. Siscovick and D. S.	Plasma phospholipid trans fatty acids, fatal ischemic heart disease, and sudden cardiac death in older adults: The cardiovascular health study	Circulation	Not specifically n-3 intervention/ exposure

PMID	Authors	Title	Journal	Rejection Reason
none	N. R. O. Matthan and E. M.; Horn and L. V.; Neuhouser and M. L.; Woodman and R.; Lichtenstein and A. H.	Plasma phospholipid fatty acid biomarkers of dietary fat quality and endogenous metabolism predict coronary heart disease risk: A nested case-control study within the women's health initiative observational study	Journal of the American Heart Association	Not specifically n-3 intervention/ exposure
none	S. E. S. Chiuve and R. K.; Moorthy and M. V.; Glynn and R. J.; Albert and C. M.	Dietary fatty acids and risk of incident atrial fibrillation in the women's health study	Circulation	not specifically n-3 intervention/ exposure
no	Silvis, N.; Vorster, H. H.; Mollentze, W. F.; Jagar, J. de; Huisman, H. W.	Metabolic and haemostatic consequences of dietary fibre and N-3 fatty acids in black type 2 (NIDDM) diabetic subjects: a placebo controlled study.	International Clinical Nutrition Review	Not specifically n-3 intervention/ exposure
24714723	Eshak ES and Iso H and Yamagishi K and Kokubo Y and Saito I and Yatsuya H and Sawada N and Inoue M and Tsugane S	Modification of the excess risk of coronary heart disease due to smoking by seafood/fish intake.	American Journal of Epidemiology	Not specifically n-3 intervention/ exposure
24360749	Wu L and Piotrowski K and Rau T and Waldmann E and Broedl UC and Demmelmair H and Koletzko B and Stark RG and Nagel JM and Mantzoros CS and Parhofer KG	Walnut-enriched diet reduces fasting non-HDL-cholesterol and apolipoprotein B in healthy Caucasian subjects: a randomized controlled cross-over clinical trial.	Metabolism: Clinical and Experimental	Not specifically n-3 intervention/ exposure
23813701	Lajous M and Willett WC and Robins J and Young JG and Rimm E and Mozaffarian D and Hernan MA	Changes in fish consumption in midlife and the risk of coronary heart disease in men and women.	American Journal of Epidemiology	Not specifically n-3 intervention/ exposure
23487436	Imamura F and Lemaitre RN and King IB and Song X and Steffen LM and Folsom AR and Siscovick DS and Mozaffarian D	Long-chain monounsaturated Fatty acids and incidence of congestive heart failure in 2 prospective cohorts.	Circulation	Not specifically n-3 intervention/ exposure
23411152	Kuhn T and Teucher B and Kaaks R and Boeing H and Weikert C and Buijsse B	Fish consumption and the risk of myocardial infarction and stroke in the German arm of the European Prospective Investigation into Cancer and Nutrition (EPIC-Germany).	The British Journal of Nutrition	Not specifically n-3 intervention/ exposure
23134888	Carvalho-Wells AL and Jackson KG and Lockyer S and Lovegrove JA and Minihane AM	APOE genotype influences triglyceride and C-reactive protein responses to altered dietary fat intake in UK adults.	The American Journal of Clinical Nutrition	Not specifically n-3 intervention/ exposure
22917075	Pintus S and Murru E and Carta G and Cordeddu L and Batetta B and Accossu S and Pistis D and Uda S and Elena Ghiani M and Mele M and Secchiari P and Almerighi G and Pintus P and Banni S	Sheep cheese naturally enriched in alpha-linolenic, conjugated linoleic and vaccenic acids improves the lipid profile and reduces anandamide in the plasma of hypercholesterolaemic subjects.	The British Journal of Nutrition	Not specifically n-3 intervention/ exposure
22190026	Horn LV and Tian L and Neuhouser ML and Howard BV and Eaton CB and Snetselaar L and Matthan NR and Lichtenstein AH	Dietary patterns are associated with disease risk among participants in the Women's Health Initiative Observational Study.	The Journal of Nutrition	Not specifically n-3 intervention/ exposure

PMID	Authors	Title	Journal	Rejection Reason
21191140	Larsson SC and Virtamo J and Wolk A	Fish consumption and risk of stroke in Swedish women.	The American Journal of Clinical Nutrition	Not specifically n-3 intervention/ exposure
20713902	A. M. S. Bernstein and Q. Hu and F. B. Stampfer and M. J. Manson and J. E. Willett and W. C.	Major dietary protein sources and risk of coronary heart disease in women	Circulation	Not specifically n-3 intervention/ exposure
19893100	Ristic-Medic D and Suzic S and Vucic V and Takic M and Tepsic J and Glibetic M	Serum and erythrocyte membrane phospholipids fatty acid composition in hyperlipidemia: effects of dietary intervention and combined diet and fibrate therapy.	General Physiology and Biophysics	Not specifically n-3 intervention/ exposure
19755403	Bjerregaard LJ and Joensen AM and Dethlefsen C and Jensen MK and Johnsen SP and Tjonneland A and Rasmussen LH and Overvad K and Schmidt EB	Fish intake and acute coronary syndrome.	European Heart Journal	Not specifically n-3 intervention/ exposure
19713172	Teas J and Baldeon ME and Chiriboga DE and Davis JR and Sarries AJ and Braverman LE	Could dietary seaweed reverse the metabolic syndrome?	Asia Pacific Journal of Clinical Nutrition	Not specifically n-3 intervention/ exposure
19423109	Vega-Lopez S and Matthan NR and Ausman LM and Ai M and Otokozawa S and Schaefer EJ and Lichtenstein AH	Substitution of vegetable oil for a partially-hydrogenated fat favorably alters cardiovascular disease risk factors in moderately hypercholesterolemic postmenopausal women.	Atherosclerosis	Not specifically n-3 intervention/ exposure
19276620	Garbagnati F and Cairella G and De Martino A and Multari M and Scognamiglio U and Venturiero V and Paolucci S	Is antioxidant and n-3 supplementation able to improve functional status in poststroke patients? Results from the Nutristroke Trial.	Cerebrovascular diseases (Basel, Switzerland)	Not specifically n-3 intervention/ exposure
18678300	Maki KC and McKenney JM and Reeves MS and Lubin BC and Dicklin MR	Effects of adding prescription omega-3 acid ethyl esters to simvastatin (20 mg/day) on lipids and lipoprotein particles in men and women with mixed dyslipidemia.	The American Journal of Cardiology	Not specifically n-3 intervention/ exposure
17764599	Messerer M and Hakansson N and Wolk A and Akesson A	Dietary supplement use and mortality in a cohort of Swedish men.	The British Journal of Nutrition	Not specifically n-3 intervention/ exposure
17563030	Fito M and Guxens M and Corella D and Saez G and Estruch R and de la Torre R and Frances F and Cabezas C and Lopez-Sabater Mdel C and Marrugat J and Garcia-Arellano A and Aros F and Ruiz-Gutierrez V and Ros E and Salas-Salvado J and Fiol M and Sola R and Covas MI	Effect of a traditional Mediterranean diet on lipoprotein oxidation: a randomized controlled trial.	Archives of Internal Medicine	Not specifically n-3 intervention/ exposure
17381974	Mukuddem-Petersen J and Stonehouse Oosthuizen W and Jerling JC and Hanekom SM and White Z	Effects of a high walnut and high cashew nut diet on selected markers of the metabolic syndrome: a controlled feeding trial.	The British Journal of Nutrition	Not specifically n-3 intervention/ exposure

PMID	Authors	Title	Journal	Rejection Reason
17237316	Carrero JJ and Fonolla J and Marti JL and Jimenez J and Boza JJ and Lopez-Huertas E	Intake of fish oil, oleic acid, folic acid, and vitamins B-6 and E for 1 year decreases plasma C-reactive protein and reduces coronary heart disease risk factors in male patients in a cardiac rehabilitation program.	The Journal of Nutrition	Not specifically n-3 intervention/ exposure
17010254	Myint PK and Welch AA and Bingham SA and Luben RN and Wareham NJ and Day NE and Khaw KT	Habitual fish consumption and risk of incident stroke: the European Prospective Investigation into Cancer (EPIC)-Norfolk prospective population study.	Public Health Nutrition	Not specifically n-3 intervention/ exposure
16054553	Chisholm A and Mc Auley K and Mann J and Williams S and Skeaff M	Cholesterol lowering effects of nuts compared with a Canola oil enriched cereal of similar fat composition.	Nutrition, Metabolism, and Cardiovascular Diseases : NMCD	Not specifically n-3 intervention/ exposure
15963403	Mozaffarian D and Bryson CL and Lemaitre RN and Burke GL and Siscovick DS	Fish intake and risk of incident heart failure.	Journal of the American College of Cardiology	Not specifically n-3 intervention/ exposure
15930443	Carrero JJ and Lopez-Huertas E and Salmeron LM and Baro L and Ros E	Daily supplementation with (n-3) PUFAs, oleic acid, folic acid, and vitamins B-6 and E increases pain-free walking distance and improves risk factors in men with peripheral vascular disease.	The Journal of Nutrition	Not specifically n-3 intervention/ exposure
15745721	Nakamura Y and Ueshima H and Okamura T and Kadowaki T and Hayakawa T and Kita Y and Tamaki S and Okayama A	Association between fish consumption and all-cause and cause-specific mortality in Japan: NIPPON DATA80, 1980-99.	The American Journal of Medicine	Not specifically n-3 intervention/ exposure
15668367	Mozaffarian D and Longstreth WT Jr and Lemaitre RN and Manolio TA and Kuller LH and Burke GL and Siscovick DS	Fish consumption and stroke risk in elderly individuals: the cardiovascular health study.	Archives of Internal Medicine	Not specifically n-3 intervention/ exposure
15668366	Laaksonen DE1, Nyyssönen K, Niskanen L, Rissanen TH, Salonen JT.	Prediction of cardiovascular mortality in middle-aged men by dietary and serum linoleic and polyunsaturatedfatty acids.	Arch Intern Med.	Not specifically n-3 intervention/ exposure
15514281	Baylin A1, Campos H.	Arachidonic acid in adipose tissue is associated with nonfatal acute myocardial infarction in the central valley ofCosta Rica.	J Nutr.	Not specifically n-3 intervention/ exposure
15262826	Mozaffarian D and Psaty BM and Rimm EB and Lemaitre RN and Burke GL and Lyles MF and Lefkowitz D and Siscovick DS	Fish intake and risk of incident atrial fibrillation.	Circulation	Not specifically n-3 intervention/ exposure
15165614	Carrero JJ and Baro L and Fonolla J and Gonzalez-Santiago M and Martinez-Ferez A and Castillo R and Jimenez J and Boza JJ and Lopez-Huertas E	Cardiovascular effects of milk enriched with omega-3 polyunsaturated fatty acids, oleic acid, folic acid, and vitamins E and B6 in volunteers with mild hyperlipidemia.	Nutrition (Burbank, Los Angeles County, Calif.)	Not specifically n-3 intervention/ exposure

PMID	Authors	Title	Journal	Rejection Reason
15159227	Brady LM and Lovegrove SS and Lesauvage SV and Gower BA and Minihane AM and Williams CM and Lovegrove JA	Increased n-6 polyunsaturated fatty acids do not attenuate the effects of long-chain n-3 polyunsaturated fatty acids on insulin sensitivity or triacylglycerol reduction in Indian Asians.	The American Journal of Clinical Nutrition	Not specifically n-3 intervention/ exposure
15087307	Matthan NR and Welty FK and Barrett PH and Harausz C and Dolnikowski GG and Parks JS and Eckel RH and Schaefer EJ and Lichtenstein AH	Dietary hydrogenated fat increases high-density lipoprotein apoA-I catabolism and decreases low-density lipoprotein apoB-100 catabolism in hypercholesterolemic women.	Arteriosclerosis, Thrombosis, and Vascular Biology	Not specifically n-3 intervention/ exposure
15051840	Clifton PM1, Keogh JB, Noakes M.	Trans fatty acids in adipose tissue and the food supply are associated with myocardial infarction.	J Nutr.	Not specifically n-3 intervention/ exposure
14717057	Wang L1, Folsom AR, Eckfeldt JH.	Plasma fatty acid composition and incidence of coronary heart disease in middle aged adults: the Atherosclerosis Risk in Communities (ARIC) Study.	Nutr Metab Cardiovasc Dis.	Not specifically n-3 intervention/ exposure
12663274	Kark JD1, Kaufmann NA, Binka F, Goldberger N, Berry EM.	Adipose tissue n-6 fatty acids and acute myocardial infarction in a population consuming a diet high in polyunsaturated fatty acids.	Am J Clin Nutr.	Not specifically n-3 intervention/ exposure
12653399	R. F. M. Gillum and M. E. Madans and J. H.	Fish consumption and hypertension incidence in African Americans and whites: the NHANES I Epidemiologic Follow-up Study	Journal of the National Medical Association	Not specifically n-3 intervention/ exposure
12642356	Mozaffarian D and Lemaitre RN and Kuller LH and Burke GL and Tracy RP and Siscovick DS	Cardiac benefits of fish consumption may depend on the type of fish meal consumed: the Cardiovascular Health Study.	Circulation	Not specifically n-3 intervention/ exposure
12433513	Singh RB and Dubnov G and Niaz MA and Ghosh S and Singh R and Rastogi SS and Manor O and Pella D and Berry EM	Effect of an Indo-Mediterranean diet on progression of coronary artery disease in high risk patients (Indo-Mediterranean Diet Heart Study): a randomised single-blind trial.	Lancet	Not specifically n-3 intervention/ exposure
11857049	Tarpila S and Aro A and Salminen I and Tarpila A and Kleemola P and Akkila J and Adlercreutz H	The effect of flaxseed supplementation in processed foods on serum fatty acids and enterolactone.	European Journal of Clinical Nutrition	Not specifically n-3 intervention/ exposure
11829698	Jula A and Marniemi J and Huupponen R and Virtanen A and Rastas M and Ronnemaa T	Effects of diet and simvastatin on serum lipids, insulin, and antioxidants in hypercholesterolemic men: a randomized controlled trial.	JAMA	Not specifically n-3 intervention/ exposure
11253967	Oomen 2001 Holland	Association between trans fatty acid intake and 10-year risk of coronary heart disease in the Zutphen Elderly Study: a prospective population-based study.	Lancet. 2001 Mar 10;357(9258):746-51.	Not specifically n-3 intervention/ exposure

PMID	Authors	Title	Journal	Rejection Reason
11226981	Iso 2001 US (NHS)	Serum triglycerides and risk of coronary heart disease among Japanese men and women.	Am J Epidemiol. 2001 Mar 1;153(5):490-9.	Not specifically n-3 intervention/ exposure
10760632	Gillum RF1, Mussolino M, Madans JH.	The relation between fish consumption, death from all causes, and incidence of coronary heart disease. the NHANES I Epidemiologic Follow-up Study.	J Clin Epidemiol. 2000 Mar 1;53(3):237-44.	Not specifically n-3 intervention/ exposure
10584044	Hu 1999 US (NHS)	Dietary saturated fats and their food sources in relation to the risk of coronary heart disease in women.	Am J Clin Nutr. 1999 Dec;70(6):1001-8.	Not specifically n-3 intervention/ exposure
10510585	Kinjo Y, Beral V, Akiba S, Key T, Mizuno S, Appleby P, Yamaguchi N, Watanabe S, Doll R.	Possible protective effect of milk, meat and fish for cerebrovascular disease mortality in Japan.	J Epidemiol. 1999 Aug;9(4):268-74.	Not specifically n-3 intervention/ exposure
10205349	Leng GC, Lee AJ, Fowkes FG, Jepson RG, Lowe GD, Skinner ER, Mowat BF.	Randomized controlled trial of gamma-linolenic acid and eicosapentaenoic acid in peripheral arterial disease.		Not specifically n-3 intervention/ exposure
9989963	DeLorgeril	Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study.	Circulation. 1999 Feb 16;99(6):779-85.	Not specifically n-3 intervention/ exposure
9415002	Mann JI, Appleby PN, Key TJ, Thorogood M.	Dietary determinants of ischaemic heart disease in health conscious individuals.	Heart. 1997 Nov;78(5):450-5.	Not specifically n-3 intervention/ exposure
9343002	Fraser 1997	Risk factors for all-cause and coronary heart disease mortality in the oldest-old. The Adventist Health Study.	Arch Intern Med. 1997 Oct 27;157(19):2249-58.	Not specifically n-3 intervention/ exposure
8610699	Gillum RF, Mussolino ME, Ingram DD.	Physical activity and stroke incidence in women and men. The NHANES I Epidemiologic Follow-up Study.	Am J Epidemiol. 1996 May 1;143(9):860-9.	Not specifically n-3 intervention/ exposure
8604960	Gillum RF1, Mussolino ME, Madans JH.	The relationship between fish consumption and stroke incidence. The NHANES I Epidemiologic Follow-up Study (National Health and Nutrition Examination Survey).	Arch Intern Med.	Not specifically n-3 intervention/ exposure
8280516	Roberts TL1, Wood DA, Riemersma RA, Gallagher PJ, Lampe FC.	Linoleic acid and risk of sudden cardiac death.	Br Heart J.	Not specifically n-3 intervention/ exposure

PMID	Authors	Title	Journal	Rejection Reason
7911176	de Lorgeril M., Renaud S., Mamelle N., Salen P., Martin JL., Monjaud I., Guidollet J., Touboul P., Delaye J.	Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease.	Lancet; 1994, 343-8911	Not specifically n-3 intervention/ exposure
5228820	Leren P	The effect of plasma cholesterol lowering diet in male survivors of myocardial infarction. A controlled clinical trial.	Acta Med Scand Suppl. 1966;466:1-92.	Not specifically n-3 intervention/ exposure
1638709	Fraser 1992a US (adventist)	Effects of traditional coronary risk factors on rates of incident coronary events in a low-risk population. The Adventist Health Study.	Circulation. 1992 Aug;86(2):406-13.	Not specifically n-3 intervention/ exposure
1617510	Bairati I., Roy L., Meyer F.	Effects of a fish oil supplement on blood pressure and serum lipids in patients treated for coronary artery disease.	The Canadian Journal of Cardiology, 8-1	Not specifically n-3 intervention/ exposure
24638908	Bonds DE and Harrington M and Worrall BB and Bertoni AG and Eaton CB and Hsia J and Robinson J and Clemons TE and Fine LJ and Chew EY	Effect of long-chain omega-3 fatty acids and lutein + zeaxanthin supplements on cardiovascular outcomes: results of the Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial.	JAMA Internal Medicine	P: Not general population (macular degeneration)
none	A. R. N. Rahbar and I. Amiri and Z.	Effects of omega-3 fatty acids on serum lipids and high sensitivity C reactive protein in cigarette smokers	Journal of Biological Sciences	Parallel RCT N<30/arm
none	A. S. B. J. G. M. Venkata Krishnan P	Effects of low dose omega-3 fatty acids on platelet functions and coagulation profile in Indian patients with type 2 diabetes mellitus with vascular complications: A prospective, preliminary study	Journal, Indian Academy of Clinical Medicine	Parallel RCT N<30/arm
none	A. Yates and Norwig and J. and Maroon and J. C. and Bost and J. and Bradley and J. P. and Duca and M. and Wecht and D. A. and Grove and R. and Iso and A. and Cobb and I. and Ross and N. and Borden and M.	Evaluation of lipid profiles and the use of omega-3 essential fatty acid in professional football players		Parallel RCT N<30/arm
none	F. P. Garmendia and R. Ronceros and G.	Effect of sacha inchi oil (Plukenetia volubilis L) on the lipid profile of patients with Hyperlipoproteinemia	Revista Peruana de Medicina de Experimental y Salud Publica	Parallel RCT N<30/arm
none	F. Shidfar and Keshavarz and A. and Jalali and M. and Miri and R. and Amri and A. and Shidfar and S. H.	Effects of purified omega-3 fatty acids on serum lipoproteins and malondialdehyde in postmenopausal fat women receiving hormone replacement therapy		Parallel RCT N<30/arm
none	H. Rus and Radoi and M. and Ciurea and C. and Nan and M. and Suta and C. and Boda and D.	Effect of treatment with omega-3 fattyacids and atorvastatin in patients with combined dyslipidemia		Parallel RCT N<30/arm
none	J. Coad and Morel and P. C. H. and Booth and C.	Effect of consuming pork meat enriched with long chain omega 3 fatty acids and selenium on markers of cardiovascular disease	Proceedings of the Massey University Advancing Pork Production Seminar, Palmerston North, New Zealand, 7th June	Parallel RCT N<30/arm

PMID	Authors	Title	Journal	Rejection Reason
none	J. D. B. Buckley and S. Murphy and K. J. Howe and P. R. C.	DHA-rich fish oil lowers heart rate during submaximal exercise in elite Australian Rules footballers	Journal of Science and Medicine in Sport	Parallel RCT N<30/arm
none	K. P. V. A. R. G. M. B. J. Bhise A	Effect of low-dose omega-3 fatty acids substitution on blood pressure, hyperinsulinemia and dyslipidemia in Indians with essential hypertension: A pilot study	Indian Journal of Clinical Biochemistry	Parallel RCT N<30/arm
none	M. J. M. H. W. S. Isley Wl	Pilot study of combined therapy with -3 fatty acids and niacin in atherogenic dyslipidemia	Journal of Clinical Lipidology	Parallel RCT N<30/arm
none	S. U. S. L. S. D. M. V. D. K. A. J. S. P. A.-K. M. U. M. I. J. Erkkila At	Effect of fatty and lean fish intake on lipoprotein subclasses in subjects with coronary heart disease: A controlled trial	Journal of Clinical Lipidology	Parallel RCT N<30/arm
none	W. R. S. T. Liu M	Effect of bread containing stable fish oil on plasma phospholipid fatty acids, triglycerides, HDL-cholesterol, and malondialdehyde in subjects with hyperlipidemia	Nutrition Research (New York, N.Y.)	Parallel RCT N<30/arm
8908382eag	Rossing P., Hansen BV., Nielsen FS., Myrup B., Hølmer G., Parving HH.	Fish oil in diabetic nephropathy.	Diabetes Care; 1996, 19-11	Parallel RCT N<30/arm
24290606	Simao AN and Lozovoy MA and Dichi I	Effect of soy product kinako and fish oil on serum lipids and glucose metabolism in women with metabolic syndrome.	Nutrition (Burbank, Los Angeles County, Calif.)	Parallel RCT N<30/arm
23888318	Hlais S and El-Bistami D and El Rahi B and Mattar MA and Obeid OA	Combined fish oil and high oleic sunflower oil supplements neutralize their individual effects on the lipid profile of healthy men.	Lipids	Parallel RCT N<30/arm
23375525	Guebre-Egziabher F and Debard C and Drai J and Denis L and Pesenti S and Bienvenu J and Vidal H and Laville M and Fouque D	Differential dose effect of fish oil on inflammation and adipose tissue gene expression in chronic kidney disease patients.	Nutrition (Burbank, Los Angeles County, Calif.)	Parallel RCT N<30/arm
23332800	Dawczynski C and Massey KA and Ness C and Kiehntopf M and Stepanow S and Platzer M and Grun M and Nicolaou A and Jahreis G	Randomized placebo-controlled intervention with n-3 LC-PUFA-supplemented yoghurt: effects on circulating eicosanoids and cardiovascular risk factors.	Clinical Nutrition (Edinburgh, Scotland)	Parallel RCT N<30/arm
22952598	Ottestad I and Hassani S and Borge GI and Kohler A and Vogt G and Hyotylainen T and Oresic M and Bronner KW and Holven KB and Ulven SM and Myhrstad MC	Fish oil supplementation alters the plasma lipidomic profile and increases long-chain PUFAs of phospholipids and triglycerides in healthy subjects.	PloS one	Parallel RCT N<30/arm
22773687	Ooi EM and Lichtenstein AH and Millar JS and Diffenderfer MR and Lamon-Fava S and Rasmussen H and Welty FK and Barrett PH and Schaefer EJ	Effects of Therapeutic Lifestyle Change diets high and low in dietary fish-derived FAs on lipoprotein metabolism in middle-aged and elderly subjects.	Journal of Lipid Research	Parallel RCT N<30/arm
22293584	Sasaki J and Miwa T and Odawara M	Administration of highly purified eicosapentaenoic acid to statin-treated diabetic patients further improves vascular function.	Endocrine Journal	Parallel RCT N<30/arm
21701083	Takaki A and Umemoto S and Ono K and Seki K and Ryoke T and Fujii A and Itagaki T and Harada M and Tanaka M and Yonezawa T and Ogawa H and Matsuzaki M	Add-on therapy of EPA reduces oxidative stress and inhibits the progression of aortic stiffness in patients with coronary artery disease and statin therapy: a randomized controlled study.	Journal of Atherosclerosis and Thrombosis	Parallel RCT N<30/arm

PMID	Authors	Title	Journal	Rejection Reason
21543294	Ozaydin M and Erdogan D and Tayyar S and Uysal BA and Dogan A and Icli A and Ozkan E and Varol E and Turker Y and Arslan A	N-3 polyunsaturated fatty acids administration does not reduce the recurrence rates of atrial fibrillation and inflammation after electrical cardioversion: a prospective randomized study.	Anadolu Kardiyoloji Dergisi : AKD = The Anatolian Journal of Cardiology	Parallel RCT N<30/arm
21232631	Kumar S and Sutherland F and Wheeler M and Heck PM and Lee G and Teh AW and Garg ML and Morgan JG and Sparks PB	Effects of chronic omega-3 polyunsaturated fatty acid supplementation on human atrial mechanical function after reversion of atrial arrhythmias to sinus rhythm: reversal of tachycardia-mediated atrial cardiomyopathy with fish oils.	Heart Rhythm : the Official Journal of the Heart Rhythm Society	Parallel RCT N<30/arm
20303788	Bouzidi N and Mekki K and Boukaddoum A and Dida N and Kaddous A and Bouchenak M	Effects of omega-3 polyunsaturated fatty-acid supplementation on redox status in chronic renal failure patients with dyslipidemia.	Journal of Renal Nutrition : The Official Journal of the Council on Renal Nutrition of the National Kidney Foundation	Parallel RCT N<30/arm
20125104	van Hees AM and Saris WH and Hul GB and Schaper NC and Timmerman BE and Lovegrove JA and Roche HM and Blaak EE	Effects of dietary fat modification on skeletal muscle fatty acid handling in the metabolic syndrome.	International Journal of Obesity (2005)	Parallel RCT N<30/arm
19854375	Maki KC and Reeves MS and Farmer M and Griinari M and Berge K and Vik H and Hubacher R and Rains TM	Krill oil supplementation increases plasma concentrations of eicosapentaenoic and docosahexaenoic acids in overweight and obese men and women.	Nutrition Research (New York, N.Y.)	Parallel RCT N<30/arm
19390588	Lankinen M and Schwab U and Erkkila A and Seppanen-Laakso T and Hannila ML and Mussalo H and Lehto S and Uusitupa M and Gylling H and Oresic M	Fatty fish intake decreases lipids related to inflammation and insulin signaling--a lipidomics approach.	PloS one	Parallel RCT N<30/arm
19261730	Egert S and Kannenberg F and Somoza V and Erbersdobler HF and Wahrburg U	Dietary alpha-linolenic acid, EPA, and DHA have differential effects on LDL fatty acid composition but similar effects on serum lipid profiles in normolipidemic humans.	The Journal of Nutrition	Parallel RCT N<30/arm
18665413	Erkkila AT and Schwab US and de Mello VD and Lappalainen T and Mussalo H and Lehto S and Kemi V and Lamberg-Allardt C and Uusitupa MI	Effects of fatty and lean fish intake on blood pressure in subjects with coronary heart disease using multiple medications.	European Journal of Nutrition	Parallel RCT N<30/arm
18460481	Kaul N and Kreml R and Austria JA and Richard MN and Edel AL and Dibrov E and Hirono S and Zettler ME and Pierce GN	A comparison of fish oil, flaxseed oil and hempseed oil supplementation on selected parameters of cardiovascular health in healthy volunteers.	Journal of the American College of Nutrition	Parallel RCT N<30/arm
17805229	Wang S and Ma AQ and Song SW and Quan QH and Zhao XF and Zheng XH	Fish oil supplementation improves large arterial elasticity in overweight hypertensive patients.	European Journal of Clinical Nutrition	Parallel RCT N<30/arm
17510682	Thomas TR and Liu Y and Linden MA and Rector RS	Interaction of exercise training and n-3 fatty acid supplementation on postprandial lipemia.	Applied Physiology, Nutrition, and Metabolism = Physiologie Appliquee, Nutrition et Metabolisme	Parallel RCT N<30/arm
17327864	Mostad IL and Bjerve KS and Lydersen S and Grill V	Effects of marine n-3 fatty acid supplementation on lipoprotein subclasses measured by nuclear magnetic resonance in subjects with type II diabetes.	European Journal of Clinical Nutrition	Parallel RCT N<30/arm

PMID	Authors	Title	Journal	Rejection Reason
16781788	Patel JV and Lee KW and Tomson J and Dubb K and Hughes EA and Lip GY	Effects of omega-3 polyunsaturated fatty acids on metabolically active hormones in patients post-myocardial infarction.	International Journal of cCardiology	Parallel RCT N<30/arm
16482073	Goyens PL and Mensink RP	Effects of alpha-linolenic acid versus those of EPA/DHA on cardiovascular risk markers in healthy elderly subjects.	European Journal of Clinical Nutrition	Parallel RCT N<30/arm
16317123	Goyens PL and Mensink RP	The dietary alpha-linolenic acid to linoleic acid ratio does not affect the serum lipoprotein profile in humans.	The Journal of Nutrition	Parallel RCT N<30/arm
16278686	Wu WH and Lu SC and Wang TF and Jou HJ and Wang TA	Effects of docosahexaenoic acid supplementation on blood lipids, estrogen metabolism, and in vivo oxidative stress in postmenopausal vegetarian women.	European Journal of Clinical Nutrition	Parallel RCT N<30/arm
15250255	Hong H and Xu ZM and Pang BS and Cui L and Wei Y and Guo WJ and Mao YL and Yang XC	Effects of simvastain combined with omega-3 fatty acids on high sensitive C-reactive protein, lipidemia, and fibrinolysis in patients with mixed dyslipidemia.	Chinese Medical Sciences Journal = Chung-kuo i hsueh k'o hsueh tsa chih / Chinese Academy of Medical Sciences	Parallel RCT N<30/arm
15226460	Li Z and Lamon-Fava S and Otvos J and Lichtenstein AH and Velez-Carrasco W and McNamara JR and Ordovas JM and Schaefer EJ	Fish consumption shifts lipoprotein subfractions to a less atherogenic pattern in humans.	The Journal of Nutrition	Parallel RCT N<30/arm
12871402	Nordoy A and Svensson B and Hansen JB	Atorvastatin and omega-3 fatty acids protect against activation of the coagulation system in patients with combined hyperlipemia.	Journal of Thrombosis and Haemostasis : JTH	Parallel RCT N<30/arm
12540386	Chan DC and Watts GF and Mori TA and Barrett PH and Redgrave TG and Beilin LJ	Randomized controlled trial of the effect of n-3 fatty acid supplementation on the metabolism of apolipoprotein B-100 and chylomicron remnants in men with visceral obesity.	The American Journal of Clinical Nutrition	Parallel RCT N<30/arm
12421024	Jain S and Gaiha M and Bhattacharjee J and Anuradha S	Effects of low-dose omega-3 fatty acid substitution in type-2 diabetes mellitus with special reference to oxidative stress--a prospective preliminary study.	The Journal of the Association of Physicians of India	Parallel RCT N<30/arm
12399272	Woodman RJ and Mori TA and Burke V and Puddey IB and Watts GF and Beilin LJ	Effects of purified eicosapentaenoic and docosahexaenoic acids on glycemic control, blood pressure, and serum lipids in type 2 diabetic patients with treated hypertension.	The American Journal of Clinical Nutrition	Parallel RCT N<30/arm
12370843	Karvonen HM and Aro A and Tapola NS and Salminen I and Uusitupa MI and Sarkkinen ES	Effect of alpha-linolenic acid-rich Camelina sativa oil on serum fatty acid composition and serum lipids in hypercholesterolemic subjects.	Metabolism: Clinical and Experimental	Parallel RCT N<30/arm
12351465	Petersen M and Pedersen H and Major-Pedersen A and Jensen T and Marckmann P	Effect of fish oil versus corn oil supplementation on LDL and HDL subclasses in type 2 diabetic patients.	Diabetes Care	Parallel RCT N<30/arm
12145002	Nestel P and Shige H and Pomeroy S and Cehun M and Abbey M and Raederstorff D	The n-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid increase systemic arterial compliance in humans.	The American Journal of Clinical Nutrition	Parallel RCT N<30/arm
11925466	Kratz M and Gulbahce E and von Eckardstein A and Cullen P and Cignarella A and Assmann G and Wahrburg U	Dietary mono- and polyunsaturated fatty acids similarly affect LDL size in healthy men and women.	The Journal of Nutrition	Parallel RCT N<30/arm

PMID	Authors	Title	Journal	Rejection Reason
10919932	Stark KD and Park EJ and Maines VA and Holub BJ	Effect of a fish-oil concentrate on serum lipids in postmenopausal women receiving and not receiving hormone replacement therapy in a placebo-controlled, double-blind trial.	The American Journal of Clinical Nutrition	Parallel RCT N<30/arm
8112187	Axelrod L., Camuso J., Williams E., Kleinman K., Briones E., Schoenfeld D.	Effects of a small quantity of omega-3 fatty acids on cardiovascular risk factors in NIDDM. A randomized, prospective, double-blind, controlled study.	Diabetes Care. 1994 Jan;17(1):37-44.	Parallel RCT N<30/arm
3020732	Haines AP., Sanders TA., Imeson JD., Mahler RF., Martin J., Mistry M., Vickers M., Wallace PG.	Effects of a fish oil supplement on platelet function, haemostatic variables and albuminuria in insulin-dependent diabetics.	Thrombosis Research; 1986, 43-6	Parallel RCT N<30/arm
19487105	Ramel A and Martinez JA and Kiely M and Bandarra NM and Thorsdottir I	Moderate consumption of fatty fish reduces diastolic blood pressure in overweight and obese European young adults during energy restriction.	Nutrition (Burbank, Los Angeles County, Calif.)	Weight loss intervention
18029476	Plat J and Jellema A and Ramakers J and Mensink RP	Weight loss, but not fish oil consumption, improves fasting and postprandial serum lipids, markers of endothelial function, and inflammatory signatures in moderately obese men.	The Journal of Nutrition	Weight loss intervention
15361771	Mori TA and Burke V and Puddey IB and Shaw JE and Beilin LJ	Effect of fish diets and weight loss on serum leptin concentration in overweight, treated-hypertensive subjects.	Journal of Hypertension	Weight loss intervention
8918511	Anderssen SA., Hjermann I., Urdal P., Torjesen PA., Holme I.	Improved carbohydrate metabolism after physical training and dietary intervention in individuals with the "atherothrombogenic syndrome'. Oslo Diet and Exercise Study (ODES). A randomized trial.	Journal of Internal Medicine. 1996 Oct; 240(4): 203-9	Weight loss intervention
1586398		The effects of nonpharmacologic interventions on blood pressure of persons with high normal levels. Results of the Trials of Hypertension Prevention, Phase I.	JAMA.	Weight loss intervention
none	S. S. B. P. S. L. E. K. M. W. R. C. L. N. M. Sindelar Ca	Serum lipids of physically active adults consuming omega-3 fatty acid-enriched eggs or conventional eggs	Nutrition Research (New York, N.Y.)	XO N<20
none	K. C. L. Maki and B. C. Reeves and M. S. Dicklin and M. R. Harris and W. S.	Prescription omega-3 acid ethyl esters plus simvastatin 20 and 80 mg: effects in mixed dyslipidemia	Journal of Clinical Lipidology	XO N<20
none	L. N. M. S. S. E. C. T. P. Lee J-Y	Consumption of omega-3 fatty acid-enriched eggs and serum lipids in humans	Journal of Nutraceuticals, Functional and Medical Foods	XO N<20
none	R. L. Purcell and S. H. Botham and K. H. Hall and W. L. Wheeler-Jones and C. P. D.	High-fat meals rich in EPA plus DHA compared with DHA only have differential effects on postprandial lipemia and plasma 8-isoprostane F2(alpha)concentrations relative to a control high-oleic acid meal: A randomized controlled trial	American Journal of Clinical Nutrition	XO N<20
22182482	Lee SP and Dart AM and Walker KZ and O'Dea K and Chin-Dusting JP and Skilton MR	Effect of altering dietary n-6:n-3 PUFA ratio on cardiovascular risk measures in patients treated with statins: a pilot study.	The British Journal of Nutrition	XO N<20

PMID	Authors	Title	Journal	Rejection Reason
21775113	Maki KC and Lawless AL and Kelley KM and Dicklin MR and Schild AL and Rains TM	Prescription omega-3-acid ethyl esters reduce fasting and postprandial triglycerides and modestly reduce pancreatic beta-cell response in subjects with primary hypertriglyceridemia.	Prostaglandins, Leukotrienes, and Essential Fatty Acids	XO N<20
19824016	Coulman KD and Liu Z and Michaelides J and Quan Hum W and Thompson LU	Fatty acids and lignans in unground whole flaxseed and sesame seed are bioavailable but have minimal antioxidant and lipid-lowering effects in postmenopausal women.	Molecular Nutrition & Food Research	XO N<20
19215678	Utarwuthipong T and Komindr S and Pakpeankitvatana V and Songchitsomboon S and Thongmuang N	Small dense low-density lipoprotein concentration and oxidative susceptibility changes after consumption of soybean oil, rice bran oil, palm oil and mixed rice bran/palm oil in hypercholesterolaemic women.	The Journal of International Medical Research	XO N<20
18991244	Ohman M and Akerfeldt T and Nilsson I and Rosen C and Hansson LO and Carlsson M and Larsson A	Biochemical effects of consumption of eggs containing omega-3 polyunsaturated fatty acids.	Upsala Journal of Medical Sciences	XO N<20
17268414	Lindqvist H and Langkilde AM and Undeland I and Radendal T and Sandberg AS	Herring (Clupea harengus) supplemented diet influences risk factors for CVD in overweight subjects.	European Journal of Clinical Nutrition	XO N<20
17103080	Schwab US and Callaway JC and Erkkila AT and Gynther J and Uusitupa MI and Jarvinen T	Effects of hempseed and flaxseed oils on the profile of serum lipids, serum total and lipoprotein lipid concentrations and haemostatic factors.	European Journal of Nutrition	XO N<20
16825681	Vega-Lopez S and Ausman LM and Jalbert SM and Erkkila AT and Lichtenstein AH	Palm and partially hydrogenated soybean oils adversely alter lipoprotein profiles compared with soybean and canola oils in moderately hyperlipidemic subjects.	The American Journal of Clinical Nutrition	XO N<20
16616012	O'Keefe JH Jr and Abuissa H and Sastre A and Steinhaus DM and Harris WS	Effects of omega-3 fatty acids on resting heart rate, heart rate recovery after exercise, and heart rate variability in men with healed myocardial infarctions and depressed ejection fractions.	The American Journal of Cardiology	XO N<20
15936647	Tahvonen RL and Schwab US and Linderborg KM and Mykkanen HM and Kallio HP	Black currant seed oil and fish oil supplements differ in their effects on fatty acid profiles of plasma lipids, and concentrations of serum total and lipoprotein lipids, plasma glucose and insulin.	The Journal of Nutritional Biochemistry	XO N<20
14767865	Calabresi L and Villa B and Canavesi M and Sirtori CR and James RW and Bernini F and Franceschini G	An omega-3 polyunsaturated fatty acid concentrate increases plasma high-density lipoprotein 2 cholesterol and paraoxonase levels in patients with familial combined hyperlipidemia.	Metabolism: Clinical and Experimental	XO N<20
12162948	Villa B and Calabresi L and Chiesa G and Rise P and Galli C and Sirtori CR	Omega-3 fatty acid ethyl esters increase heart rate variability in patients with coronary disease.	Pharmacological Research : The Official Journal of the Italian Pharmacological Society	XO N<20
11675948	Miyajima T and Tsujino T and Saito K and Yokoyama M	Effects of eicosapentaenoic acid on blood pressure, cell membrane fatty acids, and intracellular sodium concentration in essential hypertension.	Hypertension Research : Official Journal of the Japanese Society of Hypertension	XO N<20
10657575	Calabresi L and Donati D and Pazzucconi F and Sirtori CR and Franceschini G	Omacor in familial combined hyperlipidemia: effects on lipids and low density lipoprotein subclasses.	Atherosclerosis	XO N<20

Appendix C. Risk of Bias Assessment

Table C-1. Comparative studies

Author, Year PMID*	Randomization: allocation sequence adequately generated	Allocation adequately concealed	Participants adequately blinded	Outcome assessors adequately blinded	Attrition bias: Incomplete outcome data	Selective outcome reporting bias (Yes/No)	Intention-to-treat analysis? (Yes/No)	Group similarity at baseline (general)	Group similarity at baseline (Omega-3)	Similar compliance across groups	Additional bias
Baxheinrich, 2012, 22894911	Unclear	Unclear	High	Low	Low	No	No	Low	Unclear	High	
Bosch, 2012, 22686415	Unclear	Low	Low	Low	Low	No	No	Low	Low	Unclear	
Brinton, 2013, 22819432 23835245	Unclear	Low	Low	Low	Low	No	Yes	Low	Unclear	Unclear	
Brouwer, 2006, 16772624	Low	Low	Low	Low	Low	No	Yes	Low	Low	Low	
Burr, 2003, 12571649 17343767	Unclear	Low	High	Low	Low	No	Yes	Low	Low	Low	
Burr, 1989, 2571009 10578215 12032650	Unclear	High	High	High	Low	Yes	Yes	Low	Unclear	Low	
Carrepeiro, 2011, 21561620	Unclear	Unclear	Low	Low	Low	No	No	Low	Unclear	Low	Yes (Statin subgroups treated as randomized factors, but really just matched. Matching failed to make baseline lipoprotein concentrations similar.)
Carter, 2012, 22707560	Unclear	Unclear	Low	Unclear	Low	No	Yes	Low	Unclear	Unclear	
Caslake, 2008, 18779276	Low	Unclear	Low	Low	Low	No	Unclear	Low	Low	Low	
Damsgaard, 2008, 18492834	Low	Low	Low	Low	Low	No	Yes	Low	Low	Low	

Author, Year PMID*	Randomization: allocation sequence adequately generated	Allocation adequately concealed	Participants adequately blinded	Outcome assessors adequately blinded	Attrition bias: Incomplete outcome data	Selective outcome reporting bias (Yes/No)	Intention-to-treat analysis? (Yes/No)	Group similarity at baseline (general)	Group similarity at baseline (Omega-3)	Similar compliance across groups	Additional bias
Derosa, 2009, 19397392	Low	Low	Low	Low	Low	No	Yes	Low	Unclear	Unclear	
Earnest, 2012, 22811376	Low	Low	Low	Low	Low	No	No	Low	Low	Unclear	
Ebrahimi, 2009, 19593941	Unclear	Unclear	Unclear	Low/High for BP	Unclear	No	Unclear	Low	Unclear	Unclear	
Einvik, 2010, 16926660 19595382 20389249	Low	Unclear	Low	Low	Low	No	Yes	Low	Low	Low	
Eritsland, 1996, 7702027 8540453	Unclear	Low	Unclear	Unclear	Low	No	Yes (death); No (lipids)	Low	Low	Low	
Finnegan, 2003, 12663273	Low	Low	Low	Low	Low	No	No	Low	Low	Low	
Galan, 2010, 18544171 21115589 21801476 22365647	Low	Low	Low	Unclear	Low	No	Yes	Low	Low	Low	
Grieger, 2014, 24454276	Unclear	Unclear	High	Unclear	Low	No	Yes	Low	Low	Low	
Grimsgaard, 1998, 9280188 9665096	Low	Unclear	Low	Low	Low	No	No	Low	Unclear	Low	
Harrison, 2004, 15853118	Low	Low	Low	Low	High	No	Yes	Low	High	Low	
Holman, 2009, 19002433 21036355	Low	Low	Low	Low	Low	Yes	No	Low	Low	Low	
Jones, 2014, 24829493	Low	Low	Low	Low	High	No	Unclear	Low	Low	Low	
Kastelein, 2014, 24528690	Unclear	Unclear	Low	Unclear	Low	No	Yes	Low	Low	High	

Author, Year PMID*	Randomization: allocation sequence adequately generated	Allocation adequately concealed	Participants adequately blinded	Outcome assessors adequately blinded	Attrition bias: Incomplete outcome data	Selective outcome reporting bias (Yes/No)	Intention-to-treat analysis? (Yes/No)	Group similarity at baseline (general)	Group similarity at baseline (Omega-3)	Similar compliance across groups	Additional bias
Kromhout, 2010, 20362710 20929341 22110169 22301766	Low	Low	Low	Low	Low	No	Yes	Low	Low	High	
Kuhnt, 2014, 24553695	Low	Low	Low	Low	Low	No	No	Low	Low	Unclear	
Leaf, 2005, 16267249	Low	Unclear	Low	Low	Low	No	Yes	Low	Low	Low	
Liu, 2003, no PMID	Unclear	Unclear	Unclear	Low	Low	No	Yes	Low	Low	Low	
Lungershausen, 1994, 7852747	Low	Unclear	Low	Unclear	Low	No	Yes	Low	Unclear	Low	
Macchia, 2013, 23265344	Unclear	Low	Low	Low	Unclear	No	No	Low	Unclear	Unclear	
Maki, 2010, 17825687 20451686	Low	Low	Low	Low	Low	No	Yes	High	Unclear	Low	
Maki, 2013, 23998969	Unclear	Unclear	Low	Low	High	No	Yes	Low	Low	Low	
Marchioli, 2002, 10465168 11997274 17876196	Low	Unclear	High	Unclear	Low	No	Yes	Low	Unclear	Low	
Natvig, 1968, 5756076	Unclear	Low	Low	High	High	No	Yes	Unclear	Low	Low	
Nilsen, 2001, 11451717 15297084	Low	Low	Low	Low	High	Yes	Yes	Low	Unclear	Unclear	
Nodari, 2011, 21844082	Low	Low	Low	Low	Unclear	No	No	Low	Unclear	Unclear	
Nodari, 2011, 21215550	Unclear	Unclear	Low	Low	Low	No	Yes	Low	Low	Low	
Oh, 2014, 25147070	Low	Low	Low	Low	Low	No	Unclear	Low	Unclear	Unclear	
Olano-Martin, 2010, 19748619	Unclear	Unclear	Low	Low	Low	No	Unclear	Low	Low	Low	

Author, Year PMID*	Randomization: allocation sequence adequately generated	Allocation adequately concealed	Participants adequately blinded	Outcome assessors adequately blinded	Attrition bias: Incomplete outcome data	Selective outcome reporting bias (Yes/No)	Intention-to-treat analysis? (Yes/No)	Group similarity at baseline (general)	Group similarity at baseline (Omega-3)	Similar compliance across groups	Additional bias
Pase, 2015, 25565485	Low	Low	Low	Low	Low	Yes	Yes	Low	Low	Low	
Pieters, 2015, 25226826	Unclear	Unclear	Low	Low	Low	No	No	Low	Low	Low	
Raitt, 2005, 15956633	Unclear	Low	Low	Low	Low	No	No	Low	Unclear	Unclear	
Ras, 2015, 25122648	Low	Low	Low	Low	Low	Yes	Yes	Low	Unclear	Low	
Rasmussen, 2006, 16469978	Low	Low	High	Low	Low	No	Yes	Low	Low	Low	
Rauch, 2010, 21060071	Low	Low	Low	Low	Low	No	Yes	Low	Unclear	Low	Unclear (High underlying levels of fish consumption during the study could have influenced the clinical event rate during followup.)
Rodriguez-Leyva, 2013, 24126178 25694068	Low	Low	High	Low	Low	No	Yes	Low	Low	Low	
Roncaglioni, 2013, 23656645	Low	Low	Low	Low	Low	No	Yes	Low	Low	Low	
Sacks, 1994, 8021472	Unclear	Low	Low	Low	High	Yes	No	Unclear	Low	Low	
Sacks, 1995, 7759696	Unclear	Low	Low	Low	High	No	Yes	Low	Low	Low	
Sanders, 2011, 21865334	Low	Low	Low	Low	Low	No	No	Low	Low	Low	
Shaikh, 2014, 25185754	Low	Low	Low	Low	High	No	No	Low	Low	Low	
Shidfar, 2003, 12847992	Unclear	Unclear	Low	Low	High	No	Unclear	Low	Unclear	Unclear	

Author, Year PMID*	Randomization: allocation sequence adequately generated	Allocation adequately concealed	Participants adequately blinded	Outcome assessors adequately blinded	Attrition bias: Incomplete outcome data	Selective outcome reporting bias (Yes/No)	Intention-to-treat analysis? (Yes/No)	Group similarity at baseline (general)	Group similarity at baseline (Omega-3)	Similar compliance across groups	Additional bias
Sirtori, 1997, 9174486	Low	Unclear	Low	Low	Low	No	Yes	Low	Unclear	High	
Soares, 2014, 24652053	Unclear	Unclear	Low	Unclear	Low	Yes	No	Low	Unclear	Unclear	
Tardivo, 2015, 25394692	Low	Unclear	High	High	High	No	Unclear	Low	Low	Unclear	
Tatsuno, 2013, 24314359	Low	Unclear	High	High	Low	Yes	Yes	Low	Low	Low	
Tatsuno, 2013, 23725919	Low	Unclear	High	High	Low	Yes	Yes	Low	Low	Low	
Tavazzi, 2008, 18757090 19589110 21315217 23351824 23839902	Low	Low	Low	Low	Low	Yes	Yes	Low	Low	Low	
Tierney, 2011, 20938439 21839455	Low	Low	High	Low	Low	No	Yes	Low	Low	Low	
Vazquez, 2014, 24462043	Low	Low	Low	Low	Low	No	Yes	Low	Unclear	Low	
Vecka, 2012, 23183517	High	Unclear	Low	Unclear	Unclear	No	Yes	Low	Low	Unclear	
von Schacky, 1999, 10189324	Low	Low	Low	Low/High for BP	Low	No	Yes	Low	Low	Low	
Yokoyama, 2007, 17398308 18451347 18667204 19423946 20484828 22186099 22653220	Low	Low	High	Low	Low	No	Yes	Low	Unclear	Unclear	

PMID = Pubmed identifiers of all included articles.

Table C-2. Observational studies

Study PMID	Selection bias (outcome of interest not present at baseline)	Comparability/ Adjustment (adjusted for confounders or other factors)	Outcome assessors adequately blinded	Incomplete outcome data (attrition bias)	Dietary assessment instrument described (studies with FFQ)?	Nutrient exposures adequately reported	Additional Bias
Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study 9149659	Unclear	Yes (Diet and CVD risk factors)	Low	Unclear	Yes (Measured n-3 FA from ONLY diet)	No	
ARIC 19061714 22570739 23920478	Low	No	Low	Unclear	Not Applicable (biomarker)	No	
CARDIA 21205024	Low	Yes (Diet and CVD risk factors)	Low	Low	Yes (Measured n-3 FA from ONLY diet)	No	
Cardiovascular Health Study 21810709 22282329 22743310 23525429 23546563 25159901	Low	Yes (Diet and CVD risk factors)	Low	Low	Not Applicable (biomarker)	Yes	
Cohort of Swedish Men 19383731	Low	Yes (Diet and CVD risk factors)	Low	Low	Yes (Measured n-3 FA from BOTH diet and supplements)	No	
Danish National Birth Cohort 22146511	Unclear	Yes (Diet and CVD risk factors)	Low	Low	Yes (Measured n-3 FA from ONLY diet)	Yes	
Diet, Cancer and Health 15640459 19825219 21859970 23945170	Low	Yes (Diet and CVD risk factors)	Low	Low	Yes (Measured n-3 FA from ONLY diet)	Yes	
EPIC Norfolk 22802735	Low	Yes (Diet and CVD risk factors)	Low	Low	Not Applicable (biomarker)	No	
Glostrup Population Studies 21865326	Low	Yes (Diet and CVD risk factors)	Low	Low	Yes (Measured n-3 FA from ONLY diet)	Yes	

Study PMID	Selection bias (outcome of interest not present at baseline)	Comparability/ Adjustment (adjusted for confounders or other factors)	Outcome assessors adequately blinded	Incomplete outcome data (attrition bias)	Dietary assessment instrument described (studies with FFQ)?	Nutrient exposures adequately reported	Additional Bias
Guangzhou 24966412	Low	Partial (Diet factors)	Low	Low	Not Applicable (biomarker)	Yes	
Healthy Physicians Follow-up Study 7885425 12495393 19064523	Low	Yes (Diet and CVD risk factors)	Low	Low	Yes (Measured n-3 FA from BOTH diet and supplements)	Yes	
Hisayama Study 24267237	Low	Yes (Diet and CVD risk factors)	Low	Low	Yes (Measured n-3 FA from ONLY diet)	Yes	
JACC 18786479	Low	Yes (Diet and CVD risk factors)	Unclear	High	Yes (Measured n-3 FA from ONLY diet)	Yes	
Japan Public Health Center-Based Study Cohort I 16401768	Low	Yes (Diet and CVD risk factors)	Low	Low	Yes (Measured n-3 FA from ONLY diet)	No	
JELIS 21099130	Low	Yes (Diet and CVD risk factors)	Unclear	Low	Not Applicable (biomarker)	No	
Kuopio Ischemic Heart Disease Risk Factor Study 19933935	Low	Partial (Diet factors)	Low	Low	Not Applicable (biomarker)	Yes	
Malmo Diet and Cancer 25008580	Low	Yes (Diet and CVD risk factors)	Low	Low	Yes (Measured n-3 FA from BOTH diet and supplements)	No	
MESA 24351702	Low	Yes (Diet and CVD risk factors)	Low	Low	Yes (Measured n-3 FA from ONLY diet)	Yes	
MORGEN 20335635 21464993 22496770 22633188	Low	Yes (Diet and CVD risk factors)	Low	Low	Yes (Measured n-3 FA from ONLY diet)	Yes	
MRFIT 1579579	Unclear	Partial (CVD risk factors)	Low	Unclear	Yes (Instrument reported but no adequate description regarding n-3 FA intake measurement)	No	
NIPPON DATA80 24468152	Low	Partial (CVD risk factors)	Low	Low	Yes (Measured n-3 FA from ONLY diet)	Yes	

Study PMID	Selection bias (outcome of interest not present at baseline)	Comparability/ Adjustment (adjusted for confounders or other factors)	Outcome assessors adequately blinded	Incomplete outcome data (attrition bias)	Dietary assessment instrument described (studies with FFQ)?	Nutrient exposures adequately reported	Additional Bias
Nurses' Health Study 11176840 11939867 16301356	Low	Yes (Diet and CVD risk factors)	High	Low	No (No data on instrument or method used to measure n-3 FA intake)	Yes	
Osaka Acute Coronary Insufficiency Study 23047296	Low	No	Unclear	Low	Not Applicable (biomarker)	Yes	
Physician's Health Study 7598116 7829792 9424039 22952185 23098619	Low	Yes (Diet and CVD risk factors)	Low	Low	Yes (Measured n-3 FA from ONLY diet)	Yes	
Pooling Project of Cohort Studies on Diet and Coronary Disease 24964401	Low	Yes (Diet and CVD risk factors)	Low	Low	Yes (nd for whether n-3 measured from both diet and supplements)	Yes	
Rotterdam Study 16569549 19789394	Low	Yes (Diet and CVD risk factors)	Low	Unclear	Yes (Measured n-3 FA from BOTH diet and supplements)	Yes	
Scottish Heart Health Extended Cohort Study 21345851	Low	Partial (CVD risk factors)	Low	Low	Yes (Measured n-3 FA from BOTH diet and supplements)	No	
Singapore Chinese Health Study 24343844	Low	Yes (Diet and CVD risk factors)	Unclear	Low	No (No data on instrument or method used to measure n-3 FA intake)	No	
Shanghai Study 11682363	Low	Yes (Diet and CVD risk factors)	Low	Low	Yes (Measured n-3 FA from ONLY diet)	Yes	
Shanghai Women's/Men's Health Studies 23788668	Low	Partial (Diet factors)	High	Low	Yes (Measured n-3 FA from ONLY diet)	No	Yes (Difference in followup 11.2 years in women vs. 5.6 in men)
Spanish EPIC 24360762	Low	Yes (Diet and CVD risk factors)	Low	Low	Yes (Measured n-3 FA from ONLY diet)	No	

Study PMID	Selection bias (outcome of interest not present at baseline)	Comparability/ Adjustment (adjusted for confounders or other factors)	Outcome assessors adequately blinded	Incomplete outcome data (attrition bias)	Dietary assessment instrument described (studies with FFQ)?	Nutrient exposures adequately reported	Additional Bias
Swedish Mammography Study 20332801 22172525 22265275 25679993	Low	Yes (Diet and CVD risk factors)	Low	Low	Yes (Measured n-3 FA from BOTH diet and supplements)	No	
Takayama Study 12397000	Low	Yes (Diet and CVD risk factors)	Low	Low	Yes (Measured n-3 FA from ONLY diet)	Yes	
Uppsala Longitudinal Study of Adult Men 18614742	Low	Yes (Diet and CVD risk factors)	Low	Low	Not Applicable (biomarker)	Yes	
Vitamins and Lifestyle Study 24496442	Low	Yes (Diet and CVD risk factors)	Low	Low	Yes (Measured n-3 FA from ONLY diet)	Yes	
Women's Health Initiative 20211329 21610249	Low	Yes (Diet and CVD risk factors)	Low	Low	Yes (Measured n-3 FA from ONLY diet)	No	
Women's Health Study 20713915 21734059	Low	Partial (CVD risk factors)	High	Low	Yes (Measured n-3 FA from ONLY diet)	No	

PMID = Pubmed identifiers of all included articles.

Appendix D. Baseline Characteristics

Table D-1. Comparative studies, continuous measures

Author, year, PMID	Arm (N)	Male %	Race %	Age mean years	SBP mean (SD) mmHg	DBP mean (SD) mmHg	MAP mean (SD) mmHg	Total Cholesterol mean (SD) mg/dL [mmol/L]	LDL mean (SD) mg/dL [mmol/L]	HDL mean (SD) mg/dL [mmol/L]	Triglycerides mean (SD) mg/dL [mmol/L]	BMI mean (SD) Kg/m2	Weight mean (SD) Kg
Baxheinrich, 2012, 22894911	ALA [rapeseed oil] (40)			52.3 (10.6)	142.4 (18.6)	91.8 (11.8)		[5.43 (0.88)]	[3.42 (0.82)]	[1.37 (0.29)]	[1.94 (1.13)]	33.4 (4.8)	97.3 (19.7)
	Placebo [Olive oil] (41)			50.3 (9.8)	140.1 (12.4)	90.2 (7.7)		[5.49 (1.09)]	[3.49 (0.92)]	[1.43 (0.34)]	[1.64 (1.02)]	35.2 (5.1)	99.4 (16.2)
Bosch, 2012, 22686415	"Fish oil" (DHA+EPA) (6281)	65.4		63.5 (7.8)	145.6 (21.8)	84.1 (12.1)		189 (46)	112 (40)	46 (12)	median 142 (99, 196)	29.8 (5.3)	
	Placebo (6255)	64.7		63.6 (7.9)	146.0 (21.8)	84.2 (12.1)		190 (47)	112 (40)	46 (12)	median 140 (97, 195)	29.9 (5.2)	
Brinton, 2013, 23835245	EPA [2g/day] (234)	61	96 white	61.8 (9.42)				median169.0 (IQR 34.0)	median 82.0 (24)	median 38 (13)	median 254.0 (92.5)	32.9 (4.98)	
	EPA [4g/day] (226)	61	97 white	61.1 (10.03)				median 167.0 (IQR 38.0)	median 82.0 (25)	median 39 (12)	median 264.8 (93)	32.7 (4.99)	
	Placebo (227)	62	96 white	61.2 (10.05)				median 168.0 (IQR 38.0)	median 84.0 (27)	median 37 (12)	median 259.0 (81)	33.0 (5.04)	
Brouwer, 2006, 16772624	"Fish oil" (DHA+EPA) (273)	85		60.5 (12.8)	122.2 (18.8)	73.4 (10.8)						26.98 (4.4)	
	Placebo (273)	84		62.4 (11.4)	121.2 (18.5)	74.2 (9.1)						26.86 (4.01)	
Burr, 2003, 12571649	Fish + Fish oil [with or without fruit advice] (1571)	100		61	141.9	84.8		6.4				28.2	
	No intervention [with or without fruit advice] (1543)	100		61	141.6	84.6		6.4				28.1	
Burr, 1989, 2571009	Fish + Fish oil [Fish advice, either alone or in combination with fiber advice, fat advice, or both fiber a fat advice.] (1015)	100		56.7	129.7 (21.4)	79.3 (12.4)						25.8	
	No intervention [Fat advice, fiber advice, fiber a fat advice, or no advice.] (1018)	100		56.4	130.1 (21.0)	80.2 (12.5)						26	

Author, year, PMID	Arm (N)	Male %	Race %	Age mean years	SBP mean (SD) mmHg	DBP mean (SD) mmHg	MAP mean (SD) mmHg	Total Cholesterol mean (SD) mg/dL [mmol/L]	LDL mean (SD) mg/dL [mmol/L]	HDL mean (SD) mg/dL [mmol/L]	Triglycerides mean (SD) mg/dL [mmol/L]	BMI mean (SD) Kg/m2	Weight mean (SD) Kg
Carrepeiro, 2011, 21561620	Total (43)	0	65 white, 14 black, 5 Asian, 16 American Indian	61.3 (7.8)				208 (36.8)	134.8 (34.1)	50.1 (12.4)	117.5 (48.5)	28.2 (4.8)	
Carter, 2012, 22707560	"Fish oil" (DHA+EPA) [fish oil (normotensive)] (19)	90		24 (SE 2)	110 (SE 1)	66 (SE 1)	80 (SE 1)					24 (SE 1)	68 (SE 3)
	Placebo [Olive oil (normotensive)] (19)	90		24 (SE 2)	107 (SE 2)	65 (SE 1)	79 (SE 1)					24 (SE 1)	70 (SE 2)
	"Fish oil" (DHA+EPA) [fish oil prehypertensive] (15)	100		23 (SE 1)	127 (SE 1)	68 (SE 2)	88 (SE 2)					28 (SE 1)	88 (SE 4)
	Placebo [Olive oil prehypertensive] (14)	92.86		25 (SE 3)	126 (SE 2)	74 (SE 2)	92 (SE 1)					27 (SE 1)	87 (SE 2)
Caslake, 2008, 18779276	Total (312)	47.76		45 (SE 0.7)	123 (SE 1)	74 (SE 1)		[5.12 (SE 0.06)]	[3.22 (SE 0.05)]	[1.42 (SE 0.02)]	[1.26 (SE 0.03)]	25.2 (SE 0.19)	73.0 (SE 0.8)
Damsgaard, 2008, 18492834	"Fish oil" (DHA+EPA) [+ high LA (18:2 n6)] (17)			26.3 (4.8)	115 (6)			[3.99 (SE 0.11)]	[2.58 (SE 0.10)]	[1.48 (SE 0.06)]	[median 0.81]	21.9 (1.6)	73.8 (7.9)
	"Fish oil" (DHA+EPA) [+ low LA (18:2 n6)] (14)			24.9 (4.9)				[4.08 (SE 0.20)]	[2.66 (SE 0.19)]	[1.50 (SE 0.09)]	[median 1.28]	22.9 (1.9)	78.2 (10.2)
	No intervention [+ high LA (18:2 n6)] (16)			24.9 (3.9)				[3.68 (SE 0.11)]	[2.33 (SE 0.11)]	[1.36 (SE 0.04)]	[median 0.90]	23.1 (1.9)	74.3 (7.4)
	No intervention [+ low LA (18:2 n6)] (17)			25.5 (4.4)				[4.12 (SE 0.20)]	[2.71 (SE 0.18)]	[1.50 (SE 0.09)]	[median 1.01]	23.3 (1.9)	79.3 (9.3)
Derosa, 2009, 19397392	"Fish oil" (DHA+EPA) (168)	48.8		51.3 (7.2)	128.4 (6.5)	80.6 (6.8)		223.4 (15.7)	148.5 (7.2)	38.4 (4.2)	182.6 (39.7)	26.2 (1.3)	
	Placebo [sucrose, mannitol and mineral salts] (165)	49.7		50.7 (6.8)	129.6 (6.8)	81.4 (7.1)		227.5 (16.3)	149.9 (7.5)	39.7 (5.1)	189.3 (41.8)	26.0 (1.1)	

Author, year, PMID	Arm (N)	Male %	Race %	Age mean years	SBP mean (SD) mmHg	DBP mean (SD) mmHg	MAP mean (SD) mmHg	Total Cholesterol mean (SD) mg/dL [mmol/L]	LDL mean (SD) mg/dL [mmol/L]	HDL mean (SD) mg/dL [mmol/L]	Triglycerides mean (SD) mg/dL [mmol/L]	BMI mean (SD) Kg/m2	Weight mean (SD) Kg
Earnest, 2012, 22811376	Total (92)	55	77 white, 13 black, 10 Hispanic	52.9 (10.7) range 30, 70								26.3 (4.4)	80.7 (17.4)
	Placebo [placebo] (23)							[4.77 (0.99)]	[2.72 (0.83)]	[1.48 (0.51)]	[1.25 (0.57)]		
	"Fish oil" (DHA+EPA) [fish oil] (21)							[5.47 (0.96)]	[3.42 (0.79)]	[1.48 (0.49)]	[1.25 (0.70)]		
	"Fish oil" (DHA+EPA) [fish oil + multivitamin] (25)							[5.39 (1.14)]	[3.36 (0.93)]	[1.43 (0.51)]	[1.31 (0.83)]		
	Placebo [placebo + multivitamin] (23)							[5.10 (0.83)]	[3.10 (0.74)]	[1.41 (0.41)]	[1.28 (0.70)]		
Ebrahimi, 2009, 19593941	"Fish oil" (DHA+EPA) (47)			53.5 (12.7)	130.7 (14.7)	81.7 (9.7)		[5.99 (1.07)]	[3.77 (0.89)]	[1.18 (0.15)]	[median 1.76 (1.16, 2.24)]	30.3 (5.2)	68.3 (11.7)
	No intervention (42)			52.3 (11.1)	129.6 (19.8)	78.3 (13.4)		[5.75 (1.04)]	[3.71 (0.72)]	[1.12 (0.19)]	[5.75 (1.04)]	30.4 (6.1)	69.5 (14.6)
Einvik, 2010, 20389249	"Fish oil" (DHA+EPA) [with or without dietary intervention] (282)	100		70.4	149 (17)			[6.3 (1.0)]	[4.1 (1.0)]	[1.4 (0.4)]	[1.7 (0.8)]	26.3 (3.2)	
	Placebo [with or without dietary intervention] (281)	100		69.7 (3.0)	148 (19)			[6.2 (1.0)]	[4.0 (0.9)]	[1.4 (0.4)]	[1.7 (0.9)]	26.7 (3.7)	
	Placebo [no diet intervention] (68)			69 [range 64, 75]	147 (20)	83 (11)		[6.3 (1.0)]	[4.1 (1.0)]	[1.4 (0.4)]	[1.7 (0.9)]	26.6 (3.7)	
	Placebo [diet intervention] (71)			70 range 65, 75	149 (19)	82 (11)		[6.2 (1.0)]	[4.0 (0.9)]	[1.4 (0.4)]	[1.7 (0.9)]	26.8 (3.8)	
	"Fish oil" (DHA+EPA) [no diet intervention] (70)			70 range 64, 75	150 (18)	83 (12)		[6.4 (1.0)]	[4.2 (1.0)]	[1.4 (0.4)]	[1.7 (0.8)]	26.5 (3.4)	
	"Fish oil" (DHA+EPA) [diet intervention] (69)			70 range 65, 75	149 (18)	85 (11)		[6.3 (1.1)]	[4.1 (1.0)]	[1.4 (0.3)]	[1.7 (0.8)]	26.5 (3.5)	

Author, year, PMID	Arm (N)	Male %	Race %	Age mean years	SBP mean (SD) mmHg	DBP mean (SD) mmHg	MAP mean (SD) mmHg	Total Cholesterol mean (SD) mg/dL [mmol/L]	LDL mean (SD) mg/dL [mmol/L]	HDL mean (SD) mg/dL [mmol/L]	Triglycerides mean (SD) mg/dL [mmol/L]	BMI mean (SD) Kg/m2	Weight mean (SD) Kg
Eritsland, 1996, 8540453	"Fish oil" (DHA+EPA) [with aspirin or warfarin] (260)	85.8		59.9 (8.7)	144	88		[6.54 (1.14)]	[4.59 (0.97)]	[1.06 (0.31)]	[1.94 (1.05)]	25.4 (2.7)	
	No intervention [with warfarin or aspirin] (251)	87.6		59.4 (8.8)	146	88		[6.55 (1.16)]	[4.61 (1.09)]	[1.00 (0.27)]	[2.09 (1.07)]	25.5 (2.8)	
Finnegan, 2003, 12663273	Placebo [Margarine/Capsule] (30)	60		55 (SE 2)	123.2 (SE 3.7)	76 (SE 1.6)		[5.8 (SE 0.17)]	[3.63 (SE 0.16)]	[1.35 (SE 0.06)]	[1.69 (SE 0.11)]	25.8 (SE 0.6)	74.9 (SE 2.1)
	"Fish oil" (DHA+EPA) [0.8g] (30)	57		53 (SE 2)	119.6 (SE 3.7)	74.6 (SE 1.7)		[5.5 (SE 0.16)]	[3.41 (SE 0.17)]	[1.37 (SE 0.07)]	[1.65 (SE 0.14)]	27.2 (SE 0.6)	79.1 (SE 2.8)
	"Fish oil" (DHA+EPA) [1.7g] (29)	58		54 (SE 2)	118.4 (SE 2.9)	74.8 (SE 2.1)		[5.49 (SE 0.15)]	[3.42 (SE 0.14)]	[1.34 (SE 0.07)]	[1.60 (SE 0.13)]	26.1 (SE 0.6)	78.0 (SE 2.5)
	ALA [4.5g] (30)	57		52 (SE 1)	118.2 (SE 2.9)	76.0 (SE 2.0)		[5.62 (SE 0.14)]	[3.55 (SE 0.13)]	[1.29 (SE 0.06)]	[1.66 (SE 0.13)]	26.3 (SE 0.6)	77.3 (SE 2.9)
Galan, 2010, 21115589	Total (2501)	79.4		60.9 (8.8)									
	"Fish oil" (DHA+EPA) [+B vitamins] (620)	79.5		61.5 (9.3)	133.1 (21.4)	83.6 (13.2)		[median 4.5 (3.9, 5.3)]	[median 2.7 (2.2, 3.3)]	[median 1.2 (1.0, 1.4)]	[median 1.2 (0.9, 1.6)]	27.6 (4.4)	
	"Fish oil" (DHA+EPA) (633)	79.2		61.4 (9.3)	134.1 (21.9)	84.0 (12.9)		[median 4.5 (3.9, 5.3)]	[median 2.7 (2.2, 3.3)]	[median 1.2 (1.0, 1.3)]	[median 1.2 (0.9, 1.6)]	27.5 (4.0)	
	Placebo [+B vitamins] (622)	79.9		61.4 (8.7)	133.5 (22.2)	84.0 (13.7)		[median 4.6 (3.9, 5.3)]	[median 2.7 (2.2, 3.2)]	[median 1.2 (1.0, 1.4)]	[median 1.3 (0.9, 1.7)]	27.7 (4.0)	
	Placebo (626)	79.2		61.4 (8.9)	132.6 (20.0)	82.6 (12.1)		[median 4.5 (3.9, 5.1)]	[median 2.6 (2.2, 3.2)]	[median 1.1 (1.0, 1.3)]	[median 1.1 (0.9, 1.7)]	27.5 (3.8)	
Grieger, 2014, 24454276	Total (80)	49		69.5 (5.8) range 64, 85									
	Fish [mixed fish] (43)				126 (SE 2)	69 (SE 1)		[5.5 (SE 0.1)]	[3.2 (SE 0.1)]	[1.7 (SE 0.1)]	[1.1 (SE 0.1)]	26.5 (SE 0.6)	75.7 (SE 2.2)

Author, year, PMID	Arm (N)	Male %	Race %	Age mean years	SBP mean (SD) mmHg	DBP mean (SD) mmHg	MAP mean (SD) mmHg	Total Cholesterol mean (SD) mg/dL [mmol/L]	LDL mean (SD) mg/dL [mmol/L]	HDL mean (SD) mg/dL [mmol/L]	Triglycerides mean (SD) mg/dL [mmol/L]	BMI mean (SD) Kg/m2	Weight mean (SD) Kg
	Low n3 diet [Control (usual diet, eight servings of red meat per fortnight)] (37)				126 (SE 2)	67 (SE 1)		[5.5 (SE 0.2)]	[3.3 (SE 0.1)]	[1.6 (SE 0.1)]	[1.4 (SE 0.1)]	26.4 (SE 0.6)	73.8
Grimsgaard, 1998, 9665096	DHA (72)			43.2 (5.1)	121.3 (9.3)	76.1 (6.9)	90.6 (7.3)	[6.00 (0.95)]	[4.06 (0.86)]	[1.36 (0.30)]	[1.24 (0.58)]	24.9 (2.6)	
	EPA (75)			44.3 (5.2)	123.2 (9.8)	78.1 (7.3)	92.9 (8.0)	[5.98 (0.94)]	[4.06 (0.83)]	[1.33 (0.31)]	[1.23 (0.57)]	25.6 (2.9)	
	Placebo [corn oil] (77)			45.1 (5.6)	122.2 (5.7)	76.9 (8.0)	91.8 (9.1)	[6.02 (1.08)]	[4.04 (0.98)]	[1.41 (0.28)]	[1.22 (0.55)]	24.6 (2.7)	
Harrison, 2004, 15853118	DHA [food with added DHA; with or without added soya protein] (67)	50.5		52	130.9	81.1		[7.1]	[5.65]	[1.65]		27.4	
	Placebo [same food but with no added DHA; with or without added soya protein] (85)	54.4		52	134.7	81.8		[6.7]	[5.0]	[1.7]		27.2	
Holman, 2009, 19002433	"Fish oil" (DHA+EPA) [+Atorvastatin] (163)	55	91 white	median 63 (range 57, 72)	138.8 (15.5)	77.4 (9.9)		[5.1 (0.9)]	[3.3 (0.8)]	[1.1 (0.9)]	[median 1.6 (1.1, 2.1)]	30.8 (6.6)	87.5 (20.6)
	"Fish oil" (DHA+EPA) (160)	56	91 white	median 64 (range 55, 572)	135.7 (15.5)	76.9 (8.9)		[5.0 (0.8)]	[3.1 (0.7)]	[1.1 (0.7)]	[median 1.5 (1.0, 2.2)]	30.8 (6.5)	87.8 (18.6)
	Placebo [+Atorvastatin] (169)	61	92 white	median 64 (range 55, 72)	139.4 (14.8)	78.2 (9.2)		[5.0 (0.9)]	[3.2 (0.7)]	[1.1 (0.9)]	[median 1.5 (1.1, 2.3)]	30.9 (6.0)	88.4 (18.6)
	Placebo (166)	58	88 white	median 65 (range 57, 73)	139.8 (15.9)	78.8 (9.2)		[5.0 (1)]	[3.1 (0.8)]	[1.1 (0.9)]	[median 1.5 (1.2, 2.2)]	30.6 (5.8)	87.3 (18.5)
Jones, 2014, 24829493	Total (130)	54		46.46 (14.18)	120.62 (16.70)	77.04 (11.80)		[5.32 (1.05)]	[3.35 (0.93)]	[1.22 (0.29)]	[1.67 (0.88)]	29.80 (4.37)	

Author, year, PMID	Arm (N)	Male %	Race %	Age mean years	SBP mean (SD) mmHg	DBP mean (SD) mmHg	MAP mean (SD) mmHg	Total Cholesterol mean (SD) mg/dL [mmol/L]	LDL mean (SD) mg/dL [mmol/L]	HDL mean (SD) mg/dL [mmol/L]	Triglycerides mean (SD) mg/dL [mmol/L]	BMI mean (SD) Kg/m2	Weight mean (SD) Kg
Kastelein 2014 24528690	Placebo [olive oil] (98)	77.8	96 white, 4 Asian, 6.1 Hispanic	50.8 (10.6)	130.4 (12.1)	80.5 (6.2)		median 246 (range 135, 409)	median 78.2 (range 22.7, 161)	median 28.7 (range 14, 60)	median 682 (range 418, 2007)	30.4 (4.3)	
	"Fish oil" (DHA+EPA) [Omega3 2 g/d; olive oil 2 g/d] (99)	80.0	93 white, 5 Asian, 8 Hispanic, 2 other	51.1 (9.8)	130.1 (12.4)	80.9 (7.7)		Median 241 (range 131, 542)	median 77.3 (range 19.7, 182)	median 27.3 (range 13.3, 47.3)	median 717 (range 415, 1578)	31.4 (4.8)	
	"Fish oil" (DHA+EPA) [Omega3 3 g/d, olive oil 1 g/d] (97)	78.2	91.1 white, 1 black, 5.9 Asian, 4 Hispanic, 2 other	51.2 (8.8)	129.2 (11.1)	81.1 (7.5)		median 244 (range 151, 641)	median 81.0 (range 19.7, 213)	median 28.0 (range 15.3, 58.7)	median 728 (range 439, 2158)	31.8 (4.1)	
	"Fish oil" (DHA+EPA) [Omega3 4 g/d] (99)	71.7	88.9 white, 2 black, 8.1 Asian, 7.1 Hispanic, 1 other	52.9 (10.9)	129.6 (12.1)	80.7 (7.6)		median 254 (range 119, 564)	median 90.3 (range 11.7, 223)	median 28.7 (range 12.7. 69.3)	median 655 (range 435, 2095)	31.0 (5.1)	
Kromhout, 2010, 20929341	All n3 PUFAs (ALA+DHA+EPA) [EPADHA + ALA margarine] (1212)	78.1		69.1 (5.5)	140.9 (22.1)			[4.69 (0.96)]	[2.55 (0.81)]	[1.29 (0.33)]	[median 1.64 (1.19, 2.26)]	27.8 (4.0)	
	"Fish oil" (DHA+EPA) [EPADHA + ALA placebo margarine] (1192)	78.1		69.1 (5.6)	142.3 (21.6)			[4.77 (0.98)]	[2.63 (0.84)]	[1.29 (0.35)]	[median 1.63 (1.22, 2.30)]	27.7 (3.7)	
	ALA [EPA-DHA placebo + ALA margarine] (1197)	77.9		69.0 (5.6)	141.4 (21.2)			[4.70 (0.95)]	[2.57 (0.83)]	[1.28 (0.34)]	[median 1.65 (1.21, 2.31)]	27.8 (3.8)	
	Placebo [EPA-DHA placebo + ALA placebo margarine] (1236)	78.7		68.9 (5.6)	141.9 (21.6)			[4.75 (0.99)]	[2.60 (0.87)]	[1.28 (0.34)]	[median 1.69 (1.22, 2.38)]	27.8 (3.9)	

Author, year, PMID	Arm (N)	Male %	Race %	Age mean years	SBP mean (SD) mmHg	DBP mean (SD) mmHg	MAP mean (SD) mmHg	Total Cholesterol mean (SD) mg/dL [mmol/L]	LDL mean (SD) mg/dL [mmol/L]	HDL mean (SD) mg/dL [mmol/L]	Triglycerides mean (SD) mg/dL [mmol/L]	BMI mean (SD) Kg/m2	Weight mean (SD) Kg
Kuhnt 2014, 24553695	SDA+ALA (echium oil) (59)	47.5		EOI: 28 (2.9); EOII: 59 (5.7); EOIII: 61 (6.3)	EOI: 125 (10.4); EOII: 135 (19.9); EOIII: 141 (15.6)	EOI: 82 (8.9); EOII: 90 (12); EOIII: 91 (7.9)		[EOI: 4.52 (0.68); EOII: 5.71 (1.24); EOIII: 6.30 (1.02)]	[EOI: 1.48 (0.67); EOII: 1.58 (0.66); EOIII: 1.33 (0.75)]	[EOI: 1.43 (0.30); EOII: 1.58 (0.47); EOIII: 1.33 (0.32)]	[EOI: 0.89 (0.36); EOII: 1.14 (0.42); EOIII: 1.82 (0.88)]	EOI: 22 (2.3); EOII: 23.5 (2.4); EOIII: 30.1 (3.3)	
	"Fish oil" (DHA+EPA) (19)	52.6		FOI: 27 (2.5); FOII: 60 (4.2)	FOI: 136 (13.6); FOII: 136 (18.7)	FOI: 88 (7.7); FOII: 88 (7.8)		[FOI: 4.59 (0.62); FOII: 5.73 (0.80)]	[FOI: 2.49 (0.66); FOII: 3.08 (0.70)]	[FOI: 1.65 (0.34); FOII: 1.92 (0.59)]	[FOI: 0.77 (0.21); FOII: 0.90 (0.32)]	FOI: 21.5 (2.6); FOII: 24.8 (3.1)	
Leaf, 2005, 16267249	"Fish oil" (DHA+EPA) (200)	84.5	95.5 white	65.7 (0.82)									
	Placebo [olive oil] (202)	81.7	95.5 white	65.3 (0.82)									
Liu, 2003, no PMID	"Fish oil" (DHA+EPA) (29)	48.3		60 (9)				[7.00 (1.08)]	[4.67 (0.99)]	[1.53 (0.41)]	[1.66 (0.78)]		
	"Fish oil" (DHA+EPA) [Fish oil + Simvastin] (19)	21.1		62 (7)				[6.69 (0.97)]	[4.49 (0.93)]	[1.43 (0.32)]	[1.75 (0.76)]		
	No intervention [Simvastin] (18)	22.2		63 (8)				[7.04 (0.81)]	[4.46 (0.67)]	[1.66 (0.58)]	[1.54 (0.95)]		
	No intervention (22)	22.7		57 (10)				[6.77 (0.75)]	[4.50 (0.72)]	[1.53 (0.43)]	[1.61 (0.83)]		
Lungershausen, 1994, 7852747	Total (42)	30.95		61 (11.34)	132.57 (11.43)	76.52 (7.23)		[5.74 (SE 0.21)]	[4.04 (SE 0.19)]	[1.03 (SE 0.04)]		27.33 (3.93)	
Macchia, 2013, 23265344	Placebo (297)	51.9		65.9 (10.5)									83 (19)
	"Fish oil" (DHA+EPA) (289)	57.8		66.3 (12.0)									81 (16)

Author, year, PMID	Arm (N)	Male %	Race %	Age mean years	SBP mean (SD) mmHg	DBP mean (SD) mmHg	MAP mean (SD) mmHg	Total Cholesterol mean (SD) mg/dL [mmol/L]	LDL mean (SD) mg/dL [mmol/L]	HDL mean (SD) mg/dL [mmol/L]	Triglycerides mean (SD) mg/dL [mmol/L]	BMI mean (SD) Kg/m2	Weight mean (SD) Kg
Maki, 2010, 20451686	"Fish oil" (DHA+EPA) [POM3 + Simvastin] (122)	54.1	95.1 white, 1.6 black, 2.5 Asian, 0.8 Hispanic	60.3 (10.1)				183.1 (27.8) median 184.3	89.2 (21.6) median 90.7	47.3 (11.9) median 46.0	282.0 (75.8) median 267.8	31.0 (5.4)	
	Placebo [Placebo + Simvastin] (132)	60.6	96.2 white, 2.3 black, 2.3 Hispanic	59.3 (10.8)				186.0 (32.1) median 183.5	92.3 (23.2) median 88.2	44.7 (9.3) median 43.3	286.7 (77.5) median 270.7	31.5 (5.5)	
Maki, 2013, 23998969	Placebo (211)	56.7	91.6 white, 4.7 black, 1.4 Asian, 2.3 American Indian or Alaska native, native Hawaiian, or Pacific Islander, multiple, other	61.5 (9.6)	128.9 (14.3)	76.1 (7.7)		174 (29.5)	91.7 (27.3)	38.3 (9.0)	280 (70.7)	32.7 (5.3)	
	All n3 PUFAs (ALA+DHA+EPA) [2 g] (209)	57.2	96.3 white, 3.3 black, 1 other	60.9 (10)	128.3 (15)	75.7 (8.9)		179 (29.1)	92.3 (26.0)	38.7 (9.9)	284 (76.7)	33.3 (6.2)	
	All n3 PUFAs (ALA+DHA+EPA) [4 g] (207)	63.4	94.4 white, 2.3 black, 1.9 Asian, 1.4 other	60.1 (9.2)	129.7 (13.3)	77.1 (9.0)		178 (29.1)	93.6 (27.6)	38.8 (10.9)	287 (82.8)	33.3 (6.6)	
Marchioli, 2002, 11997274, Italy	"Fish oil" (DHA+EPA) [+vitamin E. (5666)	84.7		59.4				210.2	137.3	41.5	162.6	>30 (14.7%)	
	No intervention [+vitamin E. (5668)	85.1		59.4				211.6	138.5	41.7	161.9	>30(13.8%)	

Author, year, PMID	Arm (N)	Male %	Race %	Age mean years	SBP mean (SD) mmHg	DBP mean (SD) mmHg	MAP mean (SD) mmHg	Total Cholesterol mean (SD) mg/dL [mmol/L]	LDL mean (SD) mg/dL [mmol/L]	HDL mean (SD) mg/dL [mmol/L]	Triglycerides mean (SD) mg/dL [mmol/L]	BMI mean (SD) Kg/m2	Weight mean (SD) Kg
Natvig, 1968, 5756076	Placebo (6690)	100		range 49, 61									range 60, >90
	ALA (6716)	100		range 49, 61									range 60, >90
Nilsen, 2001, 11451717	"Fish oil" (DHA+EPA) (150)	76.7			124.5 (range 90,195)							25.9 (range 16.9, 41.8)	
	Placebo (150)	82.0			122.1 (range 80, 190)							26.0 (range 19.4, 33.6)	
Nodari, 2011, 21844082	All n3 PUFAs (ALA+DHA+EPA) (100)	70		70 (6)	134 (20)	82 (10)						23.8 (5.2)	77.0 (12.8)
	Placebo (99)	63.6		69 (9)	136 (16)	82 (9)						23.6 (5.3)	76.5 (10.1)
	"Fish oil" (DHA+EPA) (67)	95.5		61 (11)	119.5 (9.2)	76.0 (5.2)		187 (26)			149 (62)	25.9 (2.3)	76.9 (10.1)
	Placebo (66)	84.9		64 (9)	120.5 (12.2)	76.2 (5.1)		187 (28)			154 (76)	25.7 (2.22)	76.0 (7.5)
Oh, 2014, 25147070	Placebo (42)	54.8		54 (9)				201 (29)	111 (34)	42 (8)	281 (63)		
	"Fish oil" (DHA+EPA) [1g] (44)	50.0		55 (9)				197 (29)	109 (32)	41 (8)	286 (73)		
	"Fish oil" (DHA+EPA) [2g] (43)	53.5		54 (9)				195 (31)	109 (33)	43 (7)	267 (118)		
	"Fish oil" (DHA+EPA) [4g] (44)	52.3		55 (8)				198 (30)	110 (33)	40 (7)	287 (73)		
Olano-Martin, 2010, 19748619	Total (38)	100		range 18, 70				[range <8]			[range 1, 4]	(range 18.5, 32)	
	Placebo (38)	100		range 18, 70				[5.44 (SE 0.14)]	[3.54 (SE 0.13)]	[1.33 (SE 0.05)]	[1.39 (SE 0.08)]		
	EPA [3.3g EPA /day] (38)	100		range 18, 70				[5.56 (SE 0.16)]	[3.53 (SE 0.14)]	[1.32 (SE 0.05)]	[1.62 (SE 0.15)]		
	DHA [3.7g DHA/ day] (38)	100		range 18, 70				[5.58 (SE 0.17)]	[3.61 (SE 0.14)]	[1.31 (SE 0.05)]	[1.50 (SE 0.11)]		

Author, year, PMID	Arm (N)	Male %	Race %	Age mean years	SBP mean (SD) mmHg	DBP mean (SD) mmHg	MAP mean (SD) mmHg	Total Cholesterol mean (SD) mg/dL [mmol/L]	LDL mean (SD) mg/dL [mmol/L]	HDL mean (SD) mg/dL [mmol/L]	Triglycerides mean (SD) mg/dL [mmol/L]	BMI mean (SD) Kg/m2	Weight mean (SD) Kg
Pase 2015 25565485	“Fish oil" (DHA+EPA 3g + multivitmin) (43)	47.6		59.5 (5.6)	125.8 (21.0)	77.2 (13.3)			[3.30 (0.71)]	[1.52 (0.42)]	[1.22 (0.50)]	25.5 (3.6)	
	“Fish oil" (DHA+EPA 6g + multivitmin) (39)	47.5		58.9 (5.6)	122.6 (16.9)	75.5 (10.9)			[3.51 (0.72)]	[1.61 (0.39)]	[1.19 (0.68)]	24.4 (3.1)	
	“Fish oil" (DHA+EPA 6g) (41)	46.3		59.5 (5.9)	126.3 (16.9)	77.7 (9.8)			[3.37 (0.84)]	[1.56 (0.44)]	[1.16 (0.60)]	25.3 (4.0)	
	Placebo (37)	45.9		59.2 (6.0)	121.4 (12.5)	74.6 (12.1)			[3.27 (0.72)]	[1.57 (0.36)]	[1.00 (0.43)]	24.2 (2.8)	
Pieters 2015, 25226826	Total (32)	50		51 (15)	130 (20)	85 (12)		[5.94 (0.93)]	[3.69 (0.73)	[1.66 (0.37)]	[1.3 (0.61)]	28.9 (3)	
Raitt, 2005, 15956633	"Fish oil" (DHA+EPA) (100)	86	94 white	63 (13)									
	Placebo (100)	86	97 white	62 (13)									
Ras 2014 25122648	"Fish oil" (DHA+EPA) [2.5 g/day plant sterols + 1.8 g/day EPA+DHA] (62)	19.4		59.4 (SE 1.3)	126.7 SE (1.8)	76.8 (SE 1.0)		[6.36 (SE 0.10)]	[3.89 (SE 0.10)]	1.64 (SE 0.04)]	[1.02 (SE 0.05)]	24.3 (SE 0.4)	
	"Fish oil" (DHA+EPA) [2.5 g/day plant sterols + 1.3 g/day EPA+DHA] (62)	22.6		59.9 (SE 1.2)	129.6 SE (1.8)	79.0 (SE 0.8)		[6.60 (SE 0.12)]	[4.06 (SE 0.10)]	1.68 (SE 0.05)]	[1.09 (SE 0.06)]	25.7 (SE 0.3)	
	"Fish oil" (DHA+EPA) [2.5 g/day plant sterols + 0.9 g/day EPA+DHA] (64)	29.7		55.8 (SE 1.4)	130.0 SE (1.9)	77.6 (SE 0.9)		[6.49 (SE 0.10)]	[4.10 (SE 0.09)]	1.57 (SE 0.05)]	[1.11 (SE 0.08)]	25.1 (SE 0.3)	
	Placebo [2.5 g/day plant sterols] (64)	29.7		58.3 (SE 1.5)	127.7 SE (1.9)	77.5 (SE 1.0)		[6.39 (SE 0.11)]	[3.91 (SE 0.09)]	1.67 (SE 0.06)]	[1.13 (SE 0.07)]	24.6 (SE 0.3)	
Rasmussen, 2006, 16469978	Total (97)	59	100 white										
	Placebo [+MUFArich diet] (23)			47.0 (8.8)	123.1 (16.6)	77.8 (9.9)						26.1 (3.2)	

Author, year, PMID	Arm (N)	Male %	Race %	Age mean years	SBP mean (SD) mmHg	DBP mean (SD) mmHg	MAP mean (SD) mmHg	Total Cholesterol mean (SD) mg/dL [mmol/L]	LDL mean (SD) mg/dL [mmol/L]	HDL mean (SD) mg/dL [mmol/L]	Triglycerides mean (SD) mg/dL [mmol/L]	BMI mean (SD) Kg/m2	Weight mean (SD) Kg
	"Fish oil" (DHA+EPA) [+MUFArich diet] (24)			49.5 (7.3)	122.4 (12.9)	74.6 (9.1)						26.5 (3.1)	
	Placebo [+SFArich diet] (25)			49.3 (7.1)	121.6 (11.5)	77.2 (7.6)						26.3 (2.7)	
	"Fish oil" (DHA+EPA) [+SFArich diet] (25)			48.5 (8.0)	122.7 (11.4)	77.1 (9.0)						26.9 (3.0)	
Rauch, 2010, 21060071	All n3 PUFAs (ALA+DHA+EPA) (1919)	75.1		median 64 (54, 72)	[140 (120, 160)]							median 27.6 (25.1 ,30.4)	
	Placebo (1885)	73.7		median 64 (54, 72)	[140 (120, 160)]							median 27.3 (24.9, 30.1)	
Rodriguez-Leyva, 2013, 24126178	Total (87)			67.3 (8.5)	142.9 (20.1)	77.5 (12.8)		[4.5 (1.2)]	[2.5 (1.0)]	[1.2 (0.3)]	[1.6 (0.7)]	27.8 (4.5)	
	All n3 PUFAs (ALA+DHA+EPA) [flaxseed group] (45)			67.4 (8.06)	143.3 (22.2)	77.0 (9.5)		[4.4 (1.1)]	[2.5 (1.0)]	[1.2 (0.3)]	[1.6 (0.7)]	27.4 (4.4)	
	Placebo (42)			65.3 (9.4)	142.4 (17.5)	79.0 (15.7)		[4.5 (1.3)]	[2.6 (1.0)]	[1.2 (0.3)]	[1.7 (0.8)]	28.1 (4.4)	
Roncaglioni, 2013, 23656645	"Fish oil" (DHA+EPA) (6244)	62.3		63.9 (9.3)	140.3 (15.2)	82.9 (8.2)		215.6 (43.9)	131.8 (36.9)	50.9 (13.3)	median 150	29.3 (4.9)	
	No intervention (6269)	60.6		64.0 (9.6)	140.1 (15.1)	82.5 (8.2)		216.5 (42.2)	132.5 (36.1)	51.2 (13.4)	median 150	29.4 (5.0)	
Sacks, 1994, 8021472	Total (350)	70	range 84, 88 white	43 (6.7)									
	"Fish oil" (DHA+EPA) (175)				122.9 (8.8)	81.0 (5.1)		190 (29)		46 (13)			
	Placebo (175)				122.6 (8.3)	81.1 (4.9)		189 (32)		45 (12)			
Sacks, 1995, 7759696	"Fish oil" (DHA+EPA) (31)	93.5		62 (7)	126 (29)	76 (16)		189 (33)	122 (29)	41 (9)	128 (67)		80 (14)
	Placebo (28)	92.9		62 (7)	133 (19)	77 (7.6)		184 (28)	117 (27)	40 (12)	137 (73)		79 (15)

Author, year, PMID	Arm (N)	Male %	Race %	Age mean years	SBP mean (SD) mmHg	DBP mean (SD) mmHg	MAP mean (SD) mmHg	Total Cholesterol mean (SD) mg/dL [mmol/L]	LDL mean (SD) mg/dL [mmol/L]	HDL mean (SD) mg/dL [mmol/L]	Triglycerides mean (SD) mg/dL [mmol/L]	BMI mean (SD) Kg/m2	Weight mean (SD) Kg
Sanders, 2011, 21865334	"Fish oil" (DHA+EPA) [EPA+DHA 0.45 g/d] (80)	38.3	80.9 white, 4.3 black, 6.4 Asian, 4.3 far eastern, 4.3 other	55 (95% CI 53, 56)	121 (95% CI 118, 124)	77 (95% CI 75, 79)						25 (women); 26 (men) (95% CI 24, 26; 95% CI 25, 27)	
	"Fish oil" (DHA+EPA) [EPA+DHA 0.9 g/d] (79)	38.7	78.5 white, 6.5 black, 10.8 Asian, 4.3 other	55 (95% CI 54, 56)	122 (95% CI 119, 125)	78 (95% CI 76, 80)						26 (women); 27(men) (95% CI 24, 27; 95% CI 26, 28)	
	"Fish oil" (DHA+EPA) [EPA+DHA 1.8 g/d] (80)	39.1	85.9 white, 1.1 black, 2.2 Asian, 4.3 far eastern, 6.5 other	55 (95% CI 54, 57)	121 (95% CI 117, 124)	76 (95% CI 75, 78)						25 (women); 26 (men) (95% CI 24, 26; 95% CI 25, 27)	
	Placebo [olive oil] (71)	38.6	77.3 white, 10.2 black, 6.8 Asian, 2.3 far eastern, 3.4 other	55 (95% CI 54, 57)	120 (95% CI 117, 124)	77 (95% CI 75, 79)						26 (women); 27(men) (95% CI 25, 27; 95% CI 26, 28)	
Shaikh, 2014, 25185754	"Fish oil" (DHA+EPA) (56)	58.9		53.4			92.5	[5.0]	[3.2]	[1.05]	[2.3]	31.7	
	Placebo (corn oil) (54)	48.1		53.8			93.6	[4.6]	[2.7]	[1.1]	[2.2]	32.1	
Shidfar, 2003, 12847992	Placebo [placebo of n3 a placebo of vitamin C] (19)	36.8		54.4 (12.2)				250.7 (46.3)	167.4 (38.2)	39.2 (9.3)	311.5 (100.2)	27.6 (3)	72 (10.8)
	Placebo [500 mg vitamin C + placebo of n3] (17)	35.3		51.8 (10.7)				243.5 (35.3)	160.6 (41.5)	37.2 (5.6)	315 (98)	27.8 (2.9)	79 (8.7)

Author, year, PMID	Arm (N)	Male %	Race %	Age mean years	SBP mean (SD) mmHg	DBP mean (SD) mmHg	MAP mean (SD) mmHg	Total Cholesterol mean (SD) mg/dL [mmol/L]	LDL mean (SD) mg/dL [mmol/L]	HDL mean (SD) mg/dL [mmol/L]	Triglycerides mean (SD) mg/dL [mmol/L]	BMI mean (SD) Kg/m2	Weight mean (SD) Kg
	All n3 PUFAs (ALA+DHA+EPA) [1g n3 + placebo of vitamin C] (16)	31.25		54.4 (11.7)				243.4 (36.9)	159.6 (45.4)	39.1 (9.6)	304 (88.4)	26.9 (2.2)	74.3 (10.2)
	All n3 PUFAs (ALA+DHA+EPA) [1g n3 + 500 mg vitamin C] (16)	31.25		58.9 (7)				236.7 (49.9)	150.8 (47.4)	53.3 (10.4)	297.3 (74.1)	26.4 (2.6)	69.9 (12)
Sirtori, 1997, 9174486	All n3 PUFAs (ALA+DHA+EPA) (470)	62.6		58.2 (9.09)									74.0 (10.44)
	Placebo (465)	62.2		58.8 (8.99)									73.7 (10.08)
Soares, 2014, 24652053	Total (70)	28.6											
	Placebo [dietary intervention a placebo] (18)			51.6 (13.4)	134.4 (35.1)	85.3 (21.2)				47.3 (14.1)	199.6 (126.3)	32.8 (8.1)	
	"Fish oil" (DHA+EPA) [dietary intervention a Omega 3 supplementation] (20)			52 (12.5)	130.2 (31.7)	83.9 (23.1)				44.65 (14.9)	193.8 (93.2)	34.1 (7.9)	
	Placebo [dietary intervention a placebo and exercise] (15)			50.8 (13.4)	131.1 (36.6)	84.3 (22.4)				45.7 (15.7)	194.5 (96.3)	32.3 (8.9)	
	"Fish oil" (DHA+EPA) [dietary intervention a Omega 3 and exercise] (17)			51 (14.7)	131.6 (36.3)	78.2 (20.3)				40.8 (12.3)	198.6 (76.3)	33.5 (8.6)	
Tardivo, 2015, 25394692	"Fish oil" (DHA+EPA) [omega-3 + diet] (33)	0	100 Hispanic	55.1 (6.6)	138.8 (14.4)	86.2 (8.8)		219.1 (33.2)	134.8 (29.6)	45.9 (6.2)	192.5 (65.4)	32.8 (4.7)	
	Placebo [diet] (30)	0	100 Hispanic	55.0 (7.3)	135.5 (12.1)	85.3 (6.9)		221.5 (39.3)	134.3 (35.0)	44.6 (8.2)	188.6 (57.4)	32.0 (4.6)	

Author, year, PMID	Arm (N)	Male %	Race %	Age mean years	SBP mean (SD) mmHg	DBP mean (SD) mmHg	MAP mean (SD) mmHg	Total Cholesterol mean (SD) mg/dL [mmol/L]	LDL mean (SD) mg/dL [mmol/L]	HDL mean (SD) mg/dL [mmol/L]	Triglycerides mean (SD) mg/dL [mmol/L]	BMI mean (SD) Kg/m2	Weight mean (SD) Kg
Tatsuno, 2013, 24314359	"Fish oil" (DHA+EPA) [TAK085 2 g/day] (206)	70.8		56 (10.95)					133.2 (29.85)		254.7 (97.8)	25.9 (3.7)	
	"Fish oil" (DHA+EPA) [TAK085 4 g/day] (210)	71.5		55.9 (10.12)					129.0 (30.26)		270.0 (101.2)	26.1 (3.5)	
	EPA [EPA 1.8 g/day] (195)	71.3		55.8 (9.27)					129.3 (33.0)		264.2 (111.6)	26.3 (3.3)	
Tatsuno, 2013, 23725919	"Fish oil" (DHA+EPA) [TAK085 2 g/day] (206)	77.7		53.9 (10.8)				211.9 (31.1)	127.4 (29.1)	45.8 (9.9)	269.0 (77.52)	26.6 (3.7)	
	"Fish oil" (DHA+EPA) [TAK085 4 g/day] (210)	74.8		55.0 (10.5)				212.0 (30.2)	125.7 (28.5)	45.7 (9.9)	277.5 (97.29)	26.3 (3.9)	
	EPA [EPA 1.8 g/day] (195)	80.5		55.6 (10.5)				215.2 (33.8)	130.1 (30.5)	45.6 (10.2)	271.8 (91.53)	26.3 (3.6)	
Tavazzi, 2008, 18757090	"Fish oil" (DHA+EPA) [n3 PUFA] (3494)	77.8		67 (11)	126 (18)	77 (10)					[median 1.42 (1.05, 1.98)]	27 (5)	
	Placebo [olive oil] (3481)	78.8		67 (11)	126 (18)	77 (10)						27 (5)	
Tierney, 2011, 20938439	Total (206)	80											
	Low n3 diet [LFHCC] (106)			54.7 (SE 0.91)	139.53 (SE 1.46)	85.50 (SE 0.87)		[5.22 (SE 0.10)]	[3.17 (SE 0.11)]	[1.09 (SE 0.03)]	[1.67 (SE 0.10)]	32.51 (SE 0.42)	91.96 (SE 1.38)
	All n3 PUFAs (ALA+DHA+EPA) [LFHCC n3 (only diet with added n3 supplement)] (100)			55.39 (SE 0.96)	137.73 (SE 1.52)	85.52 (SE 0.91)		[5.38 (SE 0.11)]	[3.31 (SE 0.12)]	[1.11 (SE 0.03)]	[1.68 (SE 0.11)]	32.42 (SE 0.43)	91.20 (SE 1.43)
Vazquez, 2014, 24462043	Total (257)	52.4		57.3	140.5	83.9		197.6	119.8	46.2	170.6	32.6	
Vecka, 2012, 23183517	Total (60)	65		52.4					[3.22]	[1.19]	[3.23]		89.6

Author, year, PMID	Arm (N)	Male %	Race %	Age mean years	SBP mean (SD) mmHg	DBP mean (SD) mmHg	MAP mean (SD) mmHg	Total Cholesterol mean (SD) mg/dL [mmol/L]	LDL mean (SD) mg/dL [mmol/L]	HDL mean (SD) mg/dL [mmol/L]	Triglycerides mean (SD) mg/dL [mmol/L]	BMI mean (SD) Kg/m2	Weight mean (SD) Kg
von Schacky, 1999, 10189324	"Fish oil" (DHA+EPA) (112)	82.0		57.8 (9.7)	132.0 (18.9)	80.7 (10.5)		[6.30 (1.12)]	[4.10 (1.06)]	[1.32 (0.34)]	[2.20 (1.33)]		78.7 (12.6)
	No intervention (111)	78.6		58.9 (8.1)	129.6 (17.8)	79.8 (9.6)		[6.10 (1.13)]	[4.00 (0.91)]	[1.30 (0.36)]	[2.16 (1.10)]		78.3 (11.1)
Yokoyama, 2007, 17398308	EPA [EPA+statin (atorvastatin or simvastatin)] (9326)	32		61 (8)	135 (21)	79 (13)		[7.11 (0.67)]	[4.69 (0.76)]	[1.52 (0.46)]	[median 1.73 (1.23, 2.48)]	24 (3)	
	All arms (XO study) (9319)	31		61 (9)	135 (21)	79 (13)		[7.11 (0.68)]	[4.70 (0.75)]	[1.51 (0.44)]	[median 1.74 (1.25,2.49)]	24 (3)	

Table D-2. Comparative studies, categorical measures

Author, year, PMID	Arm (N)	DM %	CMS %	Dyslipidemia % (definition)	HTN % (definition)	Coronary revasc. %	CKD % (definition)	MI, AMI % (defintion)	CHF % (defintion)	Stroke (CVA) % (definition)	PVD %	Carotid revascu-larization % (definition)	SVT or Afib % (def.)	Ventricular tachyarr-hythmia % (defintion)
Baxheinrich, 2012, 22894911	ALA (40)		100											
	Placebo (41)		100											
Bosch, 2012, 22686415	"Fish oil" (DHA+EPA) (6281)				78.7									
	Placebo (6255)				80.3									
Brinton, 2013, 23835245	EPA [4g/day] (226)	73												
	EPA [2g/day] (234)	73												
	Placebo (227)	73												
Brouwer, 2006, 16772624	Total (273)													
	"Fish oil" (DHA+EPA) (273)	17			53 (>=160/95 mm Hg in repeated measurements, or patients taking anti-hypertensive medication)			73 (ischemic heart disease)					26 (AFib)	75

Author, year, PMID	Arm (N)	DM %	CMS %	Dyslipidemia % (definition)	HTN % (definition)	Coronary revasc. %	CKD % (definition)	MI, AMI % (defintion)	CHF % (defintion)	Stroke (CVA) % (definition)	PVD %	Carotid revascu-larization % (definition)	SVT or Afib % (def.)	Ventricular tachyarr-hythmia % (defintion)
Brouwer, 2006,	Placebo (273)	15			49 (>=160/95 mm Hg in repeated measurements, or patients taking anti-hypertensive medication)			79 (ischemic heart disease)					25 (AFib)	76
Burr, 2003, 12571649	Fish + Fish oil (1571)	12.5			48.6			49.7						
	No intervention (1543)	12.3			47.4			50.2						
Burr, 1989, 2571009	Fish + Fish oil (1015)				22.7			100						
	No intervention (1018)				24.6			100						
Carrepeiro, 2011, 21561620	Total (43)	0		50 (on statins)			0					0		
Caslake, 2008, 18779276	Total (312)	0		0 (fasting total cholesterol a TAG concentrations of >8.0 a 3.0 mmol/L, respectively)				0 (MI in the previous 2 years)						
Ebrahimi, 2009, 19593941	Total (89)													
	"Fish oil" (DHA+EPA) (47)		100											

Author, year, PMID	Arm (N)	DM %	CMS %	Dyslipidemia % (definition)	HTN % (definition)	Coronary revasc. %	CKD % (definition)	MI, AMI % (defintion)	CHF % (defintion)	Stroke (CVA) % (definition)	PVD %	Carotid revascu-larization % (definition)	SVT or Afib % (def.)	Ventricular tachyarr-hythmia % (defintion)
	No intervention (42)		100											
Einvik, 2010, 20389249	"Fish oil" (DHA+EPA) (282)	15		20 (treated hyperlipidemia)	27 (treated hypertension)									
	Placebo (281)	14		19 (treated hyperlipidemia)	29 (treated hypertension)									
	Placebo (68)	15			32 (treated hypertension)			18						
	Placebo (71)	14			26 (treated hypertension)			18						
	"Fish oil" (DHA+EPA) (70)	13			31 (treated hypertension)			17						
	"Fish oil" (DHA+EPA) (69)	13			32 (treated hypertension)			18						
Eritsland, 1996, 8540453	"Fish oil" (DHA+EPA) (260)	4.2			20									
	No intervention (251)	9.6			24.7									
Galan, 2010, 21115589	Total (2501)							46 (28 unstable angina)		26				

Author, year, PMID	Arm (N)	DM %	CMS %	Dyslipidemia % (definition)	HTN % (definition)	Coronary revasc. %	CKD % (definition)	MI, AMI % (defintion)	CHF % (defintion)	Stroke (CVA) % (definition)	PVD %	Carotid revascu-larization % (definition)	SVT or Afib % (def.)	Ventricular tachyarr-hythmia % (defintion)
	"Fish oil" (DHA+EPA) (620)							45.2 (28.4 unstable angina)		26.4				
	"Fish oil" (DHA+EPA) (633)							47.4 (29.2 unstable angina)		23.4				
	Placebo (622)							46.3 (27.0 unstable angina)		26.7				
	Placebo (626)							45.0 (29.4 unstable angina)		25.6				
Holman, 2009, 19002433	Total (658)	100												
Kastelein 2014 24528690	Placebo (98)	30.3			64.6									
	"Fish oil" (DHA+EPA) (99)	39			69									
	"Fish oil" (DHA+EPA) (97)	44.6			68.3									
	"Fish oil" (DHA+EPA) (99)	36.4			67.7									
Kromhout, 2010, 20929341	All n3 PUFAs (ALA+DHA+EPA) (1212)	20.2												

Author, year, PMID	Arm (N)	DM %	CMS %	Dyslipidemia % (definition)	HTN % (definition)	Coronary revasc. %	CKD % (definition)	MI, AMI % (defintion)	CHF % (defintion)	Stroke (CVA) % (definition)	PVD %	Carotid revascu-larization % (definition)	SVT or Afib % (def.)	Ventricular tachyarr-hythmia % (defintion)
	"Fish oil" (DHA+EPA) (1192)	22												
	ALA (1197)	21.2												
	Placebo (1236)	20.1												
Leaf, 2005, 16267249	"Fish oil" (DHA+EPA) (200)					76 (coronary artery disease)							18 (history of AFib)	
	Placebo (202)												18.8 (history of AFib)	
Lungershausen, 1994, 7852747	Total (42)				100									
Macchia, 2013, 23265344	Placebo (297)	14.7			90.8					4.4			100	
	"Fish oil" (DHA+EPA) (289)	11.1			92.2					5			100	
Maki, 2013, 23998969	Placebo (211)	72.6			87.9									
	All n3 PUFAs (ALA+DHA+EPA) [2 g] (209)	73.5			87									
	All n3 PUFAs (ALA+DHA+EPA) [4 g] (207)	68.5			83.8									
Marchioli, 2002, 11997274, Italy	"Fish oil" (DHA+EPA) (5666)	14.2						11.6						18.8

Author, year, PMID	Arm (N)	DM %	CMS %	Dyslipidemia % (definition)	HTN % (definition)	Coronary revasc. %	CKD % (definition)	MI, AMI % (defintion)	CHF % (defintion)	Stroke (CVA) % (definition)	PVD %	Carotid revascu-larization % (definition)	SVT or Afib % (def.)	Ventricular tachyarr-hythmia % (defintion)
	No intervention (5668)	15						11.9						19.4
Natvig, 1968, 5756076	Placebo (6690)							0.13						
	ALA (6716)							0.15						
Nilsen, 2001, 11451717	"Fish oil" (DHA+EPA) (150)	32.9			28.6	8.0		21.3 (previous MI)	10.0 (heart failure)					
	Placebo (150)	8.7			22.8	10.1		25.3 (previous MI)	7.4 (heart failure)					
Nodari, 2011, 21844082	All n3 PUFAs (ALA+DHA+EPA) (100)	36			47									
	Placebo (99)	33.6			40.4									
	"Fish oil" (DHA+EPA) (67)	10.4												
	Placebo (66)	23												
Oh, 2014, 25147070	Placebo (42)	5	36	100										
	"Fish oil" (DHA+EPA) [1g] (44)	7	36	100										
	"Fish oil" (DHA+EPA) [2g] (43)	33	7	100										
	"Fish oil" (DHA+EPA) [4g] (44)	36	5	100										
Olano-Martin, 2010, 19748619	Total (38)	0						0						
Pieters 2015, 25226826	Total (32)			100										

Author, year, PMID	Arm (N)	DM %	CMS %	Dyslipidemia % (definition)	HTN % (definition)	Coronary revasc. %	CKD % (definition)	MI, AMI % (defintion)	CHF % (defintion)	Stroke (CVA) % (definition)	PVD %	Carotid revascu-larization % (definition)	SVT or Afib % (def.)	Ventricular tachyarr-hythmia % (defintion)
Raitt, 2005, 15956633	"Fish oil" (DHA+EPA) (100)	46			46			55						64
	Placebo (100)	23			55			56						69
Rauch, 2010, 21060071	All n3 PUFAs (ALA+DHA+EPA) (1919)	27.6		50.5	66.9			100		5.8				
	Placebo (1885)	26.4		48.5	66.1			13.5		5.1				
Rodriguez-Leyva, 2013, 24126178	All n3 PUFAs (ALA+DHA+EPA) (45)	31.8			75.4									
	Placebo (42)	26.1			69.2									
Roncaglioni, 2013, 23656645	"Fish oil" (DHA+EPA) (6244)	59.6			84.6					4.7				
	No intervention (6269)	60.2			84.6					4.8				
Sacks, 1995, 7759696	"Fish oil" (DHA+EPA) (175)	16				52		55						
	Placebo (175)	11				43		57						
Shaikh, 2014, 25185754	"Fish oil" (DHA+EPA) (56)	10.7			32.1									
	Placebo (54)	14.8			31.5									
Shidfar, 2003, 12847992	Total (68)			100										

Author, year, PMID	Arm (N)	DM %	CMS %	Dyslipidemia % (definition)	HTN % (definition)	Coronary revasc. %	CKD % (definition)	MI, AMI % (defintion)	CHF % (defintion)	Stroke (CVA) % (definition)	PVD %	Carotid revascu-larization % (definition)	SVT or Afib % (def.)	Ventricular tachyarr-hythmia % (defintion)
Sirtori, 1997, 9174486	All n3 PUFAs (ALA+DHA+EPA) (470)	44 (diagnosed with diabetes for 2 y, who were in satisfactory metabolic control)		100 (triacylglycerol2.26-4.52 mmol/L, or 200-400 mg/dL)		68 (treated with antihypertensive drugs or SBP >= 160 mm Hg, DBP >= 95 mm Hg, or both)		0 (MI in the preceding 3 months)						
	Placebo (465)	45 (diagnosed with diabetes for 2 y, who were in satisfactory metabolic control)		100 (triacylglycerol2.26-4.52 mmol/L, or 200-400 mg/dL)		68 (treated with antihypertensive drugs or SBP >= 160 mm Hg, DBP >= 95 mm Hg, or both)		0 (MI in the preceding 3 months)						
Tatsuno, 2013, 24314359	"Fish oil" (DHA+EPA) [2 g/day] (165)	30.3 (Including impaired glucose tolerance.)			66.7									

Author, year, PMID	Arm (N)	DM %	CMS %	Dyslipidemia % (definition)	HTN % (definition)	Coronary revasc. %	CKD % (definition)	MI, AMI % (defintion)	CHF % (defintion)	Stroke (CVA) % (definition)	PVD %	Carotid revascu-larization % (definition)	SVT or Afib % (def.)	Ventricular tachyarr-hythmia % (defintion)
	"Fish oil" (DHA+EPA) [4 g/day] (171)	36.8 (Including impaired glucose tolerance)			67.3									
	EPA [1.8 g/day] (167)	42.5 (Including impaired glucose tolerance)			68.9									
Tatsuno, 2013, 23725919	"Fish oil" (DHA+EPA) [2 g/day] (206)	30.1 (Including impaired glucose tolerance.)			59.7									
	"Fish oil" (DHA+EPA) [4 g/day] (210)	33.3 (Including impaired glucose tolerance)			60.5									

Author, year, PMID	Arm (N)	DM %	CMS %	Dyslipidemia % (definition)	HTN % (definition)	Coronary revasc. %	CKD % (definition)	MI, AMI % (defintion)	CHF % (defintion)	Stroke (CVA) % (definition)	PVD %	Carotid revascu-larization % (definition)	SVT or Afib % (def.)	Ventricular tachyarr-hythmia % (defintion)
	EPA [1.8 g/day] (195)	34.4 (Including impaired glucose tolerance)			67.2									
Tavazzi, 2008, 18757090	"Fish oil" (DHA+EPA) (3494)	28.4				17.6 (CABG); 12.2 (PCI)		41.8	50 (admission for HF in the previous year)	4.8	8.4			7.1 (implantable cardiac defibrillators)
	Placebo (3481)	28.2				18.9 (CABG); 12.7 (PCI)		41.6	(admission for HF in the previous year)	5.1	9.1			7.2 (implantable cardiac defibrillators)
Tierney, 2011, 20938439	Total (206)		100											
Yokoyama, 2007, 17398308	EPA (9326)	16		100		5		6						
	All arms (XO study) (9319)	16		100		5		5						

Table D-3. Baseline Omega-3 intake, comparative studies

Author	Group (N)	Biomarker Source	Units	ALA (18:3 n3)*	EPA (20:5 n3)*	DPA (22:5 n3)*	DHA (22:6 n3)*	EPA+ DHA	EPA+ DHA+ DPA	Total n3 FA	Linoleic acid (18:2 n6)	Aracha-donic acid (20:4 n6)	Total n6 FA	n6/n3 ratio	AA/EPA ratio
Maki, 2013, 23998969	Control (205)	Plasma	mcg/mL		20.8 (10.7)	21.8 (8.0)	58.9 (18.9)					277 (77.1)			
Liu, 2003, no PMID	Control (22)	Erythrocyte	% FA		2.1 (0.3)		5.0 (0.5)					7.7 (0.3)			
Tatsuno, 2013, 24314359	EPA (166)	Plasma	µg/mL	195 (nd)	73 (nd)		184 (nd)								
Galan, 2010, 21115589	Control (169)	Plasma	% FA		[1.26 (IQR 0.84, 1.81)		Median 2.70 (IQR 2.15, 3.36)	Median 4.04 (IQR 2.99, 5.08)							
Rasmussen, 2006, 16469978	SFA (83)	Serum	%	0.31	1.5	1.07	4.67				21.02	9.45			
Burr, 2003, 12571649	Control (29)	Plasma	mg/dl		3.19 (1.75)										
Harrison, 2004, 15853118	Control (43)	Plasma	% FA				1.51 (0.15)								
Tavazzi, 2008, 18757090	Control (1203)	Plasma	mol%		0.85 (0.77)	0.78 (0.32)	3.4 (1.2)			5.1 (1.9)					
Leaf, 2005, 16267249	Control (202)	phospholipids of red blood cells	% of total FA					3.5 (SEM 1.2)							
Eritsland, 1996, 8540453	Control (251)	Serum	mg/L		33.5 (19.9)		111.4 (30.8)			170.3 (51.4)	282.7 (67.1)	105.6 (31.4)	429.9 (92.8)		
Caslake, 2008, 18779276	Control (312)	plasma phosphatidyl-choline fatty acid	% total FA		1.6 (SEM 0.04)	1.09 (0.01)	4.41 (0.07)		7.17 (0.11)		23.4 (0.15)				
Olano-Martin, 2009, 19748619	Control (38)	plasma phospholipids fatty acid	% total FA		1.7 (SEM 0.2)	1.2 (0.0)	4.8 (0.2)				23.4 (0.4)				
Grieger, 2014, 24454276	Control (37)	RBC membrane	%	0.147 (0.008 SE)	1.5 (0.1 SE)	3.0 (0.1 SE)	5.0 (2 SE)			9.7 (0.4 SE)	10.3 (0.2 SE)	12.0 (0.3 SE)	27 (0.4 SE)		
Kastelein, 2014, 24528690	Control (98)	plasma	µg/mL	Median 375 (range 105, 1182)	Median 19.5 (range 6.3, 207)		Median 85.1 (range 29.7, 411)								

Author	Group (N)	Biomarker Source	Units	ALA (18:3 n3)*	EPA (20:5 n3)*	DPA (22:5 n3)*	DHA (22:6 n3)*	EPA+ DHA	EPA+ DHA+ DPA	Total n3 FA	Linoleic acid (18:2 n6)	Aracha-donic acid (20:4 n6)	Total n6 FA	n6/n3 ratio	AA/EPA ratio
Einvik, 2010, 20389249	Control (281)	serum	% of total		Median 1.67 (IQR 1.07, 2.93)		Median 2.97 (IQR 2.23, 3.95)							Median 6.21 (IQR 4.25, 8.56)	
Einvik, 2010, 20389249	Control (68)	serum	% of total	Mean 0.59 (0.20)	Mean 2.18 (1.7)		Mean 2.98 (1.2)			Mean 6.0 (3.0)				Mean 7.0 (3.5)	
Nodari, 2011, 21215550	Control (66)	circulating free fatty acids	% total circulating FFA					1.68 (0.43)							

* mean (SD) [median (IQR)]. If a single number is given for IQR, this indicates the width of the interval (75^{th}-25^{th}).

Table D-4. Observational studies, continuous measures

Author, year, PMID	n3 Source	Male %	Race %	Age mean (SD) [median]	SBP mean (SD) [median]	DBP mean (SD [median]	Total Cholesterol mean (SD) mg/dL [mmol/L]	LDL mean (SD) mg/dL [mmol/L]	HDL mean (SD) mg/dL [mmol/L]	Triglycerides mean (SD) mg/dL [mmol/L]	BMI mean (SD)/weight mean (SD) Kg
Amiano, 2014, 24360762	Fish diet; Plant diet (ALA)	37.6		49.2 (8)							73.7 (12.6)
Ascherio, 1995, 7885425	Fish diet	100		53 (9.6) range 40,75			203				25.5 (SE 0.02)
Belin, 2011, 21610249	Fish diet; Diet (Total)	0	~84 white, ~7% black, ~3% Asian, ~5% Hispanic, ~0.4% American Indian/Alaskan Native, ~1% unknown	range 50, 79	127 (18)				64 (17)		28 (6)
Bell, 2014, 24496442	Marine oil supplement, Diet (Total)	49	93 white, 1 black, 2 Asian, 1 Hispanic, 1.5 Inuit/Eskimo, 1.5 other/missing								
Brouwer, 1996, 16569549	Diet (Total)	41% in Q3 (secondary study)		67.3 (7.6)	138 (21)	73 (11)	[6.6 (1.2)]		[1.3 (0.4)]		26.4 (3.6)
de Goede, 2010, 20335635	Diet (Total)	45		41.8	120.4 (15.9)	76.6 (10.5)	[5.2 (1.0)]		[1.4 (0.4)]		25.0 (3.9)
De Goede, 2013, 22633188	Diet (Total)	53		Cases: 50.1 (9.5), Controls: 50.0 (9.5)	Cases: 132.1 (20.2), Controls: 126.1 (16.1)	Cases: 82.9 (12.0), Controls: 80.9 (11.3)	[Cases: 5.7 (1.1), Controls: 5.6 (1.1)]		[Cases: 1.3 (0.4), Controls: 1.3 (0.3)		Cases: 25.8 (4.1), Controls: 25.9 (4.3)
de Oliveira, 2013, 24351702	Diet (Total)	46.8	26 white, 25 black, 25 Asian, 25 Hispanic	61.5 (10.2)							27.9 (5.5)
Dolecek, 1992, 24351702	Diet (Total)	100		range 35, 57							
Hara, 2013, 23047296	Diet (Total)	77.8		65 range 57, 73			191 (range 163, 222)	122 (range 100, 147)	44 (range 38, 52)	98 (range 60, 153)	23.9 (range 22.1, 26.1)
Hellstrand, 2014, 25008580	Diet (Total)	37		range 44, 74							25.6

Author, year, PMID	n3 Source	Male %	Race %	Age mean (SD) [median]	SBP mean (SD) [median]	DBP mean (SD [median]	Total Cholesterol mean (SD) mg/dL [mmol/L]	LDL mean (SD) mg/dL [mmol/L]	HDL mean (SD) mg/dL [mmol/L]	Triglycerides mean (SD) mg/dL [mmol/L]	BMI mean (SD)/weight mean (SD) Kg
Hu, 2002, 11939867	Fish diet; Plant diet (ALA)	0	98 white	range 34, 59							
Iso, 2006, 16401768	Fish diet	48		49							
Itakura, 2011, 21099130	Marine oil supplement	30.25	100 Asian	controls: 61 (9), cases: 61 (8)	controls: 134.9 (20.9), cases: 134.9 (21.4)	controls 79.2 (12.6), cases: 78.9 (12.6)					controls: 24.1 (3.3), cases 24.0 (3.2)
Joensen, 2010, 19825219	Fish diet	47.6		[men: 55.9, women 56.2]	[men: 140, women 136]		[median men: 5.9, women: 6.2]				25.9 (3.9)
Khaw, 2012, 22802735	No Data / Unclear	45.6		men: 60 (8), women 59.4 (8.5)	men: 136.1 (16.4), women: 132.6 (18.0)	men: 83.7 (10.6), women: 80 (10.7)	[men: 6.03 (1.05) 6.35 (1.20)]	[men: 3.92 (0.95), women: 4.03 (1.06)	men: 1.25 (0.33), women: 1.58 (0.42)	[men: 2.01 (1.15), women: 1.64 (1.07)]	men: 26.3 (3.1), women: 25.9 (3.9)
Koh, 2013, 24343844	Fish diet, Plant diet, Diet (Total)	44.2		56 (8)							23.2 (3.3)
Larsson, 2012, 22265275	Fish diet	0		62							25
Lemaitre, 2012, 22743310	Plant diet (ALA)	36.1	87.8 white, 11.7 black	74 (5) median 73 IQR 71-98							
Levitan, 2009, 19383731	Fish diet	100		nd							
Matsumoto, 2013, 23098619	Diet (Total)	100		68.7 (8.7)							25.8 (3.4)
Miyagawa, 2014, 24468152	Diet (Total)	43.8		49.4 (13) (Q2)	Q2: 135.5 (21.5)	Q2: 81.1 (12.1)	Q2: 188.7 (33.8)				Q2: 22.7 (3.1)
Morris, 1995, 7598116	Fish diet	100		53.2							24.9
Nagata, 2002, 12397000	Diet (Total)			men: 54.0 (12.1), women: 55.1 (13.0)							men: 22.5 (2.8), women: 22.0 (2.9)
Ninomiya, 2013, 24267237	No data / Unclear	42		61.3 (12.5)	131.8 (21.1)	78.4 (11.9)	[5.28 (0.92)]		[1.62 (0.42)]	[Median 1.10 (IQR 0.78, 1.63)]	23.1 (3.4)

Author, year, PMID	n3 Source	Male %	Race %	Age mean (SD) [median]	SBP mean (SD) [median]	DBP mean (SD [median]	Total Cholesterol mean (SD) mg/dL [mmol/L]	LDL mean (SD) mg/dL [mmol/L]	HDL mean (SD) mg/dL [mmol/L]	Triglycerides mean (SD) mg/dL [mmol/L]	BMI mean (SD)/weight mean (SD) Kg
Pietinen, 1997, 9149659	Diet (Total)	100		range 50, 69							
Strøm, 2012, 22146511	Diet (Total)	0		29.9 range 15.746.9							
Takata, 2013, 23788668	Fish diet	45.5		men: 55.1 (9.54), women: 51.8 (8.76)							
Vedtofte, 2011, 21865326	Diet (Total)	49.9		50.6 range 30.8, 60.8	123 range 104, 152						23.9 (range 19.7, 29.6)
Vedtofte, 2014, 24964401	Plant diet (ALA)	35.1		range 49, 61							
Virtanen, 2009, 19933935	Diet (Total)	100		52.8 (5.3)							
Wang, 2010, 20713915	Fish diet	0	95 white	54							25
Wang, 2011, 21734059	No Data / Unclear	0	71.6 white, 14.1 black, 13.25 Asian	54 (6.3)			208.45	122	54.1		25.5
Warensjö, 2008, 18614742	Diet (Total)	100		nd			6.9 (1.3)				25.0 (3.2)
Woodward, 2011, 21345851	Diet (Total)	53		men: 49.0 (6.9), women: 48.9 (6.6)	men: 133.2 (18.5), women: 130.0(20.0)		[men: 6.29(1.13), women: 6.49(1.31)		[men: 1.38(0.37), women: 1.68(0.42)]		
Xun, 2011, 21205024	Fish diet	46.9	50.6 black	24.9 (3.7)	110 (10.2)	68.3 (8.8)					24.4 (4.9)
Yamagishi, 2008, 18786479	Fish diet	39.5	100 Asian	55.7							men: 22.7, women 22.9
Yamagishi, 2008, 19061714	Diet (Total)	46.6	100 white	men: 54.2 (5.6), women 53.3 (5.5)	men: 120.5 (14.8), women 116.9 (17.0)	men 75.5(9.2); women 72.1 (9.1)	men: 212 (39), women 216 (42)		men: 44(12); women: 60(17)	men: 139 (94), women: 116 (73)	men: 27.7 (3.7), women: 26.2 (5)
Yuan, 2001, 11682363	Fish diet	100		55.8 (45-64)							22.2
Zeng, 2014, 24966412	Diet (Total)	25.3									

Table D-5. Observational studies, categorical measures

Author, year, PMID	DM % (definition)	Dyslipidemia % (definition)	HTN % (definition)	CHF %	Stroke (CVA) %	MI, AMI % (definiton)	SVT or Afib % (definition)
Amiano, 2014, 24360762	4.9	20.1 (hyperlipidemia)	20.1				
Ascherio, 1995, 7885425	2.4		19.3				
Belin, 2011, 21610249	4						Q2: 5
Brouwer, 1996, 16569549							
de Goede, 2010, 20335635	0.8						
De Goede, 2013, 22633188	Cases: 5.6, Controls: 0.6		Cases: 42.1, controls: 30.7				
de Oliveira, 2013, 24351702	13.1						
Dolecek, 1992, 24351702							
Hara, 2013, 23047296	35.1	50.8	67.0			100	
Hellstrand, 2014, 25008580							
Hu, 2002, 11939867							
Iso, 2006, 16401768	4	4	16				
Itakura, 2011, 21099130	controls: 16.4, cases 16.3	100	controls: 35.5, cases: 35.8				
Joensen, 2010, 19825219	men: 2.6, women: 1.5		Middle quintile: 10.0 (receiving treatment for hypertension)				
Khaw, 2012, 22802735	1.7 (history of diabetes)						
Koh, 2013, 24343844	8.9		23.7		1.1		
Larsson, 2012, 22265275	0	8 (history of high cholesterol)	20				
Lemaitre, 2012, 22743310	24						
Levitan, 2009, 19383731	7.1					4.7	
Matsumoto, 2013, 23098619							
Miyagawa, 2014, 24468152							
Morris, 1995, 7598116	2.4	5.8 (high cholesterol)	13.6				
Nagata, 2002, 12397000	men: 5.9, women: 2.7		men; 18.9, women: 17.4				
Ninomiya, 2013, 24267237	16.9		42.6				

Author, year, PMID	DM % (definition)	Dyslipidemia % (definition)	HTN % (definition)	CHF %	Stroke (CVA) %	MI, AMI % (definiton)	SVT or Afib % (definition)
Pietinen, 1997, 9149659							
Strøm, 2012, 22146511							
Takata, 2013, 23788668	men: 6.1, women: 4.2		men: 30.1, women: 23.6				
Vedtofte, 2011, 21865326						20.5 (Family history of AMI)	
Vedtofte, 2014, 24964401							
Virtanen, 2009, 19933935	4.9		46.5	5.6	1.9		
Wang, 2010, 20713915	1.25	24.6 (history of hypercholesterolemia)					
Wang, 2011, 21734059	1.7 (history of diabetes)	25.1 (history of hypercholesterolemia)					
Warensjö, 2008, 18614742	5		43				
Woodward, 2011, 21345851	men: 21, women 19						
Xun, 2011, 21205024							
Yamagishi, 2008, 18786479	men: 6, women 3		men: 18, women: 19				
Yamagishi, 2008, 19061714							
Yuan, 2001, 11682363	1.3		24.6				

Appendix E. Study Design

Table E-1. Comparative studies

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population
Baxheinrich, 2012, 22894911, Germany	Trial: Randomized Parallel, 2010 (approx.)	Industry funded/No conflict of interest (explicitly stated)	6 months	To be enrolled in the study, subjects had to meet the diagnosis criteria of the metabolic syndrome according to the definition of the International Diabetes Federation (Table 1). Exclusion criteria were CVD, severe illnesses such as renal failure or liver disease, food allergy or intolerance, pregnancy or lactation, smoking, alcohol abuse and insulin therapy or severe diabetic complications in case of diagnosed type 2 diabetes mellitus.	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease): Diabetes and/or metabolic syndrome*

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population
Bosch, 2012, 22686415, Canada, ORIGIN	Trial: Randomized Factorial Design, 2003	Industry funded	2 years	At least 50 years old; a diagnosis of diabetes with receipt of no more than one oral glucose-lowering drug, impaired glucose tolerance (plasma glucose level at 2 hours, =7.8 mM [140 mg per deciliter] and <11.1 mM [200 mg per deciliter] after a 75-g oral glucose load), or impaired fasting glucose (range, =6.1 mM [110 mg per deciliter] to <7.0 mM [126 mg per deciliter]); a history of myocardial infarction, stroke, or revascularization; angina with documented ischemia; a ratio of urinary albumin to creatinine of more than 30 mg per gram; left ventricular hypertrophy; 50% or more stenosis of a coronary, carotid, or lower-limb artery on angiography; or an ankle brachial index of less than 0.9. Participants were excluded if they were unwilling to discontinue use of a nonstudy preparation of n 3 fatty acids, had a locally measured glycated hemoglobin level of 9% or more, had undergone coronary-artery bypass grafting within the previous 4 years with no intervening cardiovascular event, had severe heart failure, or had a cancer that might affect survival.	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease): Diabetes and/or metabolic syndrome*; Hypertension; Cardiac disease; Cerebrovascular disease; Peripheral vascular disease; Arrhythmia

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population
Brinton, 2013, 23835245, US, ANCHOR	Trial: Randomized Parallel	Industry funded	12 weeks	>18 years of age at high risk for CVD (patients with clinical coronary heart disease [CHD] or CHD risk equivalents [10-year risk 20%]) as defined by the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) guidelines. On stable statin therapy (atorvastatin, rosuvastatin, or simvastatin with or without ezetimibe) for 4 weeks at doses expected to produce "optimal" LDLC levels for high-risk patients (40 and <100 mg/dL). Patients who had A1c >9.5% or were being treated with antidiabetes medication that had not been stable for 4 weeks at screening were excluded from the ANCHOR study.	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
Brouwer, 2006, 16772624, Germany, Netherlands, Sweden, UK, Poland, Czech Republic, Belgium, Austria, SOFA trial	Trial: Randomized Parallel, 2001	No industry relationship reported (funding or affiliations reported)/No Data regarding conflict of interest	12 months	Men and women >=18 years old, experienced at least 1 true, confirmed, spontaneous VT or VF in the preceding year, and either had and ICD or were about to receive one. Exclusion: receipt of an ICD for prophylactic reasons; ICD as a "bridge" to heart transplantation; refractory supraventricular arrhythmia with rapid ventricular rates despite antiarrhythmic therapy; a projected life span of <1 year; use of supplemental omega-3 PUFA during the past 3 months or consumption >8g of omega-3 PUFAs from fish or seafood per month (267 mg/d) as judged by a seafood FFQ; pregnant women; women of childbearing age who did not use adequate contraception, and patients with a known history of recent drug or alcohol abuse.. excluded patients with high baseline omega-3 intake from supplements and/or foods	Secondary Prevention (history of CVD event): Arrhythmia (at least 1 true, confirmed, spontaneous VT or VF in the preceding year, and either had and ICD or were about to receive one.)

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population
Burr, 2003, 12571649, UK, DART2	Trial: Randomized Factorial Design, 1990	Industry only donated materials (eg, supplements)	9 years	Men <70 y/o who were being treated for angina. The following subjects were excluded from the trial: men who denied ever having exertional chest pain or discomfort (except for men who never hurried whose pain was brought on by stress); men awaiting coronary artery by-pass surgery; men who already ate oily fish twice a week; men who could not tolerate oily fish or fish oil; men who appeared to be unsuitable on other grounds (eg other serious illness, likelihood of moving out of the area).	Secondary Prevention (history of CVD event): Cardiac disease (Angina)
Burr, 1989, 2571009, UK	Trial: Randomized Factorial Design, 1987 (approx.)	Industry only donated materials (eg, supplements)	2 years	The subjects were men under 70 years of age, admitted to 21 hospitals with a diagnosis of acute MI according to World Health Organization criteria. Diabetic patients, men awaiting cardiac surgery, and men who already intended to eat one of the intervention diets were excluded.	Secondary Prevention (history of CVD event): Cardiac disease (Previous MI)
Carrepeiro, 2011, 21561620, Brazil	Trial: Randomized cross-over within subgroups based on existing statin use, 2008 (approx.)	No industry relationship reported (funding or affiliations reported)	6 weeks/90 days	Female, generally healthy, 40-80 y/o. Controlled or absent cholesterolemia and hypertension, absent or moderate alcohol consumption. Exclude DM, CV intervention, kidney failure, HRT, dietary supplements w/in 6 mo.	Primary Prevention, Healthy
Carter, 2012, 22707560, US	Trial: Randomized Parallel, 2010 (approx.)	No industry relationship reported (funding or affiliations reported)	8 weeks	Normotensive (resting systolic pressure < 120 mmHg and diastolic pressure <80 mmHg) and prehypertensive (resting systolic pressure of 120-139 mmHg and.or a diastolic pressure of 80-89 mmHg. Exclusion criteria included smoking, diabetes, hypertension, autonomic dysfunction, and use of blood pressure medication. Subjects confirmed they had not been taking any omega-3 fatty acid supplements for >= 2 mo before start of study.	Primary Prevention, Healthy

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population
Caslake, 2008, 18779276, UK, FINGEN	Trial: Randomized Cross-over, 2003	Industry funded/Conflict of interest stated (CMW is a consultant to Pepsico UK and Unilever Plc. PCC is a consultant to Equazen, Royal Dutch Numico, and Mead Johnson Nutritionals and accepts speaking fees from Solvay Healthcare, Solvay Pharmaceuticals, B Braun Melsungen, and Fresenius Kabi. None of the other authors had a personal or financial conflict of interest.)	three 8-weeks intervention period separated by two 12-weeks washout periods/12 weeks	The volunteers were generally fit and healthy. Exclusion criteria for participation in the study were diagnosed diabetes or fasting glucose concentrations of >6.5 mmol/L; liver or other endocrine dysfunction; a myocardial infarction in the previous 2 y; hypolipidemic therapy or any other medication known to interfere with lipid metabolism; consumption of FA supplements or oily fish >1 time/wk; current use of a weight-reducing diet; body mass index (in kg/m2) of <18.5 or >30; or fasting total cholesterol (TC) and TAG concentrations of >8.0 and 3.0 mmol/L, respectively.	Primary Prevention, Healthy
Damsgaard, 2008, 18492834, Denmark	Trial: Randomized Factorial Design, 2005	Industry only donated materials (eg, supplements)/No conflict of interest (explicitly stated)	8 weeks	Healthy males, aged 18-40 y, with no chronic diseases, no regular medication, and no strong allergies who were smoking <5 cigarettes/week, exercising strenuously <7 h/wk, eating homemade meals >5 d/wk, and consumed butter/margarine/or oil daily.	Primary Prevention, Healthy

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population
Derosa, 2009, 19397392, Italy	Trial: Randomized Parallel	Industry only donated materials (eg, supplements)/No conflict of interest (explicitly stated)	6 months	Caucasian patients aged 18 years of either sex were eligible for inclusion in the study if they had combined dyslipidemia (defined by the International Lipid Information Bureau), identified by total cholesterol (TC) > 200 mg/dl and triglycerides (Tg) > 200 mg/dl, and who had never previously taken lipid-lowering medications. Patients were excluded if they had a genetic condition affecting lipid metabolism (e.g., familial hypercholesterolemia, type III hyperlipidemia, LPL deficiency, etc.); a history of microalbuminuria or nephrotic syndrome; an impaired hepatic function (defined as plasma aminotransferase and/or -glutamyltransferase level higher than the upper limit of normal for age and sex); an impaired renal function (defined as serum creatinine level higher than the upper limit of normal for age and sex); thyroid diseases; endocrine or metabolic disease; a history of alcohol or drug abuse; a neoplastic, infectious or autoimmune disease; poor mental condition or if they were taking any other drug that was able to influence lipid metabolism. Patients with serious cardiovascular disease (e.g., New York Heart Association class I IV congestive heart failure or a history of myocardial infarction or stroke) or cerebrovascular conditions in 6 months before study enrollment were also excluded.	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease): Dyslipidemia (total cholesterol (TC) > 200 mg/dl and triglycerides (Tg) > 200 mg/dl)

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population
Earnest, 2012, 22811376, US	Trial: Randomized Parallel, 2009 (approx.)	No Data on funding or affiliations	12 weeks	Inclusion criteria for this study necessitated that participants have a HCY concentration > 8.0 mmol/L. We excluded pregnant or lactating women from participation. Postmenopausal women both on and off hormone replacement therapy were accepted into the trial. We asked those on hormone replacement therapy to remain on their current medication and dosage schedule and notify us if the regimen was changed. Participants currently on standard medical therapy (for conditions such as hypertension, hypercholesterolemia, diabetes, arthritis, or other chronic diseases) were allowed to enter the study if they had been taking any medications for at least 6 months and agreed to remain on their current therapy during the trial.	Primary Prevention, Healthy; Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease): Diabetes and/or metabolic syndrome*; Hypertension; Dyslipidemia
Ebrahimi, 2009, 19593941, Iran	Trial: Randomized Parallel, 2007 (approx.)	No industry relationship reported (funding or affiliations reported)	6 months	People with metabolic syndrome but who had not previously taken n-3 fatty acid capsules or other nutritional supplements. People who were <40 or >70 years old were excluded from the study.	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease): Diabetes and/or metabolic syndrome*

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population
Einvik, 2010, 20389249, Norway, DOIT	Trial: Randomized Factorial Design, 1997	No industry relationship reported (funding or affiliations reported)/No Data regarding conflict of interest	3 years	The basis for recruitment in the DOIT was the 910 survivors from a population of 1232 healthy men with hypercholesterolemia (> 6.45 mmol/l) participating in the Oslo Diet and Antismoking Study, carried out from 1972 to 1977. Exclusion factors in the DOIT were: total cholesterol greater than 8mmol/l, blood pressure levels greater than 170/100mmHg, specific disease states or practical causes thought to influence longevity, or compliance (cancer, end-stage renal failure, chronic alcoholism or travel distance>200km). A total of 82 individuals were excluded and 10 individuals were unwilling to participate.	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease): Dyslipidemia (hypercholesterolemia (> 6.45 mmol/l)
Eritsland, 1996, 8540453, Norway, SHOT	Trial: Randomized Factorial Design, 1989	Industry funded/No Data regarding conflict of interest	1 year	Consecutive patients admitted for coronary artery bypass grafting without concomitant cardiac surgery, such as valve implantation or aneurysmectomy. Exclusion criteria: medical contraindications to any of the treatment principles (n = 109), refused participation (n = 57), early (~2 days) perioperative death (n = 13) or complications (n = 32), presumed lack of compliance (n = 29), indication for anticoagulation (n = 27), and administrative reasons (n = 38).	Secondary Prevention (history of CVD event): Cardiac disease (coronary artery bypass grafting without concomitant cardiac surgery)

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population
Finnegan, 2003, 12663273, UK	Trial: Randomized Parallel, 1998	Industry funded/No Data regarding conflict of interest	6 months	Moderately hyperlipidemic but otherwise healthy adults aged 25-72 y. Exclusion criteria for participation in the study were evidence of cardiovascular disease, including angina; diagnosed diabetes or a fasting glucose concentration > 6.5 mmol/L; liver or other endocrine dysfunction; pregnancy or lactation; smoking > 15 cigarettes/d; exercising strenuously > 3 times/wk; body mass index (in kg/m2) < 20 or > 32; and a hemoglobin concentration < 130 g/L in men or 120 g/L in women. Individuals who were prescribed hypolipidemic or antiinflammatory medication, took fatty acid or antioxidant supplements regularly, or consumed > 2 portions of oily fish/wk were excluded. Vegetarians and nonconsumers of margarine were also excluded. Moderate hyperlipidemia was defined as a fasting total cholesterol concentration between 4.6 and 8.0 mmol/L and a triacylglycerol concentration between 0.8 and 3.2 mmol/L.	Primary Prevention, Healthy: Dyslipidemia
Galan, 2010, 21115589, France, SU.FOL.OM3	Trial: Randomized Parallel, 2003	Industry funded	Median 4.7 years (mean 4.2, SD 1.0)	History of CVD (acute coronary event, including ACS, or cerebral ischemic event, excluding TIA, within 12 mo), 45-80 y. Exclude disease or treatment that might interfere with metabolism of homocysteine or n-3 FA (eg, methotrexate), SCr >200 mcmol/L, CrCl <40 ml/min.	Secondary Prevention (history of CVD event): Cardiac disease (Coronary event w/in 12 mo, including MI, ACS or suspected ACS); Cerebrovascular disease (CVA (not TIA))

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population
Grieger, 2014, 24454276, Australia	Trial: Randomized Parallel, 2011	Industry funded/No conflict of interest (explicitly stated)	8 weeks	Community dwelling men and women >= 64 years of age, Inclusion criteria were: BMI >= 18.5 kg/m2 usual consumption of <=1 serving of fish/seafood per week, willing to consume eight servings of fish or red meat per fortnight. Exclusion criteria were: allergies to fish/seafood, vegetarian, intake of lipid-lowering medications; intake of lipid-lowering supplements (e.g. psyllium, fish oil capsules, soy lecithin, phytoestrogens or to cease 3 weeks prior to study commencement), use of anti-inflammatory medications on a regular basis or if experiencing an acute episode within 1 week of the screening visit, presence of diabetes, liver, kidney, thyroid diseases (unless controlled and stable on replacement medication), presence of other endocrine disorders from self-reported medical history, weight loss or gain of 10% body weight in the prior 6 months, or clinically diagnosed depression or dementia..	Primary Prevention, Healthy
Grimsgaard, 1998, 9665096, Norway	Trial: Randomized Parallel, 1993	No Data on funding or affiliations/No Data regarding conflict of interest	2 months	They reported being healthy nonsmokers, did not use non-prescribed or prescribed drugs, and consumed less than four fish dishes per week in their usual diet. They also had serum cholesterol concentrations < 8.0 mmol/L, diastolic blood pressure < 95 mm Hg, and systolic blood pressure < 160 mm Hg.	Primary Prevention, Healthy

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population
Harrison, 2004, 15853118, UK	Trial: Randomized Factorial Design, 2001	Industry only donated materials (eg, supplements)	5 weeks	Men and women aged 45-59 with a total serum cholesterol >=5.7mmol/l or a mean SBP >= 130 mmHg or both. Exclusions: Those taking existing medications for blood pressure or cholesterol. Participants randomly selected from 12 general practices on the Islands of Lewis and Harris, whose inhabitants have high cholesterol.	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease): Hypertension (SBP >= 130 mmHg); Dyslipidemia (Total cholesterol >= 5.7 mmol/l)
Holman, 2009, 19002433, UK, AFORRD	Trial: Randomized Factorial Design, 2004	Industry funded	4 months	Patients with type 2 diabetes for at least 3 months, aged 18 years, with no known CVD events, and not thought by their general practitioner to be at high enough CVD risk to require immediate lipid-lowering therapy.	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease): Diabetes and/or metabolic syndrome*

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population
Jones, 2014, 24829493, Canada, COMIT	Trial: Randomized Cross-over, 2010	Industry funded/Conflict of interest stated (All authors report having received grants and funding from food companies)	4 weeks/4 weeks	Inclusion: any of the following: triglyceride level (TG) 1.7 mmol/L, high density lipoprotein cholesterol level (HDL) <1 mmol/L (males) or <1.3 mmol/L (females), blood pressure 130 mmHg (systolic) and/or 85 mmHg (diastolic) and glucose level 5.5 mmol/L, waist circumference 94 cm for men and 80 cm for women. Exclusion: thyroid disease (unless controlled by medication), diabetes mellitus, kidney disease, liver disease, current smokers, or those consuming more than two alcoholic drinks per week, or medications known to affect lipid metabolism or endothelial function (including aspirin or other non-steroidal anti-inflammatory drugs), cholestyramine, colestipol, niacin, clofibrate, gemfibrozil, probucol, or 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors.. At the beginning of the study, the Adult Treatment Panel III (ATP III) metabolic syndrome criteria for waist circumference (>102 cm for men and >88 cm for women) were followed [28]. As the trial progressed, the International Diabetes Federation (IDF) metabolic syndrome criteria for waist circumference (94 cm for men and 80 cm for women) were adopted to identify individuals in the initial stages of abdominal obesity who might benefit from dietary intervention.	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease): Hypertension (blood pressure 130 mmHg (systolic) and/or 85 mmHg (diastolic)); Dyslipidemia (TG 1.7 mmol/L, HDL <1 mmol/L (males) or <1.3 mmol/L (females)); Obesity/Overweight (waist circumference 94 cm for men and 80 cm for women); Other (glucose level 5.5 mmol/L)

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population
Kastelein, 2014, 24528690, US, Denmark, Netherlands, India, Hungary, Ukraine, Russia, EVOLVE	Trial: Randomized Parallel, 2011	Industry funded/Conflict of interest stated (The authors acknowledge that they have either received research grant funding from, or are employees of, or have ownership in Omthera Pharmaceuticals, Inc, the manufacturer of the product studied. The relationship of authors Dr Kastelein, Mr Machielse, Mr Kling, and Dr Davidson to Omthera are considered significant according to the definitions used by the Food and Drug Administration. The following authors further disclose that they have other modest relationships with industry that might pose a potential conflict of interest(s): Dr Kastelein (Amarin), Dr Maki (Abbott, Amarin, DSM, GSK, Pharmavite, Trygg Pharma), Dr Susekov (Abbott, Actavis, Amarin, Amgen, AstraZeneca, Gedeon-Richter, Genzyme, KRKA, Merck, Novartis, Pfizer, Promed,	12 weeks	Participants included men and women (nonpregnant, nonlactating) >=18 years of age with average serum TG concentrations >=500 mg/dL but <2000 mg/dL at screening (1 and 2 weeks before random assignment) who were either untreated for dyslipidemia or were using a stable (for at least 6 weeks before the first qualifying lipid measurement) dosage of a statin, CAI, or their combination. Subjects were also required to have a body mass index (calculated as weight divided by height squared; kg/m2) >=20 and be willing to maintain their customary activity level, follow the TLC diet with weight maintenance, and restrict their consumption of fish to no more than twice per week throughout the study. Persons with known lipoprotein lipase impairment or deficiency, apolipoprotein (Apo) CII deficiency, or familial dysbetalipoproteinemia were excluded from the study, as were persons with a history of pancreatitis, symptomatic gallstone disease (unless treated with cholecystectomy), uncontrolled diabetes (glycosylated hemoglobin $9%), or cancer in the past 2 years (basal cell carcinoma was not exclusionary). Persons with a recent history (past 6 months) of a cardiovascular event (ie, myocardial infarction, acute coronary syndrome, new onset angina, stroke, transient ischemic attack, or unstable congestive heart failure that required a change in treatment); revascularization procedure; aortic aneurysm; nephrotic syndrome; or pulmonary, hepatic, biliary, gastrointestinal, or immunologic disease were also excluded. Persons with uncontrolled hypothyroidism, thyroid-stimulating hormone >5 mIU/L, or poorly controlled hypertension (resting blood pressure >=160 mm Hg systolic or >=100 mm Hg diastolic) at 2	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease): Dyslipidemia (average serum TG concentrations 500-2000 mg/dL); Obesity/Overweight (body mass index >=20)

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population
Kromhout, 2010, 20929341, Netherlands, DART	Trial: Randomized Factorial Design, 2002	Industry only donated materials (eg, supplements)/No conflict of interest (explicitly stated)	40 months	Men and women 60 to 80 years of age, who had had a clinical diagnosed MI up to 10 years before randomization. Exclusion criteria: daily consumption of <10 10 g of margarine, use of n-3 fatty-acid supplements, unintended weight loss of >5 kg in the previous year, and a diagnosis of cancer with an estimated life expectancy of <1 year.	Secondary Prevention (history of CVD event): Cardiac disease (myocardial infarction)
Kuhnt 2014, 24553695, Germany	Trial: Randomized Parallel, 2011	No conflict of interest (explicitly stated)	8 weeks	Normolipidemic and normal-weight (BMI 18-25) individuals were recruited for 2 age groups: group I, 20-35 y; and group II 49-69 y. Older overweight individuals were recruited for echium oil (EO) intervention only (49-69 y; BMI >25 with markers of metabolic syndrome or BMI >= 30). Patients with markers of metabolic syndrome were mainly enlisted from the diabetes research center. This subgroup - EO III (older overweight individuals who were recruited for echium oil intervention only; 49-69 y; BMI >25 with markers of metabolic syndrome) was not included in this systematic review.	Primary Prevention, Healthy
Leaf, 2005, 16267249, US	Trial: Randomized Parallel, 1999	Industry only donated materials (eg, supplements)/No Data regarding conflict of interest	1 year	Subjects were included who had an ICD implanted because of a history of cardiac arrest, sustained ventricular tachycardia (VT), or syncope with inducible, sustained VT or ventricular fibrillation (VF) during electrophysiologic studies. The qualifying ICD implantation was required to have occurred within 12 months before entry into the study or if the patient had experienced at least 1 spontaneous ICD event for VT/VF in the preceding 12 months.. -	Secondary Prevention (history of CVD event): Arrhythmia (ICD implanted)

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population
Liu, 2003, no PMID, Sweden	Trial: Randomized Parallel, 2001 (approx.)	No Data on funding or affiliations	12 weeks	Patients with hyperlipidemia, fasting TC>6.2 mmol/L and/or fasting TG>1.8 mmol/L, were studied. The subjects had their first diagnosis of hyperlipidemia. Subjects with previously known lipid changes undergoing treatment were excluded, as well as subjects with allergy to statins, or with diabetes mellitus, liver, or renal disease, or other diseases that might influence lipid metabolism, and pregnant women. Participation in another drug study during the last month, and treatment with antimycotic drugs or antibiotics that might interfere with the effects of statins, or with other drugs that may influence lipid metabolism, were further reasons for exclusion. Patients with cancer or other serious diseases were also excluded. Subjects with obesity, high BMI, high blood pressure or insulin resistance were not excluded.	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease): Dyslipidemia (fasting TC>6.2 mmol/L and/or fasting TG>1.8 mmol/L)
Lungershausen, 1994, 7852747, Australia	Trial: Randomized Cross-over, 1992 (approx.)	Industry only donated materials (eg, supplements)	6 weeks/4-6 weeks	Volunteers with uncomplicated essential hypertension controlled by monotherapy with a beta-blocker or diuretic, or a combination of the two. Excluded if with history of unstable heart, renal, or liver disease, or with DBP >105mmHg, consumed more than 20 cigs or 40g EtOH per day, or exercised erratically. Any variation in antihypertensive drug therapy would necessitate withdrawal of the individual from the study.	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease): Hypertension (Treated for hypertension, on medication)

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population
Macchia, 2013, 23265344, Italy, Argentina, FORWARD	Trial: Randomized Parallel, 2008	Industry funded/No conflict of interest (explicitly stated)	12 months	Patients with previous persistent AF (>=2 symptomatic episodes of documented AF in the 6 months before randomization, with last episode occurring within 3 to 90 days before randomization (paroxysmal AF); or successful electrical or pharmacological cardioversion for persistent AF performed within 3 to 28 days before randomization.	Secondary Prevention (history of CVD event): Arrhythmia

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population
Maki, 2010, 20451686, US, COMBOS	Trial: Randomized Parallel, 2005	Industry funded	8 weeks	Eligible patients were men or women between the ages of 18 and 79 years who had been receiving a stable dose of a statin for the control of LDL-C levels for =>8 weeks before screening and were judged to be in good health on the basis of a medical history, physical examination, electrocardiogram, and laboratory tests, including serum chemistry, hematology, and urinalysis. Major inclusion criteria included a mean fasting TG level >=200 and <500 mg/dL, and a mean LDL-C level below or within 10% of the patient's NCEP ATPIII goal. Major exclusion criteria included poorly controlled diabetes mellitus (glycosylated hemoglobin [HbAlc] >8.0% at screening); history of a cardiovascular event, a revascularization procedure, or an aortic aneurysm or resection within 6 months of screening; history of pancreatitis; sensitivity to statins or omega-3 fatty acids; poorly controlled hypertension (resting blood pressure =>160 mm Hg systolic and/or =>100 mm Hg diastolic at 2 consecutive visits); serum creatinine level =>2.0 mg/dL; serum transaminase (aspartate aminotransferase lAST] or alanine aminotransferase [ALT]) >1.5 times the upper limit of normal (ULN) (45 U/L for ALT, 31 U/L for AST); or creatine kinase (CK) level >2 times the ULN.	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease): Dyslipidemia (mean fasting TG level _>200 and <500 mg/dL, and a mean LDL-C level below or within 10% of the patient's NCEP ATP III goal.)

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population
Maki, 2013, 23998969, US, ESPRIT TRIAL	Trial: Randomized Parallel, 2011	Industry funded	6 weeks	Participants included men and non pregnant, nonlactating women 18 years of age with fasting triglyceride (TG) levels 200 mg/dL and <500 mg/dL(after 4 weeks of the statin/diet lead-in) and at high risk for a future cardiovascular event.	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease): Dyslipidemia ((TG) levels 200 mg/dL and <500 mg/dL)
Marchioli, 2002, 11997274, Italy, GISSI-Prevention	Trial: Randomized Factorial Design, 1993	No Data on funding or affiliations	3.5 years	Patients surviving recent (< 3 months) myocardial infarction. Patients with no contraindications to supplements, provide written consent, have no unfavorable short-term outlook	Secondary Prevention (history of CVD event): Other (myocardial infarction)
Natvig, 1968, 5756076, Norway, The Norwegian Vegetable Oil Experiment of 1965-66	Trial: Randomized Parallel, 1965	Industry funded	1 year	Eligibility: male patients of industrial physicians working part time in Norway. Exclusion criteria: none.	Primary Prevention, Healthy
Nilsen, 2001, 11451717, Norway	Trial: Randomized Parallel, 1995	No Data on funding or affiliations/No Data regarding conflict of interest	6 weeks	Eligibility was based on 1) verified MI by World Health Organization criteria (29), 2) age > 18 y, 3) discontinuation of a regular supplementation of other fish-oil products, and 4) signed informed consent. Exclusion criteria consisted of 1) assumed noncompliance to protocol; 2) expected survival <2 y because of severe heart failure (New York Heart Association class IV), malignancy, or other reasons; 3) ongoing gastrointestinal bleeding or verified stomach ulcer; 4) thrombocytopenia or blood platelets <100 x10^9 /L; 5) liver insufficiency; 6) participation in any other study; and 7) residence outside the recruitment area of this study. All patients were included between the fourth and the eighth day after an acute MI	Secondary Prevention (history of CVD event): Other (MI)

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population
Nodari, 2011, 21844082, Italy	Trial: Randomized Parallel, 2006	No industry relationship reported (funding or affiliations reported)	1 year	Eligibility was determined at a screening visit that included medical history, physical examination, 12-lead ECG, chest x-ray, and 2-dimensional Doppler echocardiography, plus complete blood count, routine chemistry, thyroid function tests, and pregnancy test in fertile women.	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease): Arrhythmia
Nodari, 2011, 21215550, Italy	Trial: Randomized Parallel, 2007	No Data on funding or affiliations/No Data regarding conflict of interest	12 months	Patients aged between 18 and 75 years with a diagnosis of NICM, LV systolic dysfunction (defined as an EF 45%), and stable clinical conditions with minimal or no symptoms for at least 3 months on evidence-based medical treatment at maximum tolerated target doses for at least 6 months were considered eligible for the study. The following criteria were grounds for exclusion: presence of symptoms or evidence of coronary artery disease diagnosed through noninvasive tests, peripheral arterial disease, presence of congenital or primary valvular heart disease, persistent atrial fibrillation, inability to perform bicycle ergometry for noncardiac causes, moderately to severely reduced functional capacity, NYHA functional class IV, poor acoustic windows limiting the ability to assess echocardiographic measurements, chronic lung disease, advanced renal disease (estimated glomerular filtration rate [eGFR] <= 30 ml/min/1.73 m^2), advanced liver disease; any disease limiting life expectancy to <=1 year, contraindications to study drugs, and concomitant participation in other research studies.	Secondary Prevention (history of CVD event): Other (mild and moderate heart failure (HF) due to nonischemic dilated cardiomyopathy (NICM))

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population
Oh, 2014, 25147070, Korea	Trial: Randomized Parallel	No industry relationship reported (funding or affiliations reported)/No conflict of interest (explicitly stated)	2 months	We recruited patients from a primary care setting in the Vascular Medicine and Atherosclerosis Unit, Cardiology, Gil Medical Center, Gachon University. We excluded patients with moderate or severe hypertension, uncontrolled diabetes (HbA1c N 9%), nephrotic syndrome, hypothyroidism, coronary artery disease, or peripheral vascular disease. No patient had taken any cholesterol-lowering agent, hormone replacement therapy, or antioxidant vitamin supplements during the 2 months preceding study enrollment.	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease): Dyslipidemia (hypertriglyceridemia)
Olano-Martin, 2010, 19748619, UK	Trial: Randomized Cross-over, 2007 (approx.)	Industry funded/No Data regarding conflict of interest	3*4 weeks intervention/10 weeks wash out	Inclusion criteria for participation were as follows: male, between 18 and 70 years old, body mass index (BMI) 18.5 32 kg/m2, plasma TG 1.0 4.0 mmol/l, plasma total cholesterol (TC) <8 mmol/l, fasting glucose <7 mmol/l, haemoglobin >11 g/dl, and an E3/E3 or E3/E4 genotype. Volunteers were excluded if they had been diagnosed with cardiovascular disease (CVD), diabetes, liver disease or any other endocrine disorder, were taking medication that would affect lipoprotein metabolism, were taking fish oil supplements or consumed more than one portion of oily fish per week, had restrictions on their diet, or were competitive athletes.	Primary Prevention, Healthy

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population
Pase, 2015, 25565485, Australia	Trial: Randomized Parallel, 2010	Industry funded//Conflict of Interest: Swisse Wellness Pty Ltd., funded this trial; The National Institute of Integrative Medicine, of which Professor Avni Sali is currently director, receives financial support from Swisse Wellness Pty Ltd. Andrew Pipingas and Avni Sali are currently members of the Scientific Advisory Panel for Swisse Wellness Pty Ltd. Aside from oversight of study design and provision of supplements, Swisse Wellness Pty Ltd. was not involved in any other aspects of the conduct of the trial, including analysis or interpretation of the trial findings.	16 weeks	Participants were eligible if they did not have a diagnosis of dementia, diabetes, neurological or psychiatric disease, or cardiovascular disease. Participants taking medications, cognitive-enhancing supplements, multivitamins, or fish oil supplements were excluded. Current smokers and those with a history of drug abuse (including alcohol) were also excluded.	Primary Prevention, Healthy

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population
Pieters, 2015, 25226826, Netherlands	Trial: Randomized Cross-over, 2011	Industry funded/ No conflict of interest (explicitly stated)	6 weeks/>= 2 weeks	Healthy, overweight or slightly obese subjects with a BMI between 25 and 35 kg/m2 and aged between 18 and 70 years, who participated in earlier studies at the department. Inclusion criteria were mean serum Tg <3.0 mmol/l, stable body weight (weight gain or loss <2 kg in the previous 3 months), no indications for treatment of hyperlipidemia, no use of medication or a diet known to affect serum lipid or glucose metabolism, no active CVD, no drug or alcohol abuse, no use of an investigational product within the previous 30 days and willing to sop the consumption of vitamin supplements, fish oil capsules, fatty fish and products rich in plant stanol or sterol esters 3 weeks before the start of the study.	Primary Prevention, Increased CVD Risk: Dyslipidemia, BMI 25-35 kg/m2
Raitt, 2005, 15956633, US	Trial: Randomized Parallel, 2001	No industry relationship reported (funding or affiliations reported)	718 days (median)	Patients were eligible for entry if they were receiving an implantable cardioverter defibrillator (ICD) for an electrocardiogram-documented episode of sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) that was not the result of acute myocardial infarction or a reversible cause or who had a preexisting ICD and had received ICD therapy for an episode of electrogramdocumented VT/VF within the previous 3 months.	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease): Arrhythmia

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population
Ras, 2014, 25122648, Sweden	Trial: Randomized Parallel, 2011	Industry funded/conflict of interest: Ras, Demonty, Zebregs, and Trautwein were employed by Unilever Research and Development at the time of study conduct. Unilever markets food products enriched with plant sterols.	4 weeks	Apparently healthy; aged 25–75 y; fasting TC concentration between 5 and 8 mmol/L; BMI between 18 and 30 kg/m2; systolic blood pressure >=160 mm Hg, diastolic blood pressure >=90 mm Hg and heart rate between 50 and 100 beats/min; no use of medication that could influence the study outcomes; no use of nicotine-containing products; 10-y cardiovascular disease risk >=10 according to the Systematic Coronary Risk Evaluation (SCORE); willing to comply with the study protocol; and having signed the informed and biobank consents	Primary Prevention, Healthy
Rasmussen, 2006, 16469978, Denmark, Finland, Italy, Sweden, Australia, KANWU	Trial: Randomized Parallel, 2009 (approx.)	No industry relationship reported (funding or affiliations reported)	3 months	Healthy, aged 30-65 years with normal or moderately increased body weight (BMI 22-32 kg/m^2). Subjects with impaired glucose tolerance but without diabetes included. Excluded if: specific eating habits due to culture/religion, high habitual physical activity, high alcohol intake (>40 g/day), hepatic/cardiac/thyroid/disabling diseases. Body weight during the past 3 mo should not have changed	Primary Prevention, Healthy
Rauch, 2010, 21060071, Germany, OMEGA	Trial: Randomized Parallel, 2003	Industry funded	1 YEAR	Minimum age of 18 who were admitted to hospital for acute STEMI or non-STEMI and gave written informed consent to participate in the study.	Secondary Prevention (history of CVD event): Cardiac disease (Myocardial infarction)

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population
Rodriguez-Leyva, 2013, 24126178, Canada, FlaxPAD	Trial: Randomized Parallel, 2008	Industry funded	6 months	Patients must be >40 years old, had PAD(peripheral artery disease) for > 6 months with ankle brachial index <0.9.. exclusion criteria: inability to walk, bowel disease, moderate to severe renal failure, life expectancy <2 years with high baseline cardiac risk, allergies to any ingredient in the study product, patients who plan to undergo surgery during the course of the trial, and no more than 2 fish meals per week	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease): Peripheral vascular disease (nd)
Roncaglioni, 2013, 23656645, Italy	Trial: Randomized Parallel, 2004	No Data on funding or affiliations/No Data regarding conflict of interest	median 5 years	Participants with at least one of the following: multiple cardiovascular risk factors, clinical evidence of atherosclerotic vascular disease, or any other condition putting the patient at high cardiovascular risk in opinion of patient's general practitioner. multiple cardiovascular risk factors defined as at least four of the following(or for diabetic patients, one of the following): age >65 years, male sex, hypertension, hypercholesterolemia, current smoker, obesity, family history cardiovascular disease	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
Sacks, 1994, 8021472, US, TOHP	Trial: Randomized Parallel, 1987	No industry relationship reported (funding or affiliations reported)/No Data regarding conflict of interest	6 months	Age 30-54 years, mean diastolic blood pressure <95 mmHg, serum cholesterol <26o mg/dl and non-fasting serum glucose <200 mg/dl.	Primary Prevention, Healthy

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population
Sacks, 1995, 7759696, US	Trial: Randomized Parallel, 1993 (approx.)	No industry relationship reported (funding or affiliations reported)/No Data regarding conflict of interest	2.4 years	Eligible patients had narrowing of =>30% lumen diameter of a major coronary artery, as shown by diagnostic coronary angiography at either Brigham and Women's or Beth Israel Hospitals, a total cholesterol concentration <250 mg/dl (6.43 mmol/liter) and triglyceride level <350 mg/dl (4.0 mmol/liter) and were between the ages of 30 and 75 years. Patients with congestive heart failure; liver, renal or serious gastrointestinal disease; insulin dependent diabetes mellitus; current cigarette smoking or alcohol intake >14 drinks/week were excluded.	Secondary Prevention (history of CVD event): Dyslipidemia (total cholesterol concentration <250 mg/dl (6.43 mmol/liter) and triglyceride level <350 mg/dl (4.0 mmol/liter)); Cardiac disease (narrowing of =>30% lumen diameter of a major coronary artery)
Sanders, 2011, 21865334, UK, MARINA trial	Trial: Randomized Parallel, 2008	Industry only donated materials (eg, supplements)/No conflict of interest (explicitly stated)	12 months	Nonsmokers (confirmed by cotinine testing) men and women aged 45 70 y. Exclusions: a medical history of CVD; overall risk of cardiovascular disease >20% over the next 10 y; cancer (excluding basal cell carcinoma) in the previous 5 y; type 1 DM; uncontrolled type 2 DM; chronic renal, liver, or inflammatory bowel disease; history of substance abuse or alcoholism; pregnancy; weight change of >3 kg in preceding 2 mo; and BMI <20 and >35.	Primary Prevention, Healthy

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population
Shaikh, 2014, 25185754, Canada	Trial: Randomized Parallel	No Data on funding or affiliations/No Data regarding conflict of interest	8 weeks	Male and female study subjects >=18 years of age, with one or more risk factor for CVD, were deemed eligible for study enrollment if their fasting whole blood OS levels were 6.1 % by weight of total blood fatty acid levels, and their serum TG was between 1.02 and 5.65 mmol/L. Subjects were excluded from the study if they refused to provide informed consent, had a known allergy to fish, were premenopausal women, were currently taking hormone replacement therapy (HR), lipid-altering medication or LC n-PUFA supplements, had a history of alcohol abuse, were medically ill, had a history of ventricular arrhythmia, bleeding or clotting disorder, liver or kidney disease, autoimmune disorder or suppressed immune systems, myopathy or rhabdomyolysis, seizure disorder, or had an implantable cardioverter defibrillator. Subjects on a stable statin medication for a minimum of three months were eligible to enroll.	Primary Prevention, Increased CVD Risk (Diabetes, Hypertension)
Shidfar, 2003, 12847992, Iran	Trial: Randomized Factorial Design, 2001 (approx.)	No industry relationship reported (funding or affiliations reported)	10 weeks	Entry criteria included a serum total cholesterol and triglyceride > 200 mg/dl; body mass index <30; and no recent symptomatic diabetes, thyroid, liver, or renal disease. Patients taking sex hormones, diuretics, thyroid medications, corticosteroids, anti-hypertensives, vitamin C, oral contraceptive agents, and any medications that might interfere with the evaluation of results were excluded.	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease): Dyslipidemia (serum total cholesterol and triglyceride > 200 mg/dl)

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population
Sirtori, 1997, 9174486, Italy	Trial: Randomized Parallel, 1995 (approx.)	Industry funded/No Data regarding conflict of interest	6 month	The study protocol allowed the selection of patients of both sexes, males aged 45-75 y and females aged 55-80 y, with hyperlipoproteinemias type IIB or IV (23) associated with at least one additional risk factor: impaired glucose tolerance, NIDDM, or arterial hypertension. Patients with severe intercurrent ailments, kidney or renal disease, intestinal malabsorption, duodenal ulcer not responsive to therapy, obese individuals with a body mass index (in kg/m2) 30, as well as noncompliant or unreliable patients were excluded from the study. All patients with a history of vascular or nonvascular brain disease (including epilepsy and alcoholism), severe hyperlipidemia needing drug treatment, severe hypertension (DBP > 1 10 mm Hg, SBP > 180 mm Hg under antihypertensive treatment), myocardial infarction in the preceding 3 mo, or unstable angina were excluded.	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease): Diabetes and/or metabolic syndrome*; Hypertension (Patients treated with antihypertensive drugs or who on more than one occasion in the past year had had a systolic blood pressure (SBP) 160 mm Hg, a diastolic blood pressure (DBP) 95 mm Hg, or both, independent of drug treatment, were considered to have arterial hypertension.); Dyslipidemia (Patients with significant and stable triacylglycerol elevations (> 2.26 mmollL, or 200 mg/dL) were selected. These were defined as type IIB if serum total cholesterol was > 7.21 mmol/L (270 mg/dL) and type IV if cholesterol was 7.21 mmol/L (270 mg/dL). Patients with total cholesterol concentrations > 7.76 mmollL (300 mg/dL) with triacylglycerol concentrations 4.52 mmollL (400 mg/dL) were excluded for ethical reasons.); Other (Impaired glucose tolerance)

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population
Soares, 2014, 24652053, Brazil	Trial: Randomized Factorial Design, 2011	No industry relationship reported (funding or affiliations reported)/No conflict of interest (explicitly stated)	3 months	The participants included men and women aged between 30 and 60 years who exhibited three or more of the findings indicated by the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III): an abdominal circumference (AC) of > 88 cm for women and > 102 cm for men, a systolic arterial pressure (SAP) of 130 mmHg and a diastolic arterial pressure of 85 mmHg, a fasting glucose level of 100 mg/dL, a triglyceride level of 150 mg/dL, and a high-density lipoprotein cholesterol (HDL-C) level of < 40 mg/dL for men and < 50 mg/dL for women. Patients with absolute contraindications for physical activity because of musculoskeletal, neurological, vascular, pulmonary, and cardiac problems; those on lipid-lowering medication; those on anticoagulant medication; those who exercised regularly (30 min twice a week or more); those with a psychiatric disorder; those on antidepressant medication; those diagnosed hypothyroidism; pregnant patients; those consuming omega 3 supplements or any other food or vitamin supplements; and those who were difficult to contact and/or were lost to follow-up were excluded.	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease): Diabetes and/or metabolic syndrome*; Hypertension (systolic arterial pressure (SAP) of 130 mmHg and a diastolic arterial pressure of 85 mmHg); Dyslipidemia (a triglyceride level of 150 mg/dL, and a high-density lipoprotein cholesterol (HDL-C) level of < 40 mg/dL for men and < 50 mg/dL for women); Obesity/Overweight (abdominal circumference (AC) of > 88 cm for women and > 102 cm for men)

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population
Tardivo, 2015, 25394692, Brazil	Trial: Randomized Parallel	Industry funded/No conflict of interest (explicitly stated)	6 months	Women who had their last menstruation at least 12 months prior to this study, aged >= 45 years old and with three or more diagnostic criteria for MetS were included in the study. Exclusion criteria were: known high cardiovascular risk due to existing or pre-existing CHD, CAD, abdominal aortic stenosis or aneurysm, peripheral artery disease, chronic kidney disease, insulin-dependent diabetes; use of medications (statins, hormone therapy); history of liver disease, infection, chronic inflammatory disease, autoimmune diseases, cancer; intolerance or good allergy to fish.	Primary Prevention, Healthy

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population
Tatsuno, 2013, 24314359, Japan, ORL	Trial: Randomized Parallel, 2009	Industry funded; Authors report industry affiliation/Conflict of interest stated SUBVALUE(KK and JO are employees of Takeda Pharmaceutical Company; IT has acted as a consultant to Takeda, YS has acted as a consultant to Astellas and others)	1 year	Outpatients, aged 20 to 74 years undergoing lifestyle modification for hypertriglyceridemia, fasting triglyceride level >=150 mg/dL and < 750 mg/dL at weeks 4 and 2 during the screening period and a variation in fasting low-density lipoprotein cholesterol (LDL-C) level between weeks 4 and 2 of <25% from the highest value. All subjects were advised about lifestyle modifications (dietary or exercise or both) at all visits during the study. The main exclusion criteria were coronary artery disease, an aortic aneurysm, or significant hemorrhagic disease within 6 months before the study; pancreatitis; lipoprotein lipase deficiency, apolipoprotein C-II deficiency, and type III familial hyperlipidemia; Cushing syndrome, uremia, systemic lupus erythematosus, or serum dysproteinemia; type 1 or uncontrolled type 2 diabetes mellitus (hemoglobin A1c $8%); stage III hypertension; and hepatic impairment.. Use of concomitant medications that might affect the evaluation of efficacy was not permitted, such as fish oil supplements (including any other products, medications, or investigational drugs that contained EPA-E or DHA), insulin, androgens, estrogens, progesterones, and systemic steroids. Antihyperlipidemic drugs (with the exception of EPA-E) and antidiabetic drugs (except insulin) were allowed, provided they had been initiated at least 4 weeks before the study and the dose was not changed during the screening or treatment periods.	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease): Dyslipidemia (fasting triglyceride level >=150 mg/dL and <750 mg/dL at weeks 4 and 2 during the screening period)

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population
Tatsuno, 2013, 23725919, Japan	Trial: Randomized Parallel	Industry funded	12 weeks	Outpatients of either gender ages >=20 to ,75 years who were undergoing lifestyle modification for hypertriglyceridemia, defined as a fasting TG of between 150 and ,750 mg/dL at screening weeks 28, 24, and 22, and with ,30% variation from the greatest value. The main exclusion criteria were as follows: hepatic or renal impairment; serious cardiovascular, pancreatic, or hematological disorders; stage III hypertension; lipoprotein lipase deficiency, polipoprotein C-II deficiency and type III familial hyperlipidemia; type 1 or uncontrolled type 2 diabetes (hemoglobin A1c $8.0% at visit 1 [week –8]); drug abuse/dependency; and treatment with any investigational drug within 12 weeks of screening. Pregnant or lactating women and those of child-bearing age not practicing adequate contraception also were excluded	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease): Dyslipidemia (fasting triglyceride level >=150 mg/dL and <750 mg/dL at weeks 4 and 2 during the screening period)

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population
Tavazzi, 2008, 18757090, Italy, GISSI-HF	Trial: Randomized Parallel, 2002	Industry funded	3.9 years	Eligible patients were men and women aged 18 years or older, with clinical evidence of heart failure of any cause that was classified according to the European Society of Cardiology (ESC) guidelines as New York Heart Association (NYHA) class II IV, provided that they had had their LVEF measured within 3 months before enrolment. When LVEF was greater than 40%, the patient had to have been admitted at least once to hospital for heart failure in the preceding year to meet the inclusion criteria. Major exclusion criteria included specific indication or contraindication to n-3 PUFA; known hypersensitivity to study treatments; presence of any non-cardiac comorbidity (eg, cancer) that was unlikely to be compatible with a sufficiently long follow-up; treatment with any investigational agent within 1 month before randomisation; acute coronary syndrome or revascularisation procedure within the preceding 1 month; planned cardiac surgery, expected to be done within 3 months after randomisation; significant liver disease; and pregnant or lactating women or women of childbearing potential who were not adequately protected against becoming pregnant..	Secondary Prevention (history of CVD event): Cardiac disease (symptomatic heart failure of any cause and with any level of left ventricular ejection fraction (LVEF).)
Tierney, 2011, 20938439, Netherlands, Norway, Sweden, UK, Ireland, France, Poland, Spain, LIPGENE	Trial: Randomized Parallel, 2004	Authors report industry affiliation	3 months	3-5 characteristics of Metabolic Syndrome (see Comment about Eligibility Criteria). 1. fasting glucose conc 5.5-7 mmol/l, 2. serum TAG >1/5 mmol/l, 3. serum HDL conc <1.0 mmol/L (men) or <1.3 mmol/L (women), 4. BP : systolic >130 mm Hg, diastolic BP >85 mm, 5. Waist girth >102 cm(men) or >88 cm (women).	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease): Diabetes and/or metabolic syndrome*

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population
Vazquez, 2014, 24462043, Spain	Trial: Randomized Cross-over, 2011	Industry funded/No conflict of interest (explicitly stated)	8 weeks/0 weeks	Exclusion criteria were the following: patients taking n-3 LCFA supplements, fish allergy and positive antibodies to Anisakis spp., presence of a body mass index (BMI) 40 kg/m2, chronic kidney disease, liver failure, chronic psychopathy, neoplasia or refusal to participate in the study.	Primary Prevention, Healthy
Vecka, 2012, 23183517, Czech Republic	Non-randomized cross-over study, 2010 (approx.)	No Data on funding or affiliations	crossover trial (phase 1: 6 weeks; phase 2: 6 weeks)/not reported	The inclusion criteria were: met the IDF criteria for the metabolic syndrome, and fasting plasma triacylglycerols exceeded 1.7 mmol/l. The exclusion criteria were as follows: insulin dependent diabetes mellitus, age > 75 years, myocardial infarction or stroke in previous six months, chronic heart failure, renal or hepatic failure, obesity grade 2+ (BMI > 35 kg/m2), serious endocrinopathies, pregnancy and breastfeeding.	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease): Diabetes and/or metabolic syndrome*
von Schacky, 1999, 10189324, Canada	Trial: Randomized Parallel, 1992	No industry relationship reported (funding or affiliations reported)/No Data regarding conflict of interest	-	1) stenosis > 20% in at least one vessel 2) revascularization, PTCA or coronary bypass performed in previous 6 months in no more than one vessel.	Secondary Prevention (history of CVD event)

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population
Yokoyama, 2007, 17398308, Japan, JELIS	Trial: Randomized Parallel, 1996	Industry funded/Conflict of interest stated ('M Yokoyama received travel costs from Mochida Pharmaceutical Co Ltd, Tokyo, Japan, to participate in the scientific meeting. Other authors have no conflicts of interest.')	5 years	Inclusion criteria: Total cholesterol concentration of 6 5 mmol/L or greater, which corresponded to a LDL cholesterol of 4 4 mmol/L or greater. Exclusion criteria: acute myocardial infarction within the past 6 months, unstable angina pectoris, a history or complication of serious heart disease (such as severe arrhythmia, heart failure, cardiomyopathy, valvular disease, or congenital disease), cardiovascular reconstruction within the past 6 months, cerebrovascular disorders within the past 6 months, complications of serious hepatic or renal disease, malignant disease, uncontrollable diabetes, hyperlipidaemia due to other disorders, hyperlipidaemia caused by drugs such as steroid hormones, haemorrhage (including haemo philia, capillary fragility, gastrointestinal ulcer, urinary tract haemorrhage, haemoptysis, and vitreous haemorrhage), haemorrhagic diathesis, hypersensitivity to the study drug formulation, patients intention to undergo surgery, and judgment by the physician in charge that a patient was inappropriate for the study.	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease): Dyslipidemia (total cholesterol concentration of 6 5 mmol/L or greater, which corresponded to a LDL cholesterol of 4 4 mmol/L or greater)

Table E-2. Observational studies

Author, year, PMID, country	Study name	Study Design	Funding source/Conflict of interest	Study start date(s)	Eligibility Criteria	Study Population
Amiano, 2014, 24360762, Spain	Spanish Cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)	No industry relationship reported/No Data regarding conflict of interest	1992	20-69 years from five Spanish regions. Exclusions: diagnosis of CHD before the recruitment period and subjects with implausible dietary data	Primary Prevention, Healthy
Ascherio, 1995, 7885425, US	Health Professional Follow-up Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)	No Data on funding or affiliations/No Data regarding conflict of interest	1986	Inclusion Criteria: mail health professionals; aged 40 to 75. Exclusion Criteria: previously diagnosed stroke, myocardial infarction, coronary artery surgery, angina pectoris, peripheral arterial disease, diabetes mellitus, transient ischemic attack, or other cardiovascular disease, stroke, cancer; Daily caloric intake outside range of 800 and 4200 kcal; incompleteness of data on food consumption (more than 70 blanks out of 131 listed food items); no information on fish intake at baseline	Primary Prevention, Healthy
Belin, 2011, 21610249, US	Women's Health Initiative	Prospective, longitudinal study of intake (eg, FFQ, biomarker)	Industry funded/No Data regarding conflict of interest	nd	Women, 50-79 y, Healthy	Primary Prevention, Healthy
Bell, 2014, 24496442, US	VITAL	Prospective, longitudinal study of intake (eg, FFQ, biomarker)	No industry relationship reported (funding or affiliations reported)/No conflict of interest (explicitly stated)	2000	Men and women aged 50-76 y who completed a FFQ accurately. Patients were excluded if they reported an abnormally high (>5000 kcal for men, >4000 kcal for women) or low (<800 kcal for men, <600 kcal for women) daily energy intake, or had a condition that would affect absorption of supplements (eg gastric bypass surgery).	Primary Prevention, Healthy
Brouwer, 1996, 16569549, Netherlands	Rotterdam Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)	Industry funded/No Data regarding conflict of interest	1990	People aged 55 years and older who had no atrial fibrillation (primary study) people aged 55 years and older who had no heart failure (secondary study)	Primary Prevention, Healthy: The population is a mixture of people
de Goede, 2010, 20335635, Netherlands	MORGEN	Prospective, longitudinal study of intake (eg, FFQ, biomarker)	No Data on funding or affiliations/No conflict of interest	1993	20-65 y with no history of MI or stroke	Primary Prevention, Healthy

Author, year, PMID, country	Study name	Study Design	Funding source/Conflict of interest	Study start date(s)	Eligibility Criteria	Study Population
De Goede, 2013, 22633188, Netherlands	MORGEN	Nested Case Control	Authors report industry affiliation	1993	20-65 y with no history of MI or stroke: N=179 cases, N=179 control matched on age, gender, and enrollment date	Primary Prevention, Healthy
de Oliveira, 2013, 24351702, US	Multi-Ethnic Study of Atherosclerosis (MESA)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)	No industry relationship reported/No conflict of interest	2000	US adults aged 45-84 years, free of clinical CVD at baseline. N=6814 participants in MESA, reduced to subset of N=2837, who had plasma phospholipid FA measurements, data met quality control checks, and were not taking fish oils (under study design); N=2837 US adults, multiethnic cohort	Primary Prevention, Healthy
Dolecek, 1992, 24351702, US	Multiple Risk Factor Intervention Trial	Prospective, longitudinal study of intake (eg, FFQ, biomarker)	Industry funded/No Data regarding conflict of interest	1973	12866 middle-aged men determined to be at high risk of CHD based on smoking status, dbp, and serum cholesterol levels	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease): a mix of population
Hara, 2013, 23047296, Japan	OACIS	Prospective, longitudinal study of intake (eg, FFQ, biomarker)	No industry relationship reported/No conflict of interest	2006	Consecutive patients with AMI who were registered in the OACIS between January 2006 and December 2009 and who were discharged alive and whose blood samples were collected at least 10 days after the onset of AMI and within 14 days before and after discharge	Secondary Prevention (history of CVD event): Acute MI
Hellstrand, 2014, 25008580, Sweden	MDC (Malmo Diet and Cancer)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)	Industry funded/No Data regarding conflict of interest	1991	Participants from Malmo Diet and Cancer cohort without prevalent CVD and diabetes. Participants live in southern part of Sweden, in city of Malmo. Aged 44-74 yrs.	Primary Prevention, Healthy
Hu, 2002, 11939867, US	Nurses' Health Study (NHS)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)	No industry relationship reported/No Data regarding conflict of interest	1980	Registered female nurses a part of the Nurses' Health Study and were between the age of 34-59, and free of cardiovascular disease and cancer at baseline in 1980	Primary Prevention, Healthy
Iso, 2006, 16401768, Japan	Japan Public Health Center-Based (JPHC) Study - Cohort I	Prospective, longitudinal study of intake (eg, FFQ, biomarker)	No industry relationship reported/No Data regarding conflict of interest	January 1, 1990	Men and women who were born between 1930 and 1949 (40 to 59 years of age) and who were registered in 14 administrative districts supervised by 4 public health center (PHC) areas on January 1, 1990. We excluded men who reported myocardial infarction, angina pectoris, stroke, or cancer at baseline.	Primary Prevention, Healthy

Author, year, PMID, country	Study name	Study Design	Funding source/Conflict of interest	Study start date(s)	Eligibility Criteria	Study Population
Itakura, 2011, 21099130, Japan	JELIS	Prospective, longitudinal study of intake (eg, FFQ, biomarker)	Industry only donated materials/Authors report industry affiliation	1996-1999	Hypercholesterolemia >250mg/dL total cholesterol or >170mg/dL LDL; everyone was on a statin (10mg pravastatin or 5mg simvastatin qd)	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease): Dyslipidemia (>250mg/dL total cholesterol or >170mg/dL LDL)
Joensen, 2010, 19825219, Denmark	Danish Diet, Cancer, and Health cohort study (DCH)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)	No industry relationship reported/No conflict of interest	December 1993	Healthy, 50-64 years old. All born in Denmark, lived in the urban areas of Copenhagen and Aarhus, and not at time of invitation registered with a cancer diagnosis in the Danish Cancer Registry. Excluded those with diagnosis of ACS or cancer before entry into study. excluded 1619 individuals from study because they did not fill in questionnaire/or had diagnosis of ACS or cancer before entry into study	Primary Prevention, Healthy
Khaw, 2012, 22802735, UK	European Prospective Investigation into Cancer (EPIC) Norfolk	Nested Case Control	No industry relationship reported/No conflict of interest	1993	Men and women aged 40 79 years in Norfolk, UK	Primary Prevention, Healthy
Koh, 2013, 24343844, China	The Singapore Chinese Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)	No industry relationship reported/No conflict of interest	1993	We excluded individuals who had baseline cancer (n = 1936) or reported extreme energy intakes (<600 or >3000 kcal/day for women and <700 or >3700 kcal/day for men; n = 1023).	Primary Prevention, Healthy
Larsson, 2012, 22265275, Sweden	Swedish Mammography Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)	No industry relationship reported/No conflict of interest	1997	All women in the Swedish population register born between 1914 and 1948 and living in Vastmanland and Uppsala counties in central Sweden. Only women who completed the 1997 questionnaire are included in this study. Participants who did not provide or provided incorrect national identification numbers, who reported implausible energy intakes (>3 standard deviations from the natural logarithm transformed mean), who had a previous diagnosis of cancer (other than nonmelanoma skin cancer) or HF were excluded. Only women with no baseline history of MI or diabetes were included.	Primary Prevention, Healthy

Author, year, PMID, country	Study name	Study Design	Funding source/Conflict of interest	Study start date(s)	Eligibility Criteria	Study Population
Lemaitre, 2012, 22743310, US	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)	Authors report industry affiliation	1989	The cohort consisted of 5201 noninstitutionalized men and women aged $65 y, recruited in 1989 1990, plus an additional 687 black participants recruited in 1992 and 1993. Each paper excluded participants with their outcome of interest at baseline.	Primary Prevention, Healthy
Levitan, 2009, 19383731, Sweden	Cohort of Swedish Men	Prospective, longitudinal study of intake (eg, FFQ, biomarker)	No industry relationship reported/No conflict of interest	1997	Men. Excluded based on previous diagnosis of cancer (except non-melanoma skin cancer), implausible energy intake (.3 standard deviations from the natural logarithm transformed mean) (n = 562) or a history of HF at baseline (n = 743) were also excluded. In the primary analyses men with baseline history of MI (n = 2077) or diabetes (n = 3157) were excluded because they had higher rates of HF and may have changed their diets because of their diagnosis.	Primary Prevention, Healthy
Matsumoto, 2013, 23098619, US	Physician's Health Study (Also see Morris 7598116 entry)	Nested Case Control	No industry relationship reported/No conflict of interest	1995-2001	An ancillary study of PHS: randomly selected 1000 incident CHD cases that provided blood samples between 1995 and 2001. Density sampling technique to select 1 control who was alive and free of confirmed CHD at the time of the index case diagnosis and matched on age at blood collection (within 1 year), year of birth (within 2 years), and time of blood collection (within 3 months).	Primary Prevention, Healthy
Miyagawa, 2014, 24468152, Japan	NIPPON-DATA	Prospective, longitudinal study of intake (eg, FFQ, biomarker)	Industry funded/No conflict of interest	1980	A total of 10,546 community residents free from CVDs at baseline(4639 men and 5907 women, aged 30 and greater) from 300 randomly selected districts from all-over Japan participated in the survey, with the participation rate of about 77%. Accordingly, these participants were thought to be representative of the Japanese population. A total of 1356 men and women excluded from this analysis for the following reasons: history of CVD (n 350), missing information (e.g., nutrition, lifestyle questionnaire) at baseline (n = 124), intake of energy more than 5000 kcal/day or less than 500 kcal/day (n 139) and lost to follow-up due to incomplete residential addresses at the baseline survey (n = 1104).	Primary Prevention, Healthy

Author, year, PMID, country	Study name	Study Design	Funding source/Conflict of interest	Study start date(s)	Eligibility Criteria	Study Population
Morris, 1995, 7598116, US	Physician's Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)	No industry relationship reported/No conflict of interest	1982-1983	US male physicians, aged 40-84 years, with no history of MI, stroke, transient ischemic attacks, cancer (excluding nonmelanoma skin cancer), liver or renal disease, peptic ulcer, gout, current use of aspirin, other platelet-active drugs, or nonsteroidal anti-inflammatory agents. originally these participants were enrolled in MRFIT trial, which was terminated early	Primary Prevention, Healthy
Nagata, 2002, 12397000, Japan	Takayama Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)	No industry relationship reported/No Data regarding conflict of interest	1992	Residents of Takayama, Japan, aged 35 years or older	Primary Prevention, Healthy
Ninomiya, 2013, 24267237, Japan	Hisayama Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)	Industry funded/conflict of interest: this study was sponsored by Mochida pharmaceutical Co., Ltd. (Tokyo, Japan). The sponsor of the study had no role in the study design, conduct of the study, data collection, data interpretation or preparation of the report. Ninomiya and Kiyohara received honoraria for lecture fees from Mochida Pharmaceutical Co., Ltd. Other authors declare that they have no competing interests.	2002	A total of 3328 residents aged 40 years or older (77.6% of the total population in this age group) underwent the examination. After excluding 30 subjects who did not consent to participate in the study, 190 subjects with a history of cardiovascular disease, and 5 subjects without available data on serum fatty acid levels, the remaining 3103 participants were enrolled in the study.	Primary Prevention, Healthy

Author, year, PMID, country	Study name	Study Design	Funding source/Conflict of interest	Study start date(s)	Eligibility Criteria	Study Population
Pietinen, 1997, 9149659, Finland	The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)	Industry funded/No Data regarding conflict of interest	1985	To be eligible, they had to be 50-69 years of age men, to smoke five or more cigarettes per day at entry, and to give written informed consent. The exclusion criteria included a history of cancer or other serious disease limiting participation; use of vitamin E, vitamin A, or beta-carotene supplements in excess of predefined doses; and treatment with anticoagulant agents.	Primary Prevention, Healthy
Strøm, 2012, 22146511, Denmark	-	Prospective, longitudinal study of intake (eg, FFQ, biomarker)	Industry funded/No Data regarding conflict of interest	1996	Eligible for recruitment were all pregnant women living in Denmark who were fluent in Danish. We excluded women who reported taking fish oil as a supplement during pregnancy. Preeclampsia and gestational diabetes were excluded. finally, questionnaires with a total energy intake <4200 kJ or >16 700 kJ were excluded.	Primary Prevention, Healthy
Takata, 2013, 23788668, China	Shanghai Women s Health Study (SWHS) Shanghai Men s Health Study (SMHS)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)	No industry relationship reported/No conflict of interest	1997	Residents of 8 communities in urban Shanghai, China, who were aged 40 70 years between 1997 and 2000 for the SWHS and aged 40 74 years between 2002 and 2006 for the SMHS. We excluded participants with a reported total energy intake outside the range of 500 4,000 kcal/day (45 women, 91 men) and those with no follow-up (8 women, 14 men). We further excluded participants who died during the first year of follow-up (145 women, 248 men) to minimize the possibility of reverse causality. One male participant who did not answer all questions about smoking history was also excluded. combination of two studies: SWHS and SMHS	Primary Prevention, Healthy

Author, year, PMID, country	Study name	Study Design	Funding source/Conflict of interest	Study start date(s)	Eligibility Criteria	Study Population
Vedtofte, 2011, 21865326, Denmark	Glostrup Population Studies	Prospective, longitudinal study of intake (eg, FFQ, biomarker)	No Data on funding or affiliations/No Data regarding conflict of interest	1964	Four of the Glostrup cohorts were included in the present project: 1) the 1914 cohort: randomly sampled subjects born in 1914 and examined in 1974 or 1984; 2) the 1936 cohort: randomly sampled subjects born in 1936 and examined in 1976, 1981, and 1987; 3) the MONICA-I cohort: subjects randomly sampled from births in 1922, 1932, 1942, and 1952 and examined in 1982; and 4) the MONICA-III cohort: subjects randomly sampled from births in 1932, 1942, 1952, and 1962 and examined in 1991. Those who had been given a previous diagnosis of IHD (n = 38), those who reported that they had diabetes mellitus (n = 79), and those with missing values in the confounding variables (n = 33) were excluded.	Primary Prevention, Healthy
Vedtofte, 2014, 24964401, US, Finland, Sweden	Pooling Project of Cohort Studies on Diet and Coronary Disease	Prospective, longitudinal study of intake (eg, FFQ, biomarker)	No industry relationship reported/No conflict of interest	various across cohorts: 1966- 1992	a published prospective study with at least 150 incident CHD cases; a study determining usual dietary intake using a FFQ, a dietary history interview, or a 7 d weighed food record at baseline; a validation or a repeatability study of the dietary intake assessment method	Primary Prevention, Healthy
Virtanen, 2009, 19933935 Finland	Kuopio Ischemic Heart Disease Risk Factor Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)	No industry relationship reported/No conflict of interest	1984	Men who were 42, 48, 54, or 60 years old at the baseline examination. Subjects with a history of AF at baseline were excluded from the analyses. Also excluded men with missing data on serum PUFAs or hair methylmercury concentration.	Primary Prevention, Healthy
Wang, 2010, 20713915, US	Women's Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)	No industry relationship reported/No Data regarding conflict of interest	1992	female US health professionals, aged 39 years and free from cardiovascular disease and cancer (except nonmelanoma skin cancer). Excluded: women who had hypertension at baseline, defined as having a self-reported physician diagnosis of hypertension, self-reported current systolic BP 140 mm Hg or diastolic BP 90 mm Hg, or use of antihypertensive treatment, implausible total daily energy intake, incomplete FFQ, and prerandomization cardiovascular disease or cancer.	Primary Prevention, Healthy

Author, year, PMID, country	Study name	Study Design	Funding source/Conflict of interest	Study start date(s)	Eligibility Criteria	Study Population
Wang, 2011, 21734059, US	Women's Health Study	Nested Case Control	No industry relationship reported/No conflict of interest	1992	female U.S. health professionals, aged >=39 y and free from CVD and cancer (except nonmelanoma skin cancer)	Primary Prevention, Healthy
Warensjö, 2008, 18614742, Sweden	ULSAM	Prospective, longitudinal study of intake (eg, FFQ, biomarker)	No Data on funding or affiliations/No Data regarding conflict of interest	1970	all men born between 1920 and 1924 living in Uppsala at that time.	Primary Prevention, Healthy
Woodward, 2011, 21345851, UK	Scottish Heart Health Extended Cohort Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)	Industry funded/No conflict of interest	1984	3944 participants, predominantly aged 40 59 years, in Scotland. Anyone with evidence of CVD at baseline was excluded from all the analyses reported here.	Primary Prevention, Healthy
Xun, 2011, 21205024, US	Coronary Artery Risk Development in Young Adults (CARDIA)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)	No industry relationship reported/No Data regarding conflict of interest	1985	age 18-30 in 1985,balanced by age (18 24 and 25 30), gender, ethnicity (African American and Caucasian), and education (high school or below and beyond high school). We excluded participants who reported implausible total energy intake (<800 or >8000 kcal/d for men, and <600 or >6000 kcal/d for women), participants with missing data on exposure variables at all diet assessments, and pregnant women at any examination.	Primary Prevention, Healthy
Yamagishi, 2008, 18786479, Japan	JACC	Prospective, longitudinal study of intake (eg, FFQ, biomarker)	No industry relationship reported/No Data regarding conflict of interest	1988-1990	Nationwide community-based sample; 40-79 years old; no history of heart disease/stroke/cancer at baseline; completed fish intake on FFQ	Primary Prevention, Healthy
Yamagishi, 2008, 19061714, US	Atherosclerosis Risk in Communities (ARIC) Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)	Industry funded/No conflict of interest	1987	Aged 45-64 at baseline (1987-89), initially free of coronary heart disease, stroke and HF, and who had cholesterol ester and phospholipid plasma fatty acids measured	Primary Prevention, Healthy: The population is a mixture of people
Yuan, 2001, 11682363, China	Shanghai	Prospective, longitudinal study of intake (eg, FFQ, biomarker)	No industry relationship reported/No Data regarding conflict of interest	1986	male, age 45 64 years, and no history of cancer.	Primary Prevention, Healthy

Author, year, PMID, country	Study name	Study Design	Funding source/Conflict of interest	Study start date(s)	Eligibility Criteria	Study Population
Zeng, 2014, 24966412, China	Guangzhou	Prospective, longitudinal study of intake (eg, FFQ, biomarker)	No industry relationship reported (funding or affiliations reported)/ No conflict of interest (explicitly stated)	2008	Aged 40–75y who had been Guangzhou residents for at least 5y. Excluded participants with confirmed chronic diseases such as diabetes, CVDs, liver or renal failure, or cancer (n = 184), and those who were using antihypertensive therapy at baseline (n = 248), had missing erythrocyte FA values (n = 894), or had missing BP measurements (n = 2).	Primary Prevention, Healthy

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Study years (start date)	Country	Population
1	Baxheinrich, 2012, 22894911	2010 (approx)	Germany	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
2	Baxheinrich, 2012, 22894911	2010 (approx)	Germany	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
3	Baxheinrich, 2012, 22894911	2010 (approx)	Germany	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
4	Baxheinrich, 2012, 22894911	2010 (approx)	Germany	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
5	Baxheinrich, 2012, 22894911	2010 (approx)	Germany	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
6	Bosch, 2012, 22686415	2003	Canada	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
7	Bosch, 2012, 22686415	2003	Canada	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
8	Bosch, 2012, 22686415	2003	Canada	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
9	Bosch, 2012, 22686415	2003	Canada	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
10	Bosch, 2012, 22686415	2003	Canada	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
11	Bosch, 2012, 22686415	2003	Canada	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
12	Bosch, 2012, 22686415	2003	Canada	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
13	Bosch, 2012, 22686415	2003	Canada	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
14	Bosch, 2012, 22686415	2003	Canada	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
15	Bosch, 2012, 22686415	2003	Canada	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
16	Bosch, 2012, 22686415	2003	Canada	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Risk type	Sample size (total)
1	Baxheinrich, 2012, 22894911	Diabetes and/or metabolic syndrome	81
2	Baxheinrich, 2012, 22894911	Diabetes and/or metabolic syndrome	81
3	Baxheinrich, 2012, 22894911	Diabetes and/or metabolic syndrome	81
4	Baxheinrich, 2012, 22894911	Diabetes and/or metabolic syndrome	81
5	Baxheinrich, 2012, 22894911	Diabetes and/or metabolic syndrome	81
6	Bosch, 2012, 22686415	Diabetes and/or metabolic syndrome ; Hypertension ; Cardiac disease ; Cerebrovascular disease ; Peripheral vascular disease ; Arrhythmia	12536
7	Bosch, 2012, 22686415	Diabetes and/or metabolic syndrome ; Hypertension ; Cardiac disease ; Cerebrovascular disease ; Peripheral vascular disease ; Arrhythmia	12536
8	Bosch, 2012, 22686415	Diabetes and/or metabolic syndrome ; Hypertension ; Cardiac disease ; Cerebrovascular disease ; Peripheral vascular disease ; Arrhythmia	12536
9	Bosch, 2012, 22686415	Diabetes and/or metabolic syndrome ; Hypertension ; Cardiac disease ; Cerebrovascular disease ; Peripheral vascular disease ; Arrhythmia	12536
10	Bosch, 2012, 22686415	Diabetes and/or metabolic syndrome ; Hypertension ; Cardiac disease ; Cerebrovascular disease ; Peripheral vascular disease ; Arrhythmia	12536
11	Bosch, 2012, 22686415	Diabetes and/or metabolic syndrome ; Hypertension ; Cardiac disease ; Cerebrovascular disease ; Peripheral vascular disease ; Arrhythmia	12536
12	Bosch, 2012, 22686415	Diabetes and/or metabolic syndrome ; Hypertension ; Cardiac disease ; Cerebrovascular disease ; Peripheral vascular disease ; Arrhythmia	12536
13	Bosch, 2012, 22686415	Diabetes and/or metabolic syndrome ; Hypertension ; Cardiac disease ; Cerebrovascular disease ; Peripheral vascular disease ; Arrhythmia	12536
14	Bosch, 2012, 22686415	Diabetes and/or metabolic syndrome ; Hypertension ; Cardiac disease ; Cerebrovascular disease ; Peripheral vascular disease ; Arrhythmia	12536
15	Bosch, 2012, 22686415	Diabetes and/or metabolic syndrome ; Hypertension ; Cardiac disease ; Cerebrovascular disease ; Peripheral vascular disease ; Arrhythmia	12536
16	Bosch, 2012, 22686415	Diabetes and/or metabolic syndrome ; Hypertension ; Cardiac disease ; Cerebrovascular disease ; Peripheral vascular disease ; Arrhythmia	12536

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Age mean (SD) [median] years	Sex (% male)	Race
1	Baxheinrich, 2012, 22894911	50.3 (9.8)	nd	nd
2	Baxheinrich, 2012, 22894911	50.3 (9.8)	nd	nd
3	Baxheinrich, 2012, 22894911	50.3 (9.8)	nd	nd
4	Baxheinrich, 2012, 22894911	50.3 (9.8)	nd	nd
5	Baxheinrich, 2012, 22894911	50.3 (9.8)	nd	nd
6	Bosch, 2012, 22686415	63.6 (7.9)	64.7	nd
7	Bosch, 2012, 22686415	63.6 (7.9)	64.7	nd
8	Bosch, 2012, 22686415	63.6 (7.9)	64.7	nd
9	Bosch, 2012, 22686415	63.6 (7.9)	64.7	nd
10	Bosch, 2012, 22686415	63.6 (7.9)	64.7	nd
11	Bosch, 2012, 22686415	63.6 (7.9)	64.7	nd
12	Bosch, 2012, 22686415	63.6 (7.9)	64.7	nd
13	Bosch, 2012, 22686415	63.6 (7.9)	64.7	nd
14	Bosch, 2012, 22686415	63.6 (7.9)	64.7	nd
15	Bosch, 2012, 22686415	63.6 (7.9)	64.7	nd
16	Bosch, 2012, 22686415	63.6 (7.9)	64.7	nd

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Blood pressure SBP/DBP mmHg
1	Baxheinrich, 2012, 22894911	140.1 (12.4)/90.2 (7.7)
2	Baxheinrich, 2012, 22894911	140.1 (12.4)/90.2 (7.7)
3	Baxheinrich, 2012, 22894911	140.1 (12.4)/90.2 (7.7)
4	Baxheinrich, 2012, 22894911	140.1 (12.4)/90.2 (7.7)
5	Baxheinrich, 2012, 22894911	140.1 (12.4)/90.2 (7.7)
6	Bosch, 2012, 22686415	146.0 (21.8)/84.2 (12.1)
7	Bosch, 2012, 22686415	146.0 (21.8)/84.2 (12.1)
8	Bosch, 2012, 22686415	146.0 (21.8)/84.2 (12.1)
9	Bosch, 2012, 22686415	146.0 (21.8)/84.2 (12.1)
10	Bosch, 2012, 22686415	146.0 (21.8)/84.2 (12.1)
11	Bosch, 2012, 22686415	146.0 (21.8)/84.2 (12.1)
12	Bosch, 2012, 22686415	146.0 (21.8)/84.2 (12.1)
13	Bosch, 2012, 22686415	146.0 (21.8)/84.2 (12.1)
14	Bosch, 2012, 22686415	146.0 (21.8)/84.2 (12.1)
15	Bosch, 2012, 22686415	146.0 (21.8)/84.2 (12.1)
16	Bosch, 2012, 22686415	146.0 (21.8)/84.2 (12.1)

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Lipids: Total cholesterol/LDL/HDL/Triglycerides mean (SD) mg/dL [mmol/L]
1	Baxheinrich, 2012, 22894911	[5.49 (1.09)]/[3.49 (0.92)]/[1.43 (0.34)]/[1.64 (1.02)]
2	Baxheinrich, 2012, 22894911	[5.49 (1.09)]/[3.49 (0.92)]/[1.43 (0.34)]/[1.64 (1.02)]
3	Baxheinrich, 2012, 22894911	[5.49 (1.09)]/[3.49 (0.92)]/[1.43 (0.34)]/[1.64 (1.02)]
4	Baxheinrich, 2012, 22894911	[5.49 (1.09)]/[3.49 (0.92)]/[1.43 (0.34)]/[1.64 (1.02)]
5	Baxheinrich, 2012, 22894911	[5.49 (1.09)]/[3.49 (0.92)]/[1.43 (0.34)]/[1.64 (1.02)]
6	Bosch, 2012, 22686415	190 (47)/112 (40)/46 (12)/median 140 (97, 195)
7	Bosch, 2012, 22686415	190 (47)/112 (40)/46 (12)/median 140 (97, 195)
8	Bosch, 2012, 22686415	190 (47)/112 (40)/46 (12)/median 140 (97, 195)
9	Bosch, 2012, 22686415	190 (47)/112 (40)/46 (12)/median 140 (97, 195)
10	Bosch, 2012, 22686415	190 (47)/112 (40)/46 (12)/median 140 (97, 195)
11	Bosch, 2012, 22686415	190 (47)/112 (40)/46 (12)/median 140 (97, 195)
12	Bosch, 2012, 22686415	190 (47)/112 (40)/46 (12)/median 140 (97, 195)
13	Bosch, 2012, 22686415	190 (47)/112 (40)/46 (12)/median 140 (97, 195)
14	Bosch, 2012, 22686415	190 (47)/112 (40)/46 (12)/median 140 (97, 195)
15	Bosch, 2012, 22686415	190 (47)/112 (40)/46 (12)/median 140 (97, 195)
16	Bosch, 2012, 22686415	190 (47)/112 (40)/46 (12)/median 140 (97, 195)

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	BMI mean (SD) Kg/m2/Weight mean (SD) Kg	Baseline n-3 intake	n-3 source (Baseline)
1	Baxheinrich, 2012, 22894911	35.2 (5.1)/99.4 (16.2)	nd	nd
2	Baxheinrich, 2012, 22894911	35.2 (5.1)/99.4 (16.2)	nd	nd
3	Baxheinrich, 2012, 22894911	35.2 (5.1)/99.4 (16.2)	nd	nd
4	Baxheinrich, 2012, 22894911	35.2 (5.1)/99.4 (16.2)	nd	nd
5	Baxheinrich, 2012, 22894911	35.2 (5.1)/99.4 (16.2)	nd	nd
6	Bosch, 2012, 22686415	29.9 (5.2)	nd	nd
7	Bosch, 2012, 22686415	29.9 (5.2)	nd	nd
8	Bosch, 2012, 22686415	29.9 (5.2)	nd	nd
9	Bosch, 2012, 22686415	29.9 (5.2)	nd	nd
10	Bosch, 2012, 22686415	29.9 (5.2)	nd	nd
11	Bosch, 2012, 22686415	29.9 (5.2)	nd	nd
12	Bosch, 2012, 22686415	29.9 (5.2)	nd	nd
13	Bosch, 2012, 22686415	29.9 (5.2)	nd	nd
14	Bosch, 2012, 22686415	29.9 (5.2)	nd	nd
15	Bosch, 2012, 22686415	29.9 (5.2)	nd	nd
16	Bosch, 2012, 22686415	29.9 (5.2)	nd	nd

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	n-3 type(s)	n-3 measure	Study design	Outcome
1	Baxheinrich, 2012, 22894911	ALA vs ALA	g/d	Trial: Randomized Parallel	HDL-c
2	Baxheinrich, 2012, 22894911	ALA vs ALA	g/d	Trial: Randomized Parallel	LDL-c
3	Baxheinrich, 2012, 22894911	ALA vs ALA	g/d	Trial: Randomized Parallel	Tg
4	Baxheinrich, 2012, 22894911	ALA vs Placebo	g/d	Trial: Randomized Parallel	SBP
5	Baxheinrich, 2012, 22894911	ALA vs Placebo	g/d	Trial: Randomized Parallel	DBP
6	Bosch, 2012, 22686415	EPA+DHA vs Placebo	g/d	Trial: Randomized Factorial Design	Death, all cause
7	Bosch, 2012, 22686415	EPA+DHA vs Placebo	g/d	Trial: Randomized Factorial Design	Death, CVD (total)
8	Bosch, 2012, 22686415	EPA+DHA vs Placebo	g/d	Trial: Randomized Factorial Design	Myocardial infarction
9	Bosch, 2012, 22686415	EPA+DHA vs Placebo	g/d	Trial: Randomized Factorial Design	Revascularization
10	Bosch, 2012, 22686415	EPA+DHA vs Placebo	g/d	Trial: Randomized Factorial Design	Stroke
11	Bosch, 2012, 22686415	EPA+DHA vs Placebo	g/d	Trial: Randomized Factorial Design	Sudden cardiac death
12	Bosch, 2012, 22686415	EPA+DHA vs Placebo	g/d	Trial: Randomized Factorial Design	HDL-c
13	Bosch, 2012, 22686415	EPA+DHA vs Placebo	g/d	Trial: Randomized Factorial Design	LDL-c
14	Bosch, 2012, 22686415	EPA+DHA vs Placebo	g/d	Trial: Randomized Factorial Design	Tg
15	Bosch, 2012, 22686415	ALA+DHA+EPA vs Placebo	g/d	Trial: Randomized Factorial Design	SBP
16	Bosch, 2012, 22686415	ALA+DHA+EPA vs Placebo	g/d	Trial: Randomized Factorial Design	DBP

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Reported effect Size	Dose/intake difference	Dose-corrected effect size
1	Baxheinrich, 2012, 22894911	2.32 (-2.95, 7.59)	2.68	0.8656716
2	Baxheinrich, 2012, 22894911	1.93 (-11.97, 15.83)	2.68	0.7201493
3	Baxheinrich, 2012, 22894911	-22.12 (-59.01, 14.76)	2.68	-8.253732
4	Baxheinrich, 2012, 22894911	-1.8 (-8.3, 4.7)	3.46	-0.5202312
5	Baxheinrich, 2012, 22894911	-3.9 (-8.1, 0.3)	3.46	-1.127168
6	Bosch, 2012, 22686415	Adj HR 0.98 (0.89, 1.07)	0.84	0.976236
7	Bosch, 2012, 22686415	HR 0.98 (0.87,1.10)	0.84	0.976236
8	Bosch, 2012, 22686415	Adj HR 1.09 (0.93, 1.27)	0.84	1.10804
9	Bosch, 2012, 22686415	HR 0.96 (0.87, 1.05)	0.84	0.9525644
10	Bosch, 2012, 22686415	HR 0.92 (0.79, 1.08)	0.84	0.9055038
11	Bosch, 2012, 22686415	OR 1.11 (0.94, 1.32)	0.63	1.180161
12	Bosch, 2012, 22686415	0.10 (-0.73, 0.93)	0.465	0.2150538
13	Bosch, 2012, 22686415	0.60 (-1.62, 2.82)	0.465	1.290323
14	Bosch, 2012, 22686415	-14.50 (-22.82, -6.18)	0.84	-17.26191
15	Bosch, 2012, 22686415	0.1 (-0.6, 0.9)	0.84	0.1190476
16	Bosch, 2012, 22686415	0.1 (-0.3, 0.5)	0.84	0.1190476

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Outcome classification
1	Baxheinrich, 2012, 22894911	Secondary (per registry record DRKS00006232)
2	Baxheinrich, 2012, 22894911	Secondary (per registry record DRKS00006232)
3	Baxheinrich, 2012, 22894911	Secondary (per registry record DRKS00006232)
4	Baxheinrich, 2012, 22894911	Secondary (per registry record DRKS00006232)
5	Baxheinrich, 2012, 22894911	Secondary (per registry record DRKS00006232)
6	Bosch, 2012, 22686415	Secondary
7	Bosch, 2012, 22686415	Secondary; Primary in registry record (NCT00069784)
8	Bosch, 2012, 22686415	Primary (stated)
9	Bosch, 2012, 22686415	Secondary; Primary in registry record (NCT00069784)
10	Bosch, 2012, 22686415	Secondary; Primary in registry record (NCT00069784)
11	Bosch, 2012, 22686415	Secondary
12	Bosch, 2012, 22686415	Secondary
13	Bosch, 2012, 22686415	Secondary
14	Bosch, 2012, 22686415	Secondary
15	Bosch, 2012, 22686415	Secondary
16	Bosch, 2012, 22686415	Secondary

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Study years (start date)	Country	Population
17	Brinton, 2013, 23835245	nd	US	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
18	Brinton, 2013, 23835245	nd	US	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
19	Brinton, 2013, 23835245	nd	US	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
20	Brinton, 2013, 23835245	nd	US	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
21	Brinton, 2013, 23835245	nd	US	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
22	Brinton, 2013, 23835245	nd	US	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
23	Brinton, 2013, 23835245	nd	US	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
24	Brinton, 2013, 23835245	nd	US	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
25	Brinton, 2013, 23835245	nd	US	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
26	Brouwer, 2006, 16772624	2001	Germany, Netherlands, Sweden, UK, Poland, Czech Republic, Belgium, Austria	Secondary Prevention (history of CVD event)
27	Brouwer, 2006, 16772624	2001	Germany, Netherlands, Sweden, UK, Poland, Czech Republic, Belgium, Austria	Secondary Prevention (history of CVD event)
28	Brouwer, 2006, 16772624	2001	Germany, Netherlands, Sweden, UK, Poland, Czech Republic, Belgium, Austria,	Secondary Prevention (history of CVD event)

Row	Study	Risk type	Sample size (total)
17	Brinton, 2013, 23835245	nd	687
18	Brinton, 2013, 23835245	nd	687
19	Brinton, 2013, 23835245	nd	687
20	Brinton, 2013, 23835245	nd	687
21	Brinton, 2013, 23835245	nd	687
22	Brinton, 2013, 23835245	nd	687
23	Brinton, 2013, 23835245	nd	687
24	Brinton, 2013, 23835245	nd	687
25	Brinton, 2013, 23835245	nd	687
26	Brouwer, 2006, 16772624	Arrhythmia (at least 1 true, confirmed, spontaneous VT or VF in the preceding year, and either had and ICD or were about to receive one)	546
27	Brouwer, 2006, 16772624	Arrhythmia (at least 1 true, confirmed, spontaneous VT or VF in the preceding year, and either had and ICD or were about to receive one)	546
28	Brouwer, 2006, 16772624	Arrhythmia (at least 1 true, confirmed, spontaneous VT or VF in the preceding year, and either had and ICD or were about to receive one.)	546

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Age mean (SD) [median] years	Sex (% male)	Race
17	Brinton, 2013, 23835245	61.2 (10.05)	62	96 white
18	Brinton, 2013, 23835245	61.2 (10.05)	62	96 white
19	Brinton, 2013, 23835245	61.2 (10.05)	62	96 white
20	Brinton, 2013, 23835245	61.2 (10.05)	62	96 white
21	Brinton, 2013, 23835245	61.2 (10.05)	62	96 white
22	Brinton, 2013, 23835245	61.2 (10.05)	62	96 white
23	Brinton, 2013, 23835245	61.2 (10.05)	62	96 white
24	Brinton, 2013, 23835245	61.2 (10.05)	62	96 white
25	Brinton, 2013, 23835245	61.2 (10.05)	62	96 white
26	Brouwer, 2006, 16772624	62.4 (11.4)	84	nd
27	Brouwer, 2006, 16772624	62.4 (11.4)	84	nd
28	Brouwer, 2006, 16772624	62.4 (11.4)	84	nd

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Blood pressure SBP/DBP mmHg
17	Brinton, 2013, 23835245	nd
18	Brinton, 2013, 23835245	nd
19	Brinton, 2013, 23835245	nd
20	Brinton, 2013, 23835245	nd
21	Brinton, 2013, 23835245	nd
22	Brinton, 2013, 23835245	nd
23	Brinton, 2013, 23835245	nd
24	Brinton, 2013, 23835245	nd
25	Brinton, 2013, 23835245	nd
26	Brouwer, 2006, 16772624	121.2 (18.5)/74.2 (9.1)
27	Brouwer, 2006, 16772624	121.2 (18.5)/74.2 (9.1)
28	Brouwer, 2006, 16772624	121.2 (18.5)/74.2 (9.1)

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Lipids: Total cholesterol/LDL/HDL/Triglycerides mean (SD) mg/dL [mmol/L]
17	Brinton, 2013, 23835245	median 168.0 (IQR 38.0)/median 84.0 (27)/median 37 (12)/median 259.0 (81)
18	Brinton, 2013, 23835245	median 168.0 (IQR 38.0)/median 84.0 (27)/median 37 (12)/median 259.0 (81)
19	Brinton, 2013, 23835245	median 168.0 (IQR 38.0)/median 84.0 (27)/median 37 (12)/median 259.0 (81)
20	Brinton, 2013, 23835245	median 168.0 (IQR 38.0)/median 84.0 (27)/median 37 (12)/median 259.0 (81)
21	Brinton, 2013, 23835245	median 168.0 (IQR 38.0)/median 84.0 (27)/median 37 (12)/median 259.0 (81)
22	Brinton, 2013, 23835245	median 168.0 (IQR 38.0)/median 84.0 (27)/median 37 (12)/median 259.0 (81)
23	Brinton, 2013, 23835245	median 168.0 (IQR 38.0)/median 84.0 (27)/median 37 (12)/median 259.0 (81)
24	Brinton, 2013, 23835245	median 168.0 (IQR 38.0)/median 84.0 (27)/median 37 (12)/median 259.0 (81)
25	Brinton, 2013, 23835245	median 168.0 (IQR 38.0)/median 84.0 (27)/median 37 (12)/median 259.0 (81)
26	Brouwer, 2006, 16772624	nd
27	Brouwer, 2006, 16772624	nd
28	Brouwer, 2006, 16772624	nd

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	BMI mean (SD) Kg/m2/Weight mean (SD) Kg	Baseline n-3 intake	n-3 source (Baseline)
17	Brinton, 2013, 23835245	33.0 (5.04)	nd	nd
18	Brinton, 2013, 23835245	33.0 (5.04)	nd	nd
19	Brinton, 2013, 23835245	33.0 (5.04)	nd	nd
20	Brinton, 2013, 23835245	33.0 (5.04)	nd	nd
21	Brinton, 2013, 23835245	33.0 (5.04)	nd	nd
22	Brinton, 2013, 23835245	33.0 (5.04)	nd	nd
23	Brinton, 2013, 23835245	33.0 (5.04)	nd	nd
24	Brinton, 2013, 23835245	33.0 (5.04)	nd	nd
25	Brinton, 2013, 23835245	33.0 (5.04)	nd	nd
26	Brouwer, 2006, 16772624	26.86 (4.01)	nd	nd
27	Brouwer, 2006, 16772624	26.86 (4.01)	nd	nd
28	Brouwer, 2006, 16772624	26.86 (4.01)	nd	nd

Causality Table: Comparative Studies

Row	Study	n-3 type(s)	n-3 measure	Study design	Outcome
17	Brinton, 2013, 23835245	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	HDL-c
18	Brinton, 2013, 23835245	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	HDL-c
19	Brinton, 2013, 23835245	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Parallel	HDL-c
20	Brinton, 2013, 23835245	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	LDL-c
21	Brinton, 2013, 23835245	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	LDL-c
22	Brinton, 2013, 23835245	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Parallel	LDL-c
23	Brinton, 2013, 23835245	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Tg
24	Brinton, 2013, 23835245	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Tg
25	Brinton, 2013, 23835245	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Parallel	Tg
26	Brouwer, 2006, 16772624	EPA + DHA vs Placebo	g/d	Trial: Randomized Parallel	Arrhythmia composite
27	Brouwer, 2006, 16772624	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Death, all cause
28	Brouwer, 2006, 16772624	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Death, cardiac

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Reported effect Size	Dose/intake difference	Dose-corrected effect size
17	Brinton, 2013, 23835245	-5.00 (-8.80, -1.20)	4	-1.25
18	Brinton, 2013, 23835245	-2.30 (-5.59, 0.98)	2	-1.15
19	Brinton, 2013, 23835245	-1.00 (nd)	2	-0.5
20	Brinton, 2013, 23835245	-3.80 (-8.97, 1.37)	2	-1.9
21	Brinton, 2013, 23835245	-6.30 (-11.61, 0.99)	4	-1.575
22	Brinton, 2013, 23835245	-4.00 (nd)	2	-2
23	Brinton, 2013, 23835245	-23.20 (-34.89, -11.51)	4	-5.8
24	Brinton, 2013, 23835245	-9.80 (-17.26, -2.34)	2	-4.9
25	Brinton, 2013, 23835245	-34.40 (nd)	2	-17.2
26	Brouwer, 2006, 16772624	0.86 (0.6, 1.23)	0.84	0.8356453
27	Brouwer, 2006, 16772624	OR 0.52 (0.22, 1.25)	0.799	0.4411232
28	Brouwer, 2006, 16772624	OR 0.45 (0.17, 1.20)	0.799	0.3681062

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Outcome classification
17	Brinton, 2013, 23835245	Secondary
18	Brinton, 2013, 23835245	Secondary
19	Brinton, 2013, 23835245	Secondary
20	Brinton, 2013, 23835245	Secondary
21	Brinton, 2013, 23835245	Secondary
22	Brinton, 2013, 23835245	Secondary
23	Brinton, 2013, 23835245	Primary (stated)
24	Brinton, 2013, 23835245	Primary (stated)
25	Brinton, 2013, 23835245	Primary (stated)
26	Brouwer, 2006, 16772624	Secondary
27	Brouwer, 2006, 16772624	Secondary
28	Brouwer, 2006, 16772624	Secondary

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Study years (start date)	Country	Population
29	Brouwer, 2006, 16772624	2001	Germany, Netherlands, Sweden, UK, Poland, Czech Republic, Belgium, Austria	Secondary Prevention (history of CVD event)
30	Burr, 1989, 2571009	1987 (Approx)	UK	Secondary Prevention (history of CVD event)
31	Burr, 1989, 2571009	1987 (Approx)	UK	Secondary Prevention (history of CVD event)
32	Burr, 1989, 2571009	1987 (Approx)	UK	Secondary Prevention (history of CVD event)
34	Burr, 1989, 2571009	1987 (Approx)	UK	Secondary Prevention (history of CVD event)
35	Burr, 1989, 2571009	1987 (Approx)	UK	Secondary Prevention (history of CVD event)
36	Burr, 2003, 12571649, UK	1990	UK	Secondary Prevention (history of CVD event)
37	Burr, 2003, 12571649, UK	1990	UK	Secondary Prevention (history of CVD event)
38	Carrepeiro, 2011, 21561620	2008 (approx)	Brazil	Primary Prevention, Healthy
39	Carrepeiro, 2011, 21561620	2008 (approx)	Brazil	Primary Prevention, Healthy
40	Carrepeiro, 2011, 21561620	2008 (approx)	Brazil	Primary Prevention, Healthy
41	Carrepeiro, 2011, 21561620	2008 (approx)	Brazil	Primary Prevention, Healthy
42	Carrepeiro, 2011, 21561620	2008 (approx)	Brazil	Primary Prevention, Healthy
43	Carrepeiro, 2011, 21561620	2008 (approx)	Brazil	Primary Prevention, Healthy
44	Carter, 2012, 22707560	2010 (Approx)	US	Primary Prevention, Healthy
45	Carter, 2012, 22707560	2010 (Approx)	US	Primary Prevention, Healthy
46	Carter, 2012, 22707560	2010 (Approx)	US	Primary Prevention, Healthy
47	Carter, 2012, 22707560	2010 (Approx)	US	Primary Prevention, Healthy
48	Carter, 2012, 22707560	2010 (Approx)	US	Primary Prevention, Healthy
49	Carter, 2012, 22707560	2010 (Approx)	US	Primary Prevention, Healthy

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Risk type	Sample size (total)
29	Brouwer, 2006, 16772624	Arrhythmia (at least 1 true, confirmed, spontaneous VT or VF in the preceding year, and either had and ICD or were about to receive one)	546
30	Burr, 1989, 2571009	Cardiac disease (Previous MI)	2033
31	Burr, 1989, 2571009	Cardiac disease (Previous MI)	2033
32	Burr, 1989, 2571009	Cardiac disease (Previous MI)	2033
34	Burr, 1989, 2571009	Cardiac disease (Previous MI)	2033
35	Burr, 1989, 2571009	Cardiac disease (Previous MI)	2033
36	Burr, 2003, 12571649, UK	Cardiac disease (Angina)	3114
37	Burr, 2003, 12571649, UK	Cardiac disease (Angina)	3114
38	Carrepeiro, 2011, 21561620	na	43
39	Carrepeiro, 2011, 21561620	na	43
40	Carrepeiro, 2011, 21561620	na	43
41	Carrepeiro, 2011, 21561620	na	43
42	Carrepeiro, 2011, 21561620	na	43
43	Carrepeiro, 2011, 21561620	na	43
44	Carter, 2012, 22707560	na	67
45	Carter, 2012, 22707560	na	67
46	Carter, 2012, 22707560	na	67
47	Carter, 2012, 22707560	na	67
48	Carter, 2012, 22707560	na	67
49	Carter, 2012, 22707560	na	67

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Age mean (SD) [median] years	Sex (% male)	Race
29	Brouwer, 2006, 16772624	62.4 (11.4)	84	nd
30	Burr, 1989, 2571009	56.4	100	nd
31	Burr, 1989, 2571009	56.4	100	nd
32	Burr, 1989, 2571009	56.4	100	nd
34	Burr, 1989, 2571009	56.4	100	nd
35	Burr, 1989, 2571009	56.4	100	nd
36	Burr, 2003, 12571649, UK	61	100	nd
37	Burr, 2003, 12571649, UK	61	100	nd
38	Carrepeiro, 2011, 21561620	61.3 (7.8)	0	65 white, 14 black, 5 Asian, 16 American lian
39	Carrepeiro, 2011, 21561620	61.3 (7.8)	0	65 white, 14 black, 5 Asian, 16 American lian
40	Carrepeiro, 2011, 21561620	61.3 (7.8)	0	65 white, 14 black, 5 Asian, 16 American lian
41	Carrepeiro, 2011, 21561620	61.3 (7.8)	0	65 white, 14 black, 5 Asian, 16 American lian
42	Carrepeiro, 2011, 21561620	61.3 (7.8)	0	65 white, 14 black, 5 Asian, 16 American lian
43	Carrepeiro, 2011, 21561620	61.3 (7.8)	0	65 white, 14 black, 5 Asian, 16 American lian
44	Carter, 2012, 22707560	24 (SE 2)	90	nd
45	Carter, 2012, 22707560	24 (SE 2)	90	nd
46	Carter, 2012, 22707560	24 (SE 2)	90	nd
47	Carter, 2012, 22707560	24 (SE 2)	90	nd
48	Carter, 2012, 22707560	24 (SE 2)	90	nd
49	Carter, 2012, 22707560	24 (SE 2)	90	nd

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Blood pressure SBP/DBP mmHg
29	Brouwer, 2006, 16772624	121.2 (18.5)/74.2 (9.1)
30	Burr, 1989, 2571009	130.1 (21.0)/80.2 (12.5)
31	Burr, 1989, 2571009	130.1 (21.0)/80.2 (12.5)
32	Burr, 1989, 2571009	130.1 (21.0)/80.2 (12.5)
34	Burr, 1989, 2571009	130.1 (21.0)/80.2 (12.5)
35	Burr, 1989, 2571009	130.1 (21.0)/80.2 (12.5)
36	Burr, 2003, 12571649, UK	141.6/84.6
37	Burr, 2003, 12571649, UK	141.6/84.6
38	Carrepeiro, 2011, 21561620	nd
39	Carrepeiro, 2011, 21561620	nd
40	Carrepeiro, 2011, 21561620	nd
41	Carrepeiro, 2011, 21561620	nd
42	Carrepeiro, 2011, 21561620	nd
43	Carrepeiro, 2011, 21561620	nd
44	Carter, 2012, 22707560	normotensive: 107 (SE 2)/65 (SE 1), prehypertensive:
45	Carter, 2012, 22707560	normotensive: 107 (SE 2)/65 (SE 1), prehypertensive:
46	Carter, 2012, 22707560	normotensive: 107 (SE 2)/65 (SE 1), prehypertensive:
47	Carter, 2012, 22707560	normotensive: 107 (SE 2)/65 (SE 1), prehypertensive:
48	Carter, 2012, 22707560	normotensive: 107 (SE 2)/65 (SE 1), prehypertensive:
49	Carter, 2012, 22707560	normotensive: 107 (SE 2)/65 (SE 1), prehypertensive:

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Lipids: Total cholesterol/LDL/HDL/Triglycerides mean (SD) mg/dL [mmol/L]
29	Brouwer, 2006, 16772624	nd
30	Burr, 1989, 2571009	nd
31	Burr, 1989, 2571009	nd
32	Burr, 1989, 2571009	nd
34	Burr, 1989, 2571009	nd
35	Burr, 1989, 2571009	nd
36	Burr, 2003, 12571649, UK	6.4/nd/nd/nd
37	Burr, 2003, 12571649, UK	6.4/nd/nd/nd
38	Carrepeiro, 2011, 21561620	208 (36.8)/134.8 (34.1)/50.1 (12.4)/117.5 (48.5)
39	Carrepeiro, 2011, 21561620	208 (36.8)/134.8 (34.1)/50.1 (12.4)/117.5 (48.5)
40	Carrepeiro, 2011, 21561620	208 (36.8)/134.8 (34.1)/50.1 (12.4)/117.5 (48.5)
41	Carrepeiro, 2011, 21561620	208 (36.8)/134.8 (34.1)/50.1 (12.4)/117.5 (48.5)
42	Carrepeiro, 2011, 21561620	208 (36.8)/134.8 (34.1)/50.1 (12.4)/117.5 (48.5)
43	Carrepeiro, 2011, 21561620	208 (36.8)/134.8 (34.1)/50.1 (12.4)/117.5 (48.5)
44	Carter, 2012, 22707560	nd
45	Carter, 2012, 22707560	nd
46	Carter, 2012, 22707560	nd
47	Carter, 2012, 22707560	nd
48	Carter, 2012, 22707560	nd
49	Carter, 2012, 22707560	nd

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	BMI mean (SD) Kg/m2/Weight mean (SD) Kg	Baseline n-3 intake	n-3 source (Baseline)
29	Brouwer, 2006, 16772624	26.86 (4.01)	nd	nd
30	Burr, 1989, 2571009	26	nd	nd
31	Burr, 1989, 2571009	26	nd	nd
32	Burr, 1989, 2571009	26	nd	nd
34	Burr, 1989, 2571009	26	nd	nd
35	Burr, 1989, 2571009	26	nd	nd
36	Burr, 2003, 12571649, UK	28.1	EPA 3.19 (1.75) mg/dl	plasma
37	Burr, 2003, 12571649, UK	28.1	EPA 3.19 (1.75) mg/dl	plasma
38	Carrepeiro, 2011, 21561620	28.2 (4.8)	nd	nd
39	Carrepeiro, 2011, 21561620	28.2 (4.8)	nd	nd
40	Carrepeiro, 2011, 21561620	28.2 (4.8)	nd	nd
41	Carrepeiro, 2011, 21561620	28.2 (4.8)	nd	nd
42	Carrepeiro, 2011, 21561620	28.2 (4.8)	nd	nd
43	Carrepeiro, 2011, 21561620	28.2 (4.8)	nd	nd
44	Carter, 2012, 22707560	normotensive: 24 (SE 1)/70 (SE 2), prehypertensive 27 (SE 1)/87 (SE 2)	nd	nd
45	Carter, 2012, 22707560	normotensive: 24 (SE 1)/70 (SE 2), prehypertensive 27 (SE 1)/87 (SE 2)	nd	nd
46	Carter, 2012, 22707560	normotensive: 24 (SE 1)/70 (SE 2), prehypertensive 27 (SE 1)/87 (SE 2)	nd	nd
47	Carter, 2012, 22707560	normotensive: 24 (SE 1)/70 (SE 2), prehypertensive 27 (SE 1)/87 (SE 2)	nd	nd
48	Carter, 2012, 22707560	normotensive: 24 (SE 1)/70 (SE 2), prehypertensive 27 (SE 1)/87 (SE 2)	nd	nd
49	Carter, 2012, 22707560	normotensive: 24 (SE 1)/70 (SE 2), prehypertensive 27 (SE 1)/87 (SE 2)	nd	nd

Row	Study	n-3 type(s)	n-3 measure	Study design	Outcome
29	Brouwer, 2006, 16772624	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Myocardial infarction
30	Burr, 1989, 2571009	EPA vs EPA	g/d	Trial: Randomized Factorial Design	Death, all cause
31	Burr, 1989, 2571009	EPA vs EPA	mg/dl	Trial: Randomized Factorial Design	Death, cardiac
32	Burr, 1989, 2571009	EPA vs EPA	g/d	Trial: Randomized Factorial Design	Myocardial infarction
34	Burr, 1989, 2571009	EPA+DHA vs Placebo	g/d	Trial: Randomized Factorial Design	SBP
35	Burr, 1989, 2571009	EPA+DHA vs Placebo	g/d	Trial: Randomized Factorial Design	DBP
36	Burr, 2003, 12571649, UK	EPA+DHA vs EPA	g/d	Trial: Randomized Factorial Design	Death, all cause
37	Burr, 2003, 12571649, UK	EPA vs. EPA	g/d	Trial: Randomized Factorial Design	Death, cardiac
38	Carrepeiro, 2011, 21561620	EPA+DHA + Statin vs Placebo + Statin	g/d	Trial: Randomized Cross-over	HDL-c
39	Carrepeiro, 2011, 21561620	EPA+DHA vs Placebo	g/d	Trial: Randomized Cross-over	HDL-c
40	Carrepeiro, 2011, 21561620	EPA+DHA + Statin vs Placebo + Statin	g/d	Trial: Randomized Cross-over	LDL-c
41	Carrepeiro, 2011, 21561620	EPA+DHA vs Placebo	g/d	Trial: Randomized Cross-over	LDL-c
42	Carrepeiro, 2011, 21561620	EPA+DHA + Statin vs Placebo + Statin	g/d	Trial: Randomized Cross-over	Tg
43	Carrepeiro, 2011, 21561620	EPA+DHA vs Placebo	g/d	Trial: Randomized Cross-over	Tg
44	Carter, 2012, 22707560	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	SBP
45	Carter, 2012, 22707560	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	SBP
46	Carter, 2012, 22707560	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	DBP
47	Carter, 2012, 22707560	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	DBP
48	Carter, 2012, 22707560	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	MAP
49	Carter, 2012, 22707560	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	MAP

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Reported effect Size	Dose/intake difference	Dose-corrected effect size
29	Brouwer, 2006, 16772624	OR 0.33 (0.03, 3.20)	0.799	0.2496831
30	Burr, 1989, 2571009	Adj HR 0.95 (0.85, 1.07)	0.25	0.8145062
31	Burr, 1989, 2571009	Adj HR 0.92 (0.80, 1.07)	0.25	0.7163929
32	Burr, 1989, 2571009	Adj RR 0.84 (0.66, 1.07)	0.25	0.4978714
34	Burr, 1989, 2571009	0.40 (-1.33, 2.13)	0.357	1.120448
35	Burr, 1989, 2571009	0.19 (-0.88, 1.26)	0.357	0.5322129
36	Burr, 2003, 12571649, UK	Adj HR 1.19 (0.92, 1.54)	NA	
37	Burr, 2003, 12571649, UK	Adj HR 0.92 (0.80, 1.07)	0.25	0.7163929
38	Carrepeiro, 2011, 21561620	1.85 (nd)	2.4	0.7708333
39	Carrepeiro, 2011, 21561620	-1.34 (nd)	2.4	-0.5583333
40	Carrepeiro, 2011, 21561620	-1.54 (-3.52, 0.44)	2.4	-0.6416667
41	Carrepeiro, 2011, 21561620	-0.79 (-2.76, 1.18)	2.4	-0.3291667
42	Carrepeiro, 2011, 21561620	-1.96 (-3.95, 0.03)	2.4	-0.8166667
43	Carrepeiro, 2011, 21561620	-1.79 (-3.77, 0.19)	2.4	-0.7458333
44	Carter, 2012, 22707560	-3 (-7, 1)	2.7	-1.111111
45	Carter, 2012, 22707560	1 (-4.2, 6.2)	2.7	0.3703704
46	Carter, 2012, 22707560	-1.0 (-3.6, 1.6)	2.7	-0.3703704
47	Carter, 2012, 22707560	0 (-5.2, 5.2)	2.7	0
48	Carter, 2012, 22707560	-1 (-3.8, 1.8)	2.7	-0.3703704
49	Carter, 2012, 22707560	1 (-3.8, 5.8)	2.7	0.3703704

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Outcome classification
29	Brouwer, 2006, 16772624	Secondary
30	Burr, 1989, 2571009	Secondary
31	Burr, 1989, 2571009	Secondary
32	Burr, 1989, 2571009	Primary (stated)
34	Burr, 1989, 2571009	Secondary
35	Burr, 1989, 2571009	Secondary
36	Burr, 2003, 12571649, UK	Primary (stated)
37	Burr, 2003, 12571649, UK	Secondary
38	Carrepeiro, 2011, 21561620	Secondary
39	Carrepeiro, 2011, 21561620	Secondary
40	Carrepeiro, 2011, 21561620	Secondary
41	Carrepeiro, 2011, 21561620	Secondary
42	Carrepeiro, 2011, 21561620	Secondary
43	Carrepeiro, 2011, 21561620	Secondary
44	Carter, 2012, 22707560	Primary (stated)
45	Carter, 2012, 22707560	Primary (stated)
46	Carter, 2012, 22707560	Primary (stated)
47	Carter, 2012, 22707560	Primary (stated)
48	Carter, 2012, 22707560	Primary (stated)
49	Carter, 2012, 22707560	Primary (stated)

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Study years (start date)	Country	Population
50	Caslake, 2008, 18779276	2003	UK	Primary Prevention, Healthy
51	Caslake, 2008, 18779276	2003	UK	Primary Prevention, Healthy
52	Caslake, 2008, 18779276	2003	UK	Primary Prevention, Healthy
53	Caslake, 2008, 18779276	2003	UK	Primary Prevention, Healthy
54	Caslake, 2008, 18779276	2003	UK	Primary Prevention, Healthy
55	Caslake, 2008, 18779276	2003	UK	Primary Prevention, Healthy
56	Caslake, 2008, 18779276	2003	UK	Primary Prevention, Healthy
57	Caslake, 2008, 18779276	2003	UK	Primary Prevention, Healthy

Row	Study	Risk type	Sample size (total)
50	Caslake, 2008, 18779276	na	312
51	Caslake, 2008, 18779276	na	312
52	Caslake, 2008, 18779276	na	312
53	Caslake, 2008, 18779276	na	312
54	Caslake, 2008, 18779276	na	312
55	Caslake, 2008, 18779276	na	312
56	Caslake, 2008, 18779276	na	312
57	Caslake, 2008, 18779276	na	312

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Age mean (SD) [median] years	Sex (% male)	Race
50	Caslake, 2008, 18779276	45 (SE 0.7)	47.76	nd
51	Caslake, 2008, 18779276	45 (SE 0.7)	47.76	nd
52	Caslake, 2008, 18779276	45 (SE 0.7)	47.76	nd
53	Caslake, 2008, 18779276	45 (SE 0.7)	47.76	nd
54	Caslake, 2008, 18779276	45 (SE 0.7)	47.76	nd
55	Caslake, 2008, 18779276	45 (SE 0.7)	47.76	nd
56	Caslake, 2008, 18779276	45 (SE 0.7)	47.76	nd
57	Caslake, 2008, 18779276	45 (SE 0.7)	47.76	nd

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Blood pressure SBP/DBP mmHg
50	Caslake, 2008, 18779276	126 (SE 2)/74 (SE 2)
51	Caslake, 2008, 18779276	126 (SE 2)/74 (SE 2)
52	Caslake, 2008, 18779276	126 (SE 2)/74 (SE 2)
53	Caslake, 2008, 18779276	126 (SE 2)/74 (SE 2)
54	Caslake, 2008, 18779276	126 (SE 2)/74 (SE 2)
55	Caslake, 2008, 18779276	126 (SE 2)/74 (SE 2)
56	Caslake, 2008, 18779276	126 (SE 2)/74 (SE 2)
57	Caslake, 2008, 18779276	126 (SE 2)/74 (SE 2)

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Lipids: Total cholesterol/LDL/HDL/Triglycerides mean (SD) mg/dL [mmol/L]
50	Caslake, 2008, 18779276	[5.12 (SE 0.06)]/[3.22 (SE 0.05)]/[1.42 (SE 0.02)]/[1.26 (SE 0.03)]
51	Caslake, 2008, 18779276	[5.12 (SE 0.06)]/[3.22 (SE 0.05)]/[1.42 (SE 0.02)]/[1.26 (SE 0.03)]
52	Caslake, 2008, 18779276	[5.12 (SE 0.06)]/[3.22 (SE 0.05)]/[1.42 (SE 0.02)]/[1.26 (SE 0.03)]
53	Caslake, 2008, 18779276	[5.12 (SE 0.06)]/[3.22 (SE 0.05)]/[1.42 (SE 0.02)]/[1.26 (SE 0.03)]
54	Caslake, 2008, 18779276	[5.12 (SE 0.06)]/[3.22 (SE 0.05)]/[1.42 (SE 0.02)]/[1.26 (SE 0.03)]
55	Caslake, 2008, 18779276	[5.12 (SE 0.06)]/[3.22 (SE 0.05)]/[1.42 (SE 0.02)]/[1.26 (SE 0.03)]
56	Caslake, 2008, 18779276	[5.12 (SE 0.06)]/[3.22 (SE 0.05)]/[1.42 (SE 0.02)]/[1.26 (SE 0.03)]
57	Caslake, 2008, 18779276	[5.12 (SE 0.06)]/[3.22 (SE 0.05)]/[1.42 (SE 0.02)]/[1.26 (SE 0.03)]

Row	Study	BMI mean (SD) Kg/m2/Weight mean (SD) Kg	Baseline n-3 intake	n-3 source (Baseline)
50	Caslake, 2008, 18779276	25.2 (SE 0.19)/73.0 (SE 0.8)	EPA: 1.6 (SEM 0.04) % FA, DPA: 1.09 (0.01)% FA, DHA: 4.41 (0.07)% FA, EPA+DPA+DHA: 7.17 (0.11) % FA	plasma phosphatidylcholine fatty acid
51	Caslake, 2008, 18779276	25.2 (SE 0.19)/73.0 (SE 0.8)	EPA: 1.6 (SEM 0.04) % FA, DPA: 1.09 (0.01)% FA, DHA: 4.41 (0.07)% FA, EPA+DPA+DHA: 7.17 (0.11) % FA	plasma phosphatidylcholine fatty acid
52	Caslake, 2008, 18779276	25.2 (SE 0.19)/73.0 (SE 0.8)	EPA: 1.6 (SEM 0.04) % FA, DPA: 1.09 (0.01)% FA, DHA: 4.41 (0.07)% FA, EPA+DPA+DHA: 7.17 (0.11) % FA	plasma phosphatidylcholine fatty acid
53	Caslake, 2008, 18779276	25.2 (SE 0.19)/73.0 (SE 0.8)	EPA: 1.6 (SEM 0.04) % FA, DPA: 1.09 (0.01)% FA, DHA: 4.41 (0.07)% FA, EPA+DPA+DHA: 7.17 (0.11) % FA	plasma phosphatidylcholine fatty acid
54	Caslake, 2008, 18779276	25.2 (SE 0.19)/73.0 (SE 0.8)	EPA: 1.6 (SEM 0.04) % FA, DPA: 1.09 (0.01)% FA, DHA: 4.41 (0.07)% FA, EPA+DPA+DHA: 7.17 (0.11) % FA	plasma phosphatidylcholine fatty acid
55	Caslake, 2008, 18779276	25.2 (SE 0.19)/73.0 (SE 0.8)	EPA: 1.6 (SEM 0.04) % FA, DPA: 1.09 (0.01)% FA, DHA: 4.41 (0.07)% FA, EPA+DPA+DHA: 7.17 (0.11) % FA	plasma phosphatidylcholine fatty acid
56	Caslake, 2008, 18779276	25.2 (SE 0.19)/73.0 (SE 0.8)	EPA: 1.6 (SEM 0.04) % FA, DPA: 1.09 (0.01)% FA, DHA: 4.41 (0.07)% FA, EPA+DPA+DHA: 7.17 (0.11) % FA	plasma phosphatidylcholine fatty acid
57	Caslake, 2008, 18779276	25.2 (SE 0.19)/73.0 (SE 0.8)	EPA: 1.6 (SEM 0.04) % FA, DPA: 1.09 (0.01)% FA, DHA: 4.41 (0.07)% FA, EPA+DPA+DHA: 7.17 (0.11) % FA	plasma phosphatidylcholine fatty acid

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	n-3 type(s)	n-3 measure	Study design	Outcome
50	Caslake, 2008, 18779276	EPA+DHA vs Placebo	% FA	Trial: Randomized Cross-over	HDL-c
51	Caslake, 2008, 18779276	EPA+DHA vs Placebo	g/d	Trial: Randomized Cross-over	HDL-c
52	Caslake, 2008, 18779276	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Cross-over	HDL-c
53	Caslake, 2008, 18779276	EPA+DHA vs Placebo	g/d	Trial: Randomized Cross-over	LDL-c
54	Caslake, 2008, 18779276	EPA+DHA vs Placebo	g/d	Trial: Randomized Cross-over	LDL-c
55	Caslake, 2008, 18779276	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Cross-over	LDL-c
56	Caslake, 2008, 18779276	EPA+DHA vs Placebo	g/d	Trial: Randomized Cross-over	Tg
57	Caslake, 2008, 18779276	EPA+DHA vs Placebo	g/d	Trial: Randomized Cross-over	Tg

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Reported effect Size	Dose/intake difference	Dose-corrected effect size
50	Caslake, 2008, 18779276	2.32 (0.18, 4.46)	1.8	1.288889
51	Caslake, 2008, 18779276	2.32 (0.18, 4.46)	0.7	3.314286
52	Caslake, 2008, 18779276	0.00 (-2.14, 2.14)	1.1	0
53	Caslake, 2008, 18779276	2.70 (-2.96, 8.37)	1.8	1.5
54	Caslake, 2008, 18779276	2.70 (-2.65, 8.05)	0.7	3.857143
55	Caslake, 2008, 18779276	0.00 (-5.66, 5.66)	1.1	0
56	Caslake, 2008, 18779276	-1.42 (-23.50, -4.82)	1.8	-0.7888889
57	Caslake, 2008, 18779276	-8.00 (-17.34, 1.34)	0.7	-11.42857

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Outcome classification
50	Caslake, 2008, 18779276	Secondary
51	Caslake, 2008, 18779276	Secondary
52	Caslake, 2008, 18779276	Secondary
53	Caslake, 2008, 18779276	Primary (power analysis)
54	Caslake, 2008, 18779276	Primary (power analysis)
55	Caslake, 2008, 18779276	Primary (power analysis)
56	Caslake, 2008, 18779276	Primary (power analysis)
57	Caslake, 2008, 18779276	Primary (power analysis)

Row	Study	Study years (start date)	Country	Population
58	Caslake, 2008, 18779276	2003	UK	Primary Prevention, Healthy
59	Damsgaard, 2008, 18492834	2005	Denmark	Primary Prevention, Healthy
60	Damsgaard, 2008, 18492834	2005	Denmark	Primary Prevention, Healthy
61	Damsgaard, 2008, 18492834	2005	Denmark	Primary Prevention, Healthy
62	Damsgaard, 2008, 18492834	2005	Denmark	Primary Prevention, Healthy
63	Damsgaard, 2008, 18492834	2005	Denmark	Primary Prevention, Healthy
64	Damsgaard, 2008, 18492834	2005	Denmark	Primary Prevention, Healthy
65	Derosa, 2009, 19397392	nd	Italy	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
66	Derosa, 2009, 19397392	nd	Italy	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
67	Derosa, 2009, 19397392	nd	Italy	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
68	Derosa, 2009, 19397392	nd	Italy	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
69	Derosa, 2009, 19397392	nd	Italy	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
70	Earnest, 2012, 22811376	2009 (Approx)	US	Primary Prevention, Healthy; Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
71	Ebrahimi, 2009, 19593941	2007 (Approx)	Iran	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
72	Ebrahimi, 2009, 19593941	2007 (Approx)	Iran	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
73	Ebrahimi, 2009, 19593941	2007 (Approx)	Iran	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
74	Ebrahimi, 2009, 19593941	2007 (Approx)	Iran	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Risk type	Sample size (total)
58	Caslake, 2008, 18779276	na	312
59	Damsgaard, 2008, 18492834	na	64
60	Damsgaard, 2008, 18492834	na	64
61	Damsgaard, 2008, 18492834	na	64
62	Damsgaard, 2008, 18492834	na	64
63	Damsgaard, 2008, 18492834	na	64
64	Damsgaard, 2008, 18492834	na	64
65	Derosa, 2009, 19397392	Dyslipidemia (total cholesterol (TC) > 200 mg/dl and triglycerides (Tg) > 200 mg/dl)	333
66	Derosa, 2009, 19397392	Dyslipidemia (total cholesterol (TC) > 200 mg/dl and triglycerides (Tg) > 200 mg/dl)	333
67	Derosa, 2009, 19397392	Dyslipidemia (total cholesterol (TC) > 200 mg/dl and triglycerides (Tg) > 200 mg/dl)	333
68	Derosa, 2009, 19397392	Dyslipidemia (total cholesterol (TC) > 200 mg/dl and triglycerides (Tg) > 200 mg/dl)	333
69	Derosa, 2009, 19397392	Dyslipidemia (total cholesterol (TC) > 200 mg/dl and triglycerides (Tg) > 200 mg/dl)	333
70	Earnest, 2012, 22811376	Diabetes and/or metabolic syndrome; Hypertension ; Dyslipidemia	92
71	Ebrahimi, 2009, 19593941	Diabetes and/or metabolic syndrome	89
72	Ebrahimi, 2009, 19593941	Diabetes and/or metabolic syndrome	89
73	Ebrahimi, 2009, 19593941	Diabetes and/or metabolic syndrome	89
74	Ebrahimi, 2009, 19593941	Diabetes and/or metabolic syndrome	89

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Age mean (SD) [median] years	Sex (% male)	Race
58	Caslake, 2008, 18779276	45 (SE 0.7)	47.76	nd
59	Damsgaard, 2008, 18492834	25.5 (4.4)	100	nd
60	Damsgaard, 2008, 18492834	25.5 (4.4)	100	nd
61	Damsgaard, 2008, 18492834	25.5 (4.4)	100	nd
62	Damsgaard, 2008, 18492834	25.5 (4.4)	100	nd
63	Damsgaard, 2008, 18492834	25.5 (4.4)	100	nd
64	Damsgaard, 2008, 18492834	25.5 (4.4)	100	nd
65	Derosa, 2009, 19397392	50.7 (6.8)	49.7	nd
66	Derosa, 2009, 19397392	50.7 (6.8)	49.7	nd
67	Derosa, 2009, 19397392	50.7 (6.8)	49.7	nd
68	Derosa, 2009, 19397392	50.7 (6.8)	49.7	nd
69	Derosa, 2009, 19397392	50.7 (6.8)	49.7	nd
70	Earnest, 2012, 22811376	52.9 (10.7) [range 30, 70]	55	77 white, 13 black, 10 Hispanic
71	Ebrahimi, 2009, 19593941	52.3 (11.1)	nd	nd
72	Ebrahimi, 2009, 19593941	52.3 (11.1)	nd	nd
73	Ebrahimi, 2009, 19593941	52.3 (11.1)	nd	nd
74	Ebrahimi, 2009, 19593941	52.3 (11.1)	nd	nd

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Blood pressure SBP/DBP mmHg
58	Caslake, 2008, 18779276	126 (SE 2)/74 (SE 2)
59	Damsgaard, 2008, 18492834	115 (6)/nd
60	Damsgaard, 2008, 18492834	115 (6)/nd
61	Damsgaard, 2008, 18492834	115 (6)/nd
62	Damsgaard, 2008, 18492834	115 (6)/nd
63	Damsgaard, 2008, 18492834	115 (6)/nd
64	Damsgaard, 2008, 18492834	115 (6)/nd
65	Derosa, 2009, 19397392	129.6 (6.8)/81.4 (7.1)
66	Derosa, 2009, 19397392	129.6 (6.8)/81.4 (7.1)
67	Derosa, 2009, 19397392	129.6 (6.8)/81.4 (7.1)
68	Derosa, 2009, 19397392	129.6 (6.8)/81.4 (7.1)
69	Derosa, 2009, 19397392	129.6 (6.8)/81.4 (7.1)
70	Earnest, 2012, 22811376	nd
71	Ebrahimi, 2009, 19593941	129.6 (19.8)/78.3 (13.4)
72	Ebrahimi, 2009, 19593941	129.6 (19.8)/78.3 (13.4)
73	Ebrahimi, 2009, 19593941	129.6 (19.8)/78.3 (13.4)
74	Ebrahimi, 2009, 19593941	129.6 (19.8)/78.3 (13.4)

Row	Study	Lipids: Total cholesterol/LDL/HDL/Triglycerides mean (SD) mg/dL [mmol/L]
58	Caslake, 2008, 18779276	[5.12 (SE 0.06)]/[3.22 (SE 0.05)]/[1.42 (SE 0.02)]/[1.26 (SE 0.03)]
59	Damsgaard, 2008, 18492834	[4.12 (SE 0.20)]/[2.71 (SE 0.18)]/[1.50 (SE 0.09)]/[median 1.01]
60	Damsgaard, 2008, 18492834	[4.12 (SE 0.20)]/[2.71 (SE 0.18)]/[1.50 (SE 0.09)]/[median 1.01]
61	Damsgaard, 2008, 18492834	[4.12 (SE 0.20)]/[2.71 (SE 0.18)]/[1.50 (SE 0.09)]/[median 1.01]
62	Damsgaard, 2008, 18492834	[4.12 (SE 0.20)]/[2.71 (SE 0.18)]/[1.50 (SE 0.09)]/[median 1.01]
63	Damsgaard, 2008, 18492834	[4.12 (SE 0.20)]/[2.71 (SE 0.18)]/[1.50 (SE 0.09)]/[median 1.01]
64	Damsgaard, 2008, 18492834	[4.12 (SE 0.20)]/[2.71 (SE 0.18)]/[1.50 (SE 0.09)]/[median 1.01]
65	Derosa, 2009, 19397392	227.5 (16.3)/149.9 (7.5)/39.7 (5.1)/189.3 (41.8)
66	Derosa, 2009, 19397392	227.5 (16.3)/149.9 (7.5)/39.7 (5.1)/189.3 (41.8)
67	Derosa, 2009, 19397392	227.5 (16.3)/149.9 (7.5)/39.7 (5.1)/189.3 (41.8)
68	Derosa, 2009, 19397392	227.5 (16.3)/149.9 (7.5)/39.7 (5.1)/189.3 (41.8)
69	Derosa, 2009, 19397392	227.5 (16.3)/149.9 (7.5)/39.7 (5.1)/189.3 (41.8)
70	Earnest, 2012, 22811376	[4.77 (0.99)]/[2.72 (0.83)]/[1.48 (0.51)]/1.25 (0.57)
71	Ebrahimi, 2009, 19593941	[5.75 (1.04)]/[3.71 (0.72)]/[1.12 (0.19)]/5.75 (1.04)
72	Ebrahimi, 2009, 19593941	[5.75 (1.04)]/[3.71 (0.72)]/[1.12 (0.19)]/5.75 (1.04)
73	Ebrahimi, 2009, 19593941	[5.75 (1.04)]/[3.71 (0.72)]/[1.12 (0.19)]/5.75 (1.04)
74	Ebrahimi, 2009, 19593941	[5.75 (1.04)]/[3.71 (0.72)]/[1.12 (0.19)]/5.75 (1.04)

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	BMI mean (SD) Kg/m2/Weight mean (SD) Kg	Baseline n-3 intake	n-3 source (Baseline)
58	Caslake, 2008, 18779276	25.2 (SE 0.19)/73.0 (SE 0.8)	EPA: 1.6 (SEM 0.04) % FA, DPA: 1.09 (0.01)% FA, DHA: 4.41 (0.07)% FA, EPA+DPA+DHA: 7.17 (0.11) % FA	plasma phosphatidylcholine fatty acid
59	Damsgaard, 2008, 18492834	23.3 (1.9)/79.3 (9.3)	nd	nd
60	Damsgaard, 2008, 18492834	23.3 (1.9)/79.3 (9.3)	nd	nd
61	Damsgaard, 2008, 18492834	23.3 (1.9)/79.3 (9.3)	nd	nd
62	Damsgaard, 2008, 18492834	23.3 (1.9)/79.3 (9.3)	nd	nd
63	Damsgaard, 2008, 18492834	23.3 (1.9)/79.3 (9.3)	nd	nd
64	Damsgaard, 2008, 18492834	23.3 (1.9)/79.3 (9.3)	nd	nd
65	Derosa, 2009, 19397392	26.0 (1.1)	nd	nd
66	Derosa, 2009, 19397392	26.0 (1.1)	nd	nd
67	Derosa, 2009, 19397392	26.0 (1.1)	nd	nd
68	Derosa, 2009, 19397392	26.0 (1.1)	nd	nd
69	Derosa, 2009, 19397392	26.0 (1.1)	nd	nd
70	Earnest, 2012, 22811376	26.3 (4.4)	nd	nd
71	Ebrahimi, 2009, 19593941	30.4 (6.1)/69.5 (14.6)	nd	nd
72	Ebrahimi, 2009, 19593941	30.4 (6.1)/69.5 (14.6)	nd	nd
73	Ebrahimi, 2009, 19593941	30.4 (6.1)/69.5 (14.6)	nd	nd
74	Ebrahimi, 2009, 19593941	30.4 (6.1)/69.5 (14.6)	nd	nd

Row	Study	n-3 type(s)	n-3 measure	Study design	Outcome
58	Caslake, 2008, 18779276	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Cross-over	Tg
59	Damsgaard, 2008, 18492834	EPA+DHA + high LA vs Placebo + high LA	g/d	Trial: Randomized Factorial Design	HDL-c
60	Damsgaard, 2008, 18492834	EPA+DHA + low LA vs Placebo + low LA	g/d	Trial: Randomized Factorial Design	HDL-c
61	Damsgaard, 2008, 18492834	EPA+DHA + high LA vs Placebo + high LA	g/d	Trial: Randomized Factorial Design	LDL-c
62	Damsgaard, 2008, 18492834	EPA+DHA + low LA vs Placebo + low LA	g/d	Trial: Randomized Factorial Design	LDL-c
63	Damsgaard, 2008, 18492834	EPA+DHA + high LA vs Placebo + high LA	g/d	Trial: Randomized Factorial Design	Tg
64	Damsgaard, 2008, 18492834	EPA+DHA + low LA vs Placebo + low LA	g/d	Trial: Randomized Factorial Design	Tg
65	Derosa, 2009, 19397392	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	HDL-c
66	Derosa, 2009, 19397392	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	LDL-c
67	Derosa, 2009, 19397392	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Tg
68	Derosa, 2009, 19397392	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	SBP
69	Derosa, 2009, 19397392	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	DBP
70	Earnest, 2012, 22811376	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Tg
71	Ebrahimi, 2009, 19593941	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	HDL-c
72	Ebrahimi, 2009, 19593941	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	LDL-c
73	Ebrahimi, 2009, 19593941	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Tg
74	Ebrahimi, 2009, 19593941	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	SBP

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Reported effect Size	Dose/intake difference	Dose-corrected effect size
58	Caslake, 2008, 18779276	-6.19 (-15.04, 2.65)	1.1	-5.627273
59	Damsgaard, 2008, 18492834	0.39 (-5.67, 6.44)	3.1	0.1258065
60	Damsgaard, 2008, 18492834	3.09 (-7.83, 14.00)	3.1	0.9967742
61	Damsgaard, 2008, 18492834	3.47 (-8.98, 15.93)	3.1	1.119355
62	Damsgaard, 2008, 18492834	5.41 (-15.10, 25.91)	3.1	1.745161
63	Damsgaard, 2008, 18492834	1.70 (nd)	3.1	0.5483871
64	Damsgaard, 2008, 18492834	43.40 (nd)	3.1	14
65	Derosa, 2009, 19397392	3.90 (2.73, 5.07)	2.4	1.625
66	Derosa, 2009, 19397392	0.70 (-0.83, 2.23)	2.4	0.2916667
67	Derosa, 2009, 19397392	-59.20 (-67.35, -51.05)	2.4	-24.66667
68	Derosa, 2009, 19397392	0 (-1.4, 1.4)	2.4	0
69	Derosa, 2009, 19397392	0.2 (-1.3, 1.7)	2.4	0.0833333
70	Earnest, 2012, 22811376	82.30 (-66.53, 231.13)	2	41.15
71	Ebrahimi, 2009, 19593941	-0.39 (-13.01, 12.23)	0.3	-1.3
72	Ebrahimi, 2009, 19593941	5.41 (-50.63, 61.44)	0.3	18.03333
73	Ebrahimi, 2009, 19593941	-7.08 (nd)	0.3	-23.6
74	Ebrahimi, 2009, 19593941	-5.3 (-13.5, 2.9)	0.3	-17.66667

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Outcome classification
58	Caslake, 2008, 18779276	Primary (power analysis)
59	Damsgaard, 2008, 18492834	Primary (implied)
60	Damsgaard, 2008, 18492834	Primary (implied)
61	Damsgaard, 2008, 18492834	Primary (implied)
62	Damsgaard, 2008, 18492834	Primary (implied)
63	Damsgaard, 2008, 18492834	Primary (implied)
64	Damsgaard, 2008, 18492834	Primary (implied)
65	Derosa, 2009, 19397392	Secondary
66	Derosa, 2009, 19397392	Secondary
67	Derosa, 2009, 19397392	Secondary
68	Derosa, 2009, 19397392	Secondary
69	Derosa, 2009, 19397392	Secondary
70	Earnest, 2012, 22811376	Secondary
71	Ebrahimi, 2009, 19593941	Secondary
72	Ebrahimi, 2009, 19593941	Secondary
73	Ebrahimi, 2009, 19593941	Secondary
74	Ebrahimi, 2009, 19593941	Secondary

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Study years (start date)	Country	Population
75	Ebrahimi, 2009, 19593941	2007 (Approx)	Iran	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
76	Einvik, 2010, 20389249	1997	Norway	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
77	Einvik, 2010, 20389249	1997	Norway	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
78	Einvik, 2010, 20389249	1997	Norway	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
79	Einvik, 2010, 20389249	1997	Norway	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
80	Einvik, 2010, 20389249	1997	Norway	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
81	Einvik, 2010, 20389249	1997	Norway	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
82	Einvik, 2010, 20389249	1997	Norway	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Risk type	Sample size (total)
75	Ebrahimi, 2009, 19593941	Diabetes and/or metabolic syndrome	89
76	Einvik, 2010, 20389249	Dyslipidemia (hypercholesterolemia (> 6.45 mmol/l))	563
77	Einvik, 2010, 20389249	Dyslipidemia (hypercholesterolemia (> 6.45 mmol/l))	563
78	Einvik, 2010, 20389249	Dyslipidemia (hypercholesterolemia (> 6.45 mmol/l))	563
79	Einvik, 2010, 20389249	Dyslipidemia (hypercholesterolemia (> 6.45 mmol/l))	563
80	Einvik, 2010, 20389249	Dyslipidemia (hypercholesterolemia (> 6.45 mmol/l))	563
81	Einvik, 2010, 20389249	Dyslipidemia (hypercholesterolemia (> 6.45 mmol/l))	563
82	Einvik, 2010, 20389249	Dyslipidemia (hypercholesterolemia (> 6.45 mmol/l))	563

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Age mean (SD) [median] years	Sex (% male)	Race
75	Ebrahimi, 2009, 19593941	52.3 (11.1)	nd	nd
76	Einvik, 2010, 20389249	69.7 (3.0)	100	nd
77	Einvik, 2010, 20389249	69.7 (3.0)	100	nd
78	Einvik, 2010, 20389249	69.7 (3.0)	100	nd
79	Einvik, 2010, 20389249	69.7 (3.0)	100	nd
80	Einvik, 2010, 20389249	69.7 (3.0)	100	nd
81	Einvik, 2010, 20389249	69.7 (3.0)	100	nd
82	Einvik, 2010, 20389249	69.7 (3.0)	100	nd

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Blood pressure SBP/DBP mmHg
75	Ebrahimi, 2009, 19593941	129.6 (19.8)/78.3 (13.4)
76	Einvik, 2010, 20389249	147 (20)/83 (11)
77	Einvik, 2010, 20389249	147 (20)/83 (11)
78	Einvik, 2010, 20389249	147 (20)/83 (11)
79	Einvik, 2010, 20389249	147 (20)/83 (11)
80	Einvik, 2010, 20389249	147 (20)/83 (11)
81	Einvik, 2010, 20389249	147 (20)/83 (11)
82	Einvik, 2010, 20389249	147 (20)/83 (11)

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Lipids: Total cholesterol/LDL/HDL/Triglycerides mean (SD) mg/dL [mmol/L]
75	Ebrahimi, 2009, 19593941	[5.75 (1.04)]/[3.71 (0.72)]/[1.12 (0.19)]/5.75 (1.04)
76	Einvik, 2010, 20389249	[6.3 (1.0)]/[4.1 (1.0)]/[1.4 (0.4)]/1.7 (0.9)
77	Einvik, 2010, 20389249	[6.3 (1.0)]/[4.1 (1.0)]/[1.4 (0.4)]/1.7 (0.9)
78	Einvik, 2010, 20389249	[6.3 (1.0)]/[4.1 (1.0)]/[1.4 (0.4)]/1.7 (0.9)
79	Einvik, 2010, 20389249	[6.3 (1.0)]/[4.1 (1.0)]/[1.4 (0.4)]/1.7 (0.9)
80	Einvik, 2010, 20389249	[6.3 (1.0)]/[4.1 (1.0)]/[1.4 (0.4)]/1.7 (0.9)
81	Einvik, 2010, 20389249	[6.3 (1.0)]/[4.1 (1.0)]/[1.4 (0.4)]/1.7 (0.9)
82	Einvik, 2010, 20389249	[6.3 (1.0)]/[4.1 (1.0)]/[1.4 (0.4)]/1.7 (0.9)

Row	Study	BMI mean (SD) Kg/m2/Weight mean (SD) Kg	Baseline n-3 intake	n-3 source (Baseline)
75	Ebrahimi, 2009, 19593941	30.4 (6.1)/69.5 (14.6)	nd	nd
76	Einvik, 2010, 20389249	26.7 (3.7)	ALA: 0.59 (0.20)% FA, EPA: 2.18 (1.7)% FA, DHA: 2.98 (1.2)% FA, Total n-3 FA: 6.0 (3.0)% FA	serum
77	Einvik, 2010, 20389249	26.7 (3.7)	ALA: 0.59 (0.20)% FA, EPA: 2.18 (1.7)% FA, DHA: 2.98 (1.2)% FA, Total n-3 FA: 6.0 (3.0)% FA	serum
78	Einvik, 2010, 20389249	26.7 (3.7)	ALA: 0.59 (0.20)% FA, EPA: 2.18 (1.7)% FA, DHA: 2.98 (1.2)% FA, Total n-3 FA: 6.0 (3.0)% FA	serum
79	Einvik, 2010, 20389249	26.7 (3.7)	ALA: 0.59 (0.20)% FA, EPA: 2.18 (1.7)% FA, DHA: 2.98 (1.2)% FA, Total n-3 FA: 6.0 (3.0)% FA	serum
80	Einvik, 2010, 20389249	26.7 (3.7)	ALA: 0.59 (0.20)% FA, EPA: 2.18 (1.7)% FA, DHA: 2.98 (1.2)% FA, Total n-3 FA: 6.0 (3.0)% FA	serum
81	Einvik, 2010, 20389249	26.7 (3.7)	ALA: 0.59 (0.20)% FA, EPA: 2.18 (1.7)% FA, DHA: 2.98 (1.2)% FA, Total n-3 FA: 6.0 (3.0)% FA	serum
82	Einvik, 2010, 20389249	26.7 (3.7)	ALA: 0.59 (0.20)% FA, EPA: 2.18 (1.7)% FA, DHA: 2.98 (1.2)% FA, Total n-3 FA: 6.0 (3.0)% FA	serum

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	n-3 type(s)	n-3 measure	Study design	Outcome
75	Ebrahimi, 2009, 19593941	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	DBP
76	Einvik, 2010, 20389249	EPA+DHA vs Placebo	g/d	Trial: Randomized Factorial Design	Death, all cause
77	Einvik, 2010, 20389249	EPA+DHA + diet intervention vs placebo (Corn oil))	g/d	Trial: Randomized Factorial Design	Death, CVD (total)
78	Einvik, 2010, 20389249	EPA+DHA + diet intervention vs Placebo + diet intervention	g/d	Trial: Randomized Factorial Design	MACE
79	Einvik, 2010, 20389249	EPA+DHA +/- diet intervention vs Placebo +/- diet intervention	g/d	Trial: Randomized Factorial Design	MACE
80	Einvik, 2010, 20389249	EPA+DHA vs Placebo	g/d	Trial: Randomized Factorial Design	Total:HDL-c ratio
81	Einvik, 2010, 20389249	EPA+DHA + diet intervention vs Placebo + diet intervention	g/d	Trial: Randomized Factorial Design	Total:HDL-c ratio
82	Einvik, 2010, 20389249	EPA+DHA vs Placebo	g/d	Trial: Randomized Factorial Design	HDL-c

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Reported effect Size	Dose/intake difference	Dose-corrected effect size
75	Ebrahimi, 2009, 19593941	-4.5 (-9, 0)	0.18	-25
76	Einvik, 2010, 20389249	Adj HR 0.53 (0.27, 1.04)	4.41	0.8659195
77	Einvik, 2010, 20389249	OR 0.62 (0.24, 1.64)	2.02	0.7892664
78	Einvik, 2010, 20389249	HR 0.89 (0.55, 1.44)	2.4	0.9526042
79	Einvik, 2010, 20389249	OR 1.00 (0.56, 1.78)	2.4	1
80	Einvik, 2010, 20389249	-0.3 (-0.8, 0.2)	2.4	-0.125
81	Einvik, 2010, 20389249	-0.3 (-0.7, 0.1)	2.4	-0.125
82	Einvik, 2010, 20389249	2.70 (-2.45, 7.85)	2.4	1.125

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Outcome classification
75	Ebrahimi, 2009, 19593941	Secondary
76	Einvik, 2010, 20389249	Secondary
77	Einvik, 2010, 20389249	Secondary
78	Einvik, 2010, 20389249	Secondary
79	Einvik, 2010, 20389249	Secondary
80	Einvik, 2010, 20389249	Secondary
81	Einvik, 2010, 20389249	Secondary
82	Einvik, 2010, 20389249	Secondary

Row	Study	Study years (start date)	Country	Population
83	Einvik, 2010, 20389249	1997	Norway	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
84	Einvik, 2010, 20389249	1997	Norway	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
85	Einvik, 2010, 20389249	1997	Norway	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
86	Einvik, 2010, 20389249	1997	Norway	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
87	Einvik, 2010, 20389249	1997	Norway	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
88	Eritsland, 1996, 8540453	1989	Norway	Secondary Prevention (history of CVD event)
89	Eritsland, 1996, 8540453	1989	Norway	Secondary Prevention (history of CVD event)
90	Eritsland, 1996, 8540453	1989	Norway	Secondary Prevention (history of CVD event)
91	Eritsland, 1996, 8540453	1989	Norway	Secondary Prevention (history of CVD event)
92	Finnegan, 2003, 12663273	1998	UK	Primary Prevention, Healthy
93	Finnegan, 2003, 12663273	1998	UK	Primary Prevention, Healthy

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Risk type	Sample size (total)
83	Einvik, 2010, 20389249	Dyslipidemia (hypercholesterolemia (> 6.45 mmol/l))	563
84	Einvik, 2010, 20389249	Dyslipidemia (hypercholesterolemia (> 6.45 mmol/l))	563
85	Einvik, 2010, 20389249	Dyslipidemia (hypercholesterolemia (> 6.45 mmol/l))	563
86	Einvik, 2010, 20389249	Dyslipidemia (hypercholesterolemia (> 6.45 mmol/l))	563
87	Einvik, 2010, 20389249	Dyslipidemia (hypercholesterolemia (> 6.45 mmol/l))	563
88	Eritsland, 1996, 8540453	Cardiac disease (coronary artery bypass grafting without concomitant cardiac surgery)	511
89	Eritsland, 1996, 8540453	Cardiac disease (coronary artery bypass grafting without concomitant cardiac surgery)	511
90	Eritsland, 1996, 8540453	Cardiac disease (coronary artery bypass grafting without concomitant cardiac surgery)	511
91	Eritsland, 1996, 8540453	Cardiac disease (coronary artery bypass grafting without concomitant cardiac surgery)	511
92	Finnegan, 2003, 12663273	Dyslipidemia	119
93	Finnegan, 2003, 12663273	Dyslipidemia	119

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Age mean (SD) [median] years	Sex (% male)	Race
83	Einvik, 2010, 20389249	69.7 (3.0)	100	nd
84	Einvik, 2010, 20389249	69.7 (3.0)	100	nd
85	Einvik, 2010, 20389249	69.7 (3.0)	100	nd
86	Einvik, 2010, 20389249	69.7 (3.0)	100	nd
87	Einvik, 2010, 20389249	69.7 (3.0)	100	nd
88	Eritsland, 1996, 8540453	59.4 (8.8)	87.6	nd
89	Eritsland, 1996, 8540453	59.4 (8.8)	87.6	nd
90	Eritsland, 1996, 8540453	59.4 (8.8)	87.6	nd
91	Eritsland, 1996, 8540453	59.4 (8.8)	87.6	nd
92	Finnegan, 2003, 12663273	55 (SE 2)	60	nd
93	Finnegan, 2003, 12663273	55 (SE 2)	60	nd

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Blood pressure SBP/DBP mmHg
83	Einvik, 2010, 20389249	147 (20)/83 (11)
84	Einvik, 2010, 20389249	147 (20)/83 (11)
85	Einvik, 2010, 20389249	147 (20)/83 (11)
86	Einvik, 2010, 20389249	147 (20)/83 (11)
87	Einvik, 2010, 20389249	147 (20)/83 (11)
88	Eritsland, 1996, 8540453	146/88
89	Eritsland, 1996, 8540453	146/88
90	Eritsland, 1996, 8540453	146/88
91	Eritsland, 1996, 8540453	146/88
92	Finnegan, 2003, 12663273	123.2 (SE 3.7)/76 (SE 1.6)
93	Finnegan, 2003, 12663273	123.2 (SE 3.7)/76 (SE 1.6)

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Lipids: Total cholesterol/LDL/HDL/Triglycerides mean (SD) mg/dL [mmol/L]
83	Einvik, 2010, 20389249	[6.3 (1.0)]/[4.1 (1.0)]/[1.4 (0.4)]/1.7 (0.9)
84	Einvik, 2010, 20389249	[6.3 (1.0)]/[4.1 (1.0)]/[1.4 (0.4)]/1.7 (0.9)
85	Einvik, 2010, 20389249	[6.3 (1.0)]/[4.1 (1.0)]/[1.4 (0.4)]/1.7 (0.9)
86	Einvik, 2010, 20389249	[6.3 (1.0)]/[4.1 (1.0)]/[1.4 (0.4)]/1.7 (0.9)
87	Einvik, 2010, 20389249	[6.3 (1.0)]/[4.1 (1.0)]/[1.4 (0.4)]/1.7 (0.9)
88	Eritsland, 1996, 8540453	[6.55 (1.16)]/[4.61 (1.09)]/[1.00 (0.27)]/2.09 (1.07)
89	Eritsland, 1996, 8540453	[6.55 (1.16)]/[4.61 (1.09)]/[1.00 (0.27)]/2.09 (1.07)
90	Eritsland, 1996, 8540453	[6.55 (1.16)]/[4.61 (1.09)]/[1.00 (0.27)]/2.09 (1.07)
91	Eritsland, 1996, 8540453	[6.55 (1.16)]/[4.61 (1.09)]/[1.00 (0.27)]/2.09 (1.07)
92	Finnegan, 2003, 12663273	[5.8 (SE 0.17)]/[3.63 (SE 0.16)]/[1.35 (SE 0.06)]/[1.69 (SE 0.11)]
93	Finnegan, 2003, 12663273	[5.8 (SE 0.17)]/[3.63 (SE 0.16)]/[1.35 (SE 0.06)]/[1.69 (SE 0.11)]

Row	Study	BMI mean (SD) Kg/m2/Weight mean (SD) Kg	Baseline n-3 intake	n-3 source (Baseline)
83	Einvik, 2010, 20389249	26.7 (3.7)	ALA: 0.59 (0.20)% FA, EPA: 2.18 (1.7)% FA, DHA: 2.98 (1.2)% FA, Total n-3 FA: 6.0 (3.0)% FA	serum
84	Einvik, 2010, 20389249	26.7 (3.7)	ALA: 0.59 (0.20)% FA, EPA: 2.18 (1.7)% FA, DHA: 2.98 (1.2)% FA, Total n-3 FA: 6.0 (3.0)% FA	serum
85	Einvik, 2010, 20389249	26.7 (3.7)	ALA: 0.59 (0.20)% FA, EPA: 2.18 (1.7)% FA, DHA: 2.98 (1.2)% FA, Total n-3 FA: 6.0 (3.0)% FA	serum
86	Einvik, 2010, 20389249	26.7 (3.7)	ALA: 0.59 (0.20)% FA, EPA: 2.18 (1.7)% FA, DHA: 2.98 (1.2)% FA, Total n-3 FA: 6.0 (3.0)% FA	serum
87	Einvik, 2010, 20389249	26.7 (3.7)	ALA: 0.59 (0.20)% FA, EPA: 2.18 (1.7)% FA, DHA: 2.98 (1.2)% FA, Total n-3 FA: 6.0 (3.0)% FA	serum
88	Eritsland, 1996, 8540453	25.5 (2.8)	EPA: 33.5 (19.9) mg/L, DHA: 111.4 (30.8) mg/L, Total n-3 FA: 170.3 (51.4) mg/L	serum
89	Eritsland, 1996, 8540453	25.5 (2.8)	EPA: 33.5 (19.9) mg/L, DHA: 111.4 (30.8) mg/L, Total n-3 FA: 170.3 (51.4) mg/L	serum
90	Eritsland, 1996, 8540453	25.5 (2.8)	EPA: 33.5 (19.9) mg/L, DHA: 111.4 (30.8) mg/L, Total n-3 FA: 170.3 (51.4) mg/L	serum
91	Eritsland, 1996, 8540453	25.5 (2.8)	EPA: 33.5 (19.9) mg/L, DHA: 111.4 (30.8) mg/L, Total n-3 FA: 170.3 (51.4) mg/L	serum
92	Finnegan, 2003, 12663273	25.8 (SE 0.6)	nd	nd
93	Finnegan, 2003, 12663273	25.8 (SE 0.6)	nd	nd

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	n-3 type(s)	n-3 measure	Study design	Outcome
83	Einvik, 2010, 20389249	EPA+DHA vs Placebo	g/d	Trial: Randomized Factorial Design	Tg
84	Einvik, 2010, 20389249	EPA+DHA (no diet intervention) vs Placebo (no diet intervention)	g/d	Trial: Randomized Factorial Design	SBP
85	Einvik, 2010, 20389249	EPA+DHA (diet intervention) vs Placebo (diet intervention)	g/d	Trial: Randomized Factorial Design	SBP
86	Einvik, 2010, 20389249	EPA+DHA (no diet intervention) vs Placebo (no diet intervention)	% FA	Trial: Randomized Factorial Design	DBP
87	Einvik, 2010, 20389249	EPA+DHA (diet intervention) vs Placebo (diet intervention)	g/d	Trial: Randomized Factorial Design	DBP
88	Eritsland, 1996, 8540453	EPA+DHA vs Placebo	mg/L	Trial: Randomized Factorial Design	Death, all cause
89	Eritsland, 1996, 8540453	EPA+DHA vs Placebo	g/d	Trial: Randomized Factorial Design	HDL-c
90	Eritsland, 1996, 8540453	EPA+DHA vs Placebo	g/d	Trial: Randomized Factorial Design	LDL-c
91	Eritsland, 1996, 8540453	EPA+DHA vs Placebo	g/d	Trial: Randomized Factorial Design	Tg
92	Finnegan, 2003, 12663273	ALA vs Placebo	g/d	Trial: Randomized Parallel	HDL-c
93	Finnegan, 2003, 12663273	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	HDL-c

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Reported effect Size	Dose/intake difference	Dose-corrected effect size
83	Einvik, 2010, 20389249	-15.04 (-41.14, 11.06)	2.4	-6.266667
84	Einvik, 2010, 20389249	1 (-5.4, 7.4)	2.4	0.4166667
85	Einvik, 2010, 20389249	3 (-3.5, 9.5)	2.4	1.25
86	Einvik, 2010, 20389249	0 (-3.9, 3.9)	4.41	0
87	Einvik, 2010, 20389249	-1.1 (-5, 3)	4.41	-0.2494331
88	Eritsland, 1996, 8540453	OR 1.24 (0.42, 3.61)	3.32	1.066938
89	Eritsland, 1996, 8540453	0.77 (-4.62, 6.16)	3.4	0.2264706
90	Eritsland, 1996, 8540453	4.00 (-3.83, 11.83)	3.4	1.176471
91	Eritsland, 1996, 8540453	-32.00 (-49.61, -14.39)	3.4	-9.411765
92	Finnegan, 2003, 12663273	0.77 (-5.42, 6.97)	4.5	0.1711111
93	Finnegan, 2003, 12663273	3.09 (-3.68, 9.86)	0.8	3.8625

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Outcome classification
83	Einvik, 2010, 20389249	Secondary
84	Einvik, 2010, 20389249	Secondary
85	Einvik, 2010, 20389249	Secondary
86	Einvik, 2010, 20389249	Secondary
87	Einvik, 2010, 20389249	Secondary
88	Eritsland, 1996, 8540453	Secondary; Primary in registry record (NCT01422317)
89	Eritsland, 1996, 8540453	Secondary
90	Eritsland, 1996, 8540453	Secondary
91	Eritsland, 1996, 8540453	Secondary
92	Finnegan, 2003, 12663273	Secondary
93	Finnegan, 2003, 12663273	Secondary

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Study years (start date)	Country	Population
94	Finnegan, 2003, 12663273	1998	UK	Primary Prevention, Healthy
95	Finnegan, 2003, 12663273	1998	UK	Primary Prevention, Healthy
96	Finnegan, 2003, 12663273	1998	UK	Primary Prevention, Healthy
97	Finnegan, 2003, 12663273	1998	UK	Primary Prevention, Healthy
98	Finnegan, 2003, 12663273	1998	UK	Primary Prevention, Healthy
99	Finnegan, 2003, 12663273	1998	UK	Primary Prevention, Healthy
100	Finnegan, 2003, 12663273	1998	UK	Primary Prevention, Healthy
101	Finnegan, 2003, 12663273	1998	UK	Primary Prevention, Healthy
102	Finnegan, 2003, 12663273	1998	UK	Primary Prevention, Healthy
103	Finnegan, 2003, 12663273	1998	UK	Primary Prevention, Healthy
104	Finnegan, 2003, 12663273	1998	UK	Primary Prevention, Healthy
105	Finnegan, 2003, 12663273	1998	UK	Primary Prevention, Healthy
106	Finnegan, 2003, 12663273	1998	UK	Primary Prevention, Healthy
107	Finnegan, 2003, 12663273	1998	UK	Primary Prevention, Healthy
108	Finnegan, 2003, 12663273	1998	UK	Primary Prevention, Healthy
109	Finnegan, 2003, 12663273	1998	UK	Primary Prevention, Healthy
110	Finnegan, 2003, 12663273	1998	UK	Primary Prevention, Healthy
111	Finnegan, 2003, 12663273	1998	UK	Primary Prevention, Healthy
112	Finnegan, 2003, 12663273	1998	UK	Primary Prevention, Healthy
113	Finnegan, 2003, 12663273	1998	UK	Primary Prevention, Healthy
114	Finnegan, 2003, 12663273	1998	UK	Primary Prevention, Healthy
115	Finnegan, 2003, 12663273	1998	UK	Primary Prevention, Healthy
116	Finnegan, 2003, 12663273	1998	UK	Primary Prevention, Healthy
117	Finnegan, 2003, 12663273	1998	UK	Primary Prevention, Healthy
118	Finnegan, 2003, 12663273	1998	UK	Primary Prevention, Healthy
119	Finnegan, 2003, 12663273	1998	UK	Primary Prevention, Healthy
120	Finnegan, 2003, 12663273	1998	UK	Primary Prevention, Healthy
121	Finnegan, 2003, 12663273	1998	UK	Primary Prevention, Healthy
122	Finnegan, 2003, 12663273	1998	UK	Primary Prevention, Healthy
123	Finnegan, 2003, 12663273	1998	UK	Primary Prevention, Healthy
124	Finnegan, 2003, 12663273	1998	UK	Primary Prevention, Healthy
125	Finnegan, 2003, 12663273	1998	UK	Primary Prevention, Healthy
126	Finnegan, 2003, 12663273	1998	UK	Primary Prevention, Healthy
127	Finnegan, 2003, 12663273	1998	UK	Primary Prevention, Healthy

Row	Study	Risk type	Sample size (total)
94	Finnegan, 2003, 12663273	Dyslipidemia	119
95	Finnegan, 2003, 12663273	Dyslipidemia	119
96	Finnegan, 2003, 12663273	Dyslipidemia	119
97	Finnegan, 2003, 12663273	Dyslipidemia	119
98	Finnegan, 2003, 12663273	Dyslipidemia	119
99	Finnegan, 2003, 12663273	Dyslipidemia	119
100	Finnegan, 2003, 12663273	Dyslipidemia	119
101	Finnegan, 2003, 12663273	Dyslipidemia	119
102	Finnegan, 2003, 12663273	Dyslipidemia	119
103	Finnegan, 2003, 12663273	Dyslipidemia	119
104	Finnegan, 2003, 12663273	Dyslipidemia	119
105	Finnegan, 2003, 12663273	Dyslipidemia	119
106	Finnegan, 2003, 12663273	Dyslipidemia	119
107	Finnegan, 2003, 12663273	Dyslipidemia	119
108	Finnegan, 2003, 12663273	Dyslipidemia	119
109	Finnegan, 2003, 12663273	Dyslipidemia	119
110	Finnegan, 2003, 12663273	Dyslipidemia	119
111	Finnegan, 2003, 12663273	Dyslipidemia	119
112	Finnegan, 2003, 12663273	Dyslipidemia	119
113	Finnegan, 2003, 12663273	Dyslipidemia	119
114	Finnegan, 2003, 12663273	Dyslipidemia	119
115	Finnegan, 2003, 12663273	Dyslipidemia	119
116	Finnegan, 2003, 12663273	Dyslipidemia	119
117	Finnegan, 2003, 12663273	Dyslipidemia	119
118	Finnegan, 2003, 12663273	Dyslipidemia	119
119	Finnegan, 2003, 12663273	Dyslipidemia	119
120	Finnegan, 2003, 12663273	Dyslipidemia	119
121	Finnegan, 2003, 12663273	Dyslipidemia	119
122	Finnegan, 2003, 12663273	Dyslipidemia	119
123	Finnegan, 2003, 12663273	Dyslipidemia	119
124	Finnegan, 2003, 12663273	Dyslipidemia	119
125	Finnegan, 2003, 12663273	Dyslipidemia	119
126	Finnegan, 2003, 12663273	Dyslipidemia	119
127	Finnegan, 2003, 12663273	Dyslipidemia	119

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Age mean (SD) [median] years	Sex (% male)	Race
94	Finnegan, 2003, 12663273	55 (SE 2)	60	nd
95	Finnegan, 2003, 12663273	55 (SE 2)	60	nd
96	Finnegan, 2003, 12663273	55 (SE 2)	60	nd
97	Finnegan, 2003, 12663273	55 (SE 2)	60	nd
98	Finnegan, 2003, 12663273	55 (SE 2)	60	nd
99	Finnegan, 2003, 12663273	55 (SE 2)	60	nd
100	Finnegan, 2003, 12663273	55 (SE 2)	60	nd
101	Finnegan, 2003, 12663273	55 (SE 2)	60	nd
102	Finnegan, 2003, 12663273	55 (SE 2)	60	nd
103	Finnegan, 2003, 12663273	55 (SE 2)	60	nd
104	Finnegan, 2003, 12663273	55 (SE 2)	60	nd
105	Finnegan, 2003, 12663273	55 (SE 2)	60	nd
106	Finnegan, 2003, 12663273	55 (SE 2)	60	nd
107	Finnegan, 2003, 12663273	55 (SE 2)	60	nd
108	Finnegan, 2003, 12663273	55 (SE 2)	60	nd
109	Finnegan, 2003, 12663273	55 (SE 2)	60	nd
110	Finnegan, 2003, 12663273	55 (SE 2)	60	nd
111	Finnegan, 2003, 12663273	55 (SE 2)	60	nd
112	Finnegan, 2003, 12663273	55 (SE 2)	60	nd
113	Finnegan, 2003, 12663273	55 (SE 2)	60	nd
114	Finnegan, 2003, 12663273	55 (SE 2)	60	nd
115	Finnegan, 2003, 12663273	55 (SE 2)	60	nd
116	Finnegan, 2003, 12663273	55 (SE 2)	60	nd
117	Finnegan, 2003, 12663273	55 (SE 2)	60	nd
118	Finnegan, 2003, 12663273	55 (SE 2)	60	nd
119	Finnegan, 2003, 12663273	55 (SE 2)	60	nd
120	Finnegan, 2003, 12663273	55 (SE 2)	60	nd
121	Finnegan, 2003, 12663273	55 (SE 2)	60	nd
122	Finnegan, 2003, 12663273	55 (SE 2)	60	nd
123	Finnegan, 2003, 12663273	55 (SE 2)	60	nd
124	Finnegan, 2003, 12663273	55 (SE 2)	60	nd
125	Finnegan, 2003, 12663273	55 (SE 2)	60	nd
126	Finnegan, 2003, 12663273	55 (SE 2)	60	nd
127	Finnegan, 2003, 12663273	55 (SE 2)	60	nd

Row	Study	Blood pressure SBP/DBP mmHg
94	Finnegan, 2003, 12663273	123.2 (SE 3.7)/76 (SE 1.6)
95	Finnegan, 2003, 12663273	123.2 (SE 3.7)/76 (SE 1.6)
96	Finnegan, 2003, 12663273	123.2 (SE 3.7)/76 (SE 1.6)
97	Finnegan, 2003, 12663273	123.2 (SE 3.7)/76 (SE 1.6)
98	Finnegan, 2003, 12663273	123.2 (SE 3.7)/76 (SE 1.6)
99	Finnegan, 2003, 12663273	123.2 (SE 3.7)/76 (SE 1.6)
100	Finnegan, 2003, 12663273	123.2 (SE 3.7)/76 (SE 1.6)
101	Finnegan, 2003, 12663273	123.2 (SE 3.7)/76 (SE 1.6)
102	Finnegan, 2003, 12663273	123.2 (SE 3.7)/76 (SE 1.6)
103	Finnegan, 2003, 12663273	123.2 (SE 3.7)/76 (SE 1.6)
104	Finnegan, 2003, 12663273	123.2 (SE 3.7)/76 (SE 1.6)
105	Finnegan, 2003, 12663273	123.2 (SE 3.7)/76 (SE 1.6)
106	Finnegan, 2003, 12663273	123.2 (SE 3.7)/76 (SE 1.6)
107	Finnegan, 2003, 12663273	123.2 (SE 3.7)/76 (SE 1.6)
108	Finnegan, 2003, 12663273	123.2 (SE 3.7)/76 (SE 1.6)
109	Finnegan, 2003, 12663273	123.2 (SE 3.7)/76 (SE 1.6)
110	Finnegan, 2003, 12663273	123.2 (SE 3.7)/76 (SE 1.6)
111	Finnegan, 2003, 12663273	123.2 (SE 3.7)/76 (SE 1.6)
112	Finnegan, 2003, 12663273	123.2 (SE 3.7)/76 (SE 1.6)
113	Finnegan, 2003, 12663273	123.2 (SE 3.7)/76 (SE 1.6)
114	Finnegan, 2003, 12663273	123.2 (SE 3.7)/76 (SE 1.6)
115	Finnegan, 2003, 12663273	123.2 (SE 3.7)/76 (SE 1.6)
116	Finnegan, 2003, 12663273	123.2 (SE 3.7)/76 (SE 1.6)
117	Finnegan, 2003, 12663273	123.2 (SE 3.7)/76 (SE 1.6)
118	Finnegan, 2003, 12663273	123.2 (SE 3.7)/76 (SE 1.6)
119	Finnegan, 2003, 12663273	123.2 (SE 3.7)/76 (SE 1.6)
120	Finnegan, 2003, 12663273	123.2 (SE 3.7)/76 (SE 1.6)
121	Finnegan, 2003, 12663273	123.2 (SE 3.7)/76 (SE 1.6)
122	Finnegan, 2003, 12663273	123.2 (SE 3.7)/76 (SE 1.6)
123	Finnegan, 2003, 12663273	123.2 (SE 3.7)/76 (SE 1.6)
124	Finnegan, 2003, 12663273	123.2 (SE 3.7)/76 (SE 1.6)
125	Finnegan, 2003, 12663273	123.2 (SE 3.7)/76 (SE 1.6)
126	Finnegan, 2003, 12663273	123.2 (SE 3.7)/76 (SE 1.6)
127	Finnegan, 2003, 12663273	123.2 (SE 3.7)/76 (SE 1.6)

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Lipids: Total cholesterol/LDL/HDL/Triglycerides mean (SD) mg/dL [mmol/L]
94	Finnegan, 2003, 12663273	[5.8 (SE 0.17)]/[3.63 (SE 0.16)]/[1.35 (SE 0.06)]/[1.69 (SE 0.11)]
95	Finnegan, 2003, 12663273	[5.8 (SE 0.17)]/[3.63 (SE 0.16)]/[1.35 (SE 0.06)]/[1.69 (SE 0.11)]
96	Finnegan, 2003, 12663273	[5.8 (SE 0.17)]/[3.63 (SE 0.16)]/[1.35 (SE 0.06)]/[1.69 (SE 0.11)]
97	Finnegan, 2003, 12663273	[5.8 (SE 0.17)]/[3.63 (SE 0.16)]/[1.35 (SE 0.06)]/[1.69 (SE 0.11)]
98	Finnegan, 2003, 12663273	[5.8 (SE 0.17)]/[3.63 (SE 0.16)]/[1.35 (SE 0.06)]/[1.69 (SE 0.11)]
99	Finnegan, 2003, 12663273	[5.8 (SE 0.17)]/[3.63 (SE 0.16)]/[1.35 (SE 0.06)]/[1.69 (SE 0.11)]
100	Finnegan, 2003, 12663273	[5.8 (SE 0.17)]/[3.63 (SE 0.16)]/[1.35 (SE 0.06)]/[1.69 (SE 0.11)]
101	Finnegan, 2003, 12663273	[5.8 (SE 0.17)]/[3.63 (SE 0.16)]/[1.35 (SE 0.06)]/[1.69 (SE 0.11)]
102	Finnegan, 2003, 12663273	[5.8 (SE 0.17)]/[3.63 (SE 0.16)]/[1.35 (SE 0.06)]/[1.69 (SE 0.11)]
103	Finnegan, 2003, 12663273	[5.8 (SE 0.17)]/[3.63 (SE 0.16)]/[1.35 (SE 0.06)]/[1.69 (SE 0.11)]
104	Finnegan, 2003, 12663273	[5.8 (SE 0.17)]/[3.63 (SE 0.16)]/[1.35 (SE 0.06)]/[1.69 (SE 0.11)]
105	Finnegan, 2003, 12663273	[5.8 (SE 0.17)]/[3.63 (SE 0.16)]/[1.35 (SE 0.06)]/[1.69 (SE 0.11)]
106	Finnegan, 2003, 12663273	[5.8 (SE 0.17)]/[3.63 (SE 0.16)]/[1.35 (SE 0.06)]/[1.69 (SE 0.11)]
107	Finnegan, 2003, 12663273	[5.8 (SE 0.17)]/[3.63 (SE 0.16)]/[1.35 (SE 0.06)]/[1.69 (SE 0.11)]
108	Finnegan, 2003, 12663273	[5.8 (SE 0.17)]/[3.63 (SE 0.16)]/[1.35 (SE 0.06)]/[1.69 (SE 0.11)]
109	Finnegan, 2003, 12663273	[5.8 (SE 0.17)]/[3.63 (SE 0.16)]/[1.35 (SE 0.06)]/[1.69 (SE 0.11)]
110	Finnegan, 2003, 12663273	[5.8 (SE 0.17)]/[3.63 (SE 0.16)]/[1.35 (SE 0.06)]/[1.69 (SE 0.11)]
111	Finnegan, 2003, 12663273	[5.8 (SE 0.17)]/[3.63 (SE 0.16)]/[1.35 (SE 0.06)]/[1.69 (SE 0.11)]
112	Finnegan, 2003, 12663273	[5.8 (SE 0.17)]/[3.63 (SE 0.16)]/[1.35 (SE 0.06)]/[1.69 (SE 0.11)]
113	Finnegan, 2003, 12663273	[5.8 (SE 0.17)]/[3.63 (SE 0.16)]/[1.35 (SE 0.06)]/[1.69 (SE 0.11)]
114	Finnegan, 2003, 12663273	[5.8 (SE 0.17)]/[3.63 (SE 0.16)]/[1.35 (SE 0.06)]/[1.69 (SE 0.11)]
115	Finnegan, 2003, 12663273	[5.8 (SE 0.17)]/[3.63 (SE 0.16)]/[1.35 (SE 0.06)]/[1.69 (SE 0.11)]
116	Finnegan, 2003, 12663273	[5.8 (SE 0.17)]/[3.63 (SE 0.16)]/[1.35 (SE 0.06)]/[1.69 (SE 0.11)]
117	Finnegan, 2003, 12663273	[5.8 (SE 0.17)]/[3.63 (SE 0.16)]/[1.35 (SE 0.06)]/[1.69 (SE 0.11)]
118	Finnegan, 2003, 12663273	[5.8 (SE 0.17)]/[3.63 (SE 0.16)]/[1.35 (SE 0.06)]/[1.69 (SE 0.11)]
119	Finnegan, 2003, 12663273	[5.8 (SE 0.17)]/[3.63 (SE 0.16)]/[1.35 (SE 0.06)]/[1.69 (SE 0.11)]
120	Finnegan, 2003, 12663273	[5.8 (SE 0.17)]/[3.63 (SE 0.16)]/[1.35 (SE 0.06)]/[1.69 (SE 0.11)]
121	Finnegan, 2003, 12663273	[5.8 (SE 0.17)]/[3.63 (SE 0.16)]/[1.35 (SE 0.06)]/[1.69 (SE 0.11)]
122	Finnegan, 2003, 12663273	[5.8 (SE 0.17)]/[3.63 (SE 0.16)]/[1.35 (SE 0.06)]/[1.69 (SE 0.11)]
123	Finnegan, 2003, 12663273	[5.8 (SE 0.17)]/[3.63 (SE 0.16)]/[1.35 (SE 0.06)]/[1.69 (SE 0.11)]
124	Finnegan, 2003, 12663273	[5.8 (SE 0.17)]/[3.63 (SE 0.16)]/[1.35 (SE 0.06)]/[1.69 (SE 0.11)]
125	Finnegan, 2003, 12663273	[5.8 (SE 0.17)]/[3.63 (SE 0.16)]/[1.35 (SE 0.06)]/[1.69 (SE 0.11)]
126	Finnegan, 2003, 12663273	[5.8 (SE 0.17)]/[3.63 (SE 0.16)]/[1.35 (SE 0.06)]/[1.69 (SE 0.11)]
127	Finnegan, 2003, 12663273	[5.8 (SE 0.17)]/[3.63 (SE 0.16)]/[1.35 (SE 0.06)]/[1.69 (SE 0.11)]

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	BMI mean (SD) Kg/m2/Weight mean (SD) Kg	Baseline n-3 intake	n-3 source (Baseline)
94	Finnegan, 2003, 12663273	25.8 (SE 0.6)	nd	nd
95	Finnegan, 2003, 12663273	25.8 (SE 0.6)	nd	nd
96	Finnegan, 2003, 12663273	25.8 (SE 0.6)	nd	nd
97	Finnegan, 2003, 12663273	25.8 (SE 0.6)	nd	nd
98	Finnegan, 2003, 12663273	25.8 (SE 0.6)	nd	nd
99	Finnegan, 2003, 12663273	25.8 (SE 0.6)	nd	nd
100	Finnegan, 2003, 12663273	25.8 (SE 0.6)	nd	nd
101	Finnegan, 2003, 12663273	25.8 (SE 0.6)	nd	nd
102	Finnegan, 2003, 12663273	25.8 (SE 0.6)	nd	nd
103	Finnegan, 2003, 12663273	25.8 (SE 0.6)	nd	nd
104	Finnegan, 2003, 12663273	25.8 (SE 0.6)	nd	nd
105	Finnegan, 2003, 12663273	25.8 (SE 0.6)	nd	nd
106	Finnegan, 2003, 12663273	25.8 (SE 0.6)	nd	nd
107	Finnegan, 2003, 12663273	25.8 (SE 0.6)	nd	nd
108	Finnegan, 2003, 12663273	25.8 (SE 0.6)	nd	nd
109	Finnegan, 2003, 12663273	25.8 (SE 0.6)	nd	nd
110	Finnegan, 2003, 12663273	25.8 (SE 0.6)	nd	nd
111	Finnegan, 2003, 12663273	25.8 (SE 0.6)	nd	nd
112	Finnegan, 2003, 12663273	25.8 (SE 0.6)	nd	nd
113	Finnegan, 2003, 12663273	25.8 (SE 0.6)	nd	nd
114	Finnegan, 2003, 12663273	25.8 (SE 0.6)	nd	nd
115	Finnegan, 2003, 12663273	25.8 (SE 0.6)	nd	nd
116	Finnegan, 2003, 12663273	25.8 (SE 0.6)	nd	nd
117	Finnegan, 2003, 12663273	25.8 (SE 0.6)	nd	nd
118	Finnegan, 2003, 12663273	25.8 (SE 0.6)	nd	nd
119	Finnegan, 2003, 12663273	25.8 (SE 0.6)	nd	nd
120	Finnegan, 2003, 12663273	25.8 (SE 0.6)	nd	nd
121	Finnegan, 2003, 12663273	25.8 (SE 0.6)	nd	nd
122	Finnegan, 2003, 12663273	25.8 (SE 0.6)	nd	nd
123	Finnegan, 2003, 12663273	25.8 (SE 0.6)	nd	nd
124	Finnegan, 2003, 12663273	25.8 (SE 0.6)	nd	nd
125	Finnegan, 2003, 12663273	25.8 (SE 0.6)	nd	nd
126	Finnegan, 2003, 12663273	25.8 (SE 0.6)	nd	nd
127	Finnegan, 2003, 12663273	25.8 (SE 0.6)	nd	nd

Row	Study	n-3 type(s)	n-3 measure	Study design	Outcome
94	Finnegan, 2003, 12663273	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	HDL-c
95	Finnegan, 2003, 12663273	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Parallel	HDL-c
96	Finnegan, 2003, 12663273	EPA+DHA vs ALA	g/d	Trial: Randomized Parallel	HDL-c
97	Finnegan, 2003, 12663273	EPA+DHA vs ALA	g/d	Trial: Randomized Parallel	HDL-c
98	Finnegan, 2003, 12663273	ALA vs Placebo	g/d	Trial: Randomized Parallel	LDL-c
99	Finnegan, 2003, 12663273	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	LDL-c
100	Finnegan, 2003, 12663273	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	LDL-c
101	Finnegan, 2003, 12663273	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Parallel	LDL-c
102	Finnegan, 2003, 12663273	EPA+DHA vs ALA	g/d	Trial: Randomized Parallel	LDL-c
103	Finnegan, 2003, 12663273	EPA+DHA vs ALA	g/d	Trial: Randomized Parallel	LDL-c
104	Finnegan, 2003, 12663273	ALA vs Placebo	g/d	Trial: Randomized Parallel	Tg
105	Finnegan, 2003, 12663273	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Tg
106	Finnegan, 2003, 12663273	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Tg
107	Finnegan, 2003, 12663273	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Parallel	Tg
108	Finnegan, 2003, 12663273	EPA+DHA vs ALA	g/d	Trial: Randomized Parallel	Tg
109	Finnegan, 2003, 12663273	EPA+DHA vs ALA	g/d	Trial: Randomized Parallel	Tg
110	Finnegan, 2003, 12663273	ALA vs Placebo	g/d	Trial: Randomized Parallel	SBP
111	Finnegan, 2003, 12663273	ALA vs Placebo	g/d	Trial: Randomized Parallel	SBP
112	Finnegan, 2003, 12663273	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	SBP
113	Finnegan, 2003, 12663273	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	SBP
114	Finnegan, 2003, 12663273	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Parallel	SBP
115	Finnegan, 2003, 12663273	EPA+DHA vs ALA	g/d	Trial: Randomized Parallel	SBP
116	Finnegan, 2003, 12663273	EPA+DHA vs ALA	g/d	Trial: Randomized Parallel	SBP
117	Finnegan, 2003, 12663273	EPA+DHA vs ALA	g/d	Trial: Randomized Parallel	SBP
118	Finnegan, 2003, 12663273	EPA+DHA vs ALA	g/d	Trial: Randomized Parallel	SBP
119	Finnegan, 2003, 12663273	ALA vs Placebo	g/d	Trial: Randomized Parallel	DBP
120	Finnegan, 2003, 12663273	ALA vs Placebo	g/d	Trial: Randomized Parallel	DBP
121	Finnegan, 2003, 12663273	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	DBP
122	Finnegan, 2003, 12663273	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	DBP
123	Finnegan, 2003, 12663273	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Parallel	DBP
124	Finnegan, 2003, 12663273	EPA+DHA vs ALA	g/d	Trial: Randomized Parallel	DBP
125	Finnegan, 2003, 12663273	EPA+DHA vs ALA	g/d	Trial: Randomized Parallel	DBP
126	Finnegan, 2003, 12663273	EPA+DHA vs ALA	g/d	Trial: Randomized Parallel	DBP
127	Finnegan, 2003, 12663273	EPA+DHA vs ALA	g/d	Trial: Randomized Parallel	DBP

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Reported effect Size	Dose/intake difference	Dose-corrected effect size
94	Finnegan, 2003, 12663273	2.32 (-4.78, 9.42)	1.7	1.364706
95	Finnegan, 2003, 12663273	-0.77 (-8.56, 7.02)	0.9	-0.8555555
96	Finnegan, 2003, 12663273	2.32 (-4.66, 9.29)	NA	
97	Finnegan, 2003, 12663273	1.54 (-5.75, 8.84)	NA	
98	Finnegan, 2003, 12663273	-1.93 (-16.80, 12.94)	4.5	-0.4288889
99	Finnegan, 2003, 12663273	0.00 (-17.32, 17.32)	0.8	0
100	Finnegan, 2003, 12663273	12.74 (-3.22, 28.71)	1.7	7.494118
101	Finnegan, 2003, 12663273	12.74 (-4.76, 30.25)	0.9	14.15556
102	Finnegan, 2003, 12663273	1.93 (-14.58, 18.44)	NA	
103	Finnegan, 2003, 12663273	14.67 (-0.41, 29.75)	NA	
104	Finnegan, 2003, 12663273	23.01 (-8.88, 54.90)	4.5	5.113333
105	Finnegan, 2003, 12663273	6.19 (-23.50, 35.88)	0.8	7.7375
106	Finnegan, 2003, 12663273	-9.73 (-38.13, 18.66)	1.7	-5.723529
107	Finnegan, 2003, 12663273	-15.93 (-46.91, 15.05)	0.9	-17.7
108	Finnegan, 2003, 12663273	-16.81 (-51.02, 17.40)	NA	
109	Finnegan, 2003, 12663273	-32.74 (-65.84, 0.35)	NA	
110	Finnegan, 2003, 12663273	0 (-8.7, 8.7)	1.7	0
111	Finnegan, 2003, 12663273	5.2 (-3.9, 14.3))	4.5	1.155556
112	Finnegan, 2003, 12663273	0.5 (-8.3, 9.3)	1.7	0.2941177
113	Finnegan, 2003, 12663273	3.7 (-6.4, 13.8)	0.8	4.625
114	Finnegan, 2003, 12663273	-3.2 (-12.5, 6.1)	0.9	-3.555556
115	Finnegan, 2003, 12663273	0.5 (-7.3, 8.3)	NA	
116	Finnegan, 2003, 12663273	-4.7 (-12.9, 3.5)	NA	
117	Finnegan, 2003, 12663273	3.7 (-5.5, 12.9)	NA	
118	Finnegan, 2003, 12663273	-1.5 (-11.1, 8.1)	NA	
119	Finnegan, 2003, 12663273	-0.2 (-5.5, 5.1)	1.7	-0.1176471
120	Finnegan, 2003, 12663273	0.7 (-4.7, 6.1)	4.5	0.1555556
121	Finnegan, 2003, 12663273	-0.5 (-5.7, 4.7)	1.7	-0.2941177
122	Finnegan, 2003, 12663273	2.1 (-2.8, 7)	0.8	2.625
123	Finnegan, 2003, 12663273	-2.6 (-8, 2.8)	0.9	-2.888889
124	Finnegan, 2003, 12663273	-0.3 (-6.1, 5.5)	NA	
125	Finnegan, 2003, 12663273	-1.2 (-7.1, 4.7)	NA	
126	Finnegan, 2003, 12663273	2.3 (-3.3, 7.9)	NA	
127	Finnegan, 2003, 12663273	1.4 (-4.3, 7.1)	NA	

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Outcome classification
94	Finnegan, 2003, 12663273	Secondary
95	Finnegan, 2003, 12663273	Secondary
96	Finnegan, 2003, 12663273	Secondary
97	Finnegan, 2003, 12663273	Secondary
98	Finnegan, 2003, 12663273	Secondary
99	Finnegan, 2003, 12663273	Secondary
100	Finnegan, 2003, 12663273	Secondary
101	Finnegan, 2003, 12663273	Secondary
102	Finnegan, 2003, 12663273	Secondary
103	Finnegan, 2003, 12663273	Secondary
104	Finnegan, 2003, 12663273	Secondary
105	Finnegan, 2003, 12663273	Secondary
106	Finnegan, 2003, 12663273	Secondary
107	Finnegan, 2003, 12663273	Secondary
108	Finnegan, 2003, 12663273	Secondary
109	Finnegan, 2003, 12663273	Secondary
110	Finnegan, 2003, 12663273	Secondary
111	Finnegan, 2003, 12663273	Secondary
112	Finnegan, 2003, 12663273	Secondary
113	Finnegan, 2003, 12663273	Secondary
114	Finnegan, 2003, 12663273	Secondary
115	Finnegan, 2003, 12663273	Secondary
116	Finnegan, 2003, 12663273	Secondary
117	Finnegan, 2003, 12663273	Secondary
118	Finnegan, 2003, 12663273	Secondary
119	Finnegan, 2003, 12663273	Secondary
120	Finnegan, 2003, 12663273	Secondary
121	Finnegan, 2003, 12663273	Secondary
122	Finnegan, 2003, 12663273	Primary (power analysis)
123	Finnegan, 2003, 12663273	Primary (power analysis)
124	Finnegan, 2003, 12663273	Primary (power analysis)
125	Finnegan, 2003, 12663273	Primary (power analysis)
126	Finnegan, 2003, 12663273	Primary (power analysis)
127	Finnegan, 2003, 12663273	Primary (power analysis)

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Study years (start date)	Country	Population
128	Galan, 2010, 21115589	2003	France	Secondary Prevention (history of CVD event)
129	Galan, 2010, 21115589	2003	France	Secondary Prevention (history of CVD event)
130	Galan, 2010, 21115589	2003	France	Secondary Prevention (history of CVD event)
131	Galan, 2010, 21115589	2003	France	Secondary Prevention (history of CVD event)
132	Galan, 2010, 21115589	2003	France	Secondary Prevention (history of CVD event)
133	Galan, 2010, 21115589	2003	France	Secondary Prevention (history of CVD event)
134	Galan, 2010, 21115589	2003	France	Secondary Prevention (history of CVD event)

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Risk type	Sample size (total)
128	Galan, 2010, 21115589	Cardiac disease (Coronary event w/in 12 mo, including MI, ACS or suspected ACS); Cerebrovascular disease (CVA (not TIA))	2501
129	Galan, 2010, 21115589	Cardiac disease (Coronary event w/in 12 mo, including MI, ACS or suspected ACS); Cerebrovascular disease (CVA (not TIA))	2501
130	Galan, 2010, 21115589	Cardiac disease (Coronary event w/in 12 mo, including MI, ACS or suspected ACS); Cerebrovascular disease (CVA (not TIA))	2501
131	Galan, 2010, 21115589	Cardiac disease (Coronary event w/in 12 mo, including MI, ACS or suspected ACS); Cerebrovascular disease (CVA (not TIA))	2501
132	Galan, 2010, 21115589	Cardiac disease (Coronary event w/in 12 mo, including MI, ACS or suspected ACS); Cerebrovascular disease (CVA (not TIA))	2501
133	Galan, 2010, 21115589	Cardiac disease (Coronary event w/in 12 mo, including MI, ACS or suspected ACS); Cerebrovascular disease (CVA (not TIA))	2501
134	Galan, 2010, 21115589	Cardiac disease (Coronary event w/in 12 mo, including MI, ACS or suspected ACS); Cerebrovascular disease (CVA (not TIA))	2501

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Age mean (SD) [median] years	Sex (% male)	Race
128	Galan, 2010, 21115589	60.9 (8.8)	79.4	nd
129	Galan, 2010, 21115589	60.9 (8.8)	79.4	nd
130	Galan, 2010, 21115589	60.9 (8.8)	79.4	nd
131	Galan, 2010, 21115589	60.9 (8.8)	79.4	nd
132	Galan, 2010, 21115589	60.9 (8.8)	79.4	nd
133	Galan, 2010, 21115589	60.9 (8.8)	79.4	nd
134	Galan, 2010, 21115589	60.9 (8.8)	79.4	nd

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Blood pressure SBP/DBP mmHg
128	Galan, 2010, 21115589	132.6 (20.0)/82.6 (12.1)
129	Galan, 2010, 21115589	132.6 (20.0)/82.6 (12.1)
130	Galan, 2010, 21115589	132.6 (20.0)/82.6 (12.1)
131	Galan, 2010, 21115589	132.6 (20.0)/82.6 (12.1)
132	Galan, 2010, 21115589	132.6 (20.0)/82.6 (12.1)
133	Galan, 2010, 21115589	132.6 (20.0)/82.6 (12.1)
134	Galan, 2010, 21115589	132.6 (20.0)/82.6 (12.1)

Row	Study	Lipids: Total cholesterol/LDL/HDL/Triglycerides mean (SD) mg/dL [mmol/L]
128	Galan, 2010, 21115589	[median 4.5 (3.9, 5.1)]/[median 2.6 (2.2, 3.2)]/[median 1.1 (1.0, 1.3)]/[median 1.1 (0.9, 1.7)]
129	Galan, 2010, 21115589	[median 4.5 (3.9, 5.1)]/[median 2.6 (2.2, 3.2)]/[median 1.1 (1.0, 1.3)]/[median 1.1 (0.9, 1.7)]
130	Galan, 2010, 21115589	[median 4.5 (3.9, 5.1)]/[median 2.6 (2.2, 3.2)]/[median 1.1 (1.0, 1.3)]/[median 1.1 (0.9, 1.7)]
131	Galan, 2010, 21115589	[median 4.5 (3.9, 5.1)]/[median 2.6 (2.2, 3.2)]/[median 1.1 (1.0, 1.3)]/[median 1.1 (0.9, 1.7)]
132	Galan, 2010, 21115589	[median 4.5 (3.9, 5.1)]/[median 2.6 (2.2, 3.2)]/[median 1.1 (1.0, 1.3)]/[median 1.1 (0.9, 1.7)]
133	Galan, 2010, 21115589	[median 4.5 (3.9, 5.1)]/[median 2.6 (2.2, 3.2)]/[median 1.1 (1.0, 1.3)]/[median 1.1 (0.9, 1.7)]
134	Galan, 2010, 21115589	[median 4.5 (3.9, 5.1)]/[median 2.6 (2.2, 3.2)]/[median 1.1 (1.0, 1.3)]/[median 1.1 (0.9, 1.7)]

Row	Study	BMI mean (SD) Kg/m2/Weight mean (SD) Kg	Baseline n-3 intake	n-3 source (Baseline)
128	Galan, 2010, 21115589	27.5 (3.8)	EPA: median 1.26 (IQR 0.84, 1.81) % FA, DHA: median 2.70 (IQR 2.15, 3.36), EPA+DHA % FA: median 4.04 (IQR 2.99, 5.08) % FA	plasma
129	Galan, 2010, 21115589	27.5 (3.8)	EPA: median 1.26 (IQR 0.84, 1.81) % FA, DHA: median 2.70 (IQR 2.15, 3.36), EPA+DHA % FA: median 4.04 (IQR 2.99, 5.08) % FA	plasma
130	Galan, 2010, 21115589	27.5 (3.8)	EPA: median 1.26 (IQR 0.84, 1.81) % FA, DHA: median 2.70 (IQR 2.15, 3.36), EPA+DHA % FA: median 4.04 (IQR 2.99, 5.08) % FA	plasma
131	Galan, 2010, 21115589	27.5 (3.8)	EPA: median 1.26 (IQR 0.84, 1.81) % FA, DHA: median 2.70 (IQR 2.15, 3.36), EPA+DHA % FA: median 4.04 (IQR 2.99, 5.08) % FA	plasma
132	Galan, 2010, 21115589	27.5 (3.8)	EPA: median 1.26 (IQR 0.84, 1.81) % FA, DHA: median 2.70 (IQR 2.15, 3.36), EPA+DHA % FA: median 4.04 (IQR 2.99, 5.08) % FA	plasma
133	Galan, 2010, 21115589	27.5 (3.8)	EPA: median 1.26 (IQR 0.84, 1.81) % FA, DHA: median 2.70 (IQR 2.15, 3.36), EPA+DHA % FA: median 4.04 (IQR 2.99, 5.08) % FA	plasma
134	Galan, 2010, 21115589	27.5 (3.8)	EPA: median 1.26 (IQR 0.84, 1.81) % FA, DHA: median 2.70 (IQR 2.15, 3.36), EPA+DHA % FA: median 4.04 (IQR 2.99, 5.08) % FA	plasma

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	n-3 type(s)	n-3 measure	Study design	Outcome
128	Galan, 2010, 21115589	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Death, all cause
129	Galan, 2010, 21115589	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	MACE
130	Galan, 2010, 21115589	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Myocardial infarction
131	Galan, 2010, 21115589	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Revascularization
132	Galan, 2010, 21115589	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Parallel	Stroke
133	Galan, 2010, 21115589	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Parallel	Stroke
134	Galan, 2010, 21115589	EPA + DHA (+/- B vitamin) vs Placebo (+/- B vitamin	g/d	Trial: Randomized Parallel	SBP

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Reported effect Size	Dose/intake difference	Dose-corrected effect size
128	Galan, 2010, 21115589	Adj HR 1.03 (0.72, 1.48)	0.6	1.050498
129	Galan, 2010, 21115589	HR 1.08 (0.79, 1.47)	0.6	1.136858
130	Galan, 2010, 21115589	Adj HR 0.97 (0.66, 1.42)	0.6	0.9505017
131	Galan, 2010, 21115589	HR 0.97 (0.78, 1.22)	0.6	0.9505017
132	Galan, 2010, 21115589	HR 1.04 (0.62, 1.75)	0.6	1.067552
133	Galan, 2010, 21115589	HR 0.93 (0.60, 1.43)	0.6	0.8860772
134	Galan, 2010, 21115589	-0.06 (nd)	0.6	-0.1

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Outcome classification
128	Galan, 2010, 21115589	Secondary
129	Galan, 2010, 21115589	Secondary; Primary in registry record (ISRCTN41926726)
130	Galan, 2010, 21115589	Primary (stated); Secondary in registry record (ISRCTN41926726)
131	Galan, 2010, 21115589	Secondary
132	Galan, 2010, 21115589	Secondary
133	Galan, 2010, 21115589	Secondary
134	Galan, 2010, 21115589	Secondary

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Study years (start date)	Country	Population
135	Galan, 2010, 21115589	2003	France	Secondary Prevention (history of CVD event)
136	Galan, 2010, 21115589	2003	France	Secondary Prevention (history of CVD event)
137	Grieger, 2014, 24454276	2011	Australia	Primary Prevention, Healthy
138	Grieger, 2014, 24454276	2011	Australia	Primary Prevention, Healthy
139	Grieger, 2014, 24454276	2011	Australia	Primary Prevention, Healthy
140	Grieger, 2014, 24454276	2011	Australia	Primary Prevention, Healthy
141	Grieger, 2014, 24454276	2011	Australia	Primary Prevention, Healthy
142	Grimsgaard, 1998, 9665096	1993	Norway	Primary Prevention, Healthy
143	Grimsgaard, 1998, 9665096	1993	Norway	Primary Prevention, Healthy
144	Grimsgaard, 1998, 9665096	1993	Norway	Primary Prevention, Healthy
145	Grimsgaard, 1998, 9665096	1993	Norway	Primary Prevention, Healthy
146	Grimsgaard, 1998, 9665096	1993	Norway	Primary Prevention, Healthy
147	Grimsgaard, 1998, 9665096	1993	Norway	Primary Prevention, Healthy

Row	Study	Risk type	Sample size (total)
135	Galan, 2010, 21115589	Cardiac disease (Coronary event w/in 12 mo, including MI, ACS or suspected ACS); Cerebrovascular disease (CVA (not TIA))	2501
136	Galan, 2010, 21115589	Cardiac disease (Coronary event w/in 12 mo, including MI, ACS or suspected ACS); Cerebrovascular disease (CVA (not TIA))	2501
137	Grieger, 2014, 24454276	na	80
138	Grieger, 2014, 24454276	na	80
139	Grieger, 2014, 24454276	na	80
140	Grieger, 2014, 24454276	na	80
141	Grieger, 2014, 24454276	na	80
142	Grimsgaard, 1998, 9665096	na	147
143	Grimsgaard, 1998, 9665096	na	147
144	Grimsgaard, 1998, 9665096	na	147
145	Grimsgaard, 1998, 9665096	na	147
146	Grimsgaard, 1998, 9665096	na	147
147	Grimsgaard, 1998, 9665096	na	147

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Age mean (SD) [median] years	Sex (% male)	Race
135	Galan, 2010, 21115589	60.9 (8.8)	79.4	nd
136	Galan, 2010, 21115589	60.9 (8.8)	79.4	nd
137	Grieger, 2014, 24454276	69.5 (5.8) [range 64, 85]	49	nd
138	Grieger, 2014, 24454276	69.5 (5.8) [range 64, 85]	49	nd
139	Grieger, 2014, 24454276	69.5 (5.8) [range 64, 85]	49	nd
140	Grieger, 2014, 24454276	69.5 (5.8) [range 64, 85]	49	nd
141	Grieger, 2014, 24454276	69.5 (5.8) [range 64, 85]	49	nd
142	Grimsgaard, 1998, 9665096	45.1 (5.6)	nd	nd
143	Grimsgaard, 1998, 9665096	45.1 (5.6)	nd	nd
144	Grimsgaard, 1998, 9665096	45.1 (5.6)	nd	nd
145	Grimsgaard, 1998, 9665096	45.1 (5.6)	nd	nd
146	Grimsgaard, 1998, 9665096	45.1 (5.6)	nd	nd
147	Grimsgaard, 1998, 9665096	45.1 (5.6)	nd	nd

Row	Study	Blood pressure SBP/DBP mmHg
135	Galan, 2010, 21115589	132.6 (20.0)/82.6 (12.1)
136	Galan, 2010, 21115589	132.6 (20.0)/82.6 (12.1)
137	Grieger, 2014, 24454276	126 (SE 2)/67 (SE 1)
138	Grieger, 2014, 24454276	126 (SE 2)/67 (SE 1)
139	Grieger, 2014, 24454276	126 (SE 2)/67 (SE 1)
140	Grieger, 2014, 24454276	126 (SE 2)/67 (SE 1)
141	Grieger, 2014, 24454276	126 (SE 2)/67 (SE 1)
142	Grimsgaard, 1998, 9665096	122.2 (5.7)/76.9 (8.0)
143	Grimsgaard, 1998, 9665096	122.2 (5.7)/76.9 (8.0)
144	Grimsgaard, 1998, 9665096	122.2 (5.7)/76.9 (8.0)
145	Grimsgaard, 1998, 9665096	122.2 (5.7)/76.9 (8.0)
146	Grimsgaard, 1998, 9665096	122.2 (5.7)/76.9 (8.0)
147	Grimsgaard, 1998, 9665096	122.2 (5.7)/76.9 (8.0)

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Lipids: Total cholesterol/LDL/HDL/Triglycerides mean (SD) mg/dL [mmol/L]
135	Galan, 2010, 21115589	[median 4.5 (3.9, 5.1)]/[median 2.6 (2.2, 3.2)]/[median 1.1 (1.0, 1.3)]/[median 1.1 (0.9, 1.7)]
136	Galan, 2010, 21115589	[median 4.5 (3.9, 5.1)]/[median 2.6 (2.2, 3.2)]/[median 1.1 (1.0, 1.3)]/[median 1.1 (0.9, 1.7)]
137	Grieger, 2014, 24454276	[5.5 (SE 0.2)]/[3.3 (SE 0.1)]/[1.6 (SE 0.1)]/[1.4 (SE 0.1)]
138	Grieger, 2014, 24454276	[5.5 (SE 0.2)]/[3.3 (SE 0.1)]/[1.6 (SE 0.1)]/[1.4 (SE 0.1)]
139	Grieger, 2014, 24454276	[5.5 (SE 0.2)]/[3.3 (SE 0.1)]/[1.6 (SE 0.1)]/[1.4 (SE 0.1)]
140	Grieger, 2014, 24454276	[5.5 (SE 0.2)]/[3.3 (SE 0.1)]/[1.6 (SE 0.1)]/[1.4 (SE 0.1)]
141	Grieger, 2014, 24454276	[5.5 (SE 0.2)]/[3.3 (SE 0.1)]/[1.6 (SE 0.1)]/[1.4 (SE 0.1)]
142	Grimsgaard, 1998, 9665096	[6.02 (1.08)]/[4.04 (0.98)]/[1.41 (0.28)]/[1.22 (0.55)]
143	Grimsgaard, 1998, 9665096	[6.02 (1.08)]/[4.04 (0.98)]/[1.41 (0.28)]/[1.22 (0.55)]
144	Grimsgaard, 1998, 9665096	[6.02 (1.08)]/[4.04 (0.98)]/[1.41 (0.28)]/[1.22 (0.55)]
145	Grimsgaard, 1998, 9665096	[6.02 (1.08)]/[4.04 (0.98)]/[1.41 (0.28)]/[1.22 (0.55)]
146	Grimsgaard, 1998, 9665096	[6.02 (1.08)]/[4.04 (0.98)]/[1.41 (0.28)]/[1.22 (0.55)]
147	Grimsgaard, 1998, 9665096	[6.02 (1.08)]/[4.04 (0.98)]/[1.41 (0.28)]/[1.22 (0.55)]

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	BMI mean (SD) Kg/m2/Weight mean (SD) Kg	Baseline n-3 intake	n-3 source (Baseline)
135	Galan, 2010, 21115589	27.5 (3.8)	EPA: median 1.26 (IQR 0.84, 1.81) % FA, DHA: median 2.70 (IQR 2.15, 3.36), EPA+DHA % FA: median 4.04 (IQR 2.99, 5.08) % FA	plasma
136	Galan, 2010, 21115589	27.5 (3.8)	EPA: median 1.26 (IQR 0.84, 1.81) % FA, DHA: median 2.70 (IQR 2.15, 3.36), EPA+DHA % FA: median 4.04 (IQR 2.99, 5.08) % FA	plasma
137	Grieger, 2014, 24454276	26.4 (SE 0.6)/73.8	ALA: 0.147 (SE 0.008)%, EPA 1.5 (SE 0.1)%, DPA: 3.0 (SE 0.1)%, DHA 5.0 (SE 2)%, Total n3 FA 9.7 (SE 0.4)%	RBC membrane
138	Grieger, 2014, 24454276	26.4 (SE 0.6)/73.8	ALA: 0.147 (SE 0.008)%, EPA 1.5 (SE 0.1)%, DPA: 3.0 (SE 0.1)%, DHA 5.0 (SE 2)%, Total n3 FA 9.7 (SE 0.4)%	RBC membrane
139	Grieger, 2014, 24454276	26.4 (SE 0.6)/73.8	ALA: 0.147 (SE 0.008)%, EPA 1.5 (SE 0.1)%, DPA: 3.0 (SE 0.1)%, DHA 5.0 (SE 2)%, Total n3 FA 9.7 (SE 0.4)%	RBC membrane
140	Grieger, 2014, 24454276	26.4 (SE 0.6)/73.8	ALA: 0.147 (SE 0.008)%, EPA 1.5 (SE 0.1)%, DPA: 3.0 (SE 0.1)%, DHA 5.0 (SE 2)%, Total n3 FA 9.7 (SE 0.4)%	RBC membrane
141	Grieger, 2014, 24454276	26.4 (SE 0.6)/73.8	ALA: 0.147 (SE 0.008)%, EPA 1.5 (SE 0.1)%, DPA: 3.0 (SE 0.1)%, DHA 5.0 (SE 2)%, Total n3 FA 9.7 (SE 0.4)%	RBC membrane
142	Grimsgaard, 1998, 9665096	24.6 (2.7)	nd	nd
143	Grimsgaard, 1998, 9665096	24.6 (2.7)	nd	nd
144	Grimsgaard, 1998, 9665096	24.6 (2.7)	nd	nd
145	Grimsgaard, 1998, 9665096	24.6 (2.7)	nd	nd
146	Grimsgaard, 1998, 9665096	24.6 (2.7)	nd	nd
147	Grimsgaard, 1998, 9665096	24.6 (2.7)	nd	nd

Row	Study	n-3 type(s)	n-3 measure	Study design	Outcome
135	Galan, 2010, 21115589	EPA+DHA (+/- B vitamin) vs Placebo (+/- B vitamin	% FA	Trial: Randomized Parallel	DBP
136	Galan, 2010, 21115589	EPA + DHA (+/- B vitamin) vs Placebo (+/- B vitamin	g/d	Trial: Randomized Parallel	MAP
137	Grieger, 2014, 24454276	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	HDL-c
138	Grieger, 2014, 24454276	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	LDL-c
139	Grieger, 2014, 24454276	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Tg
140	Grieger, 2014, 24454276	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	SBP
141	Grieger, 2014, 24454276	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	DBP
142	Grimsgaard, 1998, 9665096	EPA vs Placebo	g/d	Trial: Randomized Parallel	Total:HDL-c ratio
143	Grimsgaard, 1998, 9665096	DHA vs Placebo	g/d	Trial: Randomized Parallel	Total:HDL-c ratio
144	Grimsgaard, 1998, 9665096	DHA vs EPA	g/d	Trial: Randomized Parallel	Total:HDL-c ratio
145	Grimsgaard, 1998, 9665096	EPA vs Placebo	g/d	Trial: Randomized Parallel	HDL-c
146	Grimsgaard, 1998, 9665096	DHA vs Placebo	g/d	Trial: Randomized Parallel	HDL-c
147	Grimsgaard, 1998, 9665096	DHA vs EPA	g/d	Trial: Randomized Parallel	HDL-c

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Reported effect Size	Dose/intake difference	Dose-corrected effect size
135	Galan, 2010, 21115589	0.06 (nd)	0.6	0.1
136	Galan, 2010, 21115589	0.007 (nd)	0.6	0.0116667
137	Grieger, 2014, 24454276	0.00 (-10.70, 10.70)	0.8	0
138	Grieger, 2014, 24454276	11.58 (0.88, 22.29)	0.8	14.475
139	Grieger, 2014, 24454276	0.00 (-24.53, 24.53)	0.8	0
140	Grieger, 2014, 24454276	-2.0 (-9.3, 5.3)	0.8	-2.5
141	Grieger, 2014, 24454276	0 (-4.8, 4.8)	0.8	0
142	Grimsgaard, 1998, 9665096	-0.5 (-0.8, -0.2)	3.8	-0.131579
143	Grimsgaard, 1998, 9665096	-0.5 (-0.8, -0.2)	3.6	-0.1388889
144	Grimsgaard, 1998, 9665096	0.02 (-0.3, 0.4)	NA	
145	Grimsgaard, 1998, 9665096	0.77 (-0.64, 2.19)	3.6	0.2138889
146	Grimsgaard, 1998, 9665096	-5.41 (-6.70, -4.11)	3.8	-1.423684
147	Grimsgaard, 1998, 9665096	-1.93 (-3.49, -0.37)	NA	

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Outcome classification
135	Galan, 2010, 21115589	Secondary
136	Galan, 2010, 21115589	Secondary
137	Grieger, 2014, 24454276	Secondary
138	Grieger, 2014, 24454276	Secondary
139	Grieger, 2014, 24454276	Secondary
140	Grieger, 2014, 24454276	Secondary
141	Grieger, 2014, 24454276	Secondary
142	Grimsgaard, 1998, 9665096	Primary (stated)
143	Grimsgaard, 1998, 9665096	Primary (stated)
144	Grimsgaard, 1998, 9665096	Primary (stated)
145	Grimsgaard, 1998, 9665096	Secondary
146	Grimsgaard, 1998, 9665096	Secondary
147	Grimsgaard, 1998, 9665096	Secondary

Row	Study	Study years (start date)	Country	Population
148	Grimsgaard, 1998, 9665096	1993	Norway	Primary Prevention, Healthy
149	Grimsgaard, 1998, 9665096	1993	Norway	Primary Prevention, Healthy
150	Grimsgaard, 1998, 9665096	1993	Norway	Primary Prevention, Healthy
151	Grimsgaard, 1998, 9665096	1993	Norway	Primary Prevention, Healthy
152	Grimsgaard, 1998, 9665096	1993	Norway	Primary Prevention, Healthy
153	Grimsgaard, 1998, 9665096	1993	Norway	Primary Prevention, Healthy
154	Grimsgaard, 1998, 9665096	1993	Norway	Primary Prevention, Healthy
155	Grimsgaard, 1998, 9665096	1993	Norway	Primary Prevention, Healthy
156	Grimsgaard, 1998, 9665096	1993	Norway	Primary Prevention, Healthy
157	Grimsgaard, 1998, 9665096	1993	Norway	Primary Prevention, Healthy
158	Grimsgaard, 1998, 9665096	1993	Norway	Primary Prevention, Healthy
159	Grimsgaard, 1998, 9665096	1993	Norway	Primary Prevention, Healthy
160	Grimsgaard, 1998, 9665096	1993	Norway	Primary Prevention, Healthy
161	Grimsgaard, 1998, 9665096	1993	Norway	Primary Prevention, Healthy
162	Harrison, 2004, 15853118	2001	UK	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
163	Harrison, 2004, 15853118	2001	UK	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
164	Harrison, 2004, 15853118	2001	UK	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
165	Harrison, 2004, 15853118	2001	UK	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
166	Holman, 2009, 19002433	2004	UK	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
167	Holman, 2009, 19002433	2004	UK	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
168	Holman, 2009, 19002433	2004	UK	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
169	Holman, 2009, 19002433	2004	UK	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
170	Holman, 2009, 19002433	2004	UK	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
171	Holman, 2009, 19002433	2004	UK	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
172	Holman, 2009, 19002433	2004	UK	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Risk type	Sample size (total)
148	Grimsgaard, 1998, 9665096	na	147
149	Grimsgaard, 1998, 9665096	na	147
150	Grimsgaard, 1998, 9665096	na	147
151	Grimsgaard, 1998, 9665096	na	147
152	Grimsgaard, 1998, 9665096	na	147
153	Grimsgaard, 1998, 9665096	na	147
154	Grimsgaard, 1998, 9665096	na	147
155	Grimsgaard, 1998, 9665096	na	147
156	Grimsgaard, 1998, 9665096	na	147
157	Grimsgaard, 1998, 9665096	na	147
158	Grimsgaard, 1998, 9665096	na	147
159	Grimsgaard, 1998, 9665096	na	147
160	Grimsgaard, 1998, 9665096	na	147
161	Grimsgaard, 1998, 9665096	na	147
162	Harrison, 2004, 15853118	Hypertension (SBP >= 130 mmHg); Dyslipidemia (Total cholesterol >= 5.7 mmol/l)	152
163	Harrison, 2004, 15853118	Hypertension (SBP >= 130 mmHg); Dyslipidemia (Total cholesterol >= 5.7 mmol/l)	152
164	Harrison, 2004, 15853118	Hypertension (SBP >= 130 mmHg); Dyslipidemia (Total cholesterol >= 5.7 mmol/l)	152
165	Harrison, 2004, 15853118	Hypertension (SBP >= 130 mmHg); Dyslipidemia (Total cholesterol >= 5.7 mmol/l)	152
166	Holman, 2009, 19002433	Diabetes and/or metabolic syndrome	658
167	Holman, 2009, 19002433	Diabetes and/or metabolic syndrome	658
168	Holman, 2009, 19002433	Diabetes and/or metabolic syndrome	658
169	Holman, 2009, 19002433	Diabetes and/or metabolic syndrome	658
170	Holman, 2009, 19002433	Diabetes and/or metabolic syndrome	658
171	Holman, 2009, 19002433	Diabetes and/or metabolic syndrome	658
172	Holman, 2009, 19002433	Diabetes and/or metabolic syndrome	658

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Age mean (SD) [median] years	Sex (% male)	Race
148	Grimsgaard, 1998, 9665096	45.1 (5.6)	nd	nd
149	Grimsgaard, 1998, 9665096	45.1 (5.6)	nd	nd
150	Grimsgaard, 1998, 9665096	45.1 (5.6)	nd	nd
151	Grimsgaard, 1998, 9665096	45.1 (5.6)	nd	nd
152	Grimsgaard, 1998, 9665096	45.1 (5.6)	nd	nd
153	Grimsgaard, 1998, 9665096	45.1 (5.6)	nd	nd
154	Grimsgaard, 1998, 9665096	45.1 (5.6)	nd	nd
155	Grimsgaard, 1998, 9665096	45.1 (5.6)	nd	nd
156	Grimsgaard, 1998, 9665096	45.1 (5.6)	nd	nd
157	Grimsgaard, 1998, 9665096	45.1 (5.6)	nd	nd
158	Grimsgaard, 1998, 9665096	45.1 (5.6)	nd	nd
159	Grimsgaard, 1998, 9665096	45.1 (5.6)	nd	nd
160	Grimsgaard, 1998, 9665096	45.1 (5.6)	nd	nd
161	Grimsgaard, 1998, 9665096	45.1 (5.6)	nd	nd
162	Harrison, 2004, 15853118	52	54.4	nd
163	Harrison, 2004, 15853118	52	54.4	nd
164	Harrison, 2004, 15853118	52	54.4	nd
165	Harrison, 2004, 15853118	52	54.4	nd
166	Holman, 2009, 19002433	[65 (5773)]	58	88 white
167	Holman, 2009, 19002433	[65 (5773)]	58	88 white
168	Holman, 2009, 19002433	[65 (5773)]	58	88 white
169	Holman, 2009, 19002433	[65 (5773)]	58	88 white
170	Holman, 2009, 19002433	[65 (5773)]	58	88 white
171	Holman, 2009, 19002433	[65 (5773)]	58	88 white
172	Holman, 2009, 19002433	[65 (5773)]	58	88 white

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Blood pressure SBP/DBP mmHg
148	Grimsgaard, 1998, 9665096	122.2 (5.7)/76.9 (8.0)
149	Grimsgaard, 1998, 9665096	122.2 (5.7)/76.9 (8.0)
150	Grimsgaard, 1998, 9665096	122.2 (5.7)/76.9 (8.0)
151	Grimsgaard, 1998, 9665096	122.2 (5.7)/76.9 (8.0)
152	Grimsgaard, 1998, 9665096	122.2 (5.7)/76.9 (8.0)
153	Grimsgaard, 1998, 9665096	122.2 (5.7)/76.9 (8.0)
154	Grimsgaard, 1998, 9665096	122.2 (5.7)/76.9 (8.0)
155	Grimsgaard, 1998, 9665096	122.2 (5.7)/76.9 (8.0)
156	Grimsgaard, 1998, 9665096	122.2 (5.7)/76.9 (8.0)
157	Grimsgaard, 1998, 9665096	122.2 (5.7)/76.9 (8.0)
158	Grimsgaard, 1998, 9665096	122.2 (5.7)/76.9 (8.0)
159	Grimsgaard, 1998, 9665096	122.2 (5.7)/76.9 (8.0)
160	Grimsgaard, 1998, 9665096	122.2 (5.7)/76.9 (8.0)
161	Grimsgaard, 1998, 9665096	122.2 (5.7)/76.9 (8.0)
162	Harrison, 2004, 15853118	134.7/81.8
163	Harrison, 2004, 15853118	134.7/81.8
164	Harrison, 2004, 15853118	134.7/81.8
165	Harrison, 2004, 15853118	134.7/81.8
166	Holman, 2009, 19002433	139.8 (15.9)/78.8 (9.2)
167	Holman, 2009, 19002433	139.8 (15.9)/78.8 (9.2)
168	Holman, 2009, 19002433	139.8 (15.9)/78.8 (9.2)
169	Holman, 2009, 19002433	139.8 (15.9)/78.8 (9.2)
170	Holman, 2009, 19002433	139.8 (15.9)/78.8 (9.2)
171	Holman, 2009, 19002433	139.8 (15.9)/78.8 (9.2)
172	Holman, 2009, 19002433	139.8 (15.9)/78.8 (9.2)

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Lipids: Total cholesterol/LDL/HDL/Triglycerides mean (SD) mg/dL [mmol/L]
148	Grimsgaard, 1998, 9665096	[6.02 (1.08)]/[4.04 (0.98)]/[1.41 (0.28)]/[1.22 (0.55)]
149	Grimsgaard, 1998, 9665096	[6.02 (1.08)]/[4.04 (0.98)]/[1.41 (0.28)]/[1.22 (0.55)]
150	Grimsgaard, 1998, 9665096	[6.02 (1.08)]/[4.04 (0.98)]/[1.41 (0.28)]/[1.22 (0.55)]
151	Grimsgaard, 1998, 9665096	[6.02 (1.08)]/[4.04 (0.98)]/[1.41 (0.28)]/[1.22 (0.55)]
152	Grimsgaard, 1998, 9665096	[6.02 (1.08)]/[4.04 (0.98)]/[1.41 (0.28)]/[1.22 (0.55)]
153	Grimsgaard, 1998, 9665096	[6.02 (1.08)]/[4.04 (0.98)]/[1.41 (0.28)]/[1.22 (0.55)]
154	Grimsgaard, 1998, 9665096	[6.02 (1.08)]/[4.04 (0.98)]/[1.41 (0.28)]/[1.22 (0.55)]
155	Grimsgaard, 1998, 9665096	[6.02 (1.08)]/[4.04 (0.98)]/[1.41 (0.28)]/[1.22 (0.55)]
156	Grimsgaard, 1998, 9665096	[6.02 (1.08)]/[4.04 (0.98)]/[1.41 (0.28)]/[1.22 (0.55)]
157	Grimsgaard, 1998, 9665096	[6.02 (1.08)]/[4.04 (0.98)]/[1.41 (0.28)]/[1.22 (0.55)]
158	Grimsgaard, 1998, 9665096	[6.02 (1.08)]/[4.04 (0.98)]/[1.41 (0.28)]/[1.22 (0.55)]
159	Grimsgaard, 1998, 9665096	[6.02 (1.08)]/[4.04 (0.98)]/[1.41 (0.28)]/[1.22 (0.55)]
160	Grimsgaard, 1998, 9665096	[6.02 (1.08)]/[4.04 (0.98)]/[1.41 (0.28)]/[1.22 (0.55)]
161	Grimsgaard, 1998, 9665096	[6.02 (1.08)]/[4.04 (0.98)]/[1.41 (0.28)]/[1.22 (0.55)]
162	Harrison, 2004, 15853118	[6.7]/[5.0]/[1.7]/
163	Harrison, 2004, 15853118	[6.7]/[5.0]/[1.7]/
164	Harrison, 2004, 15853118	[6.7]/[5.0]/[1.7]/
165	Harrison, 2004, 15853118	[6.7]/[5.0]/[1.7]/
166	Holman, 2009, 19002433	[5.0 (1)]/[3.1 (0.8)]/[1.1 (0.9)]/[median 1.5 (1.2, 2.2)]
167	Holman, 2009, 19002433	[5.0 (1)]/[3.1 (0.8)]/[1.1 (0.9)]/[median 1.5 (1.2, 2.2)]
168	Holman, 2009, 19002433	[5.0 (1)]/[3.1 (0.8)]/[1.1 (0.9)]/[median 1.5 (1.2, 2.2)]
169	Holman, 2009, 19002433	[5.0 (1)]/[3.1 (0.8)]/[1.1 (0.9)]/[median 1.5 (1.2, 2.2)]
170	Holman, 2009, 19002433	[5.0 (1)]/[3.1 (0.8)]/[1.1 (0.9)]/[median 1.5 (1.2, 2.2)]
171	Holman, 2009, 19002433	[5.0 (1)]/[3.1 (0.8)]/[1.1 (0.9)]/[median 1.5 (1.2, 2.2)]
172	Holman, 2009, 19002433	[5.0 (1)]/[3.1 (0.8)]/[1.1 (0.9)]/[median 1.5 (1.2, 2.2)]

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	BMI mean (SD) Kg/m2/Weight mean (SD) Kg	Baseline n-3 intake	n-3 source (Baseline)
148	Grimsgaard, 1998, 9665096	24.6 (2.7)	nd	nd
149	Grimsgaard, 1998, 9665096	24.6 (2.7)	nd	nd
150	Grimsgaard, 1998, 9665096	24.6 (2.7)	nd	nd
151	Grimsgaard, 1998, 9665096	24.6 (2.7)	nd	nd
152	Grimsgaard, 1998, 9665096	24.6 (2.7)	nd	nd
153	Grimsgaard, 1998, 9665096	24.6 (2.7)	nd	nd
154	Grimsgaard, 1998, 9665096	24.6 (2.7)	nd	nd
155	Grimsgaard, 1998, 9665096	24.6 (2.7)	nd	nd
156	Grimsgaard, 1998, 9665096	24.6 (2.7)	nd	nd
157	Grimsgaard, 1998, 9665096	24.6 (2.7)	nd	nd
158	Grimsgaard, 1998, 9665096	24.6 (2.7)	nd	nd
159	Grimsgaard, 1998, 9665096	24.6 (2.7)	nd	nd
160	Grimsgaard, 1998, 9665096	24.6 (2.7)	nd	nd
161	Grimsgaard, 1998, 9665096	24.6 (2.7)	nd	nd
162	Harrison, 2004, 15853118	27.2	DHA: 1.51 (0.15) % FA	plasma
163	Harrison, 2004, 15853118	27.2	DHA: 1.51 (0.15) % FA	plasma
164	Harrison, 2004, 15853118	27.2	DHA: 1.51 (0.15) % FA	plasma
165	Harrison, 2004, 15853118	27.2	DHA: 1.51 (0.15) % FA	plasma
166	Holman, 2009, 19002433	30.6 (5.8)/87.3 (18.5)	nd	nd
167	Holman, 2009, 19002433	30.6 (5.8)/87.3 (18.5)	nd	nd
168	Holman, 2009, 19002433	30.6 (5.8)/87.3 (18.5)	nd	nd
169	Holman, 2009, 19002433	30.6 (5.8)/87.3 (18.5)	nd	nd
170	Holman, 2009, 19002433	30.6 (5.8)/87.3 (18.5)	nd	nd
171	Holman, 2009, 19002433	30.6 (5.8)/87.3 (18.5)	nd	nd
172	Holman, 2009, 19002433	30.6 (5.8)/87.3 (18.5)	nd	nd

Row	Study	n-3 type(s)	n-3 measure	Study design	Outcome
148	Grimsgaard, 1998, 9665096	DHA vs Placebo	g/d	Trial: Randomized Parallel	LDL-c
149	Grimsgaard, 1998, 9665096	DHA vs EPA	g/d	Trial: Randomized Parallel	LDL-c
150	Grimsgaard, 1998, 9665096	EPA vs Placebo	g/d	Trial: Randomized Parallel	Tg
151	Grimsgaard, 1998, 9665096	DHA vs Placebo	g/d	Trial: Randomized Parallel	Tg
152	Grimsgaard, 1998, 9665096	DHA vs EPA	g/d	Trial: Randomized Parallel	Tg
153	Grimsgaard, 1998, 9665096	EPA vs Placebo	g/d	Trial: Randomized Parallel	SBP
154	Grimsgaard, 1998, 9665096	EPA vs DHA	g/d	Trial: Randomized Parallel	SBP
155	Grimsgaard, 1998, 9665096	DHA vs Placebo	g/d	Trial: Randomized Parallel	SBP
156	Grimsgaard, 1998, 9665096	DHA vs Placebo	g/d	Trial: Randomized Parallel	DBP
157	Grimsgaard, 1998, 9665096	EPA vs Placebo	g/d	Trial: Randomized Parallel	DBP
158	Grimsgaard, 1998, 9665096	EPA vs DHA	g/d	Trial: Randomized Parallel	DBP
159	Grimsgaard, 1998, 9665096	DHA vs Placebo	g/d	Trial: Randomized Parallel	MAP
160	Grimsgaard, 1998, 9665096	EPA vs Placebo	g/d	Trial: Randomized Parallel	MAP
161	Grimsgaard, 1998, 9665096	EPA vs DHA	g/d	Trial: Randomized Parallel	MAP
162	Harrison, 2004, 15853118	DHA vs Placebo	g/d	Trial: Randomized Factorial Design	HDL-c
163	Harrison, 2004, 15853118	DHA vs Placebo	g/d	Trial: Randomized Factorial Design	LDL-c
164	Harrison, 2004, 15853118	DHA vs Placebo	g/d	Trial: Randomized Factorial Design	SBP
165	Harrison, 2004, 15853118	DHA vs Placebo	% FA	Trial: Randomized Factorial Design	DBP
166	Holman, 2009, 19002433	EPA+DHA vs Placebo	g/d	Trial: Randomized Factorial Design	HDL-c
167	Holman, 2009, 19002433	EPA+DHA vs Placebo	g/d	Trial: Randomized Factorial Design	LDL-c
168	Holman, 2009, 19002433	EPA+DHA vs Placebo	g/d	Trial: Randomized Factorial Design	Tg
169	Holman, 2009, 19002433	EPA+DHA(+/- atorvastatin) vs Placebo (+/- atorvastatin)	g/d	Trial: Randomized Factorial Design	SBP
170	Holman, 2009, 19002433	EPA+DHA (+atorvastatin) vs Placebo (+atorvastatin)	g/d	Trial: Randomized Factorial Design	SBP
171	Holman, 2009, 19002433	EPA+DHA vs Placebo	g/d	Trial: Randomized Factorial Design	SBP
172	Holman, 2009, 19002433	EPA+DHA(+/- atorvastatin) vs Placebo (+/- atorvastatin)	g/d	Trial: Randomized Factorial Design	DBP

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Reported effect Size	Dose/intake difference	Dose-corrected effect size
148	Grimsgaard, 1998, 9665096	11.97 (7.20, 16.74)	3.8	3.15
149	Grimsgaard, 1998, 9665096	-5.79 (-11.66, 0.08)	NA	
150	Grimsgaard, 1998, 9665096	-23.01 (-33.47, -12.55)	3.6	-6.391667
151	Grimsgaard, 1998, 9665096	-8.85 (-19.45, 1.75)	3.8	-2.328947
152	Grimsgaard, 1998, 9665096	6.19 (-4.02, 16.41)	NA	
153	Grimsgaard, 1998, 9665096	-5.3 (-8.1, -2.5)	3.8	-1.394737
154	Grimsgaard, 1998, 9665096	-5.9 (-8.6,3.2)	NA	
155	Grimsgaard, 1998, 9665096	0.6 (-2.2, 3.4)	3.6	0.1666667
156	Grimsgaard, 1998, 9665096	-0.4 (-2.5, 1.7)	3.6	-0.1111111
157	Grimsgaard, 1998, 9665096	-0.6 (-2.7, 1.5)	3.8	-0.1578947
158	Grimsgaard, 1998, 9665096	-0.2 (-2.2, 1.8)	NA	
159	Grimsgaard, 1998, 9665096	0.4 (-1.9, 2.7)	3.6	0.1111111
160	Grimsgaard, 1998, 9665096	-0.4 (-2.8, 2)	3.8	-0.1052632
161	Grimsgaard, 1998, 9665096	-0.8 (-3, 1.4)	NA	
162	Harrison, 2004, 15853118	-0.17 (-0.08, 0.26)	2	-0.085
163	Harrison, 2004, 15853118	-7.45 (-45.74, 30.83)	2	-3.725
164	Harrison, 2004, 15853118	-0.94% (-4.68%, 2.79%)	2	-0.47
165	Harrison, 2004, 15853118	-2.19% (-5.57%, 1.18%)	2	-1.095
166	Holman, 2009, 19002433	0.77 (-0.10, 1.64)	2	0.385
167	Holman, 2009, 19002433	-1.16 (-11.13, 8.82)	2	-0.58
168	Holman, 2009, 19002433	-7.96 (-13.23, -2.70)	2	-3.98
169	Holman, 2009, 19002433	0.4 (nd)	1.68	0.2380952
170	Holman, 2009, 19002433	2 (-2.1, 6.1)	1.68	1.190476
171	Holman, 2009, 19002433	0 (-4, 4)	1.68	0
172	Holman, 2009, 19002433	0.6 (nd)	1.68	0.3571429

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Outcome classification
148	Grimsgaard, 1998, 9665096	Secondary
149	Grimsgaard, 1998, 9665096	Secondary
150	Grimsgaard, 1998, 9665096	Secondary
151	Grimsgaard, 1998, 9665096	Secondary
152	Grimsgaard, 1998, 9665096	Secondary
153	Grimsgaard, 1998, 9665096	Secondary
154	Grimsgaard, 1998, 9665096	Secondary
155	Grimsgaard, 1998, 9665096	Secondary
156	Grimsgaard, 1998, 9665096	Secondary
157	Grimsgaard, 1998, 9665096	Secondary
158	Grimsgaard, 1998, 9665096	Secondary
159	Grimsgaard, 1998, 9665096	Secondary
160	Grimsgaard, 1998, 9665096	Secondary
161	Grimsgaard, 1998, 9665096	Secondary
162	Harrison, 2004, 15853118	Primary (stated)
163	Harrison, 2004, 15853118	Secondary
164	Harrison, 2004, 15853118	Secondary
165	Harrison, 2004, 15853118	Primary (stated)
166	Holman, 2009, 19002433	Secondary; Primary in registry record (NCT00141232)
167	Holman, 2009, 19002433	Secondary
168	Holman, 2009, 19002433	Secondary
169	Holman, 2009, 19002433	Secondary
170	Holman, 2009, 19002433	Secondary
171	Holman, 2009, 19002433	Secondary
172	Holman, 2009, 19002433	Secondary

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Study years (start date)	Country	Population
173	Holman, 2009, 19002433	2004	UK	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
174	Holman, 2009, 19002433	2004	UK	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
175	Jones, 2014, 24829493	2010	Canada	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
176	Jones, 2014, 24829493	2010	Canada	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
177	Jones, 2014, 24829493	2010	Canada	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
178	Jones, 2014, 24829493	2010	Canada	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
179	Jones, 2014, 24829493	2010	Canada	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
180	Jones, 2014, 24829493	2010	Canada	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
181	Jones, 2014, 24829493	2010	Canada	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
182	Jones, 2014, 24829493	2010	Canada	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
183	Jones, 2014, 24829493	2010	Canada	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
184	Jones, 2014, 24829493	2010	Canada	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Risk type	Sample size (total)
173	Holman, 2009, 19002433	Diabetes and/or metabolic syndrome	658
174	Holman, 2009, 19002433	Diabetes and/or metabolic syndrome	658
175	Jones, 2014, 24829493	Hypertension (blood pressure >= 130 mmHg (systolic) and/or >=85 mmHg (diastolic)); Dyslipidemia (TG >= 1.7 mmol/L, HDL <1 mmol/L (males) or <1.3 mmol/L (females)); Obesity/Overweight (waist circumference >= 94 cm for men and >= 80 cm for women); Other (glucose level >= 5.5 mmol/L)	130
176	Jones, 2014, 24829493	Hypertension (blood pressure >= 130 mmHg (systolic) and/or >=85 mmHg (diastolic)); Dyslipidemia (TG >= 1.7 mmol/L, HDL <1 mmol/L (males) or <1.3 mmol/L (females)); Obesity/Overweight (waist circumference >= 94 cm for men and >= 80 cm for women); Other (glucose level >= 5.5 mmol/L)	130
177	Jones, 2014, 24829493	Hypertension (blood pressure >= 130 mmHg (systolic) and/or >=85 mmHg (diastolic)); Dyslipidemia (TG >= 1.7 mmol/L, HDL <1 mmol/L (males) or <1.3 mmol/L (females)); Obesity/Overweight (waist circumference >= 94 cm for men and >= 80 cm for women); Other (glucose level >= 5.5 mmol/L)	130
178	Jones, 2014, 24829493	Hypertension (blood pressure >= 130 mmHg (systolic) and/or >=85 mmHg (diastolic)); Dyslipidemia (TG >= 1.7 mmol/L, HDL <1 mmol/L (males) or <1.3 mmol/L (females)); Obesity/Overweight (waist circumference >= 94 cm for men and >= 80 cm for women); Other (glucose level >= 5.5 mmol/L)	130
179	Jones, 2014, 24829493	Hypertension (blood pressure >= 130 mmHg (systolic) and/or >=85 mmHg (diastolic)); Dyslipidemia (TG >= 1.7 mmol/L, HDL <1 mmol/L (males) or <1.3 mmol/L (females)); Obesity/Overweight (waist circumference >= 94 cm for men and >= 80 cm for women); Other (glucose level >= 5.5 mmol/L)	130
180	Jones, 2014, 24829493	Hypertension (blood pressure >= 130 mmHg (systolic) and/or >=85 mmHg (diastolic)); Dyslipidemia (TG >= 1.7 mmol/L, HDL <1 mmol/L (males) or <1.3 mmol/L (females)); Obesity/Overweight (waist circumference >= 94 cm for men and >= 80 cm for women); Other (glucose level >= 5.5 mmol/L)	130
181	Jones, 2014, 24829493	Hypertension (blood pressure >= 130 mmHg (systolic) and/or >=85 mmHg (diastolic)); Dyslipidemia (TG >= 1.7 mmol/L, HDL <1 mmol/L (males) or <1.3 mmol/L (females)); Obesity/Overweight (waist circumference >= 94 cm for men and >= 80 cm for women); Other (glucose level >= 5.5 mmol/L)	130
182	Jones, 2014, 24829493	Hypertension (blood pressure >= 130 mmHg (systolic) and/or >=85 mmHg (diastolic)); Dyslipidemia (TG >= 1.7 mmol/L, HDL <1 mmol/L (males) or <1.3 mmol/L (females)); Obesity/Overweight (waist circumference >= 94 cm for men and >= 80 cm for women); Other (glucose level >= 5.5 mmol/L)	130
183	Jones, 2014, 24829493	Hypertension (blood pressure >= 130 mmHg (systolic) and/or >=85 mmHg (diastolic)); Dyslipidemia (TG >= 1.7 mmol/L, HDL <1 mmol/L (males) or <1.3 mmol/L (females)); Obesity/Overweight (waist circumference >= 94 cm for men and >= 80 cm for women); Other (glucose level >= 5.5 mmol/L)	130
184	Jones, 2014, 24829493	Hypertension (blood pressure >= 130 mmHg (systolic) and/or >=85 mmHg (diastolic)); Dyslipidemia (TG >= 1.7 mmol/L, HDL <1 mmol/L (males) or <1.3 mmol/L (females)); Obesity/Overweight (waist circumference >= 94 cm for men and >= 80 cm for women); Other (glucose level >= 5.5 mmol/L)	130

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Age mean (SD) [median] years	Sex (% male)	Race
173	Holman, 2009, 19002433	[65 (5773)]	58	88 white
174	Holman, 2009, 19002433	[65 (5773)]	58	88 white
175	Jones, 2014, 24829493	46.46 (14.18)	54	nd
176	Jones, 2014, 24829493	46.46 (14.18)	54	nd
177	Jones, 2014, 24829493	46.46 (14.18)	54	nd
178	Jones, 2014, 24829493	46.46 (14.18)	54	nd
179	Jones, 2014, 24829493	46.46 (14.18)	54	nd
180	Jones, 2014, 24829493	46.46 (14.18)	54	nd
181	Jones, 2014, 24829493	46.46 (14.18)	54	nd
182	Jones, 2014, 24829493	46.46 (14.18)	54	nd
183	Jones, 2014, 24829493	46.46 (14.18)	54	nd
184	Jones, 2014, 24829493	46.46 (14.18)	54	nd

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Blood pressure SBP/DBP mmHg
173	Holman, 2009, 19002433	139.8 (15.9)/78.8 (9.2)
174	Holman, 2009, 19002433	139.8 (15.9)/78.8 (9.2)
175	Jones, 2014, 24829493	120.62 (16.70)/77.04 (11.80)
176	Jones, 2014, 24829493	120.62 (16.70)/77.04 (11.80)
177	Jones, 2014, 24829493	120.62 (16.70)/77.04 (11.80)
178	Jones, 2014, 24829493	120.62 (16.70)/77.04 (11.80)
179	Jones, 2014, 24829493	120.62 (16.70)/77.04 (11.80)
180	Jones, 2014, 24829493	120.62 (16.70)/77.04 (11.80)
181	Jones, 2014, 24829493	120.62 (16.70)/77.04 (11.80)
182	Jones, 2014, 24829493	120.62 (16.70)/77.04 (11.80)
183	Jones, 2014, 24829493	120.62 (16.70)/77.04 (11.80)
184	Jones, 2014, 24829493	120.62 (16.70)/77.04 (11.80)

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Lipids: Total cholesterol/LDL/HDL/Triglycerides mean (SD) mg/dL [mmol/L]
173	Holman, 2009, 19002433	[5.0 (1)]/[3.1 (0.8)]/[1.1 (0.9)]/[median 1.5 (1.2, 2.2)]
174	Holman, 2009, 19002433	[5.0 (1)]/[3.1 (0.8)]/[1.1 (0.9)]/[median 1.5 (1.2, 2.2)]
175	Jones, 2014, 24829493	[5.32 (1.05)]/[3.35 (0.93)]/[1.22 (0.29)]/[1.67 (0.88)]
176	Jones, 2014, 24829493	[5.32 (1.05)]/[3.35 (0.93)]/[1.22 (0.29)]/[1.67 (0.88)]
177	Jones, 2014, 24829493	[5.32 (1.05)]/[3.35 (0.93)]/[1.22 (0.29)]/[1.67 (0.88)]
178	Jones, 2014, 24829493	[5.32 (1.05)]/[3.35 (0.93)]/[1.22 (0.29)]/[1.67 (0.88)]
179	Jones, 2014, 24829493	[5.32 (1.05)]/[3.35 (0.93)]/[1.22 (0.29)]/[1.67 (0.88)]
180	Jones, 2014, 24829493	[5.32 (1.05)]/[3.35 (0.93)]/[1.22 (0.29)]/[1.67 (0.88)]
181	Jones, 2014, 24829493	[5.32 (1.05)]/[3.35 (0.93)]/[1.22 (0.29)]/[1.67 (0.88)]
182	Jones, 2014, 24829493	[5.32 (1.05)]/[3.35 (0.93)]/[1.22 (0.29)]/[1.67 (0.88)]
183	Jones, 2014, 24829493	[5.32 (1.05)]/[3.35 (0.93)]/[1.22 (0.29)]/[1.67 (0.88)]
184	Jones, 2014, 24829493	[5.32 (1.05)]/[3.35 (0.93)]/[1.22 (0.29)]/[1.67 (0.88)]

Row	Study	BMI mean (SD) Kg/m2/Weight mean (SD) Kg	Baseline n-3 intake	n-3 source (Baseline)
173	Holman, 2009, 19002433	30.6 (5.8)/87.3 (18.5)	nd	nd
174	Holman, 2009, 19002433	30.6 (5.8)/87.3 (18.5)	nd	nd
175	Jones, 2014, 24829493	29.8 (4.37)	nd	nd
176	Jones, 2014, 24829493	29.8 (4.37)	nd	nd
177	Jones, 2014, 24829493	29.8 (4.37)	nd	nd
178	Jones, 2014, 24829493	29.8 (4.37)	nd	nd
179	Jones, 2014, 24829493	29.8 (4.37)	nd	nd
180	Jones, 2014, 24829493	29.8 (4.37)	nd	nd
181	Jones, 2014, 24829493	29.8 (4.37)	nd	nd
182	Jones, 2014, 24829493	29.8 (4.37)	nd	nd
183	Jones, 2014, 24829493	29.8 (4.37)	nd	nd
184	Jones, 2014, 24829493	29.8 (4.37)	nd	nd

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	n-3 type(s)	n-3 measure	Study design	Outcome
173	Holman, 2009, 19002433	EPA+DHA(+/- atorvastatin) vs Placebo(+ atorvastatin)	g/d	Trial: Randomized Factorial Design	DBP
174	Holman, 2009, 19002433	EPA+DHA vs Placebo	g/d	Trial: Randomized Factorial Design	DBP
175	Jones, 2014, 24829493	ALA vs ALA	g/d	Trial: Randomized Cross-over	Total:HDL-c ratio
176	Jones, 2014, 24829493	ALA vs ALA	g/d	Trial: Randomized Cross-over	Total:HDL-c ratio
177	Jones, 2014, 24829493	ALA vs ALA	g/d	Trial: Randomized Cross-over	Total:HDL-c ratio
178	Jones, 2014, 24829493	ALA+EPA+DHA vs ALA	g/d	Trial: Randomized Cross-over	Total:HDL-c ratio
179	Jones, 2014, 24829493	ALA+EPA+DHA vs ALA	g/d	Trial: Randomized Cross-over	Total:HDL-c ratio
180	Jones, 2014, 24829493	ALA vs Placebo	g/d	Trial: Randomized Cross-over	HDL-c
181	Jones, 2014, 24829493	ALA vs ALA	g/d	Trial: Randomized Cross-over	HDL-c
182	Jones, 2014, 24829493	ALA vs ALA+DHA+EPA	g/d	Trial: Randomized Cross-over	HDL-c
183	Jones, 2014, 24829493	ALA vs Placebo	g/d	Trial: Randomized Cross-over	HDL-c
184	Jones, 2014, 24829493	ALA+DHA+EPA vs Placebo	g/d	Trial: Randomized Cross-over	HDL-c

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Reported effect Size	Dose/intake difference	Dose-corrected effect size
173	Holman, 2009, 19002433	-1 (-3.3, 1.3)	1.68	-0.5952381
174	Holman, 2009, 19002433	-1 (-3.1, 1.1)	1.68	-0.5952381
175	Jones, 2014, 24829493	0.15 (-0.18, 0.48)	5.7	0.0263158
176	Jones, 2014, 24829493	0.16 (-0.17, 0.49)	1.2	0.1333333
177	Jones, 2014, 24829493	-0.01 (-0.34, 0.32)	4.5	-0.0022222
178	Jones, 2014, 24829493	-0.16 (-0.49, 0.17)	NA	
179	Jones, 2014, 24829493	-0.31 (-0.64, 0.02)	NA	
180	Jones, 2014, 24829493	0.00 (-30.04, 30.04)	5.7	0
181	Jones, 2014, 24829493	0.77 (-29.27, 30.81)	4.5	0.1711111
182	Jones, 2014, 24829493	4.63 (-25.39, 34.66)	NA	
183	Jones, 2014, 24829493	-0.77 (-30.81, 29.27)	1.2	-0.6416667
184	Jones, 2014, 24829493	3.86 (-26.18, 33.90)	6	0.6433333

Row	Study	Outcome classification
173	Holman, 2009, 19002433	Secondary
174	Holman, 2009, 19002433	Secondary
175	Jones, 2014, 24829493	Secondary
176	Jones, 2014, 24829493	Secondary
177	Jones, 2014, 24829493	Secondary
178	Jones, 2014, 24829493	Secondary
179	Jones, 2014, 24829493	Secondary
180	Jones, 2014, 24829493	Secondary
181	Jones, 2014, 24829493	Secondary
182	Jones, 2014, 24829493	Secondary
183	Jones, 2014, 24829493	Secondary
184	Jones, 2014, 24829493	Secondary

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Study years (start date)	Country	Population
185	Jones, 2014, 24829493	2010	Canada	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
186	Jones, 2014, 24829493	2010	Canada	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
187	Jones, 2014, 24829493	2010	Canada	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
188	Jones, 2014, 24829493	2010	Canada	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
189	Jones, 2014, 24829493	2010	Canada	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
190	Jones, 2014, 24829493	2010	Canada	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
191	Jones, 2014, 24829493	2010	Canada	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
192	Jones, 2014, 24829493	2010	Canada	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
193	Jones, 2014, 24829493	2010	Canada	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
194	Jones, 2014, 24829493	2010	Canada	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
195	Jones, 2014, 24829493	2010	Canada	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
196	Jones, 2014, 24829493	2010	Canada	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)

Row	Study	Risk type	Sample size (total)
185	Jones, 2014, 24829493	Hypertension (blood pressure >= 130 mmHg (systolic) and/or >=85 mmHg (diastolic)); Dyslipidemia (TG >= 1.7 mmol/L, HDL <1 mmol/L (males) or <1.3 mmol/L (females)); Obesity/Overweight (waist circumference >= 94 cm for men and >= 80 cm for women); Other (glucose level >= 5.5 mmol/L)	130
186	Jones, 2014, 24829493	Hypertension (blood pressure >= 130 mmHg (systolic) and/or >=85 mmHg (diastolic)); Dyslipidemia (TG >= 1.7 mmol/L, HDL <1 mmol/L (males) or <1.3 mmol/L (females)); Obesity/Overweight (waist circumference >= 94 cm for men and >= 80 cm for women); Other (glucose level >= 5.5 mmol/L)	130
187	Jones, 2014, 24829493	Hypertension (blood pressure >= 130 mmHg (systolic) and/or >=85 mmHg (diastolic)); Dyslipidemia (TG >= 1.7 mmol/L, HDL <1 mmol/L (males) or <1.3 mmol/L (females)); Obesity/Overweight (waist circumference >= 94 cm for men and >= 80 cm for women); Other (glucose level >= 5.5 mmol/L)	130
188	Jones, 2014, 24829493	Hypertension (blood pressure >= 130 mmHg (systolic) and/or >=85 mmHg (diastolic)); Dyslipidemia (TG >= 1.7 mmol/L, HDL <1 mmol/L (males) or <1.3 mmol/L (females)); Obesity/Overweight (waist circumference >= 94 cm for men and >= 80 cm for women); Other (glucose level >= 5.5 mmol/L)	130
189	Jones, 2014, 24829493	Hypertension (blood pressure >= 130 mmHg (systolic) and/or >=85 mmHg (diastolic)); Dyslipidemia (TG >= 1.7 mmol/L, HDL <1 mmol/L (males) or <1.3 mmol/L (females)); Obesity/Overweight (waist circumference >= 94 cm for men and >= 80 cm for women); Other (glucose level >= 5.5 mmol/L)	130
190	Jones, 2014, 24829493	Hypertension (blood pressure >= 130 mmHg (systolic) and/or >=85 mmHg (diastolic)); Dyslipidemia (TG >= 1.7 mmol/L, HDL <1 mmol/L (males) or <1.3 mmol/L (females)); Obesity/Overweight (waist circumference >= 94 cm for men and >= 80 cm for women); Other (glucose level >= 5.5 mmol/L)	130
191	Jones, 2014, 24829493	Hypertension (blood pressure >= 130 mmHg (systolic) and/or >=85 mmHg (diastolic)); Dyslipidemia (TG >= 1.7 mmol/L, HDL <1 mmol/L (males) or <1.3 mmol/L (females)); Obesity/Overweight (waist circumference >= 94 cm for men and >= 80 cm for women); Other (glucose level >= 5.5 mmol/L)	130
192	Jones, 2014, 24829493	Hypertension (blood pressure >= 130 mmHg (systolic) and/or >=85 mmHg (diastolic)); Dyslipidemia (TG >= 1.7 mmol/L, HDL <1 mmol/L (males) or <1.3 mmol/L (females)); Obesity/Overweight (waist circumference >= 94 cm for men and >= 80 cm for women); Other (glucose level >= 5.5 mmol/L)	130
193	Jones, 2014, 24829493	Hypertension (blood pressure >= 130 mmHg (systolic) and/or >=85 mmHg (diastolic)); Dyslipidemia (TG >= 1.7 mmol/L, HDL <1 mmol/L (males) or <1.3 mmol/L (females)); Obesity/Overweight (waist circumference >= 94 cm for men and >= 80 cm for women); Other (glucose level >= 5.5 mmol/L)	130
194	Jones, 2014, 24829493	Hypertension (blood pressure >= 130 mmHg (systolic) and/or >=85 mmHg (diastolic)); Dyslipidemia (TG >= 1.7 mmol/L, HDL <1 mmol/L (males) or <1.3 mmol/L (females)); Obesity/Overweight (waist circumference >= 94 cm for men and >= 80 cm for women); Other (glucose level >= 5.5 mmol/L)	130
195	Jones, 2014, 24829493	Hypertension (blood pressure >= 130 mmHg (systolic) and/or >=85 mmHg (diastolic)); Dyslipidemia (TG >= 1.7 mmol/L, HDL <1 mmol/L (males) or <1.3 mmol/L (females)); Obesity/Overweight (waist circumference >= 94 cm for men and >= 80 cm for women); Other (glucose level >= 5.5 mmol/L)	130
196	Jones, 2014, 24829493	Hypertension (blood pressure >= 130 mmHg (systolic) and/or >=85 mmHg (diastolic)); Dyslipidemia (TG >= 1.7 mmol/L, HDL <1 mmol/L (males) or <1.3 mmol/L (females)); Obesity/Overweight (waist circumference >= 94 cm for men and >= 80 cm for women); Other (glucose level >= 5.5 mmol/L)	130

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Age mean (SD) [median] years	Sex (% male)	Race
185	Jones, 2014, 24829493	46.46 (14.18)	54	nd
186	Jones, 2014, 24829493	46.46 (14.18)	54	nd
187	Jones, 2014, 24829493	46.46 (14.18)	54	nd
188	Jones, 2014, 24829493	46.46 (14.18)	54	nd
189	Jones, 2014, 24829493	46.46 (14.18)	54	nd
190	Jones, 2014, 24829493	46.46 (14.18)	54	nd
191	Jones, 2014, 24829493	46.46 (14.18)	54	nd
192	Jones, 2014, 24829493	46.46 (14.18)	54	nd
193	Jones, 2014, 24829493	46.46 (14.18)	54	nd
194	Jones, 2014, 24829493	46.46 (14.18)	54	nd
195	Jones, 2014, 24829493	46.46 (14.18)	54	nd
196	Jones, 2014, 24829493	46.46 (14.18)	54	nd

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Blood pressure SBP/DBP mmHg
185	Jones, 2014, 24829493	120.62 (16.70)/77.04 (11.80)
186	Jones, 2014, 24829493	120.62 (16.70)/77.04 (11.80)
187	Jones, 2014, 24829493	120.62 (16.70)/77.04 (11.80)
188	Jones, 2014, 24829493	120.62 (16.70)/77.04 (11.80)
189	Jones, 2014, 24829493	120.62 (16.70)/77.04 (11.80)
190	Jones, 2014, 24829493	120.62 (16.70)/77.04 (11.80)
191	Jones, 2014, 24829493	120.62 (16.70)/77.04 (11.80)
192	Jones, 2014, 24829493	120.62 (16.70)/77.04 (11.80)
193	Jones, 2014, 24829493	120.62 (16.70)/77.04 (11.80)
194	Jones, 2014, 24829493	120.62 (16.70)/77.04 (11.80)
195	Jones, 2014, 24829493	120.62 (16.70)/77.04 (11.80)
196	Jones, 2014, 24829493	120.62 (16.70)/77.04 (11.80)

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Lipids: Total cholesterol/LDL/HDL/Triglycerides mean (SD) mg/dL [mmol/L]
185	Jones, 2014, 24829493	[5.32 (1.05)]/[3.35 (0.93)]/[1.22 (0.29)]/[1.67 (0.88)]
186	Jones, 2014, 24829493	[5.32 (1.05)]/[3.35 (0.93)]/[1.22 (0.29)]/[1.67 (0.88)]
187	Jones, 2014, 24829493	[5.32 (1.05)]/[3.35 (0.93)]/[1.22 (0.29)]/[1.67 (0.88)]
188	Jones, 2014, 24829493	[5.32 (1.05)]/[3.35 (0.93)]/[1.22 (0.29)]/[1.67 (0.88)]
189	Jones, 2014, 24829493	[5.32 (1.05)]/[3.35 (0.93)]/[1.22 (0.29)]/[1.67 (0.88)]
190	Jones, 2014, 24829493	[5.32 (1.05)]/[3.35 (0.93)]/[1.22 (0.29)]/[1.67 (0.88)]
191	Jones, 2014, 24829493	[5.32 (1.05)]/[3.35 (0.93)]/[1.22 (0.29)]/[1.67 (0.88)]
192	Jones, 2014, 24829493	[5.32 (1.05)]/[3.35 (0.93)]/[1.22 (0.29)]/[1.67 (0.88)]
193	Jones, 2014, 24829493	[5.32 (1.05)]/[3.35 (0.93)]/[1.22 (0.29)]/[1.67 (0.88)]
194	Jones, 2014, 24829493	[5.32 (1.05)]/[3.35 (0.93)]/[1.22 (0.29)]/[1.67 (0.88)]
195	Jones, 2014, 24829493	[5.32 (1.05)]/[3.35 (0.93)]/[1.22 (0.29)]/[1.67 (0.88)]
196	Jones, 2014, 24829493	[5.32 (1.05)]/[3.35 (0.93)]/[1.22 (0.29)]/[1.67 (0.88)]

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	BMI mean (SD) Kg/m2/Weight mean (SD) Kg	Baseline n-3 intake	n-3 source (Baseline)
185	Jones, 2014, 24829493	29.8 (4.37)	nd	nd
186	Jones, 2014, 24829493	29.8 (4.37)	nd	nd
187	Jones, 2014, 24829493	29.8 (4.37)	nd	nd
188	Jones, 2014, 24829493	29.8 (4.37)	nd	nd
189	Jones, 2014, 24829493	29.8 (4.37)	nd	nd
190	Jones, 2014, 24829493	29.8 (4.37)	nd	nd
191	Jones, 2014, 24829493	29.8 (4.37)	nd	nd
192	Jones, 2014, 24829493	29.8 (4.37)	nd	nd
193	Jones, 2014, 24829493	29.8 (4.37)	nd	nd
194	Jones, 2014, 24829493	29.8 (4.37)	nd	nd
195	Jones, 2014, 24829493	29.8 (4.37)	nd	nd
196	Jones, 2014, 24829493	29.8 (4.37)	nd	nd

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	n-3 type(s)	n-3 measure	Study design	Outcome
185	Jones, 2014, 24829493	ALA vs Placebo	g/d	Trial: Randomized Cross-over	LDL-c
186	Jones, 2014, 24829493	ALA vs ALA	g/d	Trial: Randomized Cross-over	LDL-c
187	Jones, 2014, 24829493	ALA vs ALA+DHA+EPA	g/d	Trial: Randomized Cross-over	LDL-c
188	Jones, 2014, 24829493	ALA vs Placebo	g/d	Trial: Randomized Cross-over	LDL-c
189	Jones, 2014, 24829493	ALA+DHA+EPA vs Placebo	g/d	Trial: Randomized Cross-over	LDL-c
190	Jones, 2014, 24829493	ALA vs Placebo	g/d	Trial: Randomized Cross-over	Tg
191	Jones, 2014, 24829493	ALA vs ALA	g/d	Trial: Randomized Cross-over	Tg
192	Jones, 2014, 24829493	ALA vs ALA+DHA+EPA	g/d	Trial: Randomized Cross-over	Tg
193	Jones, 2014, 24829493	ALA vs Placebo	g/d	Trial: Randomized Cross-over	Tg
194	Jones, 2014, 24829493	ALA + DHA + EPA vs Placebo	g/d	Trial: Randomized Cross-over	Tg
195	Jones, 2014, 24829493	ALA vs Placebo	g/d	Trial: Randomized Cross-over	SBP
196	Jones, 2014, 24829493	ALA vs Placebo	g/d	Trial: Randomized Cross-over	SBP

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Reported effect Size	Dose/intake difference	Dose-corrected effect size
185	Jones, 2014, 24829493	2.32 (-93.22, 97.86)	5.7	0.4070175
186	Jones, 2014, 24829493	1.94 (-93.60, 97.48)	4.5	0.4311111
187	Jones, 2014, 24829493	6.18 (-89.35, 101.72)	NA	
188	Jones, 2014, 24829493	0.38 (-95.16, 95.92)	1.2	0.3166667
189	Jones, 2014, 24829493	6.56 (-88.98, 102.10)	6	1.093333
190	Jones, 2014, 24829493	3.54 (-18.72, 25.80)	5.7	0.6210526
191	Jones, 2014, 24829493	-3.54 (-208.25, 201.17)	4.5	-0.7866667
192	Jones, 2014, 24829493	-34.51 (-239.22, 170.19)	0.3	-115.0333
193	Jones, 2014, 24829493	7.08 (-197.63, 211.79)	1.2	5.9
194	Jones, 2014, 24829493	-27.43 (-232.14, 177.28)	6	-4.571667
195	Jones, 2014, 24829493	-1.1 (-43.9, 41.8)	5.9	-0.1864407
196	Jones, 2014, 24829493	0.1 (-42.8, 42.9)	1.38	0.0724638

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Outcome classification
185	Jones, 2014, 24829493	Secondary
186	Jones, 2014, 24829493	Secondary
187	Jones, 2014, 24829493	Secondary
188	Jones, 2014, 24829493	Secondary
189	Jones, 2014, 24829493	Secondary
190	Jones, 2014, 24829493	Secondary
191	Jones, 2014, 24829493	Secondary
192	Jones, 2014, 24829493	Secondary
193	Jones, 2014, 24829493	Secondary
194	Jones, 2014, 24829493	Secondary
195	Jones, 2014, 24829493	Secondary
196	Jones, 2014, 24829493	Secondary

Row	Study	Study years (start date)	Country	Population
197	Jones, 2014, 24829493	2010	Canada	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
198	Jones, 2014, 24829493	2010	Canada	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
199	Jones, 2014, 24829493	2010	Canada	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
200	Jones, 2014, 24829493	2010	Canada	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
201	Jones, 2014, 24829493	2010	Canada	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
202	Jones, 2014, 24829493	2010	Canada	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
203	Jones, 2014, 24829493	2010	Canada	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
204	Jones, 2014, 24829493	2010	Canada	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
205	Kastelein, 2014, 24528690	2011	US, Denmark, Netherlands, India, Hungary, Ukraine, Russia	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
206	Kastelein, 2014, 24528690	2011	US, Denmark, Netherlands, India, Hungary, Ukraine, Russia	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)

Row	Study	Risk type	Sample size (total)
197	Jones, 2014, 24829493	Hypertension (blood pressure >= 130 mmHg (systolic) and/or >=85 mmHg (diastolic)); Dyslipidemia (TG >= 1.7 mmol/L, HDL <1 mmol/L (males) or <1.3 mmol/L (females)); Obesity/Overweight (waist circumference >= 94 cm for men and >= 80 cm for women); Other (glucose level >= 5.5 mmol/L)	130
198	Jones, 2014, 24829493	Hypertension (blood pressure >= 130 mmHg (systolic) and/or >=85 mmHg (diastolic)); Dyslipidemia (TG >= 1.7 mmol/L, HDL <1 mmol/L (males) or <1.3 mmol/L (females)); Obesity/Overweight (waist circumference >= 94 cm for men and >= 80 cm for women); Other (glucose level >= 5.5 mmol/L)	130
199	Jones, 2014, 24829493	Hypertension (blood pressure >= 130 mmHg (systolic) and/or >=85 mmHg (diastolic)); Dyslipidemia (TG >= 1.7 mmol/L, HDL <1 mmol/L (males) or <1.3 mmol/L (females)); Obesity/Overweight (waist circumference >= 94 cm for men and >= 80 cm for women); Other (glucose level >= 5.5 mmol/L)	130
200	Jones, 2014, 24829493	Hypertension (blood pressure >= 130 mmHg (systolic) and/or >=85 mmHg (diastolic)); Dyslipidemia (TG >= 1.7 mmol/L, HDL <1 mmol/L (males) or <1.3 mmol/L (females)); Obesity/Overweight (waist circumference >= 94 cm for men and >= 80 cm for women); Other (glucose level >= 5.5 mmol/L)	130
201	Jones, 2014, 24829493	Hypertension (blood pressure >= 130 mmHg (systolic) and/or >=85 mmHg (diastolic)); Dyslipidemia (TG >= 1.7 mmol/L, HDL <1 mmol/L (males) or <1.3 mmol/L (females)); Obesity/Overweight (waist circumference >= 94 cm for men and >= 80 cm for women); Other (glucose level >= 5.5 mmol/L)	130
202	Jones, 2014, 24829493	Hypertension (blood pressure >= 130 mmHg (systolic) and/or >=85 mmHg (diastolic)); Dyslipidemia (TG >= 1.7 mmol/L, HDL <1 mmol/L (males) or <1.3 mmol/L (females)); Obesity/Overweight (waist circumference >= 94 cm for men and >= 80 cm for women); Other (glucose level >= 5.5 mmol/L)	130
203	Jones, 2014, 24829493	Hypertension (blood pressure >= 130 mmHg (systolic) and/or >=85 mmHg (diastolic)); Dyslipidemia (TG >= 1.7 mmol/L, HDL <1 mmol/L (males) or <1.3 mmol/L (females)); Obesity/Overweight (waist circumference >= 94 cm for men and >= 80 cm for women); Other (glucose level >= 5.5 mmol/L)	130
204	Jones, 2014, 24829493	Hypertension (blood pressure >= 130 mmHg (systolic) and/or >=85 mmHg (diastolic)); Dyslipidemia (TG >= 1.7 mmol/L, HDL <1 mmol/L (males) or <1.3 mmol/L (females)); Obesity/Overweight (waist circumference >= 94 cm for men and >= 80 cm for women); Other (glucose level >= 5.5 mmol/L)	130
205	Kastelein, 2014, 24528690	Dyslipidemia (average serum TG concentrations 500-2000 mg/dL); Obesity/Overweight (body mass index >=20)	393
206	Kastelein, 2014, 24528690	Dyslipidemia (average serum TG concentrations 500-2000 mg/dL); Obesity/Overweight (body mass index >=20)	393

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Age mean (SD) [median] years	Sex (% male)	Race
197	Jones, 2014, 24829493	46.46 (14.18)	54	nd
198	Jones, 2014, 24829493	46.46 (14.18)	54	nd
199	Jones, 2014, 24829493	46.46 (14.18)	54	nd
200	Jones, 2014, 24829493	46.46 (14.18)	54	nd
201	Jones, 2014, 24829493	46.46 (14.18)	54	nd
202	Jones, 2014, 24829493	46.46 (14.18)	54	nd
203	Jones, 2014, 24829493	46.46 (14.18)	54	nd
204	Jones, 2014, 24829493	46.46 (14.18)	54	nd
205	Kastelein, 2014, 24528690	50.8 (10.6)	77.8	96 white, 4 Asian, 6.1 Hispanic
206	Kastelein, 2014, 24528690	50.8 (10.6)	77.8	96 white, 4 Asian, 6.1 Hispanic

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Blood pressure SBP/DBP mmHg
197	Jones, 2014, 24829493	120.62 (16.70)/77.04 (11.80)
198	Jones, 2014, 24829493	120.62 (16.70)/77.04 (11.80)
199	Jones, 2014, 24829493	120.62 (16.70)/77.04 (11.80)
200	Jones, 2014, 24829493	120.62 (16.70)/77.04 (11.80)
201	Jones, 2014, 24829493	120.62 (16.70)/77.04 (11.80)
202	Jones, 2014, 24829493	120.62 (16.70)/77.04 (11.80)
203	Jones, 2014, 24829493	120.62 (16.70)/77.04 (11.80)
204	Jones, 2014, 24829493	120.62 (16.70)/77.04 (11.80)
205	Kastelein, 2014, 24528690	130.4 (12.1)/80.5 (6.2)
206	Kastelein, 2014, 24528690	130.4 (12.1)/80.5 (6.2)

Row	Study	Lipids: Total cholesterol/LDL/HDL/Triglycerides mean (SD) mg/dL [mmol/L]
197	Jones, 2014, 24829493	[5.32 (1.05)]/[3.35 (0.93)]/[1.22 (0.29)]/[1.67 (0.88)]
198	Jones, 2014, 24829493	[5.32 (1.05)]/[3.35 (0.93)]/[1.22 (0.29)]/[1.67 (0.88)]
199	Jones, 2014, 24829493	[5.32 (1.05)]/[3.35 (0.93)]/[1.22 (0.29)]/[1.67 (0.88)]
200	Jones, 2014, 24829493	[5.32 (1.05)]/[3.35 (0.93)]/[1.22 (0.29)]/[1.67 (0.88)]
201	Jones, 2014, 24829493	[5.32 (1.05)]/[3.35 (0.93)]/[1.22 (0.29)]/[1.67 (0.88)]
202	Jones, 2014, 24829493	[5.32 (1.05)]/[3.35 (0.93)]/[1.22 (0.29)]/[1.67 (0.88)]
203	Jones, 2014, 24829493	[5.32 (1.05)]/[3.35 (0.93)]/[1.22 (0.29)]/[1.67 (0.88)]
204	Jones, 2014, 24829493	[5.32 (1.05)]/[3.35 (0.93)]/[1.22 (0.29)]/[1.67 (0.88)]
205	Kastelein, 2014, 24528690	Median 241 (range 131, 542)/median 77.3 (range 19.7, 182)/median 27.3 (range 13.3, 47.3)/median 717 (range 415, 1578)
206	Kastelein, 2014, 24528690	Median 241 (range 131, 542)/median 77.3 (range 19.7, 182)/median 27.3 (range 13.3, 47.3)/median 717 (range 415, 1578)

Row	Study	BMI mean (SD) Kg/m2/Weight mean (SD) Kg	Baseline n-3 intake	n-3 source (Baseline)
197	Jones, 2014, 24829493	29.8 (4.37)	nd	nd
198	Jones, 2014, 24829493	29.8 (4.37)	nd	nd
199	Jones, 2014, 24829493	29.8 (4.37)	nd	nd
200	Jones, 2014, 24829493	29.8 (4.37)	nd	nd
201	Jones, 2014, 24829493	29.8 (4.37)	nd	nd
202	Jones, 2014, 24829493	29.8 (4.37)	nd	nd
203	Jones, 2014, 24829493	29.8 (4.37)	nd	nd
204	Jones, 2014, 24829493	29.8 (4.37)	nd	nd
205	Kastelein, 2014, 24528690	30.4 (4.3)	ALA: median 375 (range 105, 1182) µg/mL, EPA: median 19.5 (range 6.3, 207) µg/mL, DHA: median 85.1 (range 29.7, 411) µg/mL	plasma
206	Kastelein, 2014, 24528690	30.4 (4.3)	ALA: median 375 (range 105, 1182) µg/mL, EPA: median 19.5 (range 6.3, 207) µg/mL, DHA: median 85.1 (range 29.7, 411) µg/mL	plasma

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	n-3 type(s)	n-3 measure	Study design	Outcome
197	Jones, 2014, 24829493	ALA vs ALA	g/d	Trial: Randomized Cross-over	SBP
198	Jones, 2014, 24829493	ALA + DHA + EPA vs Placebo	g/d	Trial: Randomized Cross-over	SBP
199	Jones, 2014, 24829493	ALA + DHA + EPA vs ALA	g/d	Trial: Randomized Cross-over	SBP
200	Jones, 2014, 24829493	ALA vs Placebo	g/d	Trial: Randomized Cross-over	DBP
201	Jones, 2014, 24829493	ALA vs Placebo	g/d	Trial: Randomized Cross-over	DBP
202	Jones, 2014, 24829493	ALA vs ALA	g/d	Trial: Randomized Cross-over	DBP
203	Jones, 2014, 24829493	ALA+DHA+EPA (Canola DHA) vs Placebo	g/d	Trial: Randomized Cross-over	DBP
204	Jones, 2014, 24829493	ALA+DHA+EPA (Canola DHA) vs ALA	g/d	Trial: Randomized Cross-over	DBP
205	Kastelein, 2014, 24528690	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Total:HDL-c ratio
206	Kastelein, 2014, 24528690	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Total:HDL-c ratio

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Reported effect Size	Dose/intake difference	Dose-corrected effect size
197	Jones, 2014, 24829493	-1.2 (-44, 41.7)	4.52	-0.2654867
198	Jones, 2014, 24829493	-1.1 (-43.9, 41.8)	6.24	-0.176282
199	Jones, 2014, 24829493	-1.2 (-44, 41.7)	NA	
200	Jones, 2014, 24829493	0 (-28.8, 28.8)	5.9	0
201	Jones, 2014, 24829493	-0.3 (-36.2, 35.6)	1.38	-0.2173913
202	Jones, 2014, 24829493	0.3 (-35.6, 36.2)	4.52	0.0663717
203	Jones, 2014, 24829493	-2.5 (-31.3, 26.3)	6.24	-0.400641
204	Jones, 2014, 24829493	-2.2 (-38.1, 33.8)	NA	
205	Kastelein, 2014, 24528690	-1.2 (-1.6, -0.3)	3	-0.4
206	Kastelein, 2014, 24528690	-0.8 (-1.3, -0.2)	2.25	-0.3555556

Row	Study	Outcome classification
197	Jones, 2014, 24829493	Secondary
198	Jones, 2014, 24829493	Secondary
199	Jones, 2014, 24829493	Secondary
200	Jones, 2014, 24829493	Secondary
201	Jones, 2014, 24829493	Secondary
202	Jones, 2014, 24829493	Secondary
203	Jones, 2014, 24829493	Secondary
204	Jones, 2014, 24829493	Secondary
205	Kastelein, 2014, 24528690	Secondary
206	Kastelein, 2014, 24528690	Secondary

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Study years (start date)	Country	Population
207	Kastelein, 2014, 24528690	2011	US, Denmark, Netherlands, India, Hungary, Ukraine, Russia	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
208	Kastelein, 2014, 24528690	2011	US, Denmark, Netherlands, India, Hungary, Ukraine, Russia	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
209	Kastelein, 2014, 24528690	2011	US, Denmark, Netherlands, India, Hungary, Ukraine, Russia	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
210	Kastelein, 2014, 24528690	2011	US, Denmark, Netherlands, India, Hungary, Ukraine, Russia	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
211	Kastelein, 2014, 24528690	2011	US, Denmark, Netherlands, India, Hungary, Ukraine, Russia	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
212	Kastelein, 2014, 24528690	2011	US, Denmark, Netherlands, India, Hungary, Ukraine, Russia	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
213	Kastelein, 2014, 24528690	2011	US, Denmark, Netherlands, India, Hungary, Ukraine, Russia	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)

Row	Study	Risk type	Sample size (total)
207	Kastelein, 2014, 24528690	Dyslipidemia (average serum TG concentrations 500-2000 mg/dL); Obesity/Overweight (body mass index >=20)	393
208	Kastelein, 2014, 24528690	Dyslipidemia (average serum TG concentrations 500-2000 mg/dL); Obesity/Overweight (body mass index >=20)	393
209	Kastelein, 2014, 24528690	Dyslipidemia (average serum TG concentrations 500-2000 mg/dL); Obesity/Overweight (body mass index >=20)	393
210	Kastelein, 2014, 24528690	Dyslipidemia (average serum TG concentrations 500-2000 mg/dL); Obesity/Overweight (body mass index >=20)	393
211	Kastelein, 2014, 24528690	Dyslipidemia (average serum TG concentrations 500-2000 mg/dL); Obesity/Overweight (body mass index >=20)	393
212	Kastelein, 2014, 24528690	Dyslipidemia (average serum TG concentrations 500-2000 mg/dL); Obesity/Overweight (body mass index >=20)	393
213	Kastelein, 2014, 24528690	Dyslipidemia (average serum TG concentrations 500-2000 mg/dL); Obesity/Overweight (body mass index >=20)	393

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Age mean (SD) [median] years	Sex (% male)	Race
207	Kastelein, 2014, 24528690	50.8 (10.6)	77.8	96 white, 4 Asian, 6.1 Hispanic
208	Kastelein, 2014, 24528690	50.8 (10.6)	77.8	96 white, 4 Asian, 6.1 Hispanic
209	Kastelein, 2014, 24528690	50.8 (10.6)	77.8	96 white, 4 Asian, 6.1 Hispanic
210	Kastelein, 2014, 24528690	50.8 (10.6)	77.8	96 white, 4 Asian, 6.1 Hispanic
211	Kastelein, 2014, 24528690	50.8 (10.6)	77.8	96 white, 4 Asian, 6.1 Hispanic
212	Kastelein, 2014, 24528690	50.8 (10.6)	77.8	96 white, 4 Asian, 6.1 Hispanic
213	Kastelein, 2014, 24528690	50.8 (10.6)	77.8	96 white, 4 Asian, 6.1 Hispanic

Row	Study	Blood pressure SBP/DBP mmHg
207	Kastelein, 2014, 24528690	130.4 (12.1)/80.5 (6.2)
208	Kastelein, 2014, 24528690	130.4 (12.1)/80.5 (6.2)
209	Kastelein, 2014, 24528690	130.4 (12.1)/80.5 (6.2)
210	Kastelein, 2014, 24528690	130.4 (12.1)/80.5 (6.2)
211	Kastelein, 2014, 24528690	130.4 (12.1)/80.5 (6.2)
212	Kastelein, 2014, 24528690	130.4 (12.1)/80.5 (6.2)
213	Kastelein, 2014, 24528690	130.4 (12.1)/80.5 (6.2)

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Lipids: Total cholesterol/LDL/HDL/Triglycerides mean (SD) mg/dL [mmol/L]
207	Kastelein, 2014, 24528690	Median 241 (range 131, 542)/median 77.3 (range 19.7, 182)/median 27.3 (range 13.3, 47.3)/median 717 (range 415, 1578)
208	Kastelein, 2014, 24528690	Median 241 (range 131, 542)/median 77.3 (range 19.7, 182)/median 27.3 (range 13.3, 47.3)/median 717 (range 415, 1578)
209	Kastelein, 2014, 24528690	Median 241 (range 131, 542)/median 77.3 (range 19.7, 182)/median 27.3 (range 13.3, 47.3)/median 717 (range 415, 1578)
210	Kastelein, 2014, 24528690	Median 241 (range 131, 542)/median 77.3 (range 19.7, 182)/median 27.3 (range 13.3, 47.3)/median 717 (range 415, 1578)
211	Kastelein, 2014, 24528690	Median 241 (range 131, 542)/median 77.3 (range 19.7, 182)/median 27.3 (range 13.3, 47.3)/median 717 (range 415, 1578)
212	Kastelein, 2014, 24528690	Median 241 (range 131, 542)/median 77.3 (range 19.7, 182)/median 27.3 (range 13.3, 47.3)/median 717 (range 415, 1578)
213	Kastelein, 2014, 24528690	Median 241 (range 131, 542)/median 77.3 (range 19.7, 182)/median 27.3 (range 13.3, 47.3)/median 717 (range 415, 1578)

Row	Study	BMI mean (SD) Kg/m2/Weight mean (SD) Kg	Baseline n-3 intake	n-3 source (Baseline)
207	Kastelein, 2014, 24528690	30.4 (4.3)	ALA: median 375 (range 105, 1182) µg/mL, EPA: median 19.5 (range 6.3, 207) µg/mL, DHA: median 85.1 (range 29.7, 411) µg/mL	plasma
208	Kastelein, 2014, 24528690	30.4 (4.3)	ALA: median 375 (range 105, 1182) µg/mL, EPA: median 19.5 (range 6.3, 207) µg/mL, DHA: median 85.1 (range 29.7, 411) µg/mL	plasma
209	Kastelein, 2014, 24528690	30.4 (4.3)	ALA: median 375 (range 105, 1182) µg/mL, EPA: median 19.5 (range 6.3, 207) µg/mL, DHA: median 85.1 (range 29.7, 411) µg/mL	plasma
210	Kastelein, 2014, 24528690	30.4 (4.3)	ALA: median 375 (range 105, 1182) µg/mL, EPA: median 19.5 (range 6.3, 207) µg/mL, DHA: median 85.1 (range 29.7, 411) µg/mL	plasma
211	Kastelein, 2014, 24528690	30.4 (4.3)	ALA: median 375 (range 105, 1182) µg/mL, EPA: median 19.5 (range 6.3, 207) µg/mL, DHA: median 85.1 (range 29.7, 411) µg/mL	plasma
212	Kastelein, 2014, 24528690	30.4 (4.3)	ALA: median 375 (range 105, 1182) µg/mL, EPA: median 19.5 (range 6.3, 207) µg/mL, DHA: median 85.1 (range 29.7, 411) µg/mL	plasma
213	Kastelein, 2014, 24528690	30.4 (4.3)	ALA: median 375 (range 105, 1182) µg/mL, EPA: median 19.5 (range 6.3, 207) µg/mL, DHA: median 85.1 (range 29.7, 411) µg/mL	plasma

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	n-3 type(s)	n-3 measure	Study design	Outcome
207	Kastelein, 2014, 24528690	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Total:HDL-c ratio
208	Kastelein, 2014, 24528690	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Parallel	Total:HDL-c ratio
209	Kastelein, 2014, 24528690	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Parallel	Total:HDL-c ratio
210	Kastelein, 2014, 24528690	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Parallel	Total:HDL-c ratio
211	Kastelein, 2014, 24528690	EPA+DHA vs Placebo	µg/mL	Trial: Randomized Parallel	HDL-c
212	Kastelein, 2014, 24528690	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	HDL-c
213	Kastelein, 2014, 24528690	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	HDL-c

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Reported effect Size	Dose/intake difference	Dose-corrected effect size
207	Kastelein, 2014, 24528690	-1.0 (-1.5, -0.5)	1.5	-0.6666667
208	Kastelein, 2014, 24528690	-1.2 (-1.7, -0.6)	0.75	-1.6
209	Kastelein, 2014, 24528690	-1.2 (-1.6, -0.6)	1.5	-0.8
210	Kastelein, 2014, 24528690	-0.8 (-1.3, -0.2)	0.75	-1.066667
211	Kastelein, 2014, 24528690	0.40 (nd)	1.5	0.2666667
212	Kastelein, 2014, 24528690	-0.80 (nd)	2.25	-0.3555556
213	Kastelein, 2014, 24528690	-1.00 (nd)	3	-0.3333333

Row	Study	Outcome classification
207	Kastelein, 2014, 24528690	Secondary
208	Kastelein, 2014, 24528690	Secondary
209	Kastelein, 2014, 24528690	Secondary
210	Kastelein, 2014, 24528690	Secondary
211	Kastelein, 2014, 24528690	Secondary
212	Kastelein, 2014, 24528690	Secondary
213	Kastelein, 2014, 24528690	Secondary

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Study years (start date)	Country	Population
214	Kastelein, 2014, 24528690	2011	US, Denmark, Netherlands, India, Hungary, Ukraine, Russia	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
215	Kastelein, 2014, 24528690	2011	US, Denmark, Netherlands, India, Hungary, Ukraine, Russia	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
216	Kastelein, 2014, 24528690	2011	US, Denmark, Netherlands, India, Hungary, Ukraine, Russia	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
217	Kastelein, 2014, 24528690	2011	US, Denmark, Netherlands, India, Hungary, Ukraine, Russia	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
218	Kastelein, 2014, 24528690	2011	US, Denmark, Netherlands, India, Hungary, Ukraine, Russia	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
219	Kastelein, 2014, 24528690	2011	US, Denmark, Netherlands, India, Hungary, Ukraine, Russia	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
220	Kastelein, 2014, 24528690	2011	US, Denmark, Netherlands, India, Hungary, Ukraine, Russia	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)

Row	Study	Risk type	Sample size (total)
214	Kastelein, 2014, 24528690	Dyslipidemia (average serum TG concentrations 500-2000 mg/dL); Obesity/Overweight (body mass index >=20)	393
215	Kastelein, 2014, 24528690	Dyslipidemia (average serum TG concentrations 500-2000 mg/dL); Obesity/Overweight (body mass index >=20)	393
216	Kastelein, 2014, 24528690	Dyslipidemia (average serum TG concentrations 500-2000 mg/dL); Obesity/Overweight (body mass index >=20)	393
217	Kastelein, 2014, 24528690	Dyslipidemia (average serum TG concentrations 500-2000 mg/dL); Obesity/Overweight (body mass index >=20)	393
218	Kastelein, 2014, 24528690	Dyslipidemia (average serum TG concentrations 500-2000 mg/dL); Obesity/Overweight (body mass index >=20)	393
219	Kastelein, 2014, 24528690	Dyslipidemia (average serum TG concentrations 500-2000 mg/dL); Obesity/Overweight (body mass index >=20)	393
220	Kastelein, 2014, 24528690	Dyslipidemia (average serum TG concentrations 500-2000 mg/dL); Obesity/Overweight (body mass index >=20)	393

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Age mean (SD) [median] years	Sex (% male)	Race
214	Kastelein, 2014, 24528690	50.8 (10.6)	77.8	96 white, 4 Asian, 6.1 Hispanic
215	Kastelein, 2014, 24528690	50.8 (10.6)	77.8	96 white, 4 Asian, 6.1 Hispanic
216	Kastelein, 2014, 24528690	50.8 (10.6)	77.8	96 white, 4 Asian, 6.1 Hispanic
217	Kastelein, 2014, 24528690	50.8 (10.6)	77.8	96 white, 4 Asian, 6.1 Hispanic
218	Kastelein, 2014, 24528690	50.8 (10.6)	77.8	96 white, 4 Asian, 6.1 Hispanic
219	Kastelein, 2014, 24528690	50.8 (10.6)	77.8	96 white, 4 Asian, 6.1 Hispanic
220	Kastelein, 2014, 24528690	50.8 (10.6)	77.8	96 white, 4 Asian, 6.1 Hispanic

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Blood pressure SBP/DBP mmHg
214	Kastelein, 2014, 24528690	130.4 (12.1)/80.5 (6.2)
215	Kastelein, 2014, 24528690	130.4 (12.1)/80.5 (6.2)
216	Kastelein, 2014, 24528690	130.4 (12.1)/80.5 (6.2)
217	Kastelein, 2014, 24528690	130.4 (12.1)/80.5 (6.2)
218	Kastelein, 2014, 24528690	130.4 (12.1)/80.5 (6.2)
219	Kastelein, 2014, 24528690	130.4 (12.1)/80.5 (6.2)
220	Kastelein, 2014, 24528690	130.4 (12.1)/80.5 (6.2)

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Lipids: Total cholesterol/LDL/HDL/Triglycerides mean (SD) mg/dL [mmol/L]
214	Kastelein, 2014, 24528690	Median 241 (range 131, 542)/median 77.3 (range 19.7, 182)/median 27.3 (range 13.3, 47.3)/median 717 (range 415, 1578)
215	Kastelein, 2014, 24528690	Median 241 (range 131, 542)/median 77.3 (range 19.7, 182)/median 27.3 (range 13.3, 47.3)/median 717 (range 415, 1578)
216	Kastelein, 2014, 24528690	Median 241 (range 131, 542)/median 77.3 (range 19.7, 182)/median 27.3 (range 13.3, 47.3)/median 717 (range 415, 1578)
217	Kastelein, 2014, 24528690	Median 241 (range 131, 542)/median 77.3 (range 19.7, 182)/median 27.3 (range 13.3, 47.3)/median 717 (range 415, 1578)
218	Kastelein, 2014, 24528690	Median 241 (range 131, 542)/median 77.3 (range 19.7, 182)/median 27.3 (range 13.3, 47.3)/median 717 (range 415, 1578)
219	Kastelein, 2014, 24528690	Median 241 (range 131, 542)/median 77.3 (range 19.7, 182)/median 27.3 (range 13.3, 47.3)/median 717 (range 415, 1578)
220	Kastelein, 2014, 24528690	Median 241 (range 131, 542)/median 77.3 (range 19.7, 182)/median 27.3 (range 13.3, 47.3)/median 717 (range 415, 1578)

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	BMI mean (SD) Kg/m2/Weight mean (SD) Kg	Baseline n-3 intake	n-3 source (Baseline)
214	Kastelein, 2014, 24528690	30.4 (4.3)	ALA: median 375 (range 105, 1182) µg/mL, EPA: median 19.5 (range 6.3, 207) µg/mL, DHA: median 85.1 (range 29.7, 411) µg/mL	plasma
215	Kastelein, 2014, 24528690	30.4 (4.3)	ALA: median 375 (range 105, 1182) µg/mL, EPA: median 19.5 (range 6.3, 207) µg/mL, DHA: median 85.1 (range 29.7, 411) µg/mL	plasma
216	Kastelein, 2014, 24528690	30.4 (4.3)	ALA: median 375 (range 105, 1182) µg/mL, EPA: median 19.5 (range 6.3, 207) µg/mL, DHA: median 85.1 (range 29.7, 411) µg/mL	plasma
217	Kastelein, 2014, 24528690	30.4 (4.3)	ALA: median 375 (range 105, 1182) µg/mL, EPA: median 19.5 (range 6.3, 207) µg/mL, DHA: median 85.1 (range 29.7, 411) µg/mL	plasma
218	Kastelein, 2014, 24528690	30.4 (4.3)	ALA: median 375 (range 105, 1182) µg/mL, EPA: median 19.5 (range 6.3, 207) µg/mL, DHA: median 85.1 (range 29.7, 411) µg/mL	plasma
219	Kastelein, 2014, 24528690	30.4 (4.3)	ALA: median 375 (range 105, 1182) µg/mL, EPA: median 19.5 (range 6.3, 207) µg/mL, DHA: median 85.1 (range 29.7, 411) µg/mL	plasma
220	Kastelein, 2014, 24528690	30.4 (4.3)	ALA: median 375 (range 105, 1182) µg/mL, EPA: median 19.5 (range 6.3, 207) µg/mL, DHA: median 85.1 (range 29.7, 411) µg/mL	plasma

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	n-3 type(s)	n-3 measure	Study design	Outcome
214	Kastelein, 2014, 24528690	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Parallel	HDL-c
215	Kastelein, 2014, 24528690	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Parallel	HDL-c
216	Kastelein, 2014, 24528690	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Parallel	HDL-c
217	Kastelein, 2014, 24528690	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	LDL-c
218	Kastelein, 2014, 24528690	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	LDL-c
219	Kastelein, 2014, 24528690	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	LDL-c
220	Kastelein, 2014, 24528690	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Parallel	LDL-c

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Reported effect Size	Dose/intake difference	Dose-corrected effect size
214	Kastelein, 2014, 24528690	-1.40 (nd)	1.5	-0.9333333
215	Kastelein, 2014, 24528690	-1.20 (nd)	0.75	-1.6
216	Kastelein, 2014, 24528690	-0.20 (nd)	0.75	-0.2666667
217	Kastelein, 2014, 24528690	7.90 (nd)	1.5	5.266667
218	Kastelein, 2014, 24528690	5.90 (nd)	2.25	2.622222
219	Kastelein, 2014, 24528690	11.60 (nd)	3	3.866667
220	Kastelein, 2014, 24528690	3.70 (nd)	1.5	2.466667

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Outcome classification
214	Kastelein, 2014, 24528690	Secondary
215	Kastelein, 2014, 24528690	Secondary
216	Kastelein, 2014, 24528690	Secondary
217	Kastelein, 2014, 24528690	Secondary
218	Kastelein, 2014, 24528690	Secondary
219	Kastelein, 2014, 24528690	Secondary
220	Kastelein, 2014, 24528690	Secondary

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Study years (start date)	Country	Population
221	Kastelein, 2014, 24528690	2011	US, Denmark, Netherlands, India, Hungary, Ukraine, Russia	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
222	Kastelein, 2014, 24528690	2011	US, Denmark, Netherlands, India, Hungary, Ukraine, Russia	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
223	Kastelein, 2014, 24528690	2011	US, Denmark, Netherlands, India, Hungary, Ukraine, Russia	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
224	Kastelein, 2014, 24528690	2011	US, Denmark, Netherlands, India, Hungary, Ukraine, Russia	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
225	Kastelein, 2014, 24528690	2011	US, Denmark, Netherlands, India, Hungary, Ukraine, Russia	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
226	Kastelein, 2014, 24528690	2011	US, Denmark, Netherlands, India, Hungary, Ukraine, Russia	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
227	Kastelein, 2014, 24528690	2011	US, Denmark, Netherlands, India, Hungary, Ukraine, Russia	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Risk type	Sample size (total)
221	Kastelein, 2014, 24528690	Dyslipidemia (average serum TG concentrations 500-2000 mg/dL); Obesity/Overweight (body mass index >=20)	393
222	Kastelein, 2014, 24528690	Dyslipidemia (average serum TG concentrations 500-2000 mg/dL); Obesity/Overweight (body mass index >=20)	393
223	Kastelein, 2014, 24528690	Dyslipidemia (average serum TG concentrations 500-2000 mg/dL); Obesity/Overweight (body mass index >=20)	393
224	Kastelein, 2014, 24528690	Dyslipidemia (average serum TG concentrations 500-2000 mg/dL); Obesity/Overweight (body mass index >=20)	393
225	Kastelein, 2014, 24528690	Dyslipidemia (average serum TG concentrations 500-2000 mg/dL); Obesity/Overweight (body mass index >=20)	393
226	Kastelein, 2014, 24528690	Dyslipidemia (average serum TG concentrations 500-2000 mg/dL); Obesity/Overweight (body mass index >=20)	393
227	Kastelein, 2014, 24528690	Dyslipidemia (average serum TG concentrations 500-2000 mg/dL); Obesity/Overweight (body mass index >=20)	393

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Age mean (SD) [median] years	Sex (% male)	Race
221	Kastelein, 2014, 24528690	50.8 (10.6)	77.8	96 white, 4 Asian, 6.1 Hispanic
222	Kastelein, 2014, 24528690	50.8 (10.6)	77.8	96 white, 4 Asian, 6.1 Hispanic
223	Kastelein, 2014, 24528690	50.8 (10.6)	77.8	96 white, 4 Asian, 6.1 Hispanic
224	Kastelein, 2014, 24528690	50.8 (10.6)	77.8	96 white, 4 Asian, 6.1 Hispanic
225	Kastelein, 2014, 24528690	50.8 (10.6)	77.8	96 white, 4 Asian, 6.1 Hispanic
226	Kastelein, 2014, 24528690	50.8 (10.6)	77.8	96 white, 4 Asian, 6.1 Hispanic
227	Kastelein, 2014, 24528690	50.8 (10.6)	77.8	96 white, 4 Asian, 6.1 Hispanic

Row	Study	Blood pressure SBP/DBP mmHg
221	Kastelein, 2014, 24528690	130.4 (12.1)/80.5 (6.2)
222	Kastelein, 2014, 24528690	130.4 (12.1)/80.5 (6.2)
223	Kastelein, 2014, 24528690	130.4 (12.1)/80.5 (6.2)
224	Kastelein, 2014, 24528690	130.4 (12.1)/80.5 (6.2)
225	Kastelein, 2014, 24528690	130.4 (12.1)/80.5 (6.2)
226	Kastelein, 2014, 24528690	130.4 (12.1)/80.5 (6.2)
227	Kastelein, 2014, 24528690	130.4 (12.1)/80.5 (6.2)

Row	Study	Lipids: Total cholesterol/LDL/HDL/Triglycerides mean (SD) mg/dL [mmol/L]
221	Kastelein, 2014, 24528690	Median 241 (range 131, 542)/median 77.3 (range 19.7, 182)/median 27.3 (range 13.3, 47.3)/median 717 (range 415, 1578)
222	Kastelein, 2014, 24528690	Median 241 (range 131, 542)/median 77.3 (range 19.7, 182)/median 27.3 (range 13.3, 47.3)/median 717 (range 415, 1578)
223	Kastelein, 2014, 24528690	Median 241 (range 131, 542)/median 77.3 (range 19.7, 182)/median 27.3 (range 13.3, 47.3)/median 717 (range 415, 1578)
224	Kastelein, 2014, 24528690	Median 241 (range 131, 542)/median 77.3 (range 19.7, 182)/median 27.3 (range 13.3, 47.3)/median 717 (range 415, 1578)
225	Kastelein, 2014, 24528690	Median 241 (range 131, 542)/median 77.3 (range 19.7, 182)/median 27.3 (range 13.3, 47.3)/median 717 (range 415, 1578)
226	Kastelein, 2014, 24528690	Median 241 (range 131, 542)/median 77.3 (range 19.7, 182)/median 27.3 (range 13.3, 47.3)/median 717 (range 415, 1578)
227	Kastelein, 2014, 24528690	Median 241 (range 131, 542)/median 77.3 (range 19.7, 182)/median 27.3 (range 13.3, 47.3)/median 717 (range 415, 1578)

Row	Study	BMI mean (SD) Kg/m2/Weight mean (SD) Kg	Baseline n-3 intake	n-3 source (Baseline)
221	Kastelein, 2014, 24528690	30.4 (4.3)	ALA: median 375 (range 105, 1182) µg/mL, EPA: median 19.5 (range 6.3, 207) µg/mL, DHA: median 85.1 (range 29.7, 411) µg/mL	plasma
222	Kastelein, 2014, 24528690	30.4 (4.3)	ALA: median 375 (range 105, 1182) µg/mL, EPA: median 19.5 (range 6.3, 207) µg/mL, DHA: median 85.1 (range 29.7, 411) µg/mL	plasma
223	Kastelein, 2014, 24528690	30.4 (4.3)	ALA: median 375 (range 105, 1182) µg/mL, EPA: median 19.5 (range 6.3, 207) µg/mL, DHA: median 85.1 (range 29.7, 411) µg/mL	plasma
224	Kastelein, 2014, 24528690	30.4 (4.3)	ALA: median 375 (range 105, 1182) µg/mL, EPA: median 19.5 (range 6.3, 207) µg/mL, DHA: median 85.1 (range 29.7, 411) µg/mL	plasma
225	Kastelein, 2014, 24528690	30.4 (4.3)	ALA: median 375 (range 105, 1182) µg/mL, EPA: median 19.5 (range 6.3, 207) µg/mL, DHA: median 85.1 (range 29.7, 411) µg/mL	plasma
226	Kastelein, 2014, 24528690	30.4 (4.3)	ALA: median 375 (range 105, 1182) µg/mL, EPA: median 19.5 (range 6.3, 207) µg/mL, DHA: median 85.1 (range 29.7, 411) µg/mL	plasma
227	Kastelein, 2014, 24528690	30.4 (4.3)	ALA: median 375 (range 105, 1182) µg/mL, EPA: median 19.5 (range 6.3, 207) µg/mL, DHA: median 85.1 (range 29.7, 411) µg/mL	plasma

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	n-3 type(s)	n-3 measure	Study design	Outcome
221	Kastelein, 2014, 24528690	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Parallel	LDL-c
222	Kastelein, 2014, 24528690	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Parallel	LDL-c
223	Kastelein, 2014, 24528690	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Tg
224	Kastelein, 2014, 24528690	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Tg
225	Kastelein, 2014, 24528690	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Tg
226	Kastelein, 2014, 24528690	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Parallel	Tg
227	Kastelein, 2014, 24528690	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Parallel	Tg

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Reported effect Size	Dose/intake difference	Dose-corrected effect size
221	Kastelein, 2014, 24528690	-2.00 (nd)	0.75	-2.666667
222	Kastelein, 2014, 24528690	2.00 (nd)	0.75	2.666667
223	Kastelein, 2014, 24528690	-123.00 (nd)	1.5	-82
224	Kastelein, 2014, 24528690	-144.00 (nd)	2.25	-64
225	Kastelein, 2014, 24528690	-102.00 (nd)	3	-34
226	Kastelein, 2014, 24528690	-21.00 (nd)	1.5	-14
227	Kastelein, 2014, 24528690	-32.00 (nd)	0.75	-42.66667

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Outcome classification
221	Kastelein, 2014, 24528690	Secondary
222	Kastelein, 2014, 24528690	Secondary
223	Kastelein, 2014, 24528690	Primary (stated)
224	Kastelein, 2014, 24528690	Primary (stated)
225	Kastelein, 2014, 24528690	Primary (stated)
226	Kastelein, 2014, 24528690	Primary (stated)
227	Kastelein, 2014, 24528690	Primary (stated)

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Study years (start date)	Country	Population
228	Kastelein, 2014, 24528690	2011	US, Denmark, Netherlands, India, Hungary, Ukraine, Russia	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
229	Kromhout, 2010, 20929341	2002	Netherlands	Secondary Prevention (history of CVD event)
230	Kromhout, 2010, 20929341	2002	Netherlands	Secondary Prevention (history of CVD event)
231	Kromhout, 2010, 20929341	2002	Netherlands	Secondary Prevention (history of CVD event)
232	Kromhout, 2010, 20929341	2002	Netherlands	Secondary Prevention (history of CVD event)
233	Kromhout, 2010, 20929341	2002	Netherlands	Secondary Prevention (history of CVD event)
234	Kromhout, 2010, 20929341	2002	Netherlands	Secondary Prevention (history of CVD event)
235	Kromhout, 2010, 20929341	2002	Netherlands	Secondary Prevention (history of CVD event)
236	Kromhout, 2010, 20929341	2002	Netherlands	Secondary Prevention (history of CVD event)
237	Kromhout, 2010, 20929341	2002	Netherlands	Secondary Prevention (history of CVD event)
238	Kromhout, 2010, 20929341	2002	Netherlands	Secondary Prevention (history of CVD event)
239	Kromhout, 2010, 20929341	2002	Netherlands	Secondary Prevention (history of CVD event)
240	Kromhout, 2010, 20929341	2002	Netherlands	Secondary Prevention (history of CVD event)
241	Kromhout, 2010, 20929341	2002	Netherlands	Secondary Prevention (history of CVD event)
242	Kromhout, 2010, 20929341	2002	Netherlands	Secondary Prevention (history of CVD event)
243	Kromhout, 2010, 20929341	2002	Netherlands	Secondary Prevention (history of CVD event)
244	Kromhout, 2010, 20929341	2002	Netherlands	Secondary Prevention (history of CVD event)
245	Kromhout, 2010, 20929341	2002	Netherlands	Secondary Prevention (history of CVD event)
246	Kromhout, 2010, 20929341	2002	Netherlands	Secondary Prevention (history of CVD event)
247	Kromhout, 2010, 20929341	2002	Netherlands	Secondary Prevention (history of CVD event)
248	Kromhout, 2010, 20929341	2002	Netherlands	Secondary Prevention (history of CVD event)
249	Kromhout, 2010, 20929341	2002	Netherlands	Secondary Prevention (history of CVD event)
250	Kromhout, 2010, 20929341	2002	Netherlands	Secondary Prevention (history of CVD event)

Row	Study	Risk type	Sample size (total)
228	Kastelein, 2014, 24528690	Dyslipidemia (average serum TG concentrations 500-2000 mg/dL); Obesity/Overweight (body mass index >=20)	393
229	Kromhout, 2010, 20929341	Cardiac disease (myocardial infarction)	4837
230	Kromhout, 2010, 20929341	Cardiac disease (myocardial infarction)	4837
231	Kromhout, 2010, 20929341	Cardiac disease (myocardial infarction)	4837
232	Kromhout, 2010, 20929341	Cardiac disease (myocardial infarction)	4837
233	Kromhout, 2010, 20929341	Cardiac disease (myocardial infarction)	4837
234	Kromhout, 2010, 20929341	Cardiac disease (myocardial infarction)	4837
235	Kromhout, 2010, 20929341	Cardiac disease (myocardial infarction)	4837
236	Kromhout, 2010, 20929341	Cardiac disease (myocardial infarction)	4837
237	Kromhout, 2010, 20929341	Cardiac disease (myocardial infarction)	4837
238	Kromhout, 2010, 20929341	Cardiac disease (myocardial infarction)	4837
239	Kromhout, 2010, 20929341	Cardiac disease (myocardial infarction)	4837
240	Kromhout, 2010, 20929341	Cardiac disease (myocardial infarction)	4837
241	Kromhout, 2010, 20929341	Cardiac disease (myocardial infarction)	4837
242	Kromhout, 2010, 20929341	Cardiac disease (myocardial infarction)	4837
243	Kromhout, 2010, 20929341	Cardiac disease (myocardial infarction)	4837
244	Kromhout, 2010, 20929341	Cardiac disease (myocardial infarction)	4837
245	Kromhout, 2010, 20929341	Cardiac disease (myocardial infarction)	4837
246	Kromhout, 2010, 20929341	Cardiac disease (myocardial infarction)	4837
247	Kromhout, 2010, 20929341	Cardiac disease (myocardial infarction)	4837
248	Kromhout, 2010, 20929341	Cardiac disease (myocardial infarction)	4837
249	Kromhout, 2010, 20929341	Cardiac disease (myocardial infarction)	4837
250	Kromhout, 2010, 20929341	Cardiac disease (myocardial infarction)	4837

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Age mean (SD) [median] years	Sex (% male)	Race
228	Kastelein, 2014, 24528690	50.8 (10.6)	77.8	96 white, 4 Asian, 6.1 Hispanic
229	Kromhout, 2010, 20929341	68.9 (5.6)	78.7	nd
230	Kromhout, 2010, 20929341	68.9 (5.6)	78.7	nd
231	Kromhout, 2010, 20929341	68.9 (5.6)	78.7	nd
232	Kromhout, 2010, 20929341	68.9 (5.6)	78.7	nd
233	Kromhout, 2010, 20929341	68.9 (5.6)	78.7	nd
234	Kromhout, 2010, 20929341	68.9 (5.6)	78.7	nd
235	Kromhout, 2010, 20929341	68.9 (5.6)	78.7	nd
236	Kromhout, 2010, 20929341	68.9 (5.6)	78.7	nd
237	Kromhout, 2010, 20929341	68.9 (5.6)	78.7	nd
238	Kromhout, 2010, 20929341	68.9 (5.6)	78.7	nd
239	Kromhout, 2010, 20929341	68.9 (5.6)	78.7	nd
240	Kromhout, 2010, 20929341	68.9 (5.6)	78.7	nd
241	Kromhout, 2010, 20929341	68.9 (5.6)	78.7	nd
242	Kromhout, 2010, 20929341	68.9 (5.6)	78.7	nd
243	Kromhout, 2010, 20929341	68.9 (5.6)	78.7	nd
244	Kromhout, 2010, 20929341	68.9 (5.6)	78.7	nd
245	Kromhout, 2010, 20929341	68.9 (5.6)	78.7	nd
246	Kromhout, 2010, 20929341	68.9 (5.6)	78.7	nd
247	Kromhout, 2010, 20929341	68.9 (5.6)	78.7	nd
248	Kromhout, 2010, 20929341	68.9 (5.6)	78.7	nd
249	Kromhout, 2010, 20929341	68.9 (5.6)	78.7	nd
250	Kromhout, 2010, 20929341	68.9 (5.6)	78.7	nd

Row	Study	Blood pressure SBP/DBP mmHg
228	Kastelein, 2014, 24528690	130.4 (12.1)/80.5 (6.2)
229	Kromhout, 2010, 20929341	141.9 (21.6)/nd
230	Kromhout, 2010, 20929341	141.9 (21.6)/nd
231	Kromhout, 2010, 20929341	141.9 (21.6)/nd
232	Kromhout, 2010, 20929341	141.9 (21.6)/nd
233	Kromhout, 2010, 20929341	141.9 (21.6)/nd
234	Kromhout, 2010, 20929341	141.9 (21.6)/nd
235	Kromhout, 2010, 20929341	141.9 (21.6)/nd
236	Kromhout, 2010, 20929341	141.9 (21.6)/nd
237	Kromhout, 2010, 20929341	141.9 (21.6)/nd
238	Kromhout, 2010, 20929341	141.9 (21.6)/nd
239	Kromhout, 2010, 20929341	141.9 (21.6)/nd
240	Kromhout, 2010, 20929341	141.9 (21.6)/nd
241	Kromhout, 2010, 20929341	141.9 (21.6)/nd
242	Kromhout, 2010, 20929341	141.9 (21.6)/nd
243	Kromhout, 2010, 20929341	141.9 (21.6)/nd
244	Kromhout, 2010, 20929341	141.9 (21.6)/nd
245	Kromhout, 2010, 20929341	141.9 (21.6)/nd
246	Kromhout, 2010, 20929341	141.9 (21.6)/nd
247	Kromhout, 2010, 20929341	141.9 (21.6)/nd
248	Kromhout, 2010, 20929341	141.9 (21.6)/nd
249	Kromhout, 2010, 20929341	141.9 (21.6)/nd
250	Kromhout, 2010, 20929341	141.9 (21.6)/nd

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Lipids: Total cholesterol/LDL/HDL/Triglycerides mean (SD) mg/dL [mmol/L]
228	Kastelein, 2014, 24528690	Median 241 (range 131, 542)/median 77.3 (range 19.7, 182)/median 27.3 (range 13.3, 47.3)/median 717 (range 415, 1578)
229	Kromhout, 2010, 20929341	[4.75 (0.99)]/[2.60 (0.87)]/[1.28 (0.34)]/[1.69 (1.22, 2.38)]
230	Kromhout, 2010, 20929341	[4.75 (0.99)]/[2.60 (0.87)]/[1.28 (0.34)]/[1.69 (1.22, 2.38)]
231	Kromhout, 2010, 20929341	[4.75 (0.99)]/[2.60 (0.87)]/[1.28 (0.34)]/[1.69 (1.22, 2.38)]
232	Kromhout, 2010, 20929341	[4.75 (0.99)]/[2.60 (0.87)]/[1.28 (0.34)]/[1.69 (1.22, 2.38)]
233	Kromhout, 2010, 20929341	[4.75 (0.99)]/[2.60 (0.87)]/[1.28 (0.34)]/[1.69 (1.22, 2.38)]
234	Kromhout, 2010, 20929341	[4.75 (0.99)]/[2.60 (0.87)]/[1.28 (0.34)]/[1.69 (1.22, 2.38)]
235	Kromhout, 2010, 20929341	[4.75 (0.99)]/[2.60 (0.87)]/[1.28 (0.34)]/[1.69 (1.22, 2.38)]
236	Kromhout, 2010, 20929341	[4.75 (0.99)]/[2.60 (0.87)]/[1.28 (0.34)]/[1.69 (1.22, 2.38)]
237	Kromhout, 2010, 20929341	[4.75 (0.99)]/[2.60 (0.87)]/[1.28 (0.34)]/[1.69 (1.22, 2.38)]
238	Kromhout, 2010, 20929341	[4.75 (0.99)]/[2.60 (0.87)]/[1.28 (0.34)]/[1.69 (1.22, 2.38)]
239	Kromhout, 2010, 20929341	[4.75 (0.99)]/[2.60 (0.87)]/[1.28 (0.34)]/[1.69 (1.22, 2.38)]
240	Kromhout, 2010, 20929341	[4.75 (0.99)]/[2.60 (0.87)]/[1.28 (0.34)]/[1.69 (1.22, 2.38)]
241	Kromhout, 2010, 20929341	[4.75 (0.99)]/[2.60 (0.87)]/[1.28 (0.34)]/[1.69 (1.22, 2.38)]
242	Kromhout, 2010, 20929341	[4.75 (0.99)]/[2.60 (0.87)]/[1.28 (0.34)]/[1.69 (1.22, 2.38)]
243	Kromhout, 2010, 20929341	[4.75 (0.99)]/[2.60 (0.87)]/[1.28 (0.34)]/[1.69 (1.22, 2.38)]
244	Kromhout, 2010, 20929341	[4.75 (0.99)]/[2.60 (0.87)]/[1.28 (0.34)]/[1.69 (1.22, 2.38)]
245	Kromhout, 2010, 20929341	[4.75 (0.99)]/[2.60 (0.87)]/[1.28 (0.34)]/[1.69 (1.22, 2.38)]
246	Kromhout, 2010, 20929341	[4.75 (0.99)]/[2.60 (0.87)]/[1.28 (0.34)]/[1.69 (1.22, 2.38)]
247	Kromhout, 2010, 20929341	[4.75 (0.99)]/[2.60 (0.87)]/[1.28 (0.34)]/[1.69 (1.22, 2.38)]
248	Kromhout, 2010, 20929341	[4.75 (0.99)]/[2.60 (0.87)]/[1.28 (0.34)]/[1.69 (1.22, 2.38)]
249	Kromhout, 2010, 20929341	[4.75 (0.99)]/[2.60 (0.87)]/[1.28 (0.34)]/[1.69 (1.22, 2.38)]
250	Kromhout, 2010, 20929341	[4.75 (0.99)]/[2.60 (0.87)]/[1.28 (0.34)]/[1.69 (1.22, 2.38)]

Row	Study	BMI mean (SD) Kg/m2/Weight mean (SD) Kg	Baseline n-3 intake	n-3 source (Baseline)
228	Kastelein, 2014, 24528690	30.4 (4.3)	ALA: median 375 (range 105, 1182) µg/mL, EPA: median 19.5 (range 6.3, 207) µg/mL, DHA: median 85.1 (range 29.7, 411) µg/mL	plasma
229	Kromhout, 2010, 20929341	27.8 (3.9)	nd	nd
230	Kromhout, 2010, 20929341	27.8 (3.9)	nd	nd
231	Kromhout, 2010, 20929341	27.8 (3.9)	nd	nd
232	Kromhout, 2010, 20929341	27.8 (3.9)	nd	nd
233	Kromhout, 2010, 20929341	27.8 (3.9)	nd	nd
234	Kromhout, 2010, 20929341	27.8 (3.9)	nd	nd
235	Kromhout, 2010, 20929341	27.8 (3.9)	nd	nd
236	Kromhout, 2010, 20929341	27.8 (3.9)	nd	nd
237	Kromhout, 2010, 20929341	27.8 (3.9)	nd	nd
238	Kromhout, 2010, 20929341	27.8 (3.9)	nd	nd
239	Kromhout, 2010, 20929341	27.8 (3.9)	nd	nd
240	Kromhout, 2010, 20929341	27.8 (3.9)	nd	nd
241	Kromhout, 2010, 20929341	27.8 (3.9)	nd	nd
242	Kromhout, 2010, 20929341	27.8 (3.9)	nd	nd
243	Kromhout, 2010, 20929341	27.8 (3.9)	nd	nd
244	Kromhout, 2010, 20929341	27.8 (3.9)	nd	nd
245	Kromhout, 2010, 20929341	27.8 (3.9)	nd	nd
246	Kromhout, 2010, 20929341	27.8 (3.9)	nd	nd
247	Kromhout, 2010, 20929341	27.8 (3.9)	nd	nd
248	Kromhout, 2010, 20929341	27.8 (3.9)	nd	nd
249	Kromhout, 2010, 20929341	27.8 (3.9)	nd	nd
250	Kromhout, 2010, 20929341	27.8 (3.9)	nd	nd

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	n-3 type(s)	n-3 measure	Study design	Outcome
228	Kastelein, 2014, 24528690	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Parallel	Tg
229	Kromhout, 2010, 20929341	EPA+DHA+ALA vs ALA	g/d	Trial: Randomized Factorial Design	CVD total
230	Kromhout, 2010, 20929341	EPA+DHA+ALA vs EPA+DHA	g/d	Trial: Randomized Factorial Design	CVD total
231	Kromhout, 2010, 20929341	EPA+DHA+ALA vs ALA	g/d	Trial: Randomized Factorial Design	Death, all cause
232	Kromhout, 2010, 20929341	EPA+DHA+ALA vs EPA+DHA	g/d	Trial: Randomized Factorial Design	Death, all cause
233	Kromhout, 2010, 20929341	EPA+DHA+ALA vs. ALA	g/d	Trial: Randomized Factorial Design	Death, cardiac
234	Kromhout, 2010, 20929341	EPA+DHA+ALA vs EPA+DHA	g/d	Trial: Randomized Factorial Design	Death, cardiac
235	Kromhout, 2010, 20929341	EPA+DHA+ALA vs ALA	g/d	Trial: Randomized Factorial Design	Death, CVD (total)
236	Kromhout, 2010, 20929341	EPA+DHA+ALA vs EPA+DHA	g/d	Trial: Randomized Factorial Design	Death, CVD (total)
237	Kromhout, 2010, 20929341	ALA vs Placebo	g/d	Trial: Randomized Factorial Design	Revascularization
238	Kromhout, 2010, 20929341	ALA+Statin vs Placebo + Statin	g/d	Trial: Randomized Factorial Design	Revascularization
239	Kromhout, 2010, 20929341	EPA+DHA vs Placebo	g/d	Trial: Randomized Factorial Design	Revascularization
240	Kromhout, 2010, 20929341	EPA+DHA+Statin vs Placebo + Statin	g/d	Trial: Randomized Factorial Design	Revascularization
241	Kromhout, 2010, 20929341	ALA+EPA+DHA vs Placebo	g/d	Trial: Randomized Factorial Design	Revascularization
242	Kromhout, 2010, 20929341	ALA+EPA+DHA + Statin vs Placebo + Statin	g/d	Trial: Randomized Factorial Design	Revascularization
243	Kromhout, 2010, 20929341	ALA vs Placebo	g/d	Trial: Randomized Factorial Design	Total:HDL-c ratio
244	Kromhout, 2010, 20929341	ALA + Statin vs Placebo + Statin	g/d	Trial: Randomized Factorial Design	Total:HDL-c ratio
245	Kromhout, 2010, 20929341	EPA+DHA vs Placebo	g/d	Trial: Randomized Factorial Design	Total:HDL-c ratio
246	Kromhout, 2010, 20929341	EPA+DHA + Statin vs Placebo + Statin	g/d	Trial: Randomized Factorial Design	Total:HDL-c ratio
247	Kromhout, 2010, 20929341	ALA+EPA+DHA vs Placebo	g/d	Trial: Randomized Factorial Design	Total:HDL-c ratio
248	Kromhout, 2010, 20929341	ALA+EPA+DHA + Statin vs Placebo + Statin	g/d	Trial: Randomized Factorial Design	Total:HDL-c ratio
249	Kromhout, 2010, 20929341	ALA vs Placebo	g/d	Trial: Randomized Factorial Design	HDL-c
250	Kromhout, 2010, 20929341	ALA (+EPA+DHA) vs (EPA+DHA)	g/d	Trial: Randomized Factorial Design	HDL-c

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Reported effect Size	Dose/intake difference	Dose-corrected effect size
228	Kastelein, 2014, 24528690	-21.00 (nd)	0.75	-28
229	Kromhout, 2010, 20929341	HR 0.92 (0.75, 1.13)	NA	
230	Kromhout, 2010, 20929341	HR 0.92 (0.73, 1.11)	NA	
231	Kromhout, 2010, 20929341	HR 1.01 (0.82, 1.24)	NA	
232	Kromhout, 2010, 20929341	HR 0.97 (0.79, 1.19)	NA	
233	Kromhout, 2010, 20929341	HR 0.95 (0.68,1.32)	NA	
234	Kromhout, 2010, 20929341	HR 0.92 (0.66, 1.29)	NA	
235	Kromhout, 2010, 20929341	HR 0.98 (0.72, 1.33)	NA	
236	Kromhout, 2010, 20929341	HR 0.94 (0.69, 1.27)	NA	
237	Kromhout, 2010, 20929341	HR 0.94 (0.49, 1.80)	2	0.9695359
238	Kromhout, 2010, 20929341	HR 0.98 (0.76, 1.27)	2	0.9899495
239	Kromhout, 2010, 20929341	HR 0.84 (0.44, 1.62)	0.4	0.6466931
240	Kromhout, 2010, 20929341	HR 1.06 (0.83, 1.36)	0.4	1.156817
241	Kromhout, 2010, 20929341	HR 0.48 (0.22, 1.06)	2.4	0.7365188
242	Kromhout, 2010, 20929341	HR 1.02 (0.79, 1.31)	2.4	1.008285
243	Kromhout, 2010, 20929341	0.057 (-0.19, 0.30)	2	0.0285
244	Kromhout, 2010, 20929341	0.063 (-0.012, 0.14)	2	0.0315
245	Kromhout, 2010, 20929341	0.89 (-0.15, 0.32)	0.4	2.225
246	Kromhout, 2010, 20929341	-0.062 (-0.14, 0.013)	0.4	-0.155
247	Kromhout, 2010, 20929341	0.12 (-0.13, 0.37)	2.4	0.05
248	Kromhout, 2010, 20929341	-0.036 (-0.11, 0.039)	2.4	-0.015
249	Kromhout, 2010, 20929341	-0.77 (-1.84, 0.30)	2	-0.385
250	Kromhout, 2010, 20929341	-1.54 (-2.61, -0.47)	2	-0.77

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Outcome classification
228	Kastelein, 2014, 24528690	Primary (stated)
229	Kromhout, 2010, 20929341	Secondary
230	Kromhout, 2010, 20929341	Secondary
231	Kromhout, 2010, 20929341	Primary (stated)
232	Kromhout, 2010, 20929341	Primary (stated)
233	Kromhout, 2010, 20929341	Secondary
234	Kromhout, 2010, 20929341	Secondary
235	Kromhout, 2010, 20929341	Secondary; Primary in registry record (NCT00127452)
236	Kromhout, 2010, 20929341	Secondary; Primary in registry record (NCT00127452)
237	Kromhout, 2010, 20929341	Secondary; Primary in registry record (NCT00127452)
238	Kromhout, 2010, 20929341	Secondary; Primary in registry record (NCT00127452)
239	Kromhout, 2010, 20929341	Secondary; Primary in registry record (NCT00127452)
240	Kromhout, 2010, 20929341	Secondary; Primary in registry record (NCT00127452)
241	Kromhout, 2010, 20929341	Secondary; Primary in registry record (NCT00127452)
242	Kromhout, 2010, 20929341	Secondary; Primary in registry record (NCT00127452)
243	Kromhout, 2010, 20929341	Secondary
244	Kromhout, 2010, 20929341	Secondary
245	Kromhout, 2010, 20929341	Secondary
246	Kromhout, 2010, 20929341	Secondary
247	Kromhout, 2010, 20929341	Secondary
248	Kromhout, 2010, 20929341	Secondary
249	Kromhout, 2010, 20929341	Secondary
250	Kromhout, 2010, 20929341	Secondary

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Study years (start date)	Country	Population
251	Kromhout, 2010, 20929341	2002	Netherlands	Secondary Prevention (history of CVD event)
252	Kromhout, 2010, 20929341	2002	Netherlands	Secondary Prevention (history of CVD event)
253	Kromhout, 2010, 20929341	2002	Netherlands	Secondary Prevention (history of CVD event)
254	Kromhout, 2010, 20929341	2002	Netherlands	Secondary Prevention (history of CVD event)
255	Kromhout, 2010, 20929341	2002	Netherlands	Secondary Prevention (history of CVD event)
256	Kromhout, 2010, 20929341	2002	Netherlands	Secondary Prevention (history of CVD event)
257	Kromhout, 2010, 20929341	2002	Netherlands	Secondary Prevention (history of CVD event)
258	Kromhout, 2010, 20929341	2002	Netherlands	Secondary Prevention (history of CVD event)
259	Kromhout, 2010, 20929341	2002	Netherlands	Secondary Prevention (history of CVD event)
260	Kromhout, 2010, 20929341	2002	Netherlands	Secondary Prevention (history of CVD event)
261	Kromhout, 2010, 20929341	2002	Netherlands	Secondary Prevention (history of CVD event)
262	Kromhout, 2010, 20929341	2002	Netherlands	Secondary Prevention (history of CVD event)
263	Kromhout, 2010, 20929341	2002	Netherlands	Secondary Prevention (history of CVD event)
264	Kromhout, 2010, 20929341	2002	Netherlands	Secondary Prevention (history of CVD event)
265	Kromhout, 2010, 20929341	2002	Netherlands	Secondary Prevention (history of CVD event)
266	Kromhout, 2010, 20929341	2002	Netherlands	Secondary Prevention (history of CVD event)
267	Kuhnt, 2014, 24553695	2011	Germany	Primary Prevention, HealthYoung adults 20-35 y; EOI vs FOI
268	Kuhnt, 2014, 24553695	2011	Germany	Primary Prevention, HealthOlder adults 49-69 y; EOII vs FOII
269	Kuhnt, 2014, 24553695	2011	Germany	Primary Prevention, HealthYoung adults 20-35 y; EOI vs FOI
270	Kuhnt, 2014, 24553695	2011	Germany	Primary Prevention, HealthOlder adults 49-69 y; EOII vs FOII
271	Kuhnt, 2014, 24553695	2011	Germany	Primary Prevention, HealthYoung adults 20-35 y; EOI vs FOI
272	Kuhnt, 2014, 24553695	2011	Germany	Primary Prevention, HealthOlder adults 49-69 y; EOII vs FOII
273	Kuhnt, 2014, 24553695	2011	Germany	Primary Prevention, HealthYoung adults 20-35 y; EOI vs FOI
274	Kuhnt, 2014, 24553695	2011	Germany	Primary Prevention, HealthOlder adults 49-69 y; EOII vs FOII
275	Kuhnt, 2014, 24553695	2011	Germany	Primary Prevention, HealthYoung adults 20-35 y; EOI vs FOI
276	Kuhnt, 2014, 24553695	2011	Germany	Primary Prevention, HealthOlder adults 49-69 y; EOII vs FOII
277	Kuhnt, 2014, 24553695	2011	Germany	Primary Prevention, HealthYoung adults 20-35 y; EOI vs FOI

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Risk type	Sample size (total)
251	Kromhout, 2010, 20929341	Cardiac disease (myocardial infarction)	4837
252	Kromhout, 2010, 20929341	Cardiac disease (myocardial infarction)	4837
253	Kromhout, 2010, 20929341	Cardiac disease (myocardial infarction)	4837
254	Kromhout, 2010, 20929341	Cardiac disease (myocardial infarction)	4837
255	Kromhout, 2010, 20929341	Cardiac disease (myocardial infarction)	4837
256	Kromhout, 2010, 20929341	Cardiac disease (myocardial infarction)	4837
257	Kromhout, 2010, 20929341	Cardiac disease (myocardial infarction)	4837
258	Kromhout, 2010, 20929341	Cardiac disease (myocardial infarction)	4837
259	Kromhout, 2010, 20929341	Cardiac disease (myocardial infarction)	4837
260	Kromhout, 2010, 20929341	Cardiac disease (myocardial infarction)	4837
261	Kromhout, 2010, 20929341	Cardiac disease (myocardial infarction)	4837
262	Kromhout, 2010, 20929341	Cardiac disease (myocardial infarction)	4837
263	Kromhout, 2010, 20929341	Cardiac disease (myocardial infarction)	4837
264	Kromhout, 2010, 20929341	Cardiac disease (myocardial infarction)	4837
265	Kromhout, 2010, 20929341	Cardiac disease (myocardial infarction)	4837
266	Kromhout, 2010, 20929341	Cardiac disease (myocardial infarction)	4837
267	Kuhnt, 2014, 24553695	nd	30
268	Kuhnt, 2014, 24553695	nd	29
269	Kuhnt, 2014, 24553695	nd	30
270	Kuhnt, 2014, 24553695	nd	29
271	Kuhnt, 2014, 24553695	nd	30
272	Kuhnt, 2014, 24553695	nd	29
273	Kuhnt, 2014, 24553695	nd	30
274	Kuhnt, 2014, 24553695	nd	29
275	Kuhnt, 2014, 24553695	nd	30
276	Kuhnt, 2014, 24553695	nd	29
277	Kuhnt, 2014, 24553695	nd	30

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Age mean (SD) [median] years	Sex (% male)	Race
251	Kromhout, 2010, 20929341	68.9 (5.6)	78.7	nd
252	Kromhout, 2010, 20929341	68.9 (5.6)	78.7	nd
253	Kromhout, 2010, 20929341	68.9 (5.6)	78.7	nd
254	Kromhout, 2010, 20929341	68.9 (5.6)	78.7	nd
255	Kromhout, 2010, 20929341	68.9 (5.6)	78.7	nd
256	Kromhout, 2010, 20929341	68.9 (5.6)	78.7	nd
257	Kromhout, 2010, 20929341	68.9 (5.6)	78.7	nd
258	Kromhout, 2010, 20929341	68.9 (5.6)	78.7	nd
259	Kromhout, 2010, 20929341	68.9 (5.6)	78.7	nd
260	Kromhout, 2010, 20929341	68.9 (5.6)	78.7	nd
261	Kromhout, 2010, 20929341	68.9 (5.6)	78.7	nd
262	Kromhout, 2010, 20929341	68.9 (5.6)	78.7	nd
263	Kromhout, 2010, 20929341	68.9 (5.6)	78.7	nd
264	Kromhout, 2010, 20929341	68.9 (5.6)	78.7	nd
265	Kromhout, 2010, 20929341	68.9 (5.6)	78.7	nd
266	Kromhout, 2010, 20929341	68.9 (5.6)	78.7	nd
267	Kuhnt, 2014, 24553695	27.7 (2.8)	50	nd
268	Kuhnt, 2014, 24553695	59.3 (5.3)	48	nd
269	Kuhnt, 2014, 24553695	27.7 (2.8)	50	nd
270	Kuhnt, 2014, 24553695	59.3 (5.3)	48	nd
271	Kuhnt, 2014, 24553695	27.7 (2.8)	50	nd
272	Kuhnt, 2014, 24553695	59.3 (5.3)	48	nd
273	Kuhnt, 2014, 24553695	27.7 (2.8)	50	nd
274	Kuhnt, 2014, 24553695	59.3 (5.3)	48	nd
275	Kuhnt, 2014, 24553695	27.7 (2.8)	50	nd
276	Kuhnt, 2014, 24553695	59.3 (5.3)	48	nd
277	Kuhnt, 2014, 24553695	27.7 (2.8)	50	nd

Row	Study	Blood pressure SBP/DBP mmHg
251	Kromhout, 2010, 20929341	141.9 (21.6)/nd
252	Kromhout, 2010, 20929341	141.9 (21.6)/nd
253	Kromhout, 2010, 20929341	141.9 (21.6)/nd
254	Kromhout, 2010, 20929341	141.9 (21.6)/nd
255	Kromhout, 2010, 20929341	141.9 (21.6)/nd
256	Kromhout, 2010, 20929341	141.9 (21.6)/nd
257	Kromhout, 2010, 20929341	141.9 (21.6)/nd
258	Kromhout, 2010, 20929341	141.9 (21.6)/nd
259	Kromhout, 2010, 20929341	141.9 (21.6)/nd
260	Kromhout, 2010, 20929341	141.9 (21.6)/nd
261	Kromhout, 2010, 20929341	141.9 (21.6)/nd
262	Kromhout, 2010, 20929341	141.9 (21.6)/nd
263	Kromhout, 2010, 20929341	141.9 (21.6)/nd
264	Kromhout, 2010, 20929341	141.9 (21.6)/nd
265	Kromhout, 2010, 20929341	141.9 (21.6)/nd
266	Kromhout, 2010, 20929341	141.9 (21.6)/nd
267	Kuhnt, 2014, 24553695	128.7 (12.7)/84.0 (9.0)
268	Kuhnt, 2014, 24553695	135.3 (19.5)/89.4 (10.9)
269	Kuhnt, 2014, 24553695	128.7 (12.7)/84.0 (9.0)
270	Kuhnt, 2014, 24553695	135.3 (19.5)/89.4 (10.9)
271	Kuhnt, 2014, 24553695	128.7 (12.7)/84.0 (9.0)
272	Kuhnt, 2014, 24553695	135.3 (19.5)/89.4 (10.9)
273	Kuhnt, 2014, 24553695	128.7 (12.7)/84.0 (9.0)
274	Kuhnt, 2014, 24553695	135.3 (19.5)/89.4 (10.9)
275	Kuhnt, 2014, 24553695	128.7 (12.7)/84.0 (9.0)
276	Kuhnt, 2014, 24553695	135.3 (19.5)/89.4 (10.9)
277	Kuhnt, 2014, 24553695	128.7 (12.7)/84.0 (9.0)

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Lipids: Total cholesterol/LDL/HDL/Triglycerides mean (SD) mg/dL [mmol/L]
251	Kromhout, 2010, 20929341	[4.75 (0.99)]/[2.60 (0.87)]/[1.28 (0.34)]/[1.69 (1.22, 2.38)]
252	Kromhout, 2010, 20929341	[4.75 (0.99)]/[2.60 (0.87)]/[1.28 (0.34)]/[1.69 (1.22, 2.38)]
253	Kromhout, 2010, 20929341	[4.75 (0.99)]/[2.60 (0.87)]/[1.28 (0.34)]/[1.69 (1.22, 2.38)]
254	Kromhout, 2010, 20929341	[4.75 (0.99)]/[2.60 (0.87)]/[1.28 (0.34)]/[1.69 (1.22, 2.38)]
255	Kromhout, 2010, 20929341	[4.75 (0.99)]/[2.60 (0.87)]/[1.28 (0.34)]/[1.69 (1.22, 2.38)]
256	Kromhout, 2010, 20929341	[4.75 (0.99)]/[2.60 (0.87)]/[1.28 (0.34)]/[1.69 (1.22, 2.38)]
257	Kromhout, 2010, 20929341	[4.75 (0.99)]/[2.60 (0.87)]/[1.28 (0.34)]/[1.69 (1.22, 2.38)]
258	Kromhout, 2010, 20929341	[4.75 (0.99)]/[2.60 (0.87)]/[1.28 (0.34)]/[1.69 (1.22, 2.38)]
259	Kromhout, 2010, 20929341	[4.75 (0.99)]/[2.60 (0.87)]/[1.28 (0.34)]/[1.69 (1.22, 2.38)]
260	Kromhout, 2010, 20929341	[4.75 (0.99)]/[2.60 (0.87)]/[1.28 (0.34)]/[1.69 (1.22, 2.38)]
261	Kromhout, 2010, 20929341	[4.75 (0.99)]/[2.60 (0.87)]/[1.28 (0.34)]/[1.69 (1.22, 2.38)]
262	Kromhout, 2010, 20929341	[4.75 (0.99)]/[2.60 (0.87)]/[1.28 (0.34)]/[1.69 (1.22, 2.38)]
263	Kromhout, 2010, 20929341	[4.75 (0.99)]/[2.60 (0.87)]/[1.28 (0.34)]/[1.69 (1.22, 2.38)]
264	Kromhout, 2010, 20929341	[4.75 (0.99)]/[2.60 (0.87)]/[1.28 (0.34)]/[1.69 (1.22, 2.38)]
265	Kromhout, 2010, 20929341	[4.75 (0.99)]/[2.60 (0.87)]/[1.28 (0.34)]/[1.69 (1.22, 2.38)]
266	Kromhout, 2010, 20929341	[4.75 (0.99)]/[2.60 (0.87)]/[1.28 (0.34)]/[1.69 (1.22, 2.38)]
267	Kuhnt, 2014, 24553695	[4.4 (0.7)/1.8 (0.8)/1.5 (0.3)/0.9 (0.3)]
268	Kuhnt, 2014, 24553695	[5.7 (1.1)/2.0 (1.0)/1.7 (0.5)/1.1 (0.4)]
269	Kuhnt, 2014, 24553695	[4.4 (0.7)/1.8 (0.8)/1.5 (0.3)/0.9 (0.3)]
270	Kuhnt, 2014, 24553695	[5.7 (1.1)/2.0 (1.0)/1.7 (0.5)/1.1 (0.4)]
271	Kuhnt, 2014, 24553695	[4.4 (0.7)/1.8 (0.8)/1.5 (0.3)/0.9 (0.3)]
272	Kuhnt, 2014, 24553695	[5.7 (1.1)/2.0 (1.0)/1.7 (0.5)/1.1 (0.4)]
273	Kuhnt, 2014, 24553695	[4.4 (0.7)/1.8 (0.8)/1.5 (0.3)/0.9 (0.3)]
274	Kuhnt, 2014, 24553695	[5.7 (1.1)/2.0 (1.0)/1.7 (0.5)/1.1 (0.4)]
275	Kuhnt, 2014, 24553695	[4.4 (0.7)/1.8 (0.8)/1.5 (0.3)/0.9 (0.3)]
276	Kuhnt, 2014, 24553695	[5.7 (1.1)/2.0 (1.0)/1.7 (0.5)/1.1 (0.4)]
277	Kuhnt, 2014, 24553695	[4.4 (0.7)/1.8 (0.8)/1.5 (0.3)/0.9 (0.3)]

Row	Study	BMI mean (SD) Kg/m2/Weight mean (SD) Kg	Baseline n-3 intake	n-3 source (Baseline)
251	Kromhout, 2010, 20929341	27.8 (3.9)	nd	nd
252	Kromhout, 2010, 20929341	27.8 (3.9)	nd	nd
253	Kromhout, 2010, 20929341	27.8 (3.9)	nd	nd
254	Kromhout, 2010, 20929341	27.8 (3.9)	nd	nd
255	Kromhout, 2010, 20929341	27.8 (3.9)	nd	nd
256	Kromhout, 2010, 20929341	27.8 (3.9)	nd	nd
257	Kromhout, 2010, 20929341	27.8 (3.9)	nd	nd
258	Kromhout, 2010, 20929341	27.8 (3.9)	nd	nd
259	Kromhout, 2010, 20929341	27.8 (3.9)	nd	nd
260	Kromhout, 2010, 20929341	27.8 (3.9)	nd	nd
261	Kromhout, 2010, 20929341	27.8 (3.9)	nd	nd
262	Kromhout, 2010, 20929341	27.8 (3.9)	nd	nd
263	Kromhout, 2010, 20929341	27.8 (3.9)	nd	nd
264	Kromhout, 2010, 20929341	27.8 (3.9)	nd	nd
265	Kromhout, 2010, 20929341	27.8 (3.9)	nd	nd
266	Kromhout, 2010, 20929341	27.8 (3.9)	nd	nd
267	Kuhnt, 2014, 24553695	21.8 (2.4)	nd	nd
268	Kuhnt, 2014, 24553695	23.9 (2.7)	nd	nd
269	Kuhnt, 2014, 24553695	21.8 (2.4)	nd	nd
270	Kuhnt, 2014, 24553695	23.9 (2.7)	nd	nd
271	Kuhnt, 2014, 24553695	21.8 (2.4)	nd	nd
272	Kuhnt, 2014, 24553695	23.9 (2.7)	nd	nd
273	Kuhnt, 2014, 24553695	21.8 (2.4)	nd	nd
274	Kuhnt, 2014, 24553695	23.9 (2.7)	nd	nd
275	Kuhnt, 2014, 24553695	21.8 (2.4)	nd	nd
276	Kuhnt, 2014, 24553695	23.9 (2.7)	nd	nd
277	Kuhnt, 2014, 24553695	21.8 (2.4)	nd	nd

Row	Study	n-3 type(s)	n-3 measure	Study design	Outcome
251	Kromhout, 2010, 20929341	ALA + EPA+DHA vs Placebo	g/d	Trial: Randomized Factorial Design	HDL-c
252	Kromhout, 2010, 20929341	EPA+DHA vs ALA	g/d	Trial: Randomized Factorial Design	HDL-c
253	Kromhout, 2010, 20929341	EPA+DHA vs Placebo	g/d	Trial: Randomized Factorial Design	HDL-c
254	Kromhout, 2010, 20929341	EPA+DHA (+ALA) vs (ALA)	g/d	Trial: Randomized Factorial Design	HDL-c
255	Kromhout, 2010, 20929341	EPA+DHA vs Placebo	g/d	Trial: Randomized Factorial Design	LDL-c
256	Kromhout, 2010, 20929341	EPA+DHA (+ALA) vs (ALA)	g/d	Trial: Randomized Factorial Design	LDL-c
257	Kromhout, 2010, 20929341	ALA vs Placebo	g/d	Trial: Randomized Factorial Design	LDL-c
258	Kromhout, 2010, 20929341	ALA (+EPA+DHA) vs (EPA+DHA)	g/d	Trial: Randomized Factorial Design	LDL-c
259	Kromhout, 2010, 20929341	ALA + EPA+DHA vs Placebo	g/d	Trial: Randomized Factorial Design	LDL-c
260	Kromhout, 2010, 20929341	EPA+DHA vs ALA	g/d	Trial: Randomized Factorial Design	LDL-c
261	Kromhout, 2010, 20929341	ALA vs Placebo	g/d	Trial: Randomized Factorial Design	Tg
262	Kromhout, 2010, 20929341	ALA (+EPA+DHA) vs (EPA+DHA)	g/d	Trial: Randomized Factorial Design	Tg
263	Kromhout, 2010, 20929341	ALA + EPA+DHA vs Placebo	g/d	Trial: Randomized Factorial Design	Tg
264	Kromhout, 2010, 20929341	EPA+DHA vs ALA	g/d	Trial: Randomized Factorial Design	Tg
265	Kromhout, 2010, 20929341	EPA+DHA vs Placebo	g/d	Trial: Randomized Factorial Design	Tg
266	Kromhout, 2010, 20929341	EPA+DHA (+ALA) vs (ALA)	g/d	Trial: Randomized Factorial Design	Tg
267	Kuhnt, 2014, 24553695	SDA vs EPA+DHA	g/d	Trial: Randomized Parallel	LDL:HDL-c ratio
268	Kuhnt, 2014, 24553695	SDA vs EPA+DHA	g/d	Trial: Randomized Parallel	LDL:HDL-c ratio
269	Kuhnt, 2014, 24553695	SDA vs EPA+DHA	g/d	Trial: Randomized Parallel	HDL-c
270	Kuhnt, 2014, 24553695	SDA vs EPA+DHA	g/d	Trial: Randomized Parallel	HDL-c
271	Kuhnt, 2014, 24553695	SDA vs EPA+DHA	g/d	Trial: Randomized Parallel	LDL-c
272	Kuhnt, 2014, 24553695	SDA vs EPA+DHA	g/d	Trial: Randomized Parallel	LDL-c
273	Kuhnt, 2014, 24553695	SDA vs EPA+DHA	g/d	Trial: Randomized Parallel	Tg
274	Kuhnt, 2014, 24553695	SDA vs EPA+DHA	g/d	Trial: Randomized Parallel	Tg
275	Kuhnt, 2014, 24553695	SDA vs EPA+DHA	g/d	Trial: Randomized Parallel	SBP
276	Kuhnt, 2014, 24553695	SDA vs EPA+DHA	g/d	Trial: Randomized Parallel	SBP
277	Kuhnt, 2014, 24553695	SDA vs EPA+DHA	g/d	Trial: Randomized Parallel	DBP

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Reported effect Size	Dose/intake difference	Dose-corrected effect size
251	Kromhout, 2010, 20929341	-0.39 (-1.46, 0.68)	2.4	-0.1625
252	Kromhout, 2010, 20929341	1.93 (0.86, 3.00)	NA	
253	Kromhout, 2010, 20929341	1.16 (0.09, 2.23)	0.4	2.9
254	Kromhout, 2010, 20929341	0.39 (-0.68, 1.46)	0.4	0.975
255	Kromhout, 2010, 20929341	-0.77 (-3.98, 2.44)	0.4	-1.925
256	Kromhout, 2010, 20929341	0.39 (-2.82, 3.60)	0.4	0.975
257	Kromhout, 2010, 20929341	0.39 (-2.82, 3.60)	2	0.195
258	Kromhout, 2010, 20929341	1.54 (-1.67, 4.76)	2	0.77
259	Kromhout, 2010, 20929341	0.77 (-2.44, 3.98)	2.4	0.3208333
260	Kromhout, 2010, 20929341	-1.16 (-4.37, 2.05)	NA	
261	Kromhout, 2010, 20929341	-5.31 (-15.12, 4.50)	2	-2.655
262	Kromhout, 2010, 20929341	-5.31 (-15.42, 4.80)	2	-2.655
263	Kromhout, 2010, 20929341	-7.96 (-16.64, 0.71)	2.4	-3.316667
264	Kromhout, 2010, 20929341	2.65 (-8.45, 13.76)	NA	
265	Kromhout, 2010, 20929341	-2.65 (-13.76, 8.45)	0.4	-6.625
266	Kromhout, 2010, 20929341	-2.65 (-11.33, 6.02)	0.4	-6.625
267	Kuhnt, 2014, 24553695	0.02 (-0.45, 0.49)	NA	
268	Kuhnt, 2014, 24553695	0.03 (-0.59, 0.65)	NA	
269	Kuhnt, 2014, 24553695	-4.25 (-15.69, 7.19)	NA	
270	Kuhnt, 2014, 24553695	-2.71 (-19, 13.58)	NA	
271	Kuhnt, 2014, 24553695	-3.87 (-22.48, 14.74)	NA	
272	Kuhnt, 2014, 24553695	-10.4 (-34.13, 13.33)	NA	
273	Kuhnt, 2014, 24553695	-1.75 (-17.58, 14.08)	NA	
274	Kuhnt, 2014, 24553695	13.16 (-10.1, 36.42)	NA	
275	Kuhnt, 2014, 24553695	6 (-3.12, 15.12)	NA	
276	Kuhnt, 2014, 24553695	2 (-12.7, 16.7)	NA	
277	Kuhnt, 2014, 24553695	3 (-3.1, 9.1)	NA	

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Outcome classification
251	Kromhout, 2010, 20929341	Secondary
252	Kromhout, 2010, 20929341	Secondary
253	Kromhout, 2010, 20929341	Secondary
254	Kromhout, 2010, 20929341	Secondary
255	Kromhout, 2010, 20929341	Secondary
256	Kromhout, 2010, 20929341	Secondary
257	Kromhout, 2010, 20929341	Secondary
258	Kromhout, 2010, 20929341	Secondary
259	Kromhout, 2010, 20929341	Secondary
260	Kromhout, 2010, 20929341	Secondary
261	Kromhout, 2010, 20929341	Secondary
262	Kromhout, 2010, 20929341	Secondary
263	Kromhout, 2010, 20929341	Secondary
264	Kromhout, 2010, 20929341	Secondary
265	Kromhout, 2010, 20929341	Secondary
266	Kromhout, 2010, 20929341	Secondary
267	Kuhnt, 2014, 24553695	Secondary
268	Kuhnt, 2014, 24553695	Secondary
269	Kuhnt, 2014, 24553695	Secondary
270	Kuhnt, 2014, 24553695	Secondary
271	Kuhnt, 2014, 24553695	Secondary
272	Kuhnt, 2014, 24553695	Secondary
273	Kuhnt, 2014, 24553695	Secondary
274	Kuhnt, 2014, 24553695	Secondary
275	Kuhnt, 2014, 24553695	Secondary
276	Kuhnt, 2014, 24553695	Secondary
277	Kuhnt, 2014, 24553695	Secondary

Row	Study	Study years (start date)	Country	Population
278	Kuhnt, 2014, 24553695	2011	Germany	Primary Prevention, HealthOlder adults 49-69 y; EOII vs FOII
279	Leaf, 2005, 16267249	1999	US	Secondary Prevention (history of CVD event)
280	Leaf, 2005, 16267249	1999	US	Secondary Prevention (history of CVD event)
281	Leaf, 2005, 16267249	1999	US	Secondary Prevention (history of CVD event)
282	Liu, 2003, no PMID	2001 (approx)	Sweden	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
283	Liu, 2003, no PMID	2001 (approx)	Sweden	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
284	Liu, 2003, no PMID	2001 (approx)	Sweden	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
285	Liu, 2003, no PMID	2001 (approx)	Sweden	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
286	Liu, 2003, no PMID	2001 (approx)	Sweden	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
287	Liu, 2003, no PMID	2001 (approx)	Sweden	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
288	Liu, 2003, no PMID	2001 (approx)	Sweden	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
289	Liu, 2003, no PMID	2001 (approx)	Sweden	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
290	Lungershausen, 1994	1992 (approx)	Australia	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
291	Lungershausen, 1994	1992 (approx)	Australia	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
292	Lungershausen, 1994	1992 (approx)	Australia	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
293	Lungershausen, 1994	1992 (approx)	Australia	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
294	Lungershausen, 1994	1992 (approx)	Australia	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
295	Macchia, 2013, 23265344	2008	Italy, Argentina	Secondary Prevention (history of CVD event)

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Risk type	Sample size (total)
278	Kuhnt, 2014, 24553695	nd	29
279	Leaf, 2005, 16267249	Arrhythmia (ICD implanted)	402
280	Leaf, 2005, 16267249	Arrhythmia (ICD implanted)	402
281	Leaf, 2005, 16267249	Arrhythmia (ICD implanted)	402
282	Liu, 2003, no PMID	Dyslipidemia (fasting TC>6.2 mmol/L and/or fasting TG>1.8 mmol/L)	59
283	Liu, 2003, no PMID	Dyslipidemia (fasting TC>6.2 mmol/L and/or fasting TG>1.8 mmol/L)	59
284	Liu, 2003, no PMID	Dyslipidemia (fasting TC>6.2 mmol/L and/or fasting TG>1.8 mmol/L)	59
285	Liu, 2003, no PMID	Dyslipidemia (fasting TC>6.2 mmol/L and/or fasting TG>1.8 mmol/L)	59
286	Liu, 2003, no PMID	Dyslipidemia (fasting TC>6.2 mmol/L and/or fasting TG>1.8 mmol/L)	59
287	Liu, 2003, no PMID	Dyslipidemia (fasting TC>6.2 mmol/L and/or fasting TG>1.8 mmol/L)	59
288	Liu, 2003, no PMID	Dyslipidemia (fasting TC>6.2 mmol/L and/or fasting TG>1.8 mmol/L)	59
289	Liu, 2003, no PMID	Dyslipidemia (fasting TC>6.2 mmol/L and/or fasting TG>1.8 mmol/L)	59
290	Lungershausen, 1994	Hypertension (Treated for hypertension, on medication)	42
291	Lungershausen, 1994	Hypertension (Treated for hypertension, on medication)	42
292	Lungershausen, 1994	Hypertension (Treated for hypertension, on medication)	42
293	Lungershausen, 1994	Hypertension (Treated for hypertension, on medication)	42
294	Lungershausen, 1994	Hypertension (Treated for hypertension, on medication)	42
295	Macchia, 2013, 23265344	Arrhythmia	586

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Age mean (SD) [median] years	Sex (% male)	Race
278	Kuhnt, 2014, 24553695	59.3 (5.3)	48	nd
279	Leaf, 2005, 16267249	65.3 (0.82)	81.7	95.5 white
280	Leaf, 2005, 16267249	65.3 (0.82)	81.7	95.5 white
281	Leaf, 2005, 16267249	65.3 (0.82)	81.7	95.5 white
282	Liu, 2003, no PMID	57 (10)	30.7	nd
283	Liu, 2003, no PMID	57 (10)	30.7	nd
284	Liu, 2003, no PMID	57 (10)	30.7	nd
285	Liu, 2003, no PMID	57 (10)	30.7	nd
286	Liu, 2003, no PMID	57 (10)	30.7	nd
287	Liu, 2003, no PMID	57 (10)	30.7	nd
288	Liu, 2003, no PMID	57 (10)	30.7	nd
289	Liu, 2003, no PMID	57 (10)	30.7	nd
290	Lungershausen, 1994	61 (11.34)	30.95	nd
291	Lungershausen, 1994	61 (11.34)	30.95	nd
292	Lungershausen, 1994	61 (11.34)	30.95	nd
293	Lungershausen, 1994	61 (11.34)	30.95	nd
294	Lungershausen, 1994	61 (11.34)	30.95	nd
295	Macchia, 2013, 23265344	65.9 (10.5)	51.9	nd

Row	Study	Blood pressure SBP/DBP mmHg
278	Kuhnt, 2014, 24553695	135.3 (19.5)/89.4 (10.9)
279	Leaf, 2005, 16267249	nd
280	Leaf, 2005, 16267249	nd
281	Leaf, 2005, 16267249	nd
282	Liu, 2003, no PMID	nd
283	Liu, 2003, no PMID	nd
284	Liu, 2003, no PMID	nd
285	Liu, 2003, no PMID	nd
286	Liu, 2003, no PMID	nd
287	Liu, 2003, no PMID	nd
288	Liu, 2003, no PMID	nd
289	Liu, 2003, no PMID	nd
290	Lungershausen, 1994	132.57 (11.43)/76.52 (7.23)
291	Lungershausen, 1994	132.57 (11.43)/76.52 (7.23)
292	Lungershausen, 1994	132.57 (11.43)/76.52 (7.23)
293	Lungershausen, 1994	132.57 (11.43)/76.52 (7.23)
294	Lungershausen, 1994	132.57 (11.43)/76.52 (7.23)
295	Macchia, 2013, 23265344	nd

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Lipids: Total cholesterol/LDL/HDL/Triglycerides mean (SD) mg/dL [mmol/L]
278	Kuhnt, 2014, 24553695	[5.7 (1.1)/2.0 (1.0)/1.7 (0.5)/1.1 (0.4)]
279	Leaf, 2005, 16267249	nd
280	Leaf, 2005, 16267249	nd
281	Leaf, 2005, 16267249	nd
282	Liu, 2003, no PMID	[6.77 (0.75)]/[4.50 (0.72)]/[1.53 (0.43)]/[1.61 (0.83)]
283	Liu, 2003, no PMID	[6.77 (0.75)]/[4.50 (0.72)]/[1.53 (0.43)]/[1.61 (0.83)]
284	Liu, 2003, no PMID	[6.77 (0.75)]/[4.50 (0.72)]/[1.53 (0.43)]/[1.61 (0.83)]
285	Liu, 2003, no PMID	[6.77 (0.75)]/[4.50 (0.72)]/[1.53 (0.43)]/[1.61 (0.83)]
286	Liu, 2003, no PMID	[6.77 (0.75)]/[4.50 (0.72)]/[1.53 (0.43)]/[1.61 (0.83)]
287	Liu, 2003, no PMID	[6.77 (0.75)]/[4.50 (0.72)]/[1.53 (0.43)]/[1.61 (0.83)]
288	Liu, 2003, no PMID	[6.77 (0.75)]/[4.50 (0.72)]/[1.53 (0.43)]/[1.61 (0.83)]
289	Liu, 2003, no PMID	[6.77 (0.75)]/[4.50 (0.72)]/[1.53 (0.43)]/[1.61 (0.83)]
290	Lungershausen, 1994	[5.74 (SE 0.21)]/[4.04 (SE 0.19)]/[1.03 (SE 0.04)]/
291	Lungershausen, 1994	[5.74 (SE 0.21)]/[4.04 (SE 0.19)]/[1.03 (SE 0.04)]/
292	Lungershausen, 1994	[5.74 (SE 0.21)]/[4.04 (SE 0.19)]/[1.03 (SE 0.04)]/
293	Lungershausen, 1994	[5.74 (SE 0.21)]/[4.04 (SE 0.19)]/[1.03 (SE 0.04)]/
294	Lungershausen, 1994	[5.74 (SE 0.21)]/[4.04 (SE 0.19)]/[1.03 (SE 0.04)]/
295	Macchia, 2013, 23265344	nd

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	BMI mean (SD) Kg/m2/Weight mean (SD) Kg	Baseline n-3 intake	n-3 source (Baseline)
278	Kuhnt, 2014, 24553695	23.9 (2.7)	nd	nd
279	Leaf, 2005, 16267249	nd	EPA+DHA: 3.5 (SEM 1.2) % FA	phospholipids of red blood cells
280	Leaf, 2005, 16267249	nd	EPA+DHA: 3.5 (SEM 1.2) % FA	phospholipids of red blood cells
281	Leaf, 2005, 16267249	nd	EPA+DHA: 3.5 (SEM 1.2) % FA	phospholipids of red blood cells
282	Liu, 2003, no PMID	nd	EPA: 2.1 (0.3)% FA/DHA: 5.0 (0.5)% FA	erythrocyte
283	Liu, 2003, no PMID	nd	EPA: 2.1 (0.3)% FA/DHA: 5.0 (0.5)% FA	erythrocyte
284	Liu, 2003, no PMID	nd	EPA: 2.1 (0.3)% FA/DHA: 5.0 (0.5)% FA	erythrocyte
285	Liu, 2003, no PMID	nd	EPA: 2.1 (0.3)% FA/DHA: 5.0 (0.5)% FA	erythrocyte
286	Liu, 2003, no PMID	nd	EPA: 2.1 (0.3)% FA/DHA: 5.0 (0.5)% FA	erythrocyte
287	Liu, 2003, no PMID	nd	EPA: 2.1 (0.3)% FA/DHA: 5.0 (0.5)% FA	erythrocyte
288	Liu, 2003, no PMID	nd	EPA: 2.1 (0.3)% FA/DHA: 5.0 (0.5)% FA	erythrocyte
289	Liu, 2003, no PMID	nd	EPA: 2.1 (0.3)% FA/DHA: 5.0 (0.5)% FA	erythrocyte
290	Lungershausen, 1994	27.33 (3.93)	nd	nd
291	Lungershausen, 1994	27.33 (3.93)	nd	nd
292	Lungershausen, 1994	27.33 (3.93)	nd	nd
293	Lungershausen, 1994	27.33 (3.93)	nd	nd
294	Lungershausen, 1994	27.33 (3.93)	nd	nd
295	Macchia, 2013, 23265344	weight 83 (19)	nd	nd

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	n-3 type(s)	n-3 measure	Study design	Outcome
278	Kuhnt, 2014, 24553695	SDA vs EPA+DHA	g/d	Trial: Randomized Parallel	DBP
279	Leaf, 2005, 16267249	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Death, all cause
280	Leaf, 2005, 16267249	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Death, cardiac
281	Leaf, 2005, 16267249	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Sudden cardiac death
282	Liu, 2003, no PMID	EPA+DHA+ simvastatin vs Placebo + simvastatin	g/d	Trial: Randomized Parallel	LDL:HDL-c ratio
283	Liu, 2003, no PMID	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	LDL:HDL-c ratio
284	Liu, 2003, no PMID	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	HDL-c
285	Liu, 2003, no PMID	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	HDL-c
286	Liu, 2003, no PMID	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	LDL-c
287	Liu, 2003, no PMID	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	LDL-c
288	Liu, 2003, no PMID	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Tg
289	Liu, 2003, no PMID	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Tg
290	Lungershausen, 1994	EPA+DHA vs Placebo	g/d	Trial: Randomized Cross-over	HDL-c
291	Lungershausen, 1994	EPA+DHA vs Placebo	g/d	Trial: Randomized Cross-over	LDL-c
292	Lungershausen, 1994	DHA+EPA vs Placebo	g/d	Trial: Randomized Cross-over	Tg
293	Lungershausen, 1994	EPA+DHA vs Placebo	g/d	Trial: Randomized Cross-over	SBP
294	Lungershausen, 1994	EPA+DHA vs Placebo	g/d	Trial: Randomized Cross-over	DBP
295	Macchia, 2013, 23265344	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Atrial fibrillation

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Reported effect Size	Dose/intake difference	Dose-corrected effect size
278	Kuhnt, 2014, 24553695	1 (-7.05, 9.05)	NA	
279	Leaf, 2005, 16267249	OR 1.10 (0.49, 2.47)	2.6	1.037338
280	Leaf, 2005, 16267249	OR 1.01 (0.39, 2.60)	2.6	1.003834
281	Leaf, 2005, 16267249	3.06 (0.32, 29.68)	0.6	6.449644
282	Liu, 2003, no PMID	-0.02 (-0.45, 0.41)	2.8	-0.0071429
283	Liu, 2003, no PMID	-0.1 (-0.7, 0.5)	2.8	-0.0357143
284	Liu, 2003, no PMID	2.32 (-7.32, 11.95)	2.8	0.8285714
285	Liu, 2003, no PMID	2.32 (-9.32, 13.95)	2.8	0.8285714
286	Liu, 2003, no PMID	5.41 (-13.28, 24.09)	2.8	1.932143
287	Liu, 2003, no PMID	5.02 (-17.04, 27.07)	2.8	1.792857
288	Liu, 2003, no PMID	-39.82 (-76.39, -3.26)	2.8	-14.22143
289	Liu, 2003, no PMID	-35.40 (-79.60, 8.80)	2.8	-12.64286
290	Lungershausen, 1994	0.77 (-2.71, 4.25)	3.4	0.2264706
291	Lungershausen, 1994	6.56 (-7.50, 20.56)	3.4	1.929412
292	Lungershausen, 1994	28.32 (19.65, 36.99)	3.4	8.329412
293	Lungershausen, 1994	-3.1 (-8.3, 2.1)	3.4	-0.9117647
294	Lungershausen, 1994	-1.8 (-4.8, 1.2)	3.4	-0.5294118
295	Macchia, 2013, 23265344	HR 1.28 (0.90, 1.83)	0.866	1.329839

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Outcome classification
278	Kuhnt, 2014, 24553695	Secondary
279	Leaf, 2005, 16267249	Secondary
280	Leaf, 2005, 16267249	Secondary
281	Leaf, 2005, 16267249	Secondary
282	Liu, 2003, no PMID	No data; unclear
283	Liu, 2003, no PMID	No data; unclear
284	Liu, 2003, no PMID	No data; unclear
285	Liu, 2003, no PMID	No data; unclear
286	Liu, 2003, no PMID	No data; unclear
287	Liu, 2003, no PMID	No data; unclear
288	Liu, 2003, no PMID	No data; unclear
289	Liu, 2003, no PMID	No data; unclear
290	Lungershausen, 1994	Primary (implied)
291	Lungershausen, 1994	Primary (implied)
292	Lungershausen, 1994	Primary (implied)
293	Lungershausen, 1994	Primary (implied)
294	Lungershausen, 1994	Primary (implied)
295	Macchia, 2013, 23265344	Secondary; Primary in registry record (NCT00597220)

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Study years (start date)	Country	Population
296	Macchia, 2013, 23265344	2008	Italy, Argentina	Secondary Prevention (history of CVD event)
297	Macchia, 2013, 23265344	2008	Italy, Argentina	Secondary Prevention (history of CVD event)
298	Macchia, 2013, 23265344	2008	Italy, Argentina	Secondary Prevention (history of CVD event)
299	Macchia, 2013, 23265344	2008	Italy, Argentina	Secondary Prevention (history of CVD event)
300	Maki, 2010, 20451686	2005	US	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
301	Maki, 2010, 20451686	2005	US	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
302	Maki, 2010, 20451686	2005	US	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
303	Maki, 2010, 20451686	2005	US	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
304	Maki, 2013, 23998969	2011	US	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
305	Maki, 2013, 23998969	2011	US	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
306	Maki, 2013, 23998969	2011	US	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
307	Maki, 2013, 23998969	2011	US	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)

Row	Study	Risk type	Sample size (total)
296	Macchia, 2013, 23265344	Arrhythmia	586
297	Macchia, 2013, 23265344	Arrhythmia	586
298	Macchia, 2013, 23265344	Arrhythmia	586
299	Macchia, 2013, 23265344	Arrhythmia	586
300	Maki, 2010, 20451686	Dyslipidemia (mean fasting TG level >200 and <500 mg/dL, and a mean LDL-C level below or within 10% of the patient's NCEP ATP III goal)	254
301	Maki, 2010, 20451686	Dyslipidemia (mean fasting TG level >200 and <500 mg/dL, and a mean LDL-C level below or within 10% of the patient's NCEP ATP III goal)	254
302	Maki, 2010, 20451686	Dyslipidemia (mean fasting TG level >200 and <500 mg/dL, and a mean LDL-C level below or within 10% of the patient's NCEP ATP III goal)	254
303	Maki, 2010, 20451686	Dyslipidemia (mean fasting TG level >200 and <500 mg/dL, and a mean LDL-C level below or within 10% of the patient's NCEP ATP III goal)	254
304	Maki, 2013, 23998969	Dyslipidemia ((TG) levels 200 mg/dL and <500 mg/dL)	627
305	Maki, 2013, 23998969	Dyslipidemia ((TG) levels 200 mg/dL and <500 mg/dL)	627
306	Maki, 2013, 23998969	Dyslipidemia ((TG) levels 200 mg/dL and <500 mg/dL)	627
307	Maki, 2013, 23998969	Dyslipidemia ((TG) levels 200 mg/dL and <500 mg/dL)	627

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Age mean (SD) [median] years	Sex (% male)	Race
296	Macchia, 2013, 23265344	65.9 (10.5)	51.9	nd
297	Macchia, 2013, 23265344	65.9 (10.5)	51.9	nd
298	Macchia, 2013, 23265344	65.9 (10.5)	51.9	nd
299	Macchia, 2013, 23265344	65.9 (10.5)	51.9	nd
300	Maki, 2010, 20451686	59.3 (10.8)	60.6	96.2 white, 2.3 black, 2.3 Hispanic
301	Maki, 2010, 20451686	59.3 (10.8)	60.6	96.2 white, 2.3 black, 2.3 Hispanic
302	Maki, 2010, 20451686	59.3 (10.8)	60.6	96.2 white, 2.3 black, 2.3 Hispanic
303	Maki, 2010, 20451686	59.3 (10.8)	60.6	96.2 white, 2.3 black, 2.3 Hispanic
304	Maki, 2013, 23998969	61.5 (9.6)	56.7	91.6 white, 4.7 black, 1.4 Asian, 2.3 American lian or Alaska native, native Hawaiian, or Pacific Islaer, multiple, a other
305	Maki, 2013, 23998969	61.5 (9.6)	56.7	91.6 white, 4.7 black, 1.4 Asian, 2.3 American lian or Alaska native, native Hawaiian, or Pacific Islaer, multiple, a other
306	Maki, 2013, 23998969	61.5 (9.6)	56.7	91.6 white, 4.7 black, 1.4 Asian, 2.3 American lian or Alaska native, native Hawaiian, or Pacific Islaer, multiple, a other
307	Maki, 2013, 23998969	61.5 (9.6)	56.7	91.6 white, 4.7 black, 1.4 Asian, 2.3 American lian or Alaska native, native Hawaiian, or Pacific Islaer, multiple, a other

Row	Study	Blood pressure SBP/DBP mmHg
296	Macchia, 2013, 23265344	nd
297	Macchia, 2013, 23265344	nd
298	Macchia, 2013, 23265344	nd
299	Macchia, 2013, 23265344	nd
300	Maki, 2010, 20451686	nd
301	Maki, 2010, 20451686	nd
302	Maki, 2010, 20451686	nd
303	Maki, 2010, 20451686	nd
304	Maki, 2013, 23998969	128.9 (14.3)/76.1 (7.7)
305	Maki, 2013, 23998969	128.9 (14.3)/76.1 (7.7)
306	Maki, 2013, 23998969	128.9 (14.3)/76.1 (7.7)
307	Maki, 2013, 23998969	128.9 (14.3)/76.1 (7.7)

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Lipids: Total cholesterol/LDL/HDL/Triglycerides mean (SD) mg/dL [mmol/L]
296	Macchia, 2013, 23265344	nd
297	Macchia, 2013, 23265344	nd
298	Macchia, 2013, 23265344	nd
299	Macchia, 2013, 23265344	nd
300	Maki, 2010, 20451686	186.0 (32.1) median 183.5 /92.3 (23.2) median 88.2 /44.7 (9.3) median 43.3 /286.7 (77.5) median 270.7
301	Maki, 2010, 20451686	186.0 (32.1) median 183.5 /92.3 (23.2) median 88.2 /44.7 (9.3) median 43.3 /286.7 (77.5) median 270.7
302	Maki, 2010, 20451686	186.0 (32.1) median 183.5 /92.3 (23.2) median 88.2 /44.7 (9.3) median 43.3 /286.7 (77.5) median 270.7
303	Maki, 2010, 20451686	186.0 (32.1) median 183.5 /92.3 (23.2) median 88.2 /44.7 (9.3) median 43.3 /286.7 (77.5) median 270.7
304	Maki, 2013, 23998969	174 (29.5)/91.7 (27.3)/38.3 (9.0)/280 (70.7)
305	Maki, 2013, 23998969	174 (29.5)/91.7 (27.3)/38.3 (9.0)/280 (70.7)
306	Maki, 2013, 23998969	174 (29.5)/91.7 (27.3)/38.3 (9.0)/280 (70.7)
307	Maki, 2013, 23998969	174 (29.5)/91.7 (27.3)/38.3 (9.0)/280 (70.7)

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	BMI mean (SD) Kg/m2/Weight mean (SD) Kg	Baseline n-3 intake	n-3 source (Baseline)
296	Macchia, 2013, 23265344	weight 83 (19)	nd	nd
297	Macchia, 2013, 23265344	weight 83 (19)	nd	nd
298	Macchia, 2013, 23265344	weight 83 (19)	nd	nd
299	Macchia, 2013, 23265344	weight 83 (19)	nd	nd
300	Maki, 2010, 20451686	31.5 (5.5)	nd	nd
301	Maki, 2010, 20451686	31.5 (5.5)	nd	nd
302	Maki, 2010, 20451686	31.5 (5.5)	nd	nd
303	Maki, 2010, 20451686	31.5 (5.5)	nd	nd
304	Maki, 2013, 23998969	32.7 (5.3)	EPA: 20.8 (10.7) mcg/mL, DPA: 21.8 (8.0) mcg/mL, DHA: 58.9 (18.9) mcg/mL	plasma
305	Maki, 2013, 23998969	32.7 (5.3)	EPA: 20.8 (10.7) mcg/mL, DPA: 21.8 (8.0) mcg/mL, DHA: 58.9 (18.9) mcg/mL	plasma
306	Maki, 2013, 23998969	32.7 (5.3)	EPA: 20.8 (10.7) mcg/mL, DPA: 21.8 (8.0) mcg/mL, DHA: 58.9 (18.9) mcg/mL	plasma
307	Maki, 2013, 23998969	32.7 (5.3)	EPA: 20.8 (10.7) mcg/mL, DPA: 21.8 (8.0) mcg/mL, DHA: 58.9 (18.9) mcg/mL	plasma

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	n-3 type(s)	n-3 measure	Study design	Outcome
296	Macchia, 2013, 23265344	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Congestive heart failure
297	Macchia, 2013, 23265344	ALA+EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Death, all cause
298	Macchia, 2013, 23265344	ALA+DHA+EPA vs Placebo	g/d	Trial: Randomized Parallel	MACE
299	Macchia, 2013, 23265344	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Stroke
300	Maki, 2010, 20451686	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Total:HDL-c ratio
301	Maki, 2010, 20451686	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	HDL-c
302	Maki, 2010, 20451686	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	LDL-c
303	Maki, 2010, 20451686	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Tg
304	Maki, 2013, 23998969	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Total:HDL-c ratio
305	Maki, 2013, 23998969	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Parallel	Total:HDL-c ratio
306	Maki, 2013, 23998969	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Total:HDL-c ratio
307	Maki, 2013, 23998969	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	HDL-c

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Reported effect Size	Dose/intake difference	Dose-corrected effect size
296	Macchia, 2013, 23265344	HR 0.86 (0.26, 2.81)	0.866	0.8401622
297	Macchia, 2013, 23265344	HR 0.80 (0.21, 3.00)	0.866	0.772849
298	Macchia, 2013, 23265344	HR 0.88 (0.44, 1.66)	0.866	0.8627644
299	Macchia, 2013, 23265344	HR 1.16 (0.23, 5.78)	1	1.16
300	Maki, 2010, 20451686	-0.3 (-0.52, 0.08)	3.36	-0.0892857
301	Maki, 2010, 20451686	2.50 (-0.18, 5.18)	3.36	0.7440476
302	Maki, 2010, 20451686	3.40 (-2.07, 8.87)	3.36	1.011905
303	Maki, 2010, 20451686	-68.80 (-89.32, -48.28)	3.36	-20.47619
304	Maki, 2013, 23998969	−0.2 (−0.3, −0.1)	4	-0.05
305	Maki, 2013, 23998969	−0.1 (−0.2, 0.05)	2	-0.05
306	Maki, 2013, 23998969	−0.1 (−0.2, 0.05)	2	-0.05
307	Maki, 2013, 23998969	0.5 (−1.5, 2.5)	4	

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Outcome classification
296	Macchia, 2013, 23265344	Secondary
297	Macchia, 2013, 23265344	Secondary
298	Macchia, 2013, 23265344	Secondary
299	Macchia, 2013, 23265344	Secondary
300	Maki, 2010, 20451686	Secondary; Primary in registry record (NCT00246701)
301	Maki, 2010, 20451686	Secondary; Primary in registry record (NCT00246701)
302	Maki, 2010, 20451686	Secondary; Primary in registry record (NCT00246701)
303	Maki, 2010, 20451686	Secondary; Primary in registry record (NCT00246701)
304	Maki, 2013, 23998969	Secondary; Primary in registry record (NCT01408303)
305	Maki, 2013, 23998969	Secondary; Primary in registry record (NCT01408303)
306	Maki, 2013, 23998969	Secondary; Primary in registry record (NCT01408303)
307	Maki, 2013, 23998969	Secondary; Primary in registry record (NCT01408303)

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Study years (start date)	Country	Population
308	Maki, 2013, 23998969	2011	US	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
309	Maki, 2013, 23998969	2011	US	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
310	Maki, 2013, 23998969	2011	US	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
311	Maki, 2013, 23998969	2011	US	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
312	Maki, 2013, 23998969	2011	US	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
313	Marchioli, 2002, 11997274	1993	Italy	Secondary Prevention (history of CVD event)
314	Marchioli, 2002, 11997274	1993	Italy	Secondary Prevention (history of CVD event)
315	Marchioli, 2002, 11997274	1993	Italy	Secondary Prevention (history of CVD event)
316	Marchioli, 2002, 11997274	1993	Italy	Secondary Prevention (history of CVD event)
317	Marchioli, 2002, 11997274	1993	Italy	Secondary Prevention (history of CVD event)
318	Marchioli, 2002, 11997274	1993	Italy	Secondary Prevention (history of CVD event)
319	Marchioli, 2002, 11997274	1993	Italy	Secondary Prevention (history of CVD event)
320	Natvig, 1968, 5756076	1965	Norway	Primary Prevention, Healthy
321	Natvig, 1968, 5756076	1965	Norway	Primary Prevention, Healthy

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Risk type	Sample size (total)
308	Maki, 2013, 23998969	Dyslipidemia ((TG) levels 200 mg/dL and <500 mg/dL)	627
309	Maki, 2013, 23998969	Dyslipidemia ((TG) levels 200 mg/dL and <500 mg/dL)	627
310	Maki, 2013, 23998969	Dyslipidemia ((TG) levels 200 mg/dL and <500 mg/dL)	627
311	Maki, 2013, 23998969	Dyslipidemia ((TG) levels 200 mg/dL and <500 mg/dL)	627
312	Maki, 2013, 23998969	Dyslipidemia ((TG) levels 200 mg/dL and <500 mg/dL)	627
313	Marchioli, 2002, 11997274	Other (myocardial infarction)	11334
314	Marchioli, 2002, 11997274	Other (myocardial infarction)	11334
315	Marchioli, 2002, 11997274	Other (myocardial infarction)	11334
316	Marchioli, 2002, 11997274	Other (myocardial infarction)	11334
317	Marchioli, 2002, 11997274	Other (myocardial infarction)	11334
318	Marchioli, 2002, 11997274	Other (myocardial infarction)	11334
319	Marchioli, 2002, 11997274	Other (myocardial infarction)	11334
320	Natvig, 1968, 5756076	na	13406
321	Natvig, 1968, 5756076	na	13406

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Age mean (SD) [median] years	Sex (% male)	Race
308	Maki, 2013, 23998969	61.5 (9.6)	56.7	91.6 white, 4.7 black, 1.4 Asian, 2.3 American lian or Alaska native, native Hawaiian, or Pacific Islaer, multiple, a other
309	Maki, 2013, 23998969	61.5 (9.6)	56.7	91.6 white, 4.7 black, 1.4 Asian, 2.3 American lian or Alaska native, native Hawaiian, or Pacific Islaer, multiple, a other
310	Maki, 2013, 23998969	61.5 (9.6)	56.7	91.6 white, 4.7 black, 1.4 Asian, 2.3 American lian or Alaska native, native Hawaiian, or Pacific Islaer, multiple, a other
311	Maki, 2013, 23998969	61.5 (9.6)	56.7	91.6 white, 4.7 black, 1.4 Asian, 2.3 American lian or Alaska native, native Hawaiian, or Pacific Islaer, multiple, a other
312	Maki, 2013, 23998969	61.5 (9.6)	56.7	91.6 white, 4.7 black, 1.4 Asian, 2.3 American lian or Alaska native, native Hawaiian, or Pacific Islaer, multiple, a other
313	Marchioli, 2002, 11997274	59.4	85.1	nd
314	Marchioli, 2002, 11997274	59.4	85.1	nd
315	Marchioli, 2002, 11997274	59.4	85.1	nd
316	Marchioli, 2002, 11997274	59.4	85.1	nd
317	Marchioli, 2002, 11997274	59.4	85.1	nd
318	Marchioli, 2002, 11997274	59.4	85.1	nd
319	Marchioli, 2002, 11997274	59.4	85.1	nd
320	Natvig, 1968, 5756076	range 49, 61	100	nd
321	Natvig, 1968, 5756076	range 49, 61	100	nd

Row	Study	Blood pressure SBP/DBP mmHg
308	Maki, 2013, 23998969	128.9 (14.3)/76.1 (7.7)
309	Maki, 2013, 23998969	128.9 (14.3)/76.1 (7.7)
310	Maki, 2013, 23998969	128.9 (14.3)/76.1 (7.7)
311	Maki, 2013, 23998969	128.9 (14.3)/76.1 (7.7)
312	Maki, 2013, 23998969	128.9 (14.3)/76.1 (7.7)
313	Marchioli, 2002, 11997274	nd
314	Marchioli, 2002, 11997274	nd
315	Marchioli, 2002, 11997274	nd
316	Marchioli, 2002, 11997274	nd
317	Marchioli, 2002, 11997274	nd
318	Marchioli, 2002, 11997274	nd
319	Marchioli, 2002, 11997274	nd
320	Natvig, 1968, 5756076	nd
321	Natvig, 1968, 5756076	nd

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Lipids: Total cholesterol/LDL/HDL/Triglycerides mean (SD) mg/dL [mmol/L]
308	Maki, 2013, 23998969	174 (29.5)/91.7 (27.3)/38.3 (9.0)/280 (70.7)
309	Maki, 2013, 23998969	174 (29.5)/91.7 (27.3)/38.3 (9.0)/280 (70.7)
310	Maki, 2013, 23998969	174 (29.5)/91.7 (27.3)/38.3 (9.0)/280 (70.7)
311	Maki, 2013, 23998969	174 (29.5)/91.7 (27.3)/38.3 (9.0)/280 (70.7)
312	Maki, 2013, 23998969	174 (29.5)/91.7 (27.3)/38.3 (9.0)/280 (70.7)
313	Marchioli, 2002, 11997274	211.6/138.5/41.7/161.9
314	Marchioli, 2002, 11997274	211.6/138.5/41.7/161.9
315	Marchioli, 2002, 11997274	211.6/138.5/41.7/161.9
316	Marchioli, 2002, 11997274	211.6/138.5/41.7/161.9
317	Marchioli, 2002, 11997274	211.6/138.5/41.7/161.9
318	Marchioli, 2002, 11997274	211.6/138.5/41.7/161.9
319	Marchioli, 2002, 11997274	211.6/138.5/41.7/161.9
320	Natvig, 1968, 5756076	nd
321	Natvig, 1968, 5756076	nd

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	BMI mean (SD) Kg/m2/Weight mean (SD) Kg	Baseline n-3 intake	n-3 source (Baseline)
308	Maki, 2013, 23998969	32.7 (5.3)	EPA: 20.8 (10.7) mcg/mL, DPA: 21.8 (8.0) mcg/mL, DHA: 58.9 (18.9) mcg/mL	plasma
309	Maki, 2013, 23998969	32.7 (5.3)	EPA: 20.8 (10.7) mcg/mL, DPA: 21.8 (8.0) mcg/mL, DHA: 58.9 (18.9) mcg/mL	plasma
310	Maki, 2013, 23998969	32.7 (5.3)	EPA: 20.8 (10.7) mcg/mL, DPA: 21.8 (8.0) mcg/mL, DHA: 58.9 (18.9) mcg/mL	plasma
311	Maki, 2013, 23998969	32.7 (5.3)	EPA: 20.8 (10.7) mcg/mL, DPA: 21.8 (8.0) mcg/mL, DHA: 58.9 (18.9) mcg/mL	plasma
312	Maki, 2013, 23998969	32.7 (5.3)	EPA: 20.8 (10.7) mcg/mL, DPA: 21.8 (8.0) mcg/mL, DHA: 58.9 (18.9) mcg/mL	plasma
313	Marchioli, 2002, 11997274	>30 (13.8%)	nd	nd
314	Marchioli, 2002, 11997274	>30 (13.8%)	nd	nd
315	Marchioli, 2002, 11997274	>30 (13.8%)	nd	nd
316	Marchioli, 2002, 11997274	>30 (13.8%)	nd	nd
317	Marchioli, 2002, 11997274	>30 (13.8%)	nd	nd
318	Marchioli, 2002, 11997274	>30 (13.8%)	nd	nd
319	Marchioli, 2002, 11997274	>30 (13.8%)	nd	nd
320	Natvig, 1968, 5756076	weight range 60, >90	nd	nd
321	Natvig, 1968, 5756076	weight range 60, >90	nd	nd

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	n-3 type(s)	n-3 measure	Study design	Outcome
308	Maki, 2013, 23998969	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	HDL-c
309	Maki, 2013, 23998969	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	LDL-c
310	Maki, 2013, 23998969	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	LDL-c
311	Maki, 2013, 23998969	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Tg
312	Maki, 2013, 23998969	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Parallel	Tg
313	Marchioli, 2002, 11997274	EPA+DHA vs Placebo	g/d	Trial: Randomized Factorial Design	Death, all cause
314	Marchioli, 2002, 11997274	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Death, cardiac
315	Marchioli, 2002, 11997274	EPA+DHA vs Placebo	g/d	Trial: Randomized Factorial Design	Death, CVD (total)
316	Marchioli, 2002, 11997274	EPA+DHA vs Placebo	g/d	Trial: Randomized Factorial Design	Stroke
317	Marchioli, 2002, 11997274	EPA+DHA vs Placebo	g/d	Trial: Randomized Factorial Design	HDL-c
318	Marchioli, 2002, 11997274	EPA+DHA vs Placebo	g/d	Trial: Randomized Factorial Design	LDL-c
319	Marchioli, 2002, 11997274	ALA vs Placebo	g/d	Trial: Randomized Factorial Design	Tg
320	Natvig, 1968, 5756076	ALA vs Placebo	g/d	Trial: Randomized Factorial Design	Angina, stable
321	Natvig, 1968, 5756076	ALA vs Placebo	g/d	Trial: Randomized Parallel	Death, all cause

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Reported effect Size	Dose/intake difference	Dose-corrected effect size
308	Maki, 2013, 23998969	0.1 (−1.75, 1.95)	2	
309	Maki, 2013, 23998969	-0.50 (-5.69, 4.69)	4	-0.25
310	Maki, 2013, 23998969	-3.70 (-8.88, 1.48)	2	-1.85
311	Maki, 2013, 23998969	−42 (−59.3, −24.7)	4	-0.05
312	Maki, 2013, 23998969	−28 (−44.0, −12.0)	2	-0.05
313	Marchioli, 2002, 11997274	RR 0.79 (0.66, 0.93)	0.866	0.7617044
314	Marchioli, 2002, 11997274	RR 0.65 (0.51, 0.82)	0.866	0.6080855
315	Marchioli, 2002, 11997274	RR 0.70 (0.56, 0.86)	0.866	0.6624138
316	Marchioli, 2002, 11997274	RR 1.22 (0.75, 1.97)	0.866	1.258122
317	Marchioli, 2002, 11997274	0.00 (nd)	0.866	0
318	Marchioli, 2002, 11997274	2.00 (nd)	0.866	2.309469
319	Marchioli, 2002, 11997274	-10.00 (nd)	0.866	-11.54734
320	Natvig, 1968, 5756076	OR 1.58 (0.77, 3.26)	5.2	1.091951
321	Natvig, 1968, 5756076	OR 0.93 (0.61, 1.44)	5.2	0.986141

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Outcome classification
308	Maki, 2013, 23998969	Secondary; Primary in registry record (NCT01408303)
309	Maki, 2013, 23998969	Secondary; Primary in registry record (NCT01408303)
310	Maki, 2013, 23998969	Secondary; Primary in registry record (NCT01408303)
311	Maki, 2013, 23998969	Secondary; Primary in registry record (NCT01408303)
312	Maki, 2013, 23998969	Secondary; Primary in registry record (NCT01408303)
313	Marchioli, 2002, 11997274	Primary (stated)
314	Marchioli, 2002, 11997274	Primary (stated)
315	Marchioli, 2002, 11997274	Secondary
316	Marchioli, 2002, 11997274	Secondary
317	Marchioli, 2002, 11997274	Secondary
318	Marchioli, 2002, 11997274	Secondary
319	Marchioli, 2002, 11997274	Secondary
320	Natvig, 1968, 5756076	No data; unclear
321	Natvig, 1968, 5756076	No data; unclear

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Study years (start date)	Country	Population
322	Natvig, 1968, 5756076	1965	Norway	Primary Prevention, Healthy
323	Natvig, 1968, 5756076	1965	Norway	Primary Prevention, Healthy
324	Natvig, 1968, 5756076	1965	Norway	Primary Prevention, Healthy
325	Natvig, 1968, 5756076	1965	Norway	Primary Prevention, Healthy
326	Nilsen, 2001, 11451717	1995	Norway	Secondary Prevention (history of CVD event)
327	Nilsen, 2001, 11451717	1995	Norway	Secondary Prevention (history of CVD event)
328	Nilsen, 2001, 11451717	1995	Norway	Secondary Prevention (history of CVD event)
329	Nilsen, 2001, 11451717	1995	Norway	Secondary Prevention (history of CVD event)
330	Nilsen, 2001, 11451717	1995	Norway	Secondary Prevention (history of CVD event)
331	Nilsen, 2001, 11451717	1995	Norway	Secondary Prevention (history of CVD event)
332	Nodari, 2011, 21215550	2007	Italy	Secondary Prevention (history of CVD event)
333	Nodari, 2011, 21215550	2007	Italy	Secondary Prevention (history of CVD event)
334	Nodari, 2011, 21215550	2007	Italy	Secondary Prevention (history of CVD event)
335	Nodari, 2011, 21844082	2006	Italy	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
336	Oh, 2014, 25147070	nd	Korea	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
337	Oh, 2014, 25147070	nd	Korea	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
338	Oh, 2014, 25147070	nd	Korea	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
339	Oh, 2014, 25147070	nd	Korea	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
340	Oh, 2014, 25147070	nd	Korea	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
341	Oh, 2014, 25147070	nd	Korea	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
342	Oh, 2014, 25147070	nd	Korea	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)

Row	Study	Risk type	Sample size (total)
322	Natvig, 1968, 5756076	na	13406
323	Natvig, 1968, 5756076	na	13406
324	Natvig, 1968, 5756076	na	13406
325	Natvig, 1968, 5756076	na	13406
326	Nilsen, 2001, 11451717	Other (MI)	300
327	Nilsen, 2001, 11451717	Other (MI)	300
328	Nilsen, 2001, 11451717	Other (MI)	300
329	Nilsen, 2001, 11451717	Other (MI)	300
330	Nilsen, 2001, 11451717	Other (MI)	300
331	Nilsen, 2001, 11451717	Other (MI)	300
332	Nodari, 2011, 21215550	Other (mild and moderate heart failure (HF) due to nonischemic dilated cardiomyopathy (NICM))	133
333	Nodari, 2011, 21215550	Other (mild and moderate heart failure (HF) due to nonischemic dilated cardiomyopathy (NICM))	133
334	Nodari, 2011, 21215550	Other (mild and moderate heart failure (HF) due to nonischemic dilated cardiomyopathy (NICM))	133
335	Nodari, 2011, 21844082	Arrhythmia	199
336	Oh, 2014, 25147070	Dyslipidemia (hypertriglyceridemia)	173
337	Oh, 2014, 25147070	Dyslipidemia (hypertriglyceridemia)	173
338	Oh, 2014, 25147070	Dyslipidemia (hypertriglyceridemia)	173
339	Oh, 2014, 25147070	Dyslipidemia (hypertriglyceridemia)	173
340	Oh, 2014, 25147070	Dyslipidemia (hypertriglyceridemia)	173
341	Oh, 2014, 25147070	Dyslipidemia (hypertriglyceridemia)	173
342	Oh, 2014, 25147070	Dyslipidemia (hypertriglyceridemia)	173

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Age mean (SD) [median] years	Sex (% male)	Race
322	Natvig, 1968, 5756076	range 49, 61	100	nd
323	Natvig, 1968, 5756076	range 49, 61	100	nd
324	Natvig, 1968, 5756076	range 49, 61	100	nd
325	Natvig, 1968, 5756076	range 49, 61	100	nd
326	Nilsen, 2001, 11451717		82	nd
327	Nilsen, 2001, 11451717		82	nd
328	Nilsen, 2001, 11451717		82	nd
329	Nilsen, 2001, 11451717		82	nd
330	Nilsen, 2001, 11451717		82	nd
331	Nilsen, 2001, 11451717		82	nd
332	Nodari, 2011, 21215550	64 (9)	84.9	nd
333	Nodari, 2011, 21215550	64 (9)	84.9	nd
334	Nodari, 2011, 21215550	64 (9)	84.9	nd
335	Nodari, 2011, 21844082	69 (9)	63.6	nd
336	Oh, 2014, 25147070	54 (9)	54.8	nd
337	Oh, 2014, 25147070	54 (9)	54.8	nd
338	Oh, 2014, 25147070	54 (9)	54.8	nd
339	Oh, 2014, 25147070	54 (9)	54.8	nd
340	Oh, 2014, 25147070	54 (9)	54.8	nd
341	Oh, 2014, 25147070	54 (9)	54.8	nd
342	Oh, 2014, 25147070	54 (9)	54.8	nd

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Blood pressure SBP/DBP mmHg
322	Natvig, 1968, 5756076	nd
323	Natvig, 1968, 5756076	nd
324	Natvig, 1968, 5756076	nd
325	Natvig, 1968, 5756076	nd
326	Nilsen, 2001, 11451717	122.1 (range 80, 190)/nd
327	Nilsen, 2001, 11451717	122.1 (range 80, 190)/nd
328	Nilsen, 2001, 11451717	122.1 (range 80, 190)/nd
329	Nilsen, 2001, 11451717	122.1 (range 80, 190)/nd
330	Nilsen, 2001, 11451717	122.1 (range 80, 190)/nd
331	Nilsen, 2001, 11451717	122.1 (range 80, 190)/nd
332	Nodari, 2011, 21215550	119.5 (9.2)/76 (5.2)
333	Nodari, 2011, 21215550	119.5 (9.2)/76 (5.2)
334	Nodari, 2011, 21215550	119.5 (9.2)/76 (5.2)
335	Nodari, 2011, 21844082	136 (16)/82 (9)
336	Oh, 2014, 25147070	nd
337	Oh, 2014, 25147070	nd
338	Oh, 2014, 25147070	nd
339	Oh, 2014, 25147070	nd
340	Oh, 2014, 25147070	nd
341	Oh, 2014, 25147070	nd
342	Oh, 2014, 25147070	nd

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Lipids: Total cholesterol/LDL/HDL/Triglycerides mean (SD) mg/dL [mmol/L]
322	Natvig, 1968, 5756076	nd
323	Natvig, 1968, 5756076	nd
324	Natvig, 1968, 5756076	nd
325	Natvig, 1968, 5756076	nd
326	Nilsen, 2001, 11451717	nd
327	Nilsen, 2001, 11451717	nd
328	Nilsen, 2001, 11451717	nd
329	Nilsen, 2001, 11451717	nd
330	Nilsen, 2001, 11451717	nd
331	Nilsen, 2001, 11451717	nd
332	Nodari, 2011, 21215550	187 (28)nd154 (76)
333	Nodari, 2011, 21215550	187 (28)nd154 (76)
334	Nodari, 2011, 21215550	187 (28)nd154 (76)
335	Nodari, 2011, 21844082	nd
336	Oh, 2014, 25147070	201 (29)/111 (34)/42 (8)/281 (63)
337	Oh, 2014, 25147070	201 (29)/111 (34)/42 (8)/281 (63)
338	Oh, 2014, 25147070	201 (29)/111 (34)/42 (8)/281 (63)
339	Oh, 2014, 25147070	201 (29)/111 (34)/42 (8)/281 (63)
340	Oh, 2014, 25147070	201 (29)/111 (34)/42 (8)/281 (63)
341	Oh, 2014, 25147070	201 (29)/111 (34)/42 (8)/281 (63)
342	Oh, 2014, 25147070	201 (29)/111 (34)/42 (8)/281 (63)

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	BMI mean (SD) Kg/m2/Weight mean (SD) Kg	Baseline n-3 intake	n-3 source (Baseline)
322	Natvig, 1968, 5756076	weight range 60, >90	nd	nd
323	Natvig, 1968, 5756076	weight range 60, >90	nd	nd
324	Natvig, 1968, 5756076	weight range 60, >90	nd	nd
325	Natvig, 1968, 5756076	weight range 60, >90	nd	nd
326	Nilsen, 2001, 11451717	26.0 (range 19.4, 33.6)	nd	nd
327	Nilsen, 2001, 11451717	26.0 (range 19.4, 33.6)	nd	nd
328	Nilsen, 2001, 11451717	26.0 (range 19.4, 33.6)	nd	nd
329	Nilsen, 2001, 11451717	26.0 (range 19.4, 33.6)	nd	nd
330	Nilsen, 2001, 11451717	26.0 (range 19.4, 33.6)	nd	nd
331	Nilsen, 2001, 11451717	26.0 (range 19.4, 33.6)	nd	nd
332	Nodari, 2011, 21215550	25.7 (2.22)/76.0 (7.5)	EPA+DHA: 1.68 (0.43) % FA	circulating free FA
333	Nodari, 2011, 21215550	25.7 (2.22)/76.0 (7.5)	EPA+DHA: 1.68 (0.43) % FA	circulating free FA
334	Nodari, 2011, 21215550	25.7 (2.22)/76.0 (7.5)	EPA+DHA: 1.68 (0.43) % FA	circulating free FA
335	Nodari, 2011, 21844082	23.6 (5.3)/76.5 (10.1)	nd	nd
336	Oh, 2014, 25147070	nd	nd	nd
337	Oh, 2014, 25147070	nd	nd	nd
338	Oh, 2014, 25147070	nd	nd	nd
339	Oh, 2014, 25147070	nd	nd	nd
340	Oh, 2014, 25147070	nd	nd	nd
341	Oh, 2014, 25147070	nd	nd	nd
342	Oh, 2014, 25147070	nd	nd	nd

Row	Study	n-3 type(s)	n-3 measure	Study design	Outcome
322	Natvig, 1968, 5756076	ALA vs Placebo	g/d	Trial: Randomized Parallel	Myocardial infarction
323	Natvig, 1968, 5756076	ALA vs Placebo	g/d	Trial: Randomized Parallel	Myocardial infarction
324	Natvig, 1968, 5756076	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Myocardial infarction
325	Natvig, 1968, 5756076	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Stroke
326	Nilsen, 2001, 11451717	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Angina, unstable
327	Nilsen, 2001, 11451717	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Death, all cause
328	Nilsen, 2001, 11451717	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Death, CVD (total)
329	Nilsen, 2001, 11451717	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Revascularization
330	Nilsen, 2001, 11451717	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	HDL-c
331	Nilsen, 2001, 11451717	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Tg
332	Nodari, 2011, 21215550	EPA+DHA vs Placebo	% FA	Trial: Randomized Parallel	Tg
333	Nodari, 2011, 21215550	ALA+EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	SBP
334	Nodari, 2011, 21215550	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	DBP
335	Nodari, 2011, 21844082	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Atrial fibrillation
336	Oh, 2014, 25147070	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	HDL-c
337	Oh, 2014, 25147070	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Parallel	HDL-c
338	Oh, 2014, 25147070	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Parallel	HDL-c
339	Oh, 2014, 25147070	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Parallel	HDL-c
340	Oh, 2014, 25147070	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	HDL-c
341	Oh, 2014, 25147070	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	HDL-c
342	Oh, 2014, 25147070	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	LDL-c

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Reported effect Size	Dose/intake difference	Dose-corrected effect size
322	Natvig, 1968, 5756076	OR 0.99 (0.67, 1.45)	5.2	0.9980691
323	Natvig, 1968, 5756076	OR 0.17 (0.04, 0.79)	5.2	0.7112289
324	Natvig, 1968, 5756076	OR 0.84 (0.33, 2.16)	5.2	0.9670264
325	Natvig, 1968, 5756076	OR 1.33 (0.56, 3.16)	5.2	1.056374
326	Nilsen, 2001, 11451717	OR 1.18 (0.67, 2.08)	3.52	1.048144
327	Nilsen, 2001, 11451717	OR 1.19 (0.61, 2.34)	3.464	1.0515
328	Nilsen, 2001, 11451717	1.37 (0.63, 3.01)		
329	Nilsen, 2001, 11451717	OR 0.92 (0.57, 1.47)	1.732	0.9529986
330	Nilsen, 2001, 11451717	4.73 (1.79, 7.67)	4	1.1825
331	Nilsen, 2001, 11451717	-36.90 (-55.37, -18.43)	4	-9.225
332	Nodari, 2011, 21215550	-7.00 (-29.01, 15.01)	2	-3.5
333	Nodari, 2011, 21215550	3 (-0.4, 6.4)	4.25	0.7058824
334	Nodari, 2011, 21215550	-1 .0 (-2.6, 0.6)	4.25	-0.2352941
335	Nodari, 2011, 21844082	OR 0.52 (0.26, 1.06)	1.76	0.6896651
336	Oh, 2014, 25147070	-1.00 (-4.19, 2.19)	4	-0.25
337	Oh, 2014, 25147070	-2.00 (-5.21, 1.21)	2	-1
338	Oh, 2014, 25147070	1.00 (-2.40, 4.40)	1	1
339	Oh, 2014, 25147070	1.00 (-2.17, 4.17)	2	0.5
340	Oh, 2014, 25147070	-2.00 (-5.37, 1.37)	3	-0.6666667
341	Oh, 2014, 25147070	-3.00 (-6.39, 0.39)	1	-3
342	Oh, 2014, 25147070	1.00 (-13.17, 15.17)	4	0.25

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Outcome classification
322	Natvig, 1968, 5756076	No data; unclear
323	Natvig, 1968, 5756076	No data; unclear
324	Natvig, 1968, 5756076	No data; unclear
325	Natvig, 1968, 5756076	No data; unclear
326	Nilsen, 2001, 11451717	No data; unclear
327	Nilsen, 2001, 11451717	No data; unclear
328	Nilsen, 2001, 11451717	No data; unclear
329	Nilsen, 2001, 11451717	No data; unclear
330	Nilsen, 2001, 11451717	No data; unclear
331	Nilsen, 2001, 11451717	No data; unclear
332	Nodari, 2011, 21215550	Secondary
333	Nodari, 2011, 21215550	Secondary
334	Nodari, 2011, 21215550	Secondary
335	Nodari, 2011, 21844082	Secondary; Primary in registry record (NCT01198275)
336	Oh, 2014, 25147070	Secondary
337	Oh, 2014, 25147070	Secondary
338	Oh, 2014, 25147070	Secondary
339	Oh, 2014, 25147070	Secondary
340	Oh, 2014, 25147070	Secondary
341	Oh, 2014, 25147070	Secondary
342	Oh, 2014, 25147070	Secondary

Row	Study	Study years (start date)	Country	Population
343	Oh, 2014, 25147070	nd	Korea	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
344	Oh, 2014, 25147070	nd	Korea	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
345	Oh, 2014, 25147070	nd	Korea	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
346	Oh, 2014, 25147070	nd	Korea	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
347	Oh, 2014, 25147070	nd	Korea	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
348	Oh, 2014, 25147070	nd	Korea	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
349	Oh, 2014, 25147070	nd	Korea	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
350	Oh, 2014, 25147070	nd	Korea	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
351	Oh, 2014, 25147070	nd	Korea	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
352	Oh, 2014, 25147070	nd	Korea	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
353	Oh, 2014, 25147070	nd	Korea	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
354	Olano-Martin, 2010, 19748619	2007 (approx)	UK	Primary Prevention, Healthy
355	Olano-Martin, 2010, 19748619	2007 (approx)	UK	Primary Prevention, Healthy
356	Olano-Martin, 2010, 19748619	2007 (approx)	UK	Primary Prevention, Healthy
357	Olano-Martin, 2010, 19748619	2007 (approx)	UK	Primary Prevention, Healthy

Row	Study	Risk type	Sample size (total)
343	Oh, 2014, 25147070	Dyslipidemia (hypertriglyceridemia)	173
344	Oh, 2014, 25147070	Dyslipidemia (hypertriglyceridemia)	173
345	Oh, 2014, 25147070	Dyslipidemia (hypertriglyceridemia)	173
346	Oh, 2014, 25147070	Dyslipidemia (hypertriglyceridemia)	173
347	Oh, 2014, 25147070	Dyslipidemia (hypertriglyceridemia)	173
348	Oh, 2014, 25147070	Dyslipidemia (hypertriglyceridemia)	173
349	Oh, 2014, 25147070	Dyslipidemia (hypertriglyceridemia)	173
350	Oh, 2014, 25147070	Dyslipidemia (hypertriglyceridemia)	173
351	Oh, 2014, 25147070	Dyslipidemia (hypertriglyceridemia)	173
352	Oh, 2014, 25147070	Dyslipidemia (hypertriglyceridemia)	173
353	Oh, 2014, 25147070	Dyslipidemia (hypertriglyceridemia)	173
354	Olano-Martin, 2010, 19748619	na	38
355	Olano-Martin, 2010, 19748619	na	38
356	Olano-Martin, 2010, 19748619	na	38
357	Olano-Martin, 2010, 19748619	na	38

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Age mean (SD) [median] years	Sex (% male)	Race
343	Oh, 2014, 25147070	54 (9)	54.8	nd
344	Oh, 2014, 25147070	54 (9)	54.8	nd
345	Oh, 2014, 25147070	54 (9)	54.8	nd
346	Oh, 2014, 25147070	54 (9)	54.8	nd
347	Oh, 2014, 25147070	54 (9)	54.8	nd
348	Oh, 2014, 25147070	54 (9)	54.8	nd
349	Oh, 2014, 25147070	54 (9)	54.8	nd
350	Oh, 2014, 25147070	54 (9)	54.8	nd
351	Oh, 2014, 25147070	54 (9)	54.8	nd
352	Oh, 2014, 25147070	54 (9)	54.8	nd
353	Oh, 2014, 25147070	54 (9)	54.8	nd
354	Olano-Martin, 2010, 19748619	range 18, 70	100	nd
355	Olano-Martin, 2010, 19748619	range 18, 70	100	nd
356	Olano-Martin, 2010, 19748619	range 18, 70	100	nd
357	Olano-Martin, 2010, 19748619	range 18, 70	100	nd

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Blood pressure SBP/DBP mmHg
343	Oh, 2014, 25147070	nd
344	Oh, 2014, 25147070	nd
345	Oh, 2014, 25147070	nd
346	Oh, 2014, 25147070	nd
347	Oh, 2014, 25147070	nd
348	Oh, 2014, 25147070	nd
349	Oh, 2014, 25147070	nd
350	Oh, 2014, 25147070	nd
351	Oh, 2014, 25147070	nd
352	Oh, 2014, 25147070	nd
353	Oh, 2014, 25147070	nd
354	Olano-Martin, 2010, 19748619	nd
355	Olano-Martin, 2010, 19748619	nd
356	Olano-Martin, 2010, 19748619	nd
357	Olano-Martin, 2010, 19748619	nd

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Lipids: Total cholesterol/LDL/HDL/Triglycerides mean (SD) mg/dL [mmol/L]
343	Oh, 2014, 25147070	201 (29)/111 (34)/42 (8)/281 (63)
344	Oh, 2014, 25147070	201 (29)/111 (34)/42 (8)/281 (63)
345	Oh, 2014, 25147070	201 (29)/111 (34)/42 (8)/281 (63)
346	Oh, 2014, 25147070	201 (29)/111 (34)/42 (8)/281 (63)
347	Oh, 2014, 25147070	201 (29)/111 (34)/42 (8)/281 (63)
348	Oh, 2014, 25147070	201 (29)/111 (34)/42 (8)/281 (63)
349	Oh, 2014, 25147070	201 (29)/111 (34)/42 (8)/281 (63)
350	Oh, 2014, 25147070	201 (29)/111 (34)/42 (8)/281 (63)
351	Oh, 2014, 25147070	201 (29)/111 (34)/42 (8)/281 (63)
352	Oh, 2014, 25147070	201 (29)/111 (34)/42 (8)/281 (63)
353	Oh, 2014, 25147070	201 (29)/111 (34)/42 (8)/281 (63)
354	Olano-Martin, 2010, 19748619	[5.44 (SE 0.14)]/[3.54 (SE 0.13)]/[1.33 (SE 0.05)]/[1.39 (SE 0.08)]
355	Olano-Martin, 2010, 19748619	[5.44 (SE 0.14)]/[3.54 (SE 0.13)]/[1.33 (SE 0.05)]/[1.39 (SE 0.08)]
356	Olano-Martin, 2010, 19748619	[5.44 (SE 0.14)]/[3.54 (SE 0.13)]/[1.33 (SE 0.05)]/[1.39 (SE 0.08)]
357	Olano-Martin, 2010, 19748619	[5.44 (SE 0.14)]/[3.54 (SE 0.13)]/[1.33 (SE 0.05)]/[1.39 (SE 0.08)]

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	BMI mean (SD) Kg/m2/Weight mean (SD) Kg	Baseline n-3 intake	n-3 source (Baseline)
343	Oh, 2014, 25147070	nd	nd	nd
344	Oh, 2014, 25147070	nd	nd	nd
345	Oh, 2014, 25147070	nd	nd	nd
346	Oh, 2014, 25147070	nd	nd	nd
347	Oh, 2014, 25147070	nd	nd	nd
348	Oh, 2014, 25147070	nd	nd	nd
349	Oh, 2014, 25147070	nd	nd	nd
350	Oh, 2014, 25147070	nd	nd	nd
351	Oh, 2014, 25147070	nd	nd	nd
352	Oh, 2014, 25147070	nd	nd	nd
353	Oh, 2014, 25147070	nd	nd	nd
354	Olano-Martin, 2010, 19748619	range 18.5, 32	EPA: 1.7 (SEM 0.2)% FA, DPA: 1.2 (0.0)% FA, DHA: 4.8 (0.2)% FA	plasma phospholipids fatty acid
355	Olano-Martin, 2010, 19748619	range 18.5, 32	EPA: 1.7 (SEM 0.2)% FA, DPA: 1.2 (0.0)% FA, DHA: 4.8 (0.2)% FA	plasma phospholipids fatty acid
356	Olano-Martin, 2010, 19748619	range 18.5, 32	EPA: 1.7 (SEM 0.2)% FA, DPA: 1.2 (0.0)% FA, DHA: 4.8 (0.2)% FA	plasma phospholipids fatty acid
357	Olano-Martin, 2010, 19748619	range 18.5, 32	EPA: 1.7 (SEM 0.2)% FA, DPA: 1.2 (0.0)% FA, DHA: 4.8 (0.2)% FA	plasma phospholipids fatty acid

Row	Study	n-3 type(s)	n-3 measure	Study design	Outcome
343	Oh, 2014, 25147070	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Parallel	LDL-c
344	Oh, 2014, 25147070	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Parallel	LDL-c
345	Oh, 2014, 25147070	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Parallel	LDL-c
346	Oh, 2014, 25147070	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	LDL-c
347	Oh, 2014, 25147070	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	LDL-c
348	Oh, 2014, 25147070	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Tg
349	Oh, 2014, 25147070	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Parallel	Tg
350	Oh, 2014, 25147070	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Parallel	Tg
351	Oh, 2014, 25147070	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Parallel	Tg
352	Oh, 2014, 25147070	EPA vs Placebo	g/d	Trial: Randomized Parallel	Tg
353	Oh, 2014, 25147070	EPA vs DHA	% FA	Trial: Randomized Parallel	Tg
354	Olano-Martin, 2010, 19748619	DHA vs Placebo	g/d	Trial: Randomized Parallel	HDL-c
355	Olano-Martin, 2010, 19748619	EPA vs Placebo	g/d	Trial: Randomized Cross-over	HDL-c
356	Olano-Martin, 2010, 19748619	EPA vs DHA	g/d	Trial: Randomized Cross-over	HDL-c
357	Olano-Martin, 2010, 19748619	DHA vs Placebo	g/d	Trial: Randomized Cross-over	LDL-c

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Reported effect Size	Dose/intake difference	Dose-corrected effect size
343	Oh, 2014, 25147070	6.00 (-8.15, 20.15)	2	3
344	Oh, 2014, 25147070	3.00 (-11.07, 17.07)	1	3
345	Oh, 2014, 25147070	-5.00 (-18.77, 8.77)	2	-2.5
346	Oh, 2014, 25147070	-2.00 (-15.69, 11.69)	3	-0.6666667
347	Oh, 2014, 25147070	3.00 (-10.66, 16.66)	1	3
348	Oh, 2014, 25147070	-62.00 (-102.52, -21.48)	4	-15.5
349	Oh, 2014, 25147070	-30.00 (-73.10, 13.10)	2	-15
350	Oh, 2014, 25147070	-23.00 (-60.64, 14.64)	1	-23
351	Oh, 2014, 25147070	-32.00 (-77.22, 13.22)	2	-16
352	Oh, 2014, 25147070	-39.00 (-79.06, 1.06)	3	-13
353	Oh, 2014, 25147070	-7.00 (-49.67, 35.67)	1	-7
354	Olano-Martin, 2010, 19748619	-0.77 (-6.43, 4.89)	3.3	-0.2333333
355	Olano-Martin, 2010, 19748619	-1.16 (-6.51, 4.19)	NA	
356	Olano-Martin, 2010, 19748619	0.39 (-5.27, 6.05)	3.7	0.1054054
357	Olano-Martin, 2010, 19748619	2.70 (-12.17, 17.57)	3.3	0.8181818

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Outcome classification
343	Oh, 2014, 25147070	Secondary
344	Oh, 2014, 25147070	Secondary
345	Oh, 2014, 25147070	Secondary
346	Oh, 2014, 25147070	Secondary
347	Oh, 2014, 25147070	Secondary
348	Oh, 2014, 25147070	Secondary
349	Oh, 2014, 25147070	Secondary
350	Oh, 2014, 25147070	Secondary
351	Oh, 2014, 25147070	Secondary
352	Oh, 2014, 25147070	Secondary
353	Oh, 2014, 25147070	Secondary
354	Olano-Martin, 2010, 19748619	Secondary
355	Olano-Martin, 2010, 19748619	Secondary
356	Olano-Martin, 2010, 19748619	Secondary
357	Olano-Martin, 2010, 19748619	Primary (stated)

Row	Study	Study years (start date)	Country	Population
358	Olano-Martin, 2010, 19748619	2007 (approx)	UK	Primary Prevention, Healthy
359	Olano-Martin, 2010, 19748619	2007 (approx)	UK	Primary Prevention, Healthy
360	Olano-Martin, 2010, 19748619	2007 (approx)	UK	Primary Prevention, Healthy
361	Olano-Martin, 2010, 19748619	2007 (approx)	UK	Primary Prevention, Healthy
362	Olano-Martin, 2010, 19748619	2007 (approx)	UK	Primary Prevention, Healthy
363	Pase, 2015, 25565485	2015	Australia	Primary Prevention, Healthy
364	Pase, 2015, 25565485	2015	Australia	Primary Prevention, Healthy
365	Pase, 2015, 25565485	2015	Australia	Primary Prevention, Healthy
366	Pase, 2015, 25565485	2015	Australia	Primary Prevention, Healthy
367	Pieters_2015_25226826	2011	Netherlands	Primary Prevention, Increased CVD Risk
368	Pieters_2015_25226826	2011	Netherlands	Primary Prevention, Increased CVD Risk
369	Pieters_2015_25226826	2011	Netherlands	Primary Prevention, Increased CVD Risk
370	Pieters_2015_25226826	2011	Netherlands	Primary Prevention, Increased CVD Risk
371	Pieters_2015_25226826	2011	Netherlands	Primary Prevention, Increased CVD Risk
372	Pieters_2015_25226826	2011	Netherlands	Primary Prevention, Increased CVD Risk
373	Raitt_2005_15956633,	2001	US	Primary Prevention, Increased CVD Risk
374	Raitt_2005_15956633,	2001	US	Primary Prevention, Increased CVD Risk
375	Raitt_2005_15956633,	2001	US	Primary Prevention, Increased CVD Risk
376	Raitt_2005_15956633,	2001	US	Primary Prevention, Increased CVD Risk
377	Raitt_2005_15956633,	2001	US	Primary Prevention, Increased CVD Risk

Row	Study	Risk type	Sample size (total)
358	Olano-Martin, 2010, 19748619	na	38
359	Olano-Martin, 2010, 19748619	na	38
360	Olano-Martin, 2010, 19748619	na	38
361	Olano-Martin, 2010, 19748619	na	38
362	Olano-Martin, 2010, 19748619	na	38
363	Pase, 2015, 25565485	na	160
364	Pase, 2015, 25565485	na	160
365	Pase, 2015, 25565485	na	160
366	Pase, 2015, 25565485	na	160
367	Pieters_2015_25226826	Overweight hypertiglyceridemic	32
368	Pieters_2015_25226826	Overweight hypertiglyceridemic	32
369	Pieters_2015_25226826	Overweight hypertiglyceridemic	32
370	Pieters_2015_25226826	Overweight hypertiglyceridemic	32
371	Pieters_2015_25226826	Overweight hypertiglyceridemic	32
372	Pieters_2015_25226826	Overweight hypertiglyceridemic	32
373	Raitt_2005_15956633,	Arrhythmia	200
374	Raitt_2005_15956633,	Arrhythmia	200
375	Raitt_2005_15956633,	Arrhythmia	200
376	Raitt_2005_15956633,	Arrhythmia	200
377	Raitt_2005_15956633,	Arrhythmia	200

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Age mean (SD) [median] years	Sex (% male)	Race
358	Olano-Martin, 2010, 19748619	range 18, 70	100	nd
359	Olano-Martin, 2010, 19748619	range 18, 70	100	nd
360	Olano-Martin, 2010, 19748619	range 18, 70	100	nd
361	Olano-Martin, 2010, 19748619	range 18, 70	100	nd
362	Olano-Martin, 2010, 19748619	range 18, 70	100	nd
363	Pase, 2015, 25565485	59.3 (5.7)	46.9	nd
364	Pase, 2015, 25565485	59.3 (5.7)	46.9	nd
365	Pase, 2015, 25565485	59.3 (5.7)	46.9	nd
366	Pase, 2015, 25565485	59.3 (5.7)	46.9	nd
367	Pieters_2015_25226826	51 (15)	47.2	nd
368	Pieters_2015_25226826	51 (15)	47.2	nd
369	Pieters_2015_25226826	51 (15)	47.2	nd
370	Pieters_2015_25226826	51 (15)	47.2	nd
371	Pieters_2015_25226826	51 (15)	47.2	nd
372	Pieters_2015_25226826	51 (15)	47.2	nd
373	Raitt_2005_15956633,	63.5 (13)	86	95.5% white
374	Raitt_2005_15956633,	63.5 (13)	86	95.5% white
375	Raitt_2005_15956633,	63.5 (13)	86	95.5% white
376	Raitt_2005_15956633,	63.5 (13)	86	95.5% white
377	Raitt_2005_15956633,	63.5 (13)	86	95.5% white

Row	Study	Blood pressure SBP/DBP mmHg
358	Olano-Martin, 2010, 19748619	nd
359	Olano-Martin, 2010, 19748619	nd
360	Olano-Martin, 2010, 19748619	nd
361	Olano-Martin, 2010, 19748619	nd
362	Olano-Martin, 2010, 19748619	nd
363	Pase, 2015, 25565485	124.1 (19.1)/76.3 (11.6)
364	Pase, 2015, 25565485	124.1 (19.1)/76.3 (11.6)
365	Pase, 2015, 25565485	124.1 (19.1)/76.3 (11.6)
366	Pase, 2015, 25565485	124.1 (19.1)/76.3 (11.6)
367	Pieters_2015_25226826	nd
368	Pieters_2015_25226826	nd
369	Pieters_2015_25226826	nd
370	Pieters_2015_25226826	nd
371	Pieters_2015_25226826	nd
372	Pieters_2015_25226826	nd
373	Raitt_2005_15956633,	nd
374	Raitt_2005_15956633,	nd
375	Raitt_2005_15956633,	nd
376	Raitt_2005_15956633,	nd
377	Raitt_2005_15956633,	nd

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Lipids: Total cholesterol/LDL/HDL/Triglycerides mean (SD) mg/dL [mmol/L]
358	Olano-Martin, 2010, 19748619	[5.44 (SE 0.14)]/[3.54 (SE 0.13)]/[1.33 (SE 0.05)]/[1.39 (SE 0.08)]
359	Olano-Martin, 2010, 19748619	[5.44 (SE 0.14)]/[3.54 (SE 0.13)]/[1.33 (SE 0.05)]/[1.39 (SE 0.08)]
360	Olano-Martin, 2010, 19748619	[5.44 (SE 0.14)]/[3.54 (SE 0.13)]/[1.33 (SE 0.05)]/[1.39 (SE 0.08)]
361	Olano-Martin, 2010, 19748619	[5.44 (SE 0.14)]/[3.54 (SE 0.13)]/[1.33 (SE 0.05)]/[1.39 (SE 0.08)]
362	Olano-Martin, 2010, 19748619	[5.44 (SE 0.14)]/[3.54 (SE 0.13)]/[1.33 (SE 0.05)]/[1.39 (SE 0.08)]
363	Pase, 2015, 25565485	[nd/3.36 (0.75)/1.56 (0.40)/1.20 (0.62)
364	Pase, 2015, 25565485	[nd/3.36 (0.75)/1.56 (0.40)/1.20 (0.62)
365	Pase, 2015, 25565485	[nd/3.36 (0.75)/1.56 (0.40)/1.20 (0.62)
366	Pase, 2015, 25565485	[nd/3.36 (0.75)/1.56 (0.40)/1.20 (0.62)
367	Pieters_2015_25226826	[5.94 (0.93)/3.69 (0.73)/1.66 (0.37)/1.30 (0.61)]
368	Pieters_2015_25226826	[5.94 (0.93)/3.69 (0.73)/1.66 (0.37)/1.30 (0.61)]
369	Pieters_2015_25226826	[5.94 (0.93)/3.69 (0.73)/1.66 (0.37)/1.30 (0.61)]
370	Pieters_2015_25226826	[5.94 (0.93)/3.69 (0.73)/1.66 (0.37)/1.30 (0.61)]
371	Pieters_2015_25226826	[5.94 (0.93)/3.69 (0.73)/1.66 (0.37)/1.30 (0.61)]
372	Pieters_2015_25226826	[5.94 (0.93)/3.69 (0.73)/1.66 (0.37)/1.30 (0.61)]
373	Raitt_2005_15956633,	nd
374	Raitt_2005_15956633,	nd
375	Raitt_2005_15956633,	nd
376	Raitt_2005_15956633,	nd
377	Raitt_2005_15956633,	nd

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	BMI mean (SD) Kg/m2/Weight mean (SD) Kg	Baseline n-3 intake	n-3 source (Baseline)
358	Olano-Martin, 2010, 19748619	range 18.5, 32	EPA: 1.7 (SEM 0.2)% FA, DPA: 1.2 (0.0)% FA, DHA: 4.8 (0.2)% FA	plasma phospholipids fatty acid
359	Olano-Martin, 2010, 19748619	range 18.5, 32	EPA: 1.7 (SEM 0.2)% FA, DPA: 1.2 (0.0)% FA, DHA: 4.8 (0.2)% FA	plasma phospholipids fatty acid
360	Olano-Martin, 2010, 19748619	range 18.5, 32	EPA: 1.7 (SEM 0.2)% FA, DPA: 1.2 (0.0)% FA, DHA: 4.8 (0.2)% FA	plasma phospholipids fatty acid
361	Olano-Martin, 2010, 19748619	range 18.5, 32	EPA: 1.7 (SEM 0.2)% FA, DPA: 1.2 (0.0)% FA, DHA: 4.8 (0.2)% FA	plasma phospholipids fatty acid
362	Olano-Martin, 2010, 19748619	range 18.5, 32	EPA: 1.7 (SEM 0.2)% FA, DPA: 1.2 (0.0)% FA, DHA: 4.8 (0.2)% FA	plasma phospholipids fatty acid
363	Pase, 2015, 25565485	24.9 (3.4)	nd	nd
364	Pase, 2015, 25565485	24.9 (3.4)	nd	nd
365	Pase, 2015, 25565485	24.9 (3.4)	nd	nd
366	Pase, 2015, 25565485	24.9 (3.4)	nd	nd
367	Pieters_2015_25226826	28.9 (3)	nd	nd
368	Pieters_2015_25226826	28.9 (3)	nd	nd
369	Pieters_2015_25226826	28.9 (3)	nd	nd
370	Pieters_2015_25226826	28.9 (3)	nd	nd
371	Pieters_2015_25226826	28.9 (3)	nd	nd
372	Pieters_2015_25226826	28.9 (3)	nd	nd
373	Raitt_2005_15956633,	nd	nd	nd
374	Raitt_2005_15956633,	nd	nd	nd
375	Raitt_2005_15956633,	nd	nd	nd
376	Raitt_2005_15956633,	nd	nd	nd
377	Raitt_2005_15956633,	nd	nd	nd

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	n-3 type(s)	n-3 measure	Study design	Outcome
358	Olano-Martin, 2010, 19748619	EPA vs Placebo	g/d	Trial: Randomized Cross-over	LDL-c
359	Olano-Martin, 2010, 19748619	EPA vs DHA	g/d	Trial: Randomized Cross-over	LDL-c
360	Olano-Martin, 2010, 19748619	DHA vs Placebo	g/d	Trial: Randomized Cross-over	Tg
361	Olano-Martin, 2010, 19748619	EPH + DHA vs Placebo	g/d	Trial: Randomized Cross-over	Tg
362	Olano-Martin, 2010, 19748619	EPA+DHA vs Placebo	g/d	Trial: Randomized Cross-over	Tg
363	Pase, 2015, 25565485	EPA+DHA (0.48) vs Placebo	g/d	Trial: Randomized Cross-over	SBP
364	Pase, 2015, 25565485	EPA+DHA (0.48) vs EPA+DHA (0.28)	g/d	Trial: Randomized Parallel	SBP
365	Pase, 2015, 25565485	EPA+DHA (0.48) vs Placebo	g/d	Trial: Randomized Parallel	DBP
366	Pase, 2015, 25565485	EPA+DHA (0.48) vs EPA+DHA (0.28)	g/d	Trial: Randomized Parallel	DBP
367	Pieters_2015_25226826	SDA 1.2; ALA 3.03 vs Placebo	g/d	Trial: Randomized Cross-over	Total:HDL-c ratio
368	Pieters_2015_25226826	SDA 1.2; ALA 3.03 vs Placebo	g/d	Trial: Randomized Cross-over	HDL-c
369	Pieters_2015_25226826	SDA 1.2; ALA 3.03 vs Placebo	g/d	Trial: Randomized Cross-over	LDL-c
370	Pieters_2015_25226826	SDA 1.2; ALA 3.03 vs Placebo	g/d	Trial: Randomized Cross-over	Tg
371	Pieters_2015_25226826	SDA 1.2; ALA 3.03 vs Placebo	g/d	Trial: Randomized Cross-over	SBP
372	Pieters_2015_25226826	SDA 1.2; ALA 3.03 vs Placebo	g/d	Trial: Randomized Cross-over	DBP
373	Raitt_2005_15956633,	EPA 0.756 + DHA 0.54 vs. Placebo	g/d	Trial: Randomized Parallel	Death, cardiac
374	Raitt_2005_15956633,	EPA 0.756 + DHA 0.54 vs. Placebo	g/d	Trial: Randomized Parallel	Death, all cause
375	Raitt_2005_15956633,	EPA 0.756 + DHA 0.54 vs. Placebo	g/d	Trial: Randomized Parallel	Myocardial infarction
376	Raitt_2005_15956633,	EPA 0.756 + DHA 0.54 vs. Placebo	g/d	Trial: Randomized Parallel	Revascularization
377	Raitt_2005_15956633,	EPA 0.756 + DHA 0.54 vs. Placebo	g/d	Trial: Randomized Parallel	Sudden Cardiac Death

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Reported effect Size	Dose/intake difference	Dose-corrected effect size
358	Olano-Martin, 2010, 19748619	-6.18 (-21.77, 9.41)	NA	
359	Olano-Martin, 2010, 19748619	8.88 (-5.32, 23.08)	3.7	2.4
360	Olano-Martin, 2010, 19748619	-41.64 (-69.92, -13.36)	3.3	-12.61818
361	Olano-Martin, 2010, 19748619	-3.54 (-27.69, 20.61)	NA	
362	Olano-Martin, 2010, 19748619	-27.43 (-51.59, -3.27)	3.7	-7.413514
363	Pase, 2015, 25565485	-6.9 (-13.96, 0.16)	0.48	-14.38
364	Pase, 2015, 25565485	-1 (-9.04, 7.04)	0.2	-5
365	Pase, 2015, 25565485	-3.5 (-8.2, 1.2)	0.48	-7.29
366	Pase, 2015, 25565485	-1.5 (-6.99, 3.99)	0.2	-7.5
367	Pieters_2015_25226826	-0.06 (-0.22, 0.1)	1.2	-0.05
368	Pieters_2015_25226826	1.16 (-0.39, 2.71)	1.2	0.97
369	Pieters_2015_25226826	-1.55 (-6.2, 3.1)	1.2	-1.29
370	Pieters_2015_25226826	9.73 (-4.73, 24.19)	1.2	8.11
371	Pieters_2015_25226826	2.00 (-3.73, 7.73)	1.2	1.67
372	Pieters_2015_25226826	1.00 (-1.84, 3.84)	1.2	0.83
373	Raitt_2005_15956633,	0.39 (0.07, 2.05)	1.8	0.22
374	Raitt_2005_15956633,	0.38 (0.11, 1.24)	1.8	0.21
375	Raitt_2005_15956633,	0.33 (0.03, 3.19)	1.8	0.18
376	Raitt_2005_15956633,	0.49 (0.09, 2.74)	1.8	0.27
377	Raitt_2005_15956633,	5.1 (0.24, 107.64)	1.8	2.83

Row	Study	Outcome classification
358	Olano-Martin, 2010, 19748619	Primary (stated)
359	Olano-Martin, 2010, 19748619	Primary (stated)
360	Olano-Martin, 2010, 19748619	Secondary
361	Olano-Martin, 2010, 19748619	Secondary
362	Olano-Martin, 2010, 19748619	Secondary
363	Pase, 2015, 25565485	Secondary
364	Pase, 2015, 25565485	Secondary
365	Pase, 2015, 25565485	Secondary
366	Pase, 2015, 25565485	Secondary
367	Pieters_2015_25226826	Secondary
368	Pieters_2015_25226826	Secondary
369	Pieters_2015_25226826	Secondary
370	Pieters_2015_25226826	Primary (stated)
371	Pieters_2015_25226826	Secondary
372	Pieters_2015_25226826	Secondary
373	Raitt_2005_15956633,	Secondary
374	Raitt_2005_15956633,	Secondary
375	Raitt_2005_15956633,	Secondary
376	Raitt_2005_15956633,	Secondary
377	Raitt_2005_15956633,	Secondary

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Study years (start date)	Country	Population
378	Raitt_2005_15956633,	2001	US	Primary Prevention, Increased CVD Risk
379	Raitt_2005_15956633,	2001	US	Primary Prevention, Increased CVD Risk
380	Ras 2014 25122648	2011	Sweden	Primary Prevention, Healthy
381	Ras 2014 25122649	2011	Sweden	Primary Prevention, Healthy
382	Ras 2014 25122650	2011	Sweden	Primary Prevention, Healthy
383	Ras 2014 25122651	2011	Sweden	Primary Prevention, Healthy
384	Ras 2014 25122651	2011	Sweden	Primary Prevention, Healthy
385	Ras 2014 25122651	2011	Sweden	Primary Prevention, Healthy
386	Ras 2014 25122652	2011	Sweden	Primary Prevention, Healthy
387	Ras 2014 25122653	2011	Sweden	Primary Prevention, Healthy
388	Ras 2014 25122654	2011	Sweden	Primary Prevention, Healthy
389	Ras 2014 25122655	2011	Sweden	Primary Prevention, Healthy
390	Ras 2014 25122655	2011	Sweden	Primary Prevention, Healthy
391	Ras 2014 25122655	2011	Sweden	Primary Prevention, Healthy
392	Ras 2014 25122656	2011	Sweden	Primary Prevention, Healthy
393	Ras 2014 25122657	2011	Sweden	Primary Prevention, Healthy
394	Ras 2014 25122658	2011	Sweden	Primary Prevention, Healthy
395	Ras 2014 25122659	2011	Sweden	Primary Prevention, Healthy
396	Ras 2014 25122659	2011	Sweden	Primary Prevention, Healthy
397	Ras 2014 25122659	2011	Sweden	Primary Prevention, Healthy
398	Rasmussen, 2006, 16469978	2009 (Approx)	Denmark, Finland, Italy, Sweden, Australia	Primary Prevention, Healthy
399	Rasmussen, 2006, 16469978	2009 (Approx)	Denmark, Finland, Italy, Sweden, Australia	Primary Prevention, Healthy

Row	Study	Risk type	Sample size (total)
378	Raitt_2005_15956633,	Arrhythmia	200
379	Raitt_2005_15956633,	Arrhythmia	200
380	Ras 2014 25122648	na	314
381	Ras 2014 25122649	na	314
382	Ras 2014 25122650	na	314
383	Ras 2014 25122651	na	314
384	Ras 2014 25122651	na	314
385	Ras 2014 25122651	na	314
386	Ras 2014 25122652	na	314
387	Ras 2014 25122653	na	314
388	Ras 2014 25122654	na	314
389	Ras 2014 25122655	na	314
390	Ras 2014 25122655	na	314
391	Ras 2014 25122655	na	314
392	Ras 2014 25122656	na	314
393	Ras 2014 25122657	na	314
394	Ras 2014 25122658	na	314
395	Ras 2014 25122659	na	314
396	Ras 2014 25122659	na	314
397	Ras 2014 25122659	na	314
398	Rasmussen, 2006, 16469978	na	97
399	Rasmussen, 2006, 16469978	na	97

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Age mean (SD) [median] years	Sex (% male)	Race
378	Raitt_2005_15956633,	63.5 (13)	86	95.5% white
379	Raitt_2005_15956633,	63.5 (13)	86	95.5% white
380	Ras 2014 25122648	57.9 (0.6)	26.8	nd
381	Ras 2014 25122649	57.9 (0.6)	26.8	nd
382	Ras 2014 25122650	57.9 (0.6)	26.8	nd
383	Ras 2014 25122651	57.9 (0.6)	26.8	nd
384	Ras 2014 25122651	57.9 (0.6)	26.8	nd
385	Ras 2014 25122651	57.9 (0.6)	26.8	nd
386	Ras 2014 25122652	57.9 (0.6)	26.8	nd
387	Ras 2014 25122653	57.9 (0.6)	26.8	nd
388	Ras 2014 25122654	57.9 (0.6)	26.8	nd
389	Ras 2014 25122655	57.9 (0.6)	26.8	nd
390	Ras 2014 25122655	57.9 (0.6)	26.8	nd
391	Ras 2014 25122655	57.9 (0.6)	26.8	nd
392	Ras 2014 25122656	57.9 (0.6)	26.8	nd
393	Ras 2014 25122657	57.9 (0.6)	26.8	nd
394	Ras 2014 25122658	57.9 (0.6)	26.8	nd
395	Ras 2014 25122659	57.9 (0.6)	26.8	nd
396	Ras 2014 25122659	57.9 (0.6)	26.8	nd
397	Ras 2014 25122659	57.9 (0.6)	26.8	nd
398	Rasmussen, 2006, 16469978	48.5	nd	nd
399	Rasmussen, 2006, 16469978	48.5	nd	nd

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Blood pressure SBP/DBP mmHg
378	Raitt_2005_15956633,	nd
379	Raitt_2005_15956633,	nd
380	Ras 2014 25122648	128.2 (0.8)/77.7 (0.4)
381	Ras 2014 25122649	128.2 (0.8)/77.7 (0.4)
382	Ras 2014 25122650	128.2 (0.8)/77.7 (0.4)
383	Ras 2014 25122651	128.2 (0.8)/77.7 (0.4)
384	Ras 2014 25122651	128.2 (0.8)/77.7 (0.4)
385	Ras 2014 25122651	128.2 (0.8)/77.7 (0.4)
386	Ras 2014 25122652	128.2 (0.8)/77.7 (0.4)
387	Ras 2014 25122653	128.2 (0.8)/77.7 (0.4)
388	Ras 2014 25122654	128.2 (0.8)/77.7 (0.4)
389	Ras 2014 25122655	128.2 (0.8)/77.7 (0.4)
390	Ras 2014 25122655	128.2 (0.8)/77.7 (0.4)
391	Ras 2014 25122655	128.2 (0.8)/77.7 (0.4)
392	Ras 2014 25122656	128.2 (0.8)/77.7 (0.4)
393	Ras 2014 25122657	128.2 (0.8)/77.7 (0.4)
394	Ras 2014 25122658	128.2 (0.8)/77.7 (0.4)
395	Ras 2014 25122659	128.2 (0.8)/77.7 (0.4)
396	Ras 2014 25122659	128.2 (0.8)/77.7 (0.4)
397	Ras 2014 25122659	128.2 (0.8)/77.7 (0.4)
398	Rasmussen, 2006, 16469978	122.7 (11.4)/77.1 (9.0)
399	Rasmussen, 2006, 16469978	122.7 (11.4)/77.1 (9.0)

Row	Study	Lipids: Total cholesterol/LDL/HDL/Triglycerides mean (SD) mg/dL [mmol/L]
378	Raitt_2005_15956633,	nd
379	Raitt_2005_15956633,	nd
380	Ras 2014 25122648	[6.45 (0.05)/4.00 (0.04)/1.63 (0.02)/1.09 (0.03)]
381	Ras 2014 25122649	[6.45 (0.05)/4.00 (0.04)/1.63 (0.02)/1.09 (0.03)]
382	Ras 2014 25122650	[6.45 (0.05)/4.00 (0.04)/1.63 (0.02)/1.09 (0.03)]
383	Ras 2014 25122651	[6.45 (0.05)/4.00 (0.04)/1.63 (0.02)/1.09 (0.03)]
384	Ras 2014 25122651	[6.45 (0.05)/4.00 (0.04)/1.63 (0.02)/1.09 (0.03)]
385	Ras 2014 25122651	[6.45 (0.05)/4.00 (0.04)/1.63 (0.02)/1.09 (0.03)]
386	Ras 2014 25122652	[6.45 (0.05)/4.00 (0.04)/1.63 (0.02)/1.09 (0.03)]
387	Ras 2014 25122653	[6.45 (0.05)/4.00 (0.04)/1.63 (0.02)/1.09 (0.03)]
388	Ras 2014 25122654	[6.45 (0.05)/4.00 (0.04)/1.63 (0.02)/1.09 (0.03)]
389	Ras 2014 25122655	[6.45 (0.05)/4.00 (0.04)/1.63 (0.02)/1.09 (0.03)]
390	Ras 2014 25122655	[6.45 (0.05)/4.00 (0.04)/1.63 (0.02)/1.09 (0.03)]
391	Ras 2014 25122655	[6.45 (0.05)/4.00 (0.04)/1.63 (0.02)/1.09 (0.03)]
392	Ras 2014 25122656	[6.45 (0.05)/4.00 (0.04)/1.63 (0.02)/1.09 (0.03)]
393	Ras 2014 25122657	[6.45 (0.05)/4.00 (0.04)/1.63 (0.02)/1.09 (0.03)]
394	Ras 2014 25122658	[6.45 (0.05)/4.00 (0.04)/1.63 (0.02)/1.09 (0.03)]
395	Ras 2014 25122659	[6.45 (0.05)/4.00 (0.04)/1.63 (0.02)/1.09 (0.03)]
396	Ras 2014 25122659	[6.45 (0.05)/4.00 (0.04)/1.63 (0.02)/1.09 (0.03)]
397	Ras 2014 25122659	[6.45 (0.05)/4.00 (0.04)/1.63 (0.02)/1.09 (0.03)]
398	Rasmussen, 2006, 16469978	nd
399	Rasmussen, 2006, 16469978	nd

Row	Study	BMI mean (SD) Kg/m2/Weight mean (SD) Kg	Baseline n-3 intake	n-3 source (Baseline)
378	Raitt_2005_15956633,	nd	nd	nd
379	Raitt_2005_15956633,	nd	nd	nd
380	Ras 2014 25122648	25.0 (0.1)	nd	nd
381	Ras 2014 25122649	25.0 (0.1)	nd	nd
382	Ras 2014 25122650	25.0 (0.1)	nd	nd
383	Ras 2014 25122651	25.0 (0.1)	nd	nd
384	Ras 2014 25122651	25.0 (0.1)	nd	nd
385	Ras 2014 25122651	25.0 (0.1)	nd	nd
386	Ras 2014 25122652	25.0 (0.1)	nd	nd
387	Ras 2014 25122653	25.0 (0.1)	nd	nd
388	Ras 2014 25122654	25.0 (0.1)	nd	nd
389	Ras 2014 25122655	25.0 (0.1)	nd	nd
390	Ras 2014 25122655	25.0 (0.1)	nd	nd
391	Ras 2014 25122655	25.0 (0.1)	nd	nd
392	Ras 2014 25122656	25.0 (0.1)	nd	nd
393	Ras 2014 25122657	25.0 (0.1)	nd	nd
394	Ras 2014 25122658	25.0 (0.1)	nd	nd
395	Ras 2014 25122659	25.0 (0.1)	nd	nd
396	Ras 2014 25122659	25.0 (0.1)	nd	nd
397	Ras 2014 25122659	25.0 (0.1)	nd	nd
398	Rasmussen, 2006, 16469978	26.9 (3.0)	ALA: 0.31% FA, EPA: 1.5% FA, DPA: 1.07% FA, DHA 4.67 % FA	serum
399	Rasmussen, 2006, 16469978	26.9 (3.0)	ALA: 0.31% FA, EPA: 1.5% FA, DPA: 1.07% FA, DHA 4.67 % FA	serum

Row	Study	n-3 type(s)	n-3 measure	Study design	Outcome
378	Raitt_2005_15956633,	EPA 0.756 + DHA 0.54 vs. Placebo	g/d	Trial: Randomized Parallel	Congestive Heart Failure
379	Raitt_2005_15956633,	EPA 0.756 + DHA 0.54 vs. Placebo	g/d	Trial: Randomized Parallel	Angina pectoris
380	Ras 2014 25122648	EPA+DHA 0.9 vs Placebo	g/d	Trial: Randomized Parallel	LDL-c
381	Ras 2014 25122649	EPA+DHA 1.3 vs Placebo	g/d	Trial: Randomized Parallel	LDL-c
382	Ras 2014 25122650	EPA+DHA 1.8 vs Placebo	g/d	Trial: Randomized Parallel	LDL-c
383	Ras 2014 25122651	EPA+DHA 1.8 vs EPA+DHA 0.9	g/d	Trial: Randomized Parallel	LDL-c
384	Ras 2014 25122651	EPA+DHA 1.8 vs EPA+DHA 1.3	g/d	Trial: Randomized Parallel	LDL-c
385	Ras 2014 25122651	EPA+DHA 1.3 vs EPA+DHA 0.9	g/d	Trial: Randomized Parallel	LDL-c
386	Ras 2014 25122652	EPA+DHA 0.9 vs Placebo	g/d	Trial: Randomized Parallel	HDL-c
387	Ras 2014 25122653	EPA+DHA 1.3 vs Placebo	g/d	Trial: Randomized Parallel	HDL-c
388	Ras 2014 25122654	EPA+DHA 1.8 vs Placebo	g/d	Trial: Randomized Parallel	HDL-c
389	Ras 2014 25122655	EPA+DHA 1.8 vs EPA+DHA 0.9	g/d	Trial: Randomized Parallel	HDL-c
390	Ras 2014 25122655	EPA+DHA 1.8 vs EPA+DHA 1.3	g/d	Trial: Randomized Parallel	HDL-c
391	Ras 2014 25122655	EPA+DHA 1.3 vs EPA+DHA 0.9	g/d	Trial: Randomized Parallel	HDL-c
392	Ras 2014 25122656	EPA+DHA 0.9 vs Placebo	g/d	Trial: Randomized Parallel	Tg
393	Ras 2014 25122657	EPA+DHA 1.3 vs Placebo	g/d	Trial: Randomized Parallel	Tg
394	Ras 2014 25122658	EPA+DHA 1.8 vs Placebo	g/d	Trial: Randomized Parallel	Tg
395	Ras 2014 25122659	EPA+DHA 1.8 vs EPA+DHA 0.9	g/d	Trial: Randomized Parallel	Tg
396	Ras 2014 25122659	EPA+DHA 1.8 vs EPA+DHA 1.3	g/d	Trial: Randomized Parallel	Tg
397	Ras 2014 25122659	EPA+DHA 1.3 vs EPA+DHA 0.9	g/d	Trial: Randomized Parallel	Tg
398	Rasmussen, 2006, 16469978	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	LDL-c
399	Rasmussen, 2006, 16469978	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	LDL-c

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Reported effect Size	Dose/intake difference	Dose-corrected effect size
378	Raitt_2005_15956633,	1.19 (0.52, 2.73)	1.8	0.66
379	Raitt_2005_15956633,	1.48 (0.54, 4.05)	1.8	0.82
380	Ras 2014 25122648	-1.9 (nd)	0.9	-2.11
381	Ras 2014 25122649	-1.5 (nd)	1.3	-1.15
382	Ras 2014 25122650	-3.1 (nd)	1.8	-1.72
383	Ras 2014 25122651	-1.2 (nd)	0.9	-1.33
384	Ras 2014 25122651	-1.5 (nd)	0.5	-3
385	Ras 2014 25122651	0.39 (nd)	0.4	0.98
386	Ras 2014 25122652	0.7 (nd)	0.9	0.78
387	Ras 2014 25122653	3.5 (nd)	1.3	2.69
388	Ras 2014 25122654	3.9 (nd)	1.8	2.17
389	Ras 2014 25122655	3.1 (nd)	0.9	3.44
390	Ras 2014 25122655	0.39 (nd)	0.5	0.78
391	Ras 2014 25122655	2.7 (nd)	0.4	6.75
392	Ras 2014 25122656	-2.5 (nd)	0.9	-2.78
393	Ras 2014 25122657	-4.8 (nd)	1.3	-3.69
394	Ras 2014 25122658	-10.7 (nd)	1.8	-5.94
395	Ras 2014 25122659	-8.3 (nd)	0.9	-9.22
396	Ras 2014 25122659	-5.9 (nd)	0.5	-11.8
397	Ras 2014 25122659	-2.3 (nd)	0.4	-5.75
398	Rasmussen, 2006, 16469978	1.13 (-9.48, 11.74)	2.4	0.4708333
399	Rasmussen, 2006, 16469978	7.07 (-0.16, 14.30)	2.4	2.945833

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Outcome classification
378	Raitt_2005_15956633,	Secondary
379	Raitt_2005_15956633,	Secondary
380	Ras 2014 25122648	Secondary; Primary in registry record (NCT01313988)
381	Ras 2014 25122649	Secondary; Primary in registry record (NCT01313988)
382	Ras 2014 25122650	Secondary; Primary in registry record (NCT01313988)
383	Ras 2014 25122651	Secondary; Primary in registry record (NCT01313988)
384	Ras 2014 25122651	Secondary; Primary in registry record (NCT01313988)
385	Ras 2014 25122651	Secondary; Primary in registry record (NCT01313988)
386	Ras 2014 25122652	Secondary; Primary in registry record (NCT01313988)
387	Ras 2014 25122653	Secondary; Primary in registry record (NCT01313988)
388	Ras 2014 25122654	Secondary; Primary in registry record (NCT01313988)
389	Ras 2014 25122655	Secondary; Primary in registry record (NCT01313988)
390	Ras 2014 25122655	Secondary; Primary in registry record (NCT01313988)
391	Ras 2014 25122655	Secondary; Primary in registry record (NCT01313988)
392	Ras 2014 25122656	Primary (power analysis)
393	Ras 2014 25122657	Primary (power analysis)
394	Ras 2014 25122658	Primary (power analysis)
395	Ras 2014 25122659	Primary (power analysis)
396	Ras 2014 25122659	Primary (power analysis)
397	Ras 2014 25122659	Primary (power analysis)
398	Rasmussen, 2006, 16469978	Primary (stated)
399	Rasmussen, 2006, 16469978	Primary (stated)

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Study years (start date)	Country	Population
400	Rasmussen, 2006, 16469978	2009 (Approx)	Denmark, Finland, Italy, Sweden, Australia	Primary Prevention, Healthy
401	Rasmussen, 2006, 16469978	2009 (Approx)	Denmark, Finland, Italy, Sweden, Australia	Primary Prevention, Healthy
402	Rauch, 2010, 21060071	2003	Germany	Secondary Prevention (history of CVD event)
403	Rauch, 2010, 21060071	2003	Germany	Secondary Prevention (history of CVD event)
404	Rauch, 2010, 21060071	2003	Germany	Secondary Prevention (history of CVD event)
405	Rauch, 2010, 21060071	2003	Germany	Secondary Prevention (history of CVD event)
406	Rauch, 2010, 21060071	2003	Germany	Secondary Prevention (history of CVD event)
407	Rodriguez-Leyva, 2013, 24126178	2008	Canada	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
408	Rodriguez-Leyva, 2013, 24126178	2008	Canada	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
409	Rodriguez-Leyva, 2013, 24126178	2008	Canada	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
410	Rodriguez-Leyva, 2013, 24126178	2008	Canada	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
411	Rodriguez-Leyva, 2013, 24126178	2008	Canada	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
412	Rodriguez-Leyva, 2013, 24126178	2008	Canada	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
413	Rodriguez-Leyva, 2013, 24126178	2008	Canada	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
414	Roncaglioni, 2013, 23656645	2004	Italy	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
415	Roncaglioni, 2013, 23656645	2004	Italy	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
416	Roncaglioni, 2013, 23656645	2004	Italy	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Risk type	Sample size (total)
400	Rasmussen, 2006, 16469978	na	97
401	Rasmussen, 2006, 16469978	na	97
402	Rauch, 2010, 21060071	Cardiac disease (Myocardial infarction)	3804
403	Rauch, 2010, 21060071	Cardiac disease (Myocardial infarction)	3804
404	Rauch, 2010, 21060071	Cardiac disease (Myocardial infarction)	3804
405	Rauch, 2010, 21060071	Cardiac disease (Myocardial infarction)	3804
406	Rauch, 2010, 21060071	Cardiac disease (Myocardial infarction)	3804
407	Rodriguez-Leyva, 2013, 24126178	Peripheral vascular disease	87
408	Rodriguez-Leyva, 2013, 24126178	Peripheral vascular disease	87
409	Rodriguez-Leyva, 2013, 24126178	Peripheral vascular disease	87
410	Rodriguez-Leyva, 2013, 24126178	Peripheral vascular disease	87
411	Rodriguez-Leyva, 2013, 24126178	Peripheral vascular disease	87
412	Rodriguez-Leyva, 2013, 24126178	Peripheral vascular disease	87
413	Rodriguez-Leyva, 2013, 24126178	Peripheral vascular disease	87
414	Roncaglioni, 2013, 23656645	nd	12513
415	Roncaglioni, 2013, 23656645	nd	12513
416	Roncaglioni, 2013, 23656645	nd	12513

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Age mean (SD) [median] years	Sex (% male)	Race
400	Rasmussen, 2006, 16469978	48.5	nd	nd
401	Rasmussen, 2006, 16469978	48.5	nd	nd
402	Rauch, 2010, 21060071	[64 (54, 72)]	73.7	nd
403	Rauch, 2010, 21060071	[64 (54, 72)]	73.7	nd
404	Rauch, 2010, 21060071	[64 (54, 72)]	73.7	nd
405	Rauch, 2010, 21060071	[64 (54, 72)]	73.7	nd
406	Rauch, 2010, 21060071	[64 (54, 72)]	73.7	nd
407	Rodriguez-Leyva, 2013, 24126178	67.3 (8.5)	nd	nd
408	Rodriguez-Leyva, 2013, 24126178	67.3 (8.5)	nd	nd
409	Rodriguez-Leyva, 2013, 24126178	67.3 (8.5)	nd	nd
410	Rodriguez-Leyva, 2013, 24126178	67.3 (8.5)	nd	nd
411	Rodriguez-Leyva, 2013, 24126178	67.3 (8.5)	nd	nd
412	Rodriguez-Leyva, 2013, 24126178	67.3 (8.5)	nd	nd
413	Rodriguez-Leyva, 2013, 24126178	67.3 (8.5)	nd	nd
414	Roncaglioni, 2013, 23656645	64.0 (9.6)	60.6	nd
415	Roncaglioni, 2013, 23656645	64.0 (9.6)	60.6	nd
416	Roncaglioni, 2013, 23656645	64.0 (9.6)	60.6	nd

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Blood pressure SBP/DBP mmHg
400	Rasmussen, 2006, 16469978	122.7 (11.4)/77.1 (9.0)
401	Rasmussen, 2006, 16469978	122.7 (11.4)/77.1 (9.0)
402	Rauch, 2010, 21060071	median 140 (IQR 120, 160)]/nd
403	Rauch, 2010, 21060071	median 140 (IQR 120, 160)]/nd
404	Rauch, 2010, 21060071	median 140 (IQR 120, 160)]/nd
405	Rauch, 2010, 21060071	median 140 (IQR 120, 160)]/nd
406	Rauch, 2010, 21060071	median 140 (IQR 120, 160)]/nd
407	Rodriguez-Leyva, 2013, 24126178	142.9 (20.1)/77.5 (12.8)
408	Rodriguez-Leyva, 2013, 24126178	142.9 (20.1)/77.5 (12.8)
409	Rodriguez-Leyva, 2013, 24126178	142.9 (20.1)/77.5 (12.8)
410	Rodriguez-Leyva, 2013, 24126178	142.9 (20.1)/77.5 (12.8)
411	Rodriguez-Leyva, 2013, 24126178	142.9 (20.1)/77.5 (12.8)
412	Rodriguez-Leyva, 2013, 24126178	142.9 (20.1)/77.5 (12.8)
413	Rodriguez-Leyva, 2013, 24126178	142.9 (20.1)/77.5 (12.8)
414	Roncaglioni, 2013, 23656645	140.1 (15.1)/82.5 (8.2)
415	Roncaglioni, 2013, 23656645	140.1 (15.1)/82.5 (8.2)
416	Roncaglioni, 2013, 23656645	140.1 (15.1)/82.5 (8.2)

Row	Study	Lipids: Total cholesterol/LDL/HDL/Triglycerides mean (SD) mg/dL [mmol/L]
400	Rasmussen, 2006, 16469978	nd
401	Rasmussen, 2006, 16469978	nd
402	Rauch, 2010, 21060071	nd
403	Rauch, 2010, 21060071	nd
404	Rauch, 2010, 21060071	nd
405	Rauch, 2010, 21060071	nd
406	Rauch, 2010, 21060071	nd
407	Rodriguez-Leyva, 2013, 24126178	[4.5 (1.2)]/[2.5 (1.0)]/[1.2 (0.3)]/[1.6 (0.7)]
408	Rodriguez-Leyva, 2013, 24126178	[4.5 (1.2)]/[2.5 (1.0)]/[1.2 (0.3)]/[1.6 (0.7)]
409	Rodriguez-Leyva, 2013, 24126178	[4.5 (1.2)]/[2.5 (1.0)]/[1.2 (0.3)]/[1.6 (0.7)]
410	Rodriguez-Leyva, 2013, 24126178	[4.5 (1.2)]/[2.5 (1.0)]/[1.2 (0.3)]/[1.6 (0.7)]
411	Rodriguez-Leyva, 2013, 24126178	[4.5 (1.2)]/[2.5 (1.0)]/[1.2 (0.3)]/[1.6 (0.7)]
412	Rodriguez-Leyva, 2013, 24126178	[4.5 (1.2)]/[2.5 (1.0)]/[1.2 (0.3)]/[1.6 (0.7)]
413	Rodriguez-Leyva, 2013, 24126178	[4.5 (1.2)]/[2.5 (1.0)]/[1.2 (0.3)]/[1.6 (0.7)]
414	Roncaglioni, 2013, 23656645	216.5 (42.2)/132.5 (36.1)/51.2 (13.4)/median 150
415	Roncaglioni, 2013, 23656645	216.5 (42.2)/132.5 (36.1)/51.2 (13.4)/median 150
416	Roncaglioni, 2013, 23656645	216.5 (42.2)/132.5 (36.1)/51.2 (13.4)/median 150

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	BMI mean (SD) Kg/m2/Weight mean (SD) Kg	Baseline n-3 intake	n-3 source (Baseline)
400	Rasmussen, 2006, 16469978	26.9 (3.0)	ALA: 0.31% FA, EPA: 1.5% FA, DPA: 1.07% FA, DHA 4.67 % FA	serum
401	Rasmussen, 2006, 16469978	26.9 (3.0)	ALA: 0.31% FA, EPA: 1.5% FA, DPA: 1.07% FA, DHA 4.67 % FA	serum
402	Rauch, 2010, 21060071	median 27.3 (24.9, 30.1)	nd	nd
403	Rauch, 2010, 21060071	median 27.3 (24.9, 30.1)	nd	nd
404	Rauch, 2010, 21060071	median 27.3 (24.9, 30.1)	nd	nd
405	Rauch, 2010, 21060071	median 27.3 (24.9, 30.1)	nd	nd
406	Rauch, 2010, 21060071	median 27.3 (24.9, 30.1)	nd	nd
407	Rodriguez-Leyva, 2013, 24126178	27.8 (4.5)	nd	nd
408	Rodriguez-Leyva, 2013, 24126178	27.8 (4.5)	nd	nd
409	Rodriguez-Leyva, 2013, 24126178	27.8 (4.5)	nd	nd
410	Rodriguez-Leyva, 2013, 24126178	27.8 (4.5)	nd	nd
411	Rodriguez-Leyva, 2013, 24126178	27.8 (4.5)	nd	nd
412	Rodriguez-Leyva, 2013, 24126178	27.8 (4.5)	nd	nd
413	Rodriguez-Leyva, 2013, 24126178	27.8 (4.5)	nd	nd
414	Roncaglioni, 2013, 23656645	29.4 (5.0)	nd	nd
415	Roncaglioni, 2013, 23656645	29.4 (5.0)	nd	nd
416	Roncaglioni, 2013, 23656645	29.4 (5.0)	nd	nd

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	n-3 type(s)	n-3 measure	Study design	Outcome
400	Rasmussen, 2006, 16469978	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	SBP
401	Rasmussen, 2006, 16469978	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	DBP
402	Rauch, 2010, 21060071	ALA+EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Death, all cause
403	Rauch, 2010, 21060071	ALA+EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Revascularization
404	Rauch, 2010, 21060071	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Sudden cardiac death
405	Rauch, 2010, 21060071	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	LDL-c
406	Rauch, 2010, 21060071	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Tg
407	Rodriguez-Leyva, 2013, 24126178	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	LDL:HDL-c ratio
408	Rodriguez-Leyva, 2013, 24126178	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Total:HDL-c ratio
409	Rodriguez-Leyva, 2013, 24126178	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	HDL-c
410	Rodriguez-Leyva, 2013, 24126178	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	LDL-c
411	Rodriguez-Leyva, 2013, 24126178	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Tg
412	Rodriguez-Leyva, 2013, 24126178	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	SBP
413	Rodriguez-Leyva, 2013, 24126178	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	DBP
414	Roncaglioni, 2013, 23656645	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Congestive heart failure
415	Roncaglioni, 2013, 23656645	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Congestive heart failure
416	Roncaglioni, 2013, 23656645	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Death, all cause

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Reported effect Size	Dose/intake difference	Dose-corrected effect size
400	Rasmussen, 2006, 16469978	−0.4 (−2.6, 1.8)	2.4	-0.1666667
401	Rasmussen, 2006, 16469978	−0.6 (−2.8, 0.8)	2.4	-0.1666667
402	Rauch, 2010, 21060071	OR 1.25 (0.90, 1.72)	0.84	1.304275
403	Rauch, 2010, 21060071	OR 0.93 (0.80, 1.08)	0.84	0.917233
404	Rauch, 2010, 21060071	0.95 (0.56, 1.6)	1	0.95
405	Rauch, 2010, 21060071	0.00 (nd)	1	0
406	Rauch, 2010, 21060071	-5.00 (nd)	1	-5
407	Rodriguez-Leyva, 2013, 24126178	0.1 (−0.3, 0.5)	5.9	
408	Rodriguez-Leyva, 2013, 24126178	0.2 (−0.3, 0.7)	5.9	
409	Rodriguez-Leyva, 2013, 24126178	−3.5 (−8.2, 1.2)	5.9	
410	Rodriguez-Leyva, 2013, 24126178	0 (−16.6, 16.6)	5.9	
411	Rodriguez-Leyva, 2013, 24126178	26.5 (−4.4, 57.5)	5.9	
412	Rodriguez-Leyva, 2013, 24126178	-7.3 (-15.4, 0.8)	5.9	-1.237288
413	Rodriguez-Leyva, 2013, 24126178	−2.1 (−7.2, 3.0)	5.9	-1.237288
414	Roncaglioni, 2013, 23656645	HR 1.00 (0.53, 1.88)	0.85	1
415	Roncaglioni, 2013, 23656645	HR 0.67 (0.52, 0.87)	0.85	0.6242839
416	Roncaglioni, 2013, 23656645	HR 1.03 (0.88, 1.19)	0.85	1.035387

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Outcome classification
400	Rasmussen, 2006, 16469978	Secondary
401	Rasmussen, 2006, 16469978	Secondary
402	Rauch, 2010, 21060071	Secondary
403	Rauch, 2010, 21060071	Secondary
404	Rauch, 2010, 21060071	Secondary; Primary in registry record (NCT00251134)
405	Rauch, 2010, 21060071	Secondary
406	Rauch, 2010, 21060071	Primary (stated); Secondary in registry record (NCT00317707)
407	Rodriguez-Leyva, 2013, 24126178	Primary (stated)
408	Rodriguez-Leyva, 2013, 24126178	Primary (stated)
409	Rodriguez-Leyva, 2013, 24126178	Secondary
410	Rodriguez-Leyva, 2013, 24126178	Secondary
411	Rodriguez-Leyva, 2013, 24126178	Secondary
412	Rodriguez-Leyva, 2013, 24126178	Secondary
413	Rodriguez-Leyva, 2013, 24126178	Secondary
414	Roncaglioni, 2013, 23656645	Secondary
415	Roncaglioni, 2013, 23656645	Secondary
416	Roncaglioni, 2013, 23656645	Secondary

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Study years (start date)	Country	Population
417	Roncaglioni, 2013, 23656645	2004	Italy	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
418	Roncaglioni, 2013, 23656645	2004	Italy	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
419	Roncaglioni, 2013, 23656645	2004	Italy	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
420	Roncaglioni, 2013, 23656645	2004	Italy	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
421	Roncaglioni, 2013, 23656645	2004	Italy	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
422	Roncaglioni, 2013, 23656645	2004	Italy	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
423	Roncaglioni, 2013, 23656645	2004	Italy	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
424	Roncaglioni, 2013, 23656645	2004	Italy	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
425	Roncaglioni, 2013, 23656645	2004	Italy	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
426	Roncaglioni, 2013, 23656645	2004	Italy	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
427	Sacks, 1994, 8021472	1987	US	Primary Prevention, Healthy
428	Sacks, 1994, 8021472	1987	US	Primary Prevention, Healthy
429	Sacks, 1994, 8021472	1987	US	Primary Prevention, Healthy
430	Sacks, 1994, 8021472	1987	US	Primary Prevention, Healthy
431	Sacks, 1995, 7759696	1993 (approx)	US	Secondary Prevention (history of CVD event)
432	Sacks, 1995, 7759696	1993 (approx)	US	Secondary Prevention (history of CVD event)
433	Sacks, 1995, 7759696	1993 (approx)	US	Secondary Prevention (history of CVD event)
434	Sacks, 1995, 7759696	1993 (approx)	US	Secondary Prevention (history of CVD event)

Row	Study	Risk type	Sample size (total)
417	Roncaglioni, 2013, 23656645	nd	12513
418	Roncaglioni, 2013, 23656645	nd	12513
419	Roncaglioni, 2013, 23656645	nd	12513
420	Roncaglioni, 2013, 23656645	nd	12513
421	Roncaglioni, 2013, 23656645	nd	12513
422	Roncaglioni, 2013, 23656645	nd	12513
423	Roncaglioni, 2013, 23656645	nd	12513
424	Roncaglioni, 2013, 23656645	nd	12513
425	Roncaglioni, 2013, 23656645	nd	12513
426	Roncaglioni, 2013, 23656645	nd	12513
427	Sacks, 1994, 8021472	na	350
428	Sacks, 1994, 8021472	na	350
429	Sacks, 1994, 8021472	na	350
430	Sacks, 1994, 8021472	na	350
431	Sacks, 1995, 7759696	Dyslipidemia (total cholesterol concentration <250 mg/dl (6.43 mmol/liter) and triglyceride level <350 mg/dl (4.0 mmol/liter)); Cardiac disease (narrowing of =>30% lumen diameter of a major coronary artery)	59
432	Sacks, 1995, 7759696	Dyslipidemia (total cholesterol concentration <250 mg/dl (6.43 mmol/liter) and triglyceride level <350 mg/dl (4.0 mmol/liter)); Cardiac disease (narrowing of =>30% lumen diameter of a major coronary artery)	59
433	Sacks, 1995, 7759696	Dyslipidemia (total cholesterol concentration <250 mg/dl (6.43 mmol/liter) and triglyceride level <350 mg/dl (4.0 mmol/liter)); Cardiac disease (narrowing of =>30% lumen diameter of a major coronary artery)	59
434	Sacks, 1995, 7759696	Dyslipidemia (total cholesterol concentration <250 mg/dl (6.43 mmol/liter) and triglyceride level <350 mg/dl (4.0 mmol/liter)); Cardiac disease (narrowing of =>30% lumen diameter of a major coronary artery)	59

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Age mean (SD) [median] years	Sex (% male)	Race
417	Roncaglioni, 2013, 23656645	64.0 (9.6)	60.6	nd
418	Roncaglioni, 2013, 23656645	64.0 (9.6)	60.6	nd
419	Roncaglioni, 2013, 23656645	64.0 (9.6)	60.6	nd
420	Roncaglioni, 2013, 23656645	64.0 (9.6)	60.6	nd
421	Roncaglioni, 2013, 23656645	64.0 (9.6)	60.6	nd
422	Roncaglioni, 2013, 23656645	64.0 (9.6)	60.6	nd
423	Roncaglioni, 2013, 23656645	64.0 (9.6)	60.6	nd
424	Roncaglioni, 2013, 23656645	64.0 (9.6)	60.6	nd
425	Roncaglioni, 2013, 23656645	64.0 (9.6)	60.6	nd
426	Roncaglioni, 2013, 23656645	64.0 (9.6)	60.6	nd
427	Sacks, 1994, 8021472	43 (6.7)	70	range 84, 88 white
428	Sacks, 1994, 8021472	43 (6.7)	70	range 84, 88 white
429	Sacks, 1994, 8021472	43 (6.7)	70	range 84, 88 white
430	Sacks, 1994, 8021472	43 (6.7)	70	range 84, 88 white
431	Sacks, 1995, 7759696	62 (7)	92.9	nd
432	Sacks, 1995, 7759696	62 (7)	92.9	nd
433	Sacks, 1995, 7759696	62 (7)	92.9	nd
434	Sacks, 1995, 7759696	62 (7)	92.9	nd

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Blood pressure SBP/DBP mmHg
417	Roncaglioni, 2013, 23656645	140.1 (15.1)/82.5 (8.2)
418	Roncaglioni, 2013, 23656645	140.1 (15.1)/82.5 (8.2)
419	Roncaglioni, 2013, 23656645	140.1 (15.1)/82.5 (8.2)
420	Roncaglioni, 2013, 23656645	140.1 (15.1)/82.5 (8.2)
421	Roncaglioni, 2013, 23656645	140.1 (15.1)/82.5 (8.2)
422	Roncaglioni, 2013, 23656645	140.1 (15.1)/82.5 (8.2)
423	Roncaglioni, 2013, 23656645	140.1 (15.1)/82.5 (8.2)
424	Roncaglioni, 2013, 23656645	140.1 (15.1)/82.5 (8.2)
425	Roncaglioni, 2013, 23656645	140.1 (15.1)/82.5 (8.2)
426	Roncaglioni, 2013, 23656645	140.1 (15.1)/82.5 (8.2)
427	Sacks, 1994, 8021472	122.6 (8.3)/81.1 (4.9)
428	Sacks, 1994, 8021472	122.6 (8.3)/81.1 (4.9)
429	Sacks, 1994, 8021472	122.6 (8.3)/81.1 (4.9)
430	Sacks, 1994, 8021472	122.6 (8.3)/81.1 (4.9)
431	Sacks, 1995, 7759696	133 (19)/77 (7.6)
432	Sacks, 1995, 7759696	133 (19)/77 (7.6)
433	Sacks, 1995, 7759696	133 (19)/77 (7.6)
434	Sacks, 1995, 7759696	133 (19)/77 (7.6)

Row	Study	Lipids: Total cholesterol/LDL/HDL/Triglycerides mean (SD) mg/dL [mmol/L]
417	Roncaglioni, 2013, 23656645	216.5 (42.2)/132.5 (36.1)/51.2 (13.4)/median 150
418	Roncaglioni, 2013, 23656645	216.5 (42.2)/132.5 (36.1)/51.2 (13.4)/median 150
419	Roncaglioni, 2013, 23656645	216.5 (42.2)/132.5 (36.1)/51.2 (13.4)/median 150
420	Roncaglioni, 2013, 23656645	216.5 (42.2)/132.5 (36.1)/51.2 (13.4)/median 150
421	Roncaglioni, 2013, 23656645	216.5 (42.2)/132.5 (36.1)/51.2 (13.4)/median 150
422	Roncaglioni, 2013, 23656645	216.5 (42.2)/132.5 (36.1)/51.2 (13.4)/median 150
423	Roncaglioni, 2013, 23656645	216.5 (42.2)/132.5 (36.1)/51.2 (13.4)/median 150
424	Roncaglioni, 2013, 23656645	216.5 (42.2)/132.5 (36.1)/51.2 (13.4)/median 150
425	Roncaglioni, 2013, 23656645	216.5 (42.2)/132.5 (36.1)/51.2 (13.4)/median 150
426	Roncaglioni, 2013, 23656645	216.5 (42.2)/132.5 (36.1)/51.2 (13.4)/median 150
427	Sacks, 1994, 8021472	189 (32)/ /45 (12)/
428	Sacks, 1994, 8021472	189 (32)/ /45 (12)/
429	Sacks, 1994, 8021472	189 (32)/ /45 (12)/
430	Sacks, 1994, 8021472	189 (32)/ /45 (12)/
431	Sacks, 1995, 7759696	184 (28)/117 (27)/40 (12)/137 (73)
432	Sacks, 1995, 7759696	184 (28)/117 (27)/40 (12)/137 (73)
433	Sacks, 1995, 7759696	184 (28)/117 (27)/40 (12)/137 (73)
434	Sacks, 1995, 7759696	184 (28)/117 (27)/40 (12)/137 (73)

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	BMI mean (SD) Kg/m2/Weight mean (SD) Kg	Baseline n-3 intake	n-3 source (Baseline)
417	Roncaglioni, 2013, 23656645	29.4 (5.0)	nd	nd
418	Roncaglioni, 2013, 23656645	29.4 (5.0)	nd	nd
419	Roncaglioni, 2013, 23656645	29.4 (5.0)	nd	nd
420	Roncaglioni, 2013, 23656645	29.4 (5.0)	nd	nd
421	Roncaglioni, 2013, 23656645	29.4 (5.0)	nd	nd
422	Roncaglioni, 2013, 23656645	29.4 (5.0)	nd	nd
423	Roncaglioni, 2013, 23656645	29.4 (5.0)	nd	nd
424	Roncaglioni, 2013, 23656645	29.4 (5.0)	nd	nd
425	Roncaglioni, 2013, 23656645	29.4 (5.0)	nd	nd
426	Roncaglioni, 2013, 23656645	29.4 (5.0)	nd	nd
427	Sacks, 1994, 8021472	nd	nd	nd
428	Sacks, 1994, 8021472	nd	nd	nd
429	Sacks, 1994, 8021472	nd	nd	nd
430	Sacks, 1994, 8021472	nd	nd	nd
431	Sacks, 1995, 7759696	weight 79 (15)	nd	nd
432	Sacks, 1995, 7759696	weight 79 (15)	nd	nd
433	Sacks, 1995, 7759696	weight 79 (15)	nd	nd
434	Sacks, 1995, 7759696	weight 79 (15)	nd	nd

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	n-3 type(s)	n-3 measure	Study design	Outcome
417	Roncaglioni, 2013, 23656645	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Death, CVD (total)
418	Roncaglioni, 2013, 23656645	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Death, stroke
419	Roncaglioni, 2013, 23656645	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	MACE
420	Roncaglioni, 2013, 23656645	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Myocardial infarction
421	Roncaglioni, 2013, 23656645	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Sudden cardiac death
422	Roncaglioni, 2013, 23656645	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	HDL-c
423	Roncaglioni, 2013, 23656645	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	LDL-c
424	Roncaglioni, 2013, 23656645	EPA+DHA +DPA vs Placebo	g/d	Trial: Randomized Parallel	Tg
425	Roncaglioni, 2013, 23656645	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	SBP
426	Roncaglioni, 2013, 23656645	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	DBP
427	Sacks, 1994, 8021472	DHA vs Placebo	g/d	Trial: Randomized Parallel	Angina, unstable
428	Sacks, 1994, 8021472	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	HDL-c
429	Sacks, 1994, 8021472	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	SBP
430	Sacks, 1994, 8021472	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	DBP
431	Sacks, 1995, 7759696	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Congestive heart failure
432	Sacks, 1995, 7759696	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Death, cardiac
433	Sacks, 1995, 7759696	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Myocardial infarction
434	Sacks, 1995, 7759696	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Stroke

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Reported effect Size	Dose/intake difference	Dose-corrected effect size
417	Roncaglioni, 2013, 23656645	HR 1.03 (0.82, 1.30)	0.85	1.035387
418	Roncaglioni, 2013, 23656645	HR 1.05 (0.55, 2.00)	0.85	1.05908
419	Roncaglioni, 2013, 23656645	HR 0.98 (0.88, 1.08)	0.85	0.9765123
420	Roncaglioni, 2013, 23656645	HR 0.76 (0.34, 1.74)	0.85	0.7240703
421	Roncaglioni, 2013, 23656645	OR 1.28 (0.88, 1.89)	0.85	1.336994
422	Roncaglioni, 2013, 23656645	0.55 (0.03, 1.07)	0.85	0.6470588
423	Roncaglioni, 2013, 23656645	-0.35 (-1.79, 1.09)	0.85	-0.4117647
424	Roncaglioni, 2013, 23656645	-8.08 (-11.43, -4.74)	0.85	-9.505882
425	Roncaglioni, 2013, 23656645	0.2 (-0.4, 0.7)	0.85	0.2352941
426	Roncaglioni, 2013, 23656645	-0.2 (-25, 24.6)	0.85	-0.2352941
427	Sacks, 1994, 8021472	OR 0.64 (0.13, 3.16)	2.4	0.8303127
428	Sacks, 1994, 8021472	1.8 (-1.0,4.5)	2.4	0.75
429	Sacks, 1994, 8021472	1.2 (-0.3, 2.8)	2.4	0.5
430	Sacks, 1994, 8021472	-0.5 (-1.5, 0.5)	2.4	-0.2083333
431	Sacks, 1995, 7759696	nd	6	
432	Sacks, 1995, 7759696	RD -3.6% (-10.4%, 3.3%)	6	
433	Sacks, 1995, 7759696	OR 0.43 (0.04, 5.06)	6	0.8687832
434	Sacks, 1995, 7759696	OR 2.8 (0.11, 71.63)	4.8	1.239247

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Outcome classification
417	Roncaglioni, 2013, 23656645	Primary (stated, a priori)
418	Roncaglioni, 2013, 23656645	Secondary
419	Roncaglioni, 2013, 23656645	Primary (stated, added at 1 year)
420	Roncaglioni, 2013, 23656645	Secondary
421	Roncaglioni, 2013, 23656645	Secondary
422	Roncaglioni, 2013, 23656645	Secondary
423	Roncaglioni, 2013, 23656645	Secondary
424	Roncaglioni, 2013, 23656645	Secondary
425	Roncaglioni, 2013, 23656645	Secondary
426	Roncaglioni, 2013, 23656645	Secondary
427	Sacks, 1994, 8021472	Primary (stated)
428	Sacks, 1994, 8021472	Secondary
429	Sacks, 1994, 8021472	Secondary
430	Sacks, 1994, 8021472	Secondary
431	Sacks, 1995, 7759696	Secondary
432	Sacks, 1995, 7759696	Secondary
433	Sacks, 1995, 7759696	Secondary
434	Sacks, 1995, 7759696	Secondary

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Study years (start date)	Country	Population
435	Sacks, 1995, 7759696	1993 (approx)	US	Secondary Prevention (history of CVD event)
436	Sacks, 1995, 7759696	1993 (approx)	US	Secondary Prevention (history of CVD event)
437	Sacks, 1995, 7759696	1993 (approx)	US	Secondary Prevention (history of CVD event)
438	Sacks, 1995, 7759696	1993 (approx)	US	Secondary Prevention (history of CVD event)
439	Sacks, 1995, 7759696	1993 (approx)	US	Secondary Prevention (history of CVD event)
440	Sacks, 1995, 7759696	1993 (approx)	US	Secondary Prevention (history of CVD event)
441	Sanders, 2011, 21865334	2008	UK	Primary Prevention, Healthy
442	Sanders, 2011, 21865334	2008	UK	Primary Prevention, Healthy
443	Sanders, 2011, 21865334	2008	UK	Primary Prevention, Healthy
444	Sanders, 2011, 21865334	2008	UK	Primary Prevention, Healthy
445	Sanders, 2011, 21865334	2008	UK	Primary Prevention, Healthy
446	Sanders, 2011, 21865334	2008	UK	Primary Prevention, Healthy
447	Sanders, 2011, 21865334	2008	UK	Primary Prevention, Healthy
448	Sanders, 2011, 21865334	2008	UK	Primary Prevention, Healthy
449	Sanders, 2011, 21865334	2008	UK	Primary Prevention, Healthy
450	Sanders, 2011, 21865334	2008	UK	Primary Prevention, Healthy

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Risk type	Sample size (total)
435	Sacks, 1995, 7759696	Dyslipidemia (total cholesterol concentration <250 mg/dl (6.43 mmol/liter) and triglyceride level <350 mg/dl (4.0 mmol/liter)); Cardiac disease (narrowing of =>30% lumen diameter of a major coronary artery)	59
436	Sacks, 1995, 7759696	Dyslipidemia (total cholesterol concentration <250 mg/dl (6.43 mmol/liter) and triglyceride level <350 mg/dl (4.0 mmol/liter)); Cardiac disease (narrowing of =>30% lumen diameter of a major coronary artery)	59
437	Sacks, 1995, 7759696	Dyslipidemia (total cholesterol concentration <250 mg/dl (6.43 mmol/liter) and triglyceride level <350 mg/dl (4.0 mmol/liter)); Cardiac disease (narrowing of =>30% lumen diameter of a major coronary artery)	59
438	Sacks, 1995, 7759696	Dyslipidemia (total cholesterol concentration <250 mg/dl (6.43 mmol/liter) and triglyceride level <350 mg/dl (4.0 mmol/liter)); Cardiac disease (narrowing of =>30% lumen diameter of a major coronary artery)	59
439	Sacks, 1995, 7759696	Dyslipidemia (total cholesterol concentration <250 mg/dl (6.43 mmol/liter) and triglyceride level <350 mg/dl (4.0 mmol/liter)); Cardiac disease (narrowing of =>30% lumen diameter of a major coronary artery)	59
440	Sacks, 1995, 7759696	Dyslipidemia (total cholesterol concentration <250 mg/dl (6.43 mmol/liter) and triglyceride level <350 mg/dl (4.0 mmol/liter)); Cardiac disease (narrowing of =>30% lumen diameter of a major coronary artery)	59
441	Sanders, 2011, 21865334	na	310
442	Sanders, 2011, 21865334	na	310
443	Sanders, 2011, 21865334	na	310
444	Sanders, 2011, 21865334	na	310
445	Sanders, 2011, 21865334	na	310
446	Sanders, 2011, 21865334	na	310
447	Sanders, 2011, 21865334	na	310
448	Sanders, 2011, 21865334	na	310
449	Sanders, 2011, 21865334	na	310
450	Sanders, 2011, 21865334	na	310

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Age mean (SD) [median] years	Sex (% male)	Race
435	Sacks, 1995, 7759696	62 (7)	92.9	nd
436	Sacks, 1995, 7759696	62 (7)	92.9	nd
437	Sacks, 1995, 7759696	62 (7)	92.9	nd
438	Sacks, 1995, 7759696	62 (7)	92.9	nd
439	Sacks, 1995, 7759696	62 (7)	92.9	nd
440	Sacks, 1995, 7759696	62 (7)	92.9	nd
441	Sanders, 2011, 21865334	55 (95% CI 54, 57)	38.6	77.3 white, 10.2 black, 6.8 Asian, 2.3 far eastern, 3.4 other
442	Sanders, 2011, 21865334	55 (95% CI 54, 57)	38.6	77.3 white, 10.2 black, 6.8 Asian, 2.3 far eastern, 3.4 other
443	Sanders, 2011, 21865334	55 (95% CI 54, 57)	38.6	77.3 white, 10.2 black, 6.8 Asian, 2.3 far eastern, 3.4 other
444	Sanders, 2011, 21865334	55 (95% CI 54, 57)	38.6	77.3 white, 10.2 black, 6.8 Asian, 2.3 far eastern, 3.4 other
445	Sanders, 2011, 21865334	55 (95% CI 54, 57)	38.6	77.3 white, 10.2 black, 6.8 Asian, 2.3 far eastern, 3.4 other
446	Sanders, 2011, 21865334	55 (95% CI 54, 57)	38.6	77.3 white, 10.2 black, 6.8 Asian, 2.3 far eastern, 3.4 other
447	Sanders, 2011, 21865334	55 (95% CI 54, 57)	38.6	77.3 white, 10.2 black, 6.8 Asian, 2.3 far eastern, 3.4 other
448	Sanders, 2011, 21865334	55 (95% CI 54, 57)	38.6	77.3 white, 10.2 black, 6.8 Asian, 2.3 far eastern, 3.4 other
449	Sanders, 2011, 21865334	55 (95% CI 54, 57)	38.6	77.3 white, 10.2 black, 6.8 Asian, 2.3 far eastern, 3.4 other
450	Sanders, 2011, 21865334	55 (95% CI 54, 57)	38.6	77.3 white, 10.2 black, 6.8 Asian, 2.3 far eastern, 3.4 other

Row	Study	Blood pressure SBP/DBP mmHg
435	Sacks, 1995, 7759696	133 (19)/77 (7.6)
436	Sacks, 1995, 7759696	133 (19)/77 (7.6)
437	Sacks, 1995, 7759696	133 (19)/77 (7.6)
438	Sacks, 1995, 7759696	133 (19)/77 (7.6)
439	Sacks, 1995, 7759696	133 (19)/77 (7.6)
440	Sacks, 1995, 7759696	133 (19)/77 (7.6)
441	Sanders, 2011, 21865334	120 (95% CI 117, 124)/77 (95% CI 75, 79)
442	Sanders, 2011, 21865334	120 (95% CI 117, 124)/77 (95% CI 75, 79)
443	Sanders, 2011, 21865334	120 (95% CI 117, 124)/77 (95% CI 75, 79)
444	Sanders, 2011, 21865334	120 (95% CI 117, 124)/77 (95% CI 75, 79)
445	Sanders, 2011, 21865334	120 (95% CI 117, 124)/77 (95% CI 75, 79)
446	Sanders, 2011, 21865334	120 (95% CI 117, 124)/77 (95% CI 75, 79)
447	Sanders, 2011, 21865334	120 (95% CI 117, 124)/77 (95% CI 75, 79)
448	Sanders, 2011, 21865334	120 (95% CI 117, 124)/77 (95% CI 75, 79)
449	Sanders, 2011, 21865334	120 (95% CI 117, 124)/77 (95% CI 75, 79)
450	Sanders, 2011, 21865334	120 (95% CI 117, 124)/77 (95% CI 75, 79)

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Lipids: Total cholesterol/LDL/HDL/Triglycerides mean (SD) mg/dL [mmol/L]
435	Sacks, 1995, 7759696	184 (28)/117 (27)/40 (12)/137 (73)
436	Sacks, 1995, 7759696	184 (28)/117 (27)/40 (12)/137 (73)
437	Sacks, 1995, 7759696	184 (28)/117 (27)/40 (12)/137 (73)
438	Sacks, 1995, 7759696	184 (28)/117 (27)/40 (12)/137 (73)
439	Sacks, 1995, 7759696	184 (28)/117 (27)/40 (12)/137 (73)
440	Sacks, 1995, 7759696	184 (28)/117 (27)/40 (12)/137 (73)
441	Sanders, 2011, 21865334	nd
442	Sanders, 2011, 21865334	nd
443	Sanders, 2011, 21865334	nd
444	Sanders, 2011, 21865334	nd
445	Sanders, 2011, 21865334	nd
446	Sanders, 2011, 21865334	nd
447	Sanders, 2011, 21865334	nd
448	Sanders, 2011, 21865334	nd
449	Sanders, 2011, 21865334	nd
450	Sanders, 2011, 21865334	nd

Row	Study	BMI mean (SD) Kg/m2/Weight mean (SD) Kg	Baseline n-3 intake	n-3 source (Baseline)
435	Sacks, 1995, 7759696	weight 79 (15)	nd	nd
436	Sacks, 1995, 7759696	weight 79 (15)	nd	nd
437	Sacks, 1995, 7759696	weight 79 (15)	nd	nd
438	Sacks, 1995, 7759696	weight 79 (15)	nd	nd
439	Sacks, 1995, 7759696	weight 79 (15)	nd	nd
440	Sacks, 1995, 7759696	weight 79 (15)	nd	nd
441	Sanders, 2011, 21865334	26 (95% CI 25, 27) (women); 27 (95% CI 26, 28) (men)	nd	nd
442	Sanders, 2011, 21865334	26 (95% CI 25, 27) (women); 27 (95% CI 26, 28) (men)	nd	nd
443	Sanders, 2011, 21865334	26 (95% CI 25, 27) (women); 27 (95% CI 26, 28) (men)	nd	nd
444	Sanders, 2011, 21865334	26 (95% CI 25, 27) (women); 27 (95% CI 26, 28) (men)	nd	nd
445	Sanders, 2011, 21865334	26 (95% CI 25, 27) (women); 27 (95% CI 26, 28) (men)	nd	nd
446	Sanders, 2011, 21865334	26 (95% CI 25, 27) (women); 27 (95% CI 26, 28) (men)	nd	nd
447	Sanders, 2011, 21865334	26 (95% CI 25, 27) (women); 27 (95% CI 26, 28) (men)	nd	nd
448	Sanders, 2011, 21865334	26 (95% CI 25, 27) (women); 27 (95% CI 26, 28) (men)	nd	nd
449	Sanders, 2011, 21865334	26 (95% CI 25, 27) (women); 27 (95% CI 26, 28) (men)	nd	nd
450	Sanders, 2011, 21865334	26 (95% CI 25, 27) (women); 27 (95% CI 26, 28) (men)	nd	nd

Row	Study	n-3 type(s)	n-3 measure	Study design	Outcome
435	Sacks, 1995, 7759696	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	HDL-c
436	Sacks, 1995, 7759696	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	HDL-c
437	Sacks, 1995, 7759696	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	LDL-c
438	Sacks, 1995, 7759696	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Tg
439	Sacks, 1995, 7759696	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	SBP
440	Sacks, 1995, 7759696	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	DBP
441	Sanders, 2011, 21865334	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Total:HDL-c ratio
442	Sanders, 2011, 21865334	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Parallel	Total:HDL-c ratio
443	Sanders, 2011, 21865334	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Parallel	Total:HDL-c ratio
444	Sanders, 2011, 21865334	ALA+EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Total:HDL-c ratio
445	Sanders, 2011, 21865334	ALA+EPA+DHA+ vitamin C vs Placebo + vitamin C	g/d	Trial: Randomized Parallel	Total:HDL-c ratio
446	Sanders, 2011, 21865334	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Total:HDL-c ratio
447	Sanders, 2011, 21865334	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	HDL-c
448	Sanders, 2011, 21865334	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Parallel	HDL-c
449	Sanders, 2011, 21865334	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Parallel	HDL-c
450	Sanders, 2011, 21865334	ALA+EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	HDL-c

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Reported effect Size	Dose/intake difference	Dose-corrected effect size
435	Sacks, 1995, 7759696	1.80 (-0.92, 4.52)	2	0.9
436	Sacks, 1995, 7759696	-1.00 (-6.86, 4.86)	6	-0.1666667
437	Sacks, 1995, 7759696	5.00 (-9.07, 19.07)	6	0.8333333
438	Sacks, 1995, 7759696	-33.00 (-66.57, 0.57)	6	-5.5
439	Sacks, 1995, 7759696	-1.0 (-14,.0 12.0)	6	-0.1666667
440	Sacks, 1995, 7759696	1 .0 (-4.6, 6.6)	6	0.1666667
441	Sanders, 2011, 21865334	−0.07 (−0.35, 0.21)	1.8	
442	Sanders, 2011, 21865334	−0.03 (−0.31, 0.25)	0.9	
443	Sanders, 2011, 21865334	−0.01 (−0.29, 0.27)	0.45	
444	Sanders, 2011, 21865334	−0.04 (−0.30, 0.22)	1.8	
445	Sanders, 2011, 21865334	−0.06 (−0.33, 0.21)	1.8	
446	Sanders, 2011, 21865334	−0.02 (−0.28, 0.24)	0.9	
447	Sanders, 2011, 21865334	3.9 (−1.6, 9.3)	1.8	
448	Sanders, 2011, 21865334	0 (−5.5, 5.5)	0.9	
449	Sanders, 2011, 21865334	3.9 (−1.6, 9.3)	0.45	
450	Sanders, 2011, 21865334	3.9 (−1.6, 9.3)	1.8	

Row	Study	Outcome classification
435	Sacks, 1995, 7759696	Secondary
436	Sacks, 1995, 7759696	Secondary
437	Sacks, 1995, 7759696	Secondary
438	Sacks, 1995, 7759696	Secondary
439	Sacks, 1995, 7759696	Secondary
440	Sacks, 1995, 7759696	Secondary
441	Sanders, 2011, 21865334	Secondary
442	Sanders, 2011, 21865334	Secondary
443	Sanders, 2011, 21865334	Secondary
444	Sanders, 2011, 21865334	Secondary
445	Sanders, 2011, 21865334	Secondary
446	Sanders, 2011, 21865334	Secondary
447	Sanders, 2011, 21865334	Secondary
448	Sanders, 2011, 21865334	Secondary
449	Sanders, 2011, 21865334	Secondary
450	Sanders, 2011, 21865334	Secondary

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Study years (start date)	Country	Population
451	Sanders, 2011, 21865334	2008	UK	Primary Prevention, Healthy
452	Sanders, 2011, 21865334	2008	UK	Primary Prevention, Healthy
453	Sanders, 2011, 21865334	2008	UK	Primary Prevention, Healthy
454	Sanders, 2011, 21865334	2008	UK	Primary Prevention, Healthy
455	Sanders, 2011, 21865334	2008	UK	Primary Prevention, Healthy
456	Sanders, 2011, 21865334	2008	UK	Primary Prevention, Healthy
457	Sanders, 2011, 21865334	2008	UK	Primary Prevention, Healthy
458	Sanders, 2011, 21865334	2008	UK	Primary Prevention, Healthy
459	Sanders, 2011, 21865334	2008	UK	Primary Prevention, Healthy
460	Sanders, 2011, 21865334	2008	UK	Primary Prevention, Healthy
461	Sanders, 2011, 21865334	2008	UK	Primary Prevention, Healthy
462	Sanders, 2011, 21865334	2008	UK	Primary Prevention, Healthy
463	Sanders, 2011, 21865334	2008	UK	Primary Prevention, Healthy
464	Sanders, 2011, 21865334	2008	UK	Primary Prevention, Healthy
465	Sanders, 2011, 21865334	2008	UK	Primary Prevention, Healthy
466	Sanders, 2011, 21865334	2008	UK	Primary Prevention, Healthy

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Risk type	Sample size (total)
451	Sanders, 2011, 21865334	na	310
452	Sanders, 2011, 21865334	na	310
453	Sanders, 2011, 21865334	na	310
454	Sanders, 2011, 21865334	na	310
455	Sanders, 2011, 21865334	na	310
456	Sanders, 2011, 21865334	na	310
457	Sanders, 2011, 21865334	na	310
458	Sanders, 2011, 21865334	na	310
459	Sanders, 2011, 21865334	na	310
460	Sanders, 2011, 21865334	na	310
461	Sanders, 2011, 21865334	na	310
462	Sanders, 2011, 21865334	na	310
463	Sanders, 2011, 21865334	na	310
464	Sanders, 2011, 21865334	na	310
465	Sanders, 2011, 21865334	na	310
466	Sanders, 2011, 21865334	na	310

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Age mean (SD) [median] years	Sex (% male)	Race
451	Sanders, 2011, 21865334	55 (95% CI 54, 57)	38.6	77.3 white, 10.2 black, 6.8 Asian, 2.3 far eastern, 3.4 other
452	Sanders, 2011, 21865334	55 (95% CI 54, 57)	38.6	77.3 white, 10.2 black, 6.8 Asian, 2.3 far eastern, 3.4 other
453	Sanders, 2011, 21865334	55 (95% CI 54, 57)	38.6	77.3 white, 10.2 black, 6.8 Asian, 2.3 far eastern, 3.4 other
454	Sanders, 2011, 21865334	55 (95% CI 54, 57)	38.6	77.3 white, 10.2 black, 6.8 Asian, 2.3 far eastern, 3.4 other
455	Sanders, 2011, 21865334	55 (95% CI 54, 57)	38.6	77.3 white, 10.2 black, 6.8 Asian, 2.3 far eastern, 3.4 other
456	Sanders, 2011, 21865334	55 (95% CI 54, 57)	38.6	77.3 white, 10.2 black, 6.8 Asian, 2.3 far eastern, 3.4 other
457	Sanders, 2011, 21865334	55 (95% CI 54, 57)	38.6	77.3 white, 10.2 black, 6.8 Asian, 2.3 far eastern, 3.4 other
458	Sanders, 2011, 21865334	55 (95% CI 54, 57)	38.6	77.3 white, 10.2 black, 6.8 Asian, 2.3 far eastern, 3.4 other
459	Sanders, 2011, 21865334	55 (95% CI 54, 57)	38.6	77.3 white, 10.2 black, 6.8 Asian, 2.3 far eastern, 3.4 other
460	Sanders, 2011, 21865334	55 (95% CI 54, 57)	38.6	77.3 white, 10.2 black, 6.8 Asian, 2.3 far eastern, 3.4 other
461	Sanders, 2011, 21865334	55 (95% CI 54, 57)	38.6	77.3 white, 10.2 black, 6.8 Asian, 2.3 far eastern, 3.4 other
462	Sanders, 2011, 21865334	55 (95% CI 54, 57)	38.6	77.3 white, 10.2 black, 6.8 Asian, 2.3 far eastern, 3.4 other
463	Sanders, 2011, 21865334	55 (95% CI 54, 57)	38.6	77.3 white, 10.2 black, 6.8 Asian, 2.3 far eastern, 3.4 other
464	Sanders, 2011, 21865334	55 (95% CI 54, 57)	38.6	77.3 white, 10.2 black, 6.8 Asian, 2.3 far eastern, 3.4 other
465	Sanders, 2011, 21865334	55 (95% CI 54, 57)	38.6	77.3 white, 10.2 black, 6.8 Asian, 2.3 far eastern, 3.4 other
466	Sanders, 2011, 21865334	55 (95% CI 54, 57)	38.6	77.3 white, 10.2 black, 6.8 Asian, 2.3 far eastern, 3.4 other

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Blood pressure SBP/DBP mmHg
451	Sanders, 2011, 21865334	120 (95% CI 117, 124)/77 (95% CI 75, 79)
452	Sanders, 2011, 21865334	120 (95% CI 117, 124)/77 (95% CI 75, 79)
453	Sanders, 2011, 21865334	120 (95% CI 117, 124)/77 (95% CI 75, 79)
454	Sanders, 2011, 21865334	120 (95% CI 117, 124)/77 (95% CI 75, 79)
455	Sanders, 2011, 21865334	120 (95% CI 117, 124)/77 (95% CI 75, 79)
456	Sanders, 2011, 21865334	120 (95% CI 117, 124)/77 (95% CI 75, 79)
457	Sanders, 2011, 21865334	120 (95% CI 117, 124)/77 (95% CI 75, 79)
458	Sanders, 2011, 21865334	120 (95% CI 117, 124)/77 (95% CI 75, 79)
459	Sanders, 2011, 21865334	120 (95% CI 117, 124)/77 (95% CI 75, 79)
460	Sanders, 2011, 21865334	120 (95% CI 117, 124)/77 (95% CI 75, 79)
461	Sanders, 2011, 21865334	120 (95% CI 117, 124)/77 (95% CI 75, 79)
462	Sanders, 2011, 21865334	120 (95% CI 117, 124)/77 (95% CI 75, 79)
463	Sanders, 2011, 21865334	120 (95% CI 117, 124)/77 (95% CI 75, 79)
464	Sanders, 2011, 21865334	120 (95% CI 117, 124)/77 (95% CI 75, 79)
465	Sanders, 2011, 21865334	120 (95% CI 117, 124)/77 (95% CI 75, 79)
466	Sanders, 2011, 21865334	120 (95% CI 117, 124)/77 (95% CI 75, 79)

Row	Study	Lipids: Total cholesterol/LDL/HDL/Triglycerides mean (SD) mg/dL [mmol/L]
451	Sanders, 2011, 21865334	nd
452	Sanders, 2011, 21865334	nd
453	Sanders, 2011, 21865334	nd
454	Sanders, 2011, 21865334	nd
455	Sanders, 2011, 21865334	nd
456	Sanders, 2011, 21865334	nd
457	Sanders, 2011, 21865334	nd
458	Sanders, 2011, 21865334	nd
459	Sanders, 2011, 21865334	nd
460	Sanders, 2011, 21865334	nd
461	Sanders, 2011, 21865334	nd
462	Sanders, 2011, 21865334	nd
463	Sanders, 2011, 21865334	nd
464	Sanders, 2011, 21865334	nd
465	Sanders, 2011, 21865334	nd
466	Sanders, 2011, 21865334	nd

Row	Study	BMI mean (SD) Kg/m2/Weight mean (SD) Kg	Baseline n-3 intake	n-3 source (Baseline)
451	Sanders, 2011, 21865334	26 (95% CI 25, 27) (women); 27 (95% CI 26, 28) (men)	nd	nd
452	Sanders, 2011, 21865334	26 (95% CI 25, 27) (women); 27 (95% CI 26, 28) (men)	nd	nd
453	Sanders, 2011, 21865334	26 (95% CI 25, 27) (women); 27 (95% CI 26, 28) (men)	nd	nd
454	Sanders, 2011, 21865334	26 (95% CI 25, 27) (women); 27 (95% CI 26, 28) (men)	nd	nd
455	Sanders, 2011, 21865334	26 (95% CI 25, 27) (women); 27 (95% CI 26, 28) (men)	nd	nd
456	Sanders, 2011, 21865334	26 (95% CI 25, 27) (women); 27 (95% CI 26, 28) (men)	nd	nd
457	Sanders, 2011, 21865334	26 (95% CI 25, 27) (women); 27 (95% CI 26, 28) (men)	nd	nd
458	Sanders, 2011, 21865334	26 (95% CI 25, 27) (women); 27 (95% CI 26, 28) (men)	nd	nd
459	Sanders, 2011, 21865334	26 (95% CI 25, 27) (women); 27 (95% CI 26, 28) (men)	nd	nd
460	Sanders, 2011, 21865334	26 (95% CI 25, 27) (women); 27 (95% CI 26, 28) (men)	nd	nd
461	Sanders, 2011, 21865334	26 (95% CI 25, 27) (women); 27 (95% CI 26, 28) (men)	nd	nd
462	Sanders, 2011, 21865334	26 (95% CI 25, 27) (women); 27 (95% CI 26, 28) (men)	nd	nd
463	Sanders, 2011, 21865334	26 (95% CI 25, 27) (women); 27 (95% CI 26, 28) (men)	nd	nd
464	Sanders, 2011, 21865334	26 (95% CI 25, 27) (women); 27 (95% CI 26, 28) (men)	nd	nd
465	Sanders, 2011, 21865334	26 (95% CI 25, 27) (women); 27 (95% CI 26, 28) (men)	nd	nd
466	Sanders, 2011, 21865334	26 (95% CI 25, 27) (women); 27 (95% CI 26, 28) (men)	nd	nd

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	n-3 type(s)	n-3 measure	Study design	Outcome
451	Sanders, 2011, 21865334	ALA+EPA+DHA+ vitamin C vs Placebo + vitamin C	g/d	Trial: Randomized Parallel	HDL-c
452	Sanders, 2011, 21865334	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	HDL-c
453	Sanders, 2011, 21865334	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	LDL-c
454	Sanders, 2011, 21865334	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Parallel	LDL-c
455	Sanders, 2011, 21865334	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Parallel	LDL-c
456	Sanders, 2011, 21865334	ALA+EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	LDL-c
457	Sanders, 2011, 21865334	ALA+EPA+DHA+ vitamin C vs Placebo + vitamin C	g/d	Trial: Randomized Parallel	LDL-c
458	Sanders, 2011, 21865334	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	LDL-c
459	Sanders, 2011, 21865334	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Tg
460	Sanders, 2011, 21865334	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Parallel	Tg
461	Sanders, 2011, 21865334	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Parallel	Tg
462	Sanders, 2011, 21865334	ALA+EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Tg
463	Sanders, 2011, 21865334	ALA+EPA+DHA+ vitamin C vs Placebo + vitamin C	g/d	Trial: Randomized Parallel	Tg
464	Sanders, 2011, 21865334	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Tg
465	Sanders, 2011, 21865334	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	SBP
466	Sanders, 2011, 21865334	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Parallel	SBP

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Reported effect Size	Dose/intake difference	Dose-corrected effect size
451	Sanders, 2011, 21865334	0 (−5.5, 5.5)	1.8	
452	Sanders, 2011, 21865334	−3.9 (−9.3, 1.6)	0.9	
453	Sanders, 2011, 21865334	3.9 (−5.6, 13.6)	1.8	
454	Sanders, 2011, 21865334	0 (−10.2, 10.2)	0.9	
455	Sanders, 2011, 21865334	7.7 (−2.5, 17.9)	0.45	
456	Sanders, 2011, 21865334	3.9 (−6.4, 14.1)	1.8	
457	Sanders, 2011, 21865334	−11.6 (−22.5, −0.66) −3.9 (−13.5, 5.8)	1.8	
458	Sanders, 2011, 21865334	−7.7 (−18.6, 3.2)	0.9	
459	Sanders, 2011, 21865334	−15.0 (−27.4, −2.7)	1.8	
460	Sanders, 2011, 21865334	−3.5 (−16.5, 9.4)	0.9	
461	Sanders, 2011, 21865334	−2.7 (−15.8, 10.5)	0.45	
462	Sanders, 2011, 21865334	−11.5 (−24.2, 1.2)	1.8	
463	Sanders, 2011, 21865334	−12.4 (−88.4, 63.7)	1.8	
464	Sanders, 2011, 21865334	−0.9 (−77.0, 75.3)	0.9	
465	Sanders, 2011, 21865334	-0.3 (-4.3, 3.7)	1.8	
466	Sanders, 2011, 21865334	-0.8 (-4.8, 3.2)	0.9	

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Outcome classification
451	Sanders, 2011, 21865334	Secondary
452	Sanders, 2011, 21865334	Secondary
453	Sanders, 2011, 21865334	Secondary
454	Sanders, 2011, 21865334	Secondary
455	Sanders, 2011, 21865334	Secondary
456	Sanders, 2011, 21865334	Secondary
457	Sanders, 2011, 21865334	Secondary
458	Sanders, 2011, 21865334	Secondary
459	Sanders, 2011, 21865334	Secondary
460	Sanders, 2011, 21865334	Secondary
461	Sanders, 2011, 21865334	Secondary
462	Sanders, 2011, 21865334	Secondary
463	Sanders, 2011, 21865334	Secondary
464	Sanders, 2011, 21865334	Secondary
465	Sanders, 2011, 21865334	Secondary
466	Sanders, 2011, 21865334	Secondary

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Study years (start date)	Country	Population
467	Sanders, 2011, 21865334	2008	UK	Primary Prevention, Healthy
468	Sanders, 2011, 21865334	2008	UK	Primary Prevention, Healthy
469	Sanders, 2011, 21865334	2008	UK	Primary Prevention, Healthy
470	Sanders, 2011, 21865334	2008	UK	Primary Prevention, Healthy
471	Sanders, 2011, 21865334	2008	UK	Primary Prevention, Healthy
472	Sanders, 2011, 21865334	2008	UK	Primary Prevention, Healthy
473	Sanders, 2011, 21865334	2008	UK	Primary Prevention, Healthy
474	Sanders, 2011, 21865334	2008	UK	Primary Prevention, Healthy
475	Sanders, 2011, 21865334	2008	UK	Primary Prevention, Healthy
476	Sanders, 2011, 21865334	2008	UK	Primary Prevention, Healthy
477	Sanders, 2011, 21865334	2008	UK	Primary Prevention, Healthy
478	Sanders, 2011, 21865334	2008	UK	Primary Prevention, Healthy
479	Sanders, 2011, 21865334	2008	UK	Primary Prevention, Healthy
480	Sanders, 2011, 21865334	2008	UK	Primary Prevention, Healthy
481	Sanders, 2011, 21865334	2008	UK	Primary Prevention, Healthy
482	Sanders, 2011, 21865334	2008	UK	Primary Prevention, Healthy
483	Shaikh 2014 25185754	nd	Canada	Primary Prevention, Healthy

Row	Study	Risk type	Sample size (total)
467	Sanders, 2011, 21865334	na	310
468	Sanders, 2011, 21865334	na	310
469	Sanders, 2011, 21865334	na	310
470	Sanders, 2011, 21865334	na	310
471	Sanders, 2011, 21865334	na	310
472	Sanders, 2011, 21865334	na	310
473	Sanders, 2011, 21865334	na	310
474	Sanders, 2011, 21865334	na	310
475	Sanders, 2011, 21865334	na	310
476	Sanders, 2011, 21865334	na	310
477	Sanders, 2011, 21865334	na	310
478	Sanders, 2011, 21865334	na	310
479	Sanders, 2011, 21865334	na	310
480	Sanders, 2011, 21865334	na	310
481	Sanders, 2011, 21865334	na	310
482	Sanders, 2011, 21865334	na	310
483	Shaikh 2014 25185754	na	110

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Age mean (SD) [median] years	Sex (% male)	Race
467	Sanders, 2011, 21865334	55 (95% CI 54, 57)	38.6	77.3 white, 10.2 black, 6.8 Asian, 2.3 far eastern, 3.4 other
468	Sanders, 2011, 21865334	55 (95% CI 54, 57)	38.6	77.3 white, 10.2 black, 6.8 Asian, 2.3 far eastern, 3.4 other
469	Sanders, 2011, 21865334	55 (95% CI 54, 57)	38.6	77.3 white, 10.2 black, 6.8 Asian, 2.3 far eastern, 3.4 other
470	Sanders, 2011, 21865334	55 (95% CI 54, 57)	38.6	77.3 white, 10.2 black, 6.8 Asian, 2.3 far eastern, 3.4 other
471	Sanders, 2011, 21865334	55 (95% CI 54, 57)	38.6	77.3 white, 10.2 black, 6.8 Asian, 2.3 far eastern, 3.4 other
472	Sanders, 2011, 21865334	55 (95% CI 54, 57)	38.6	77.3 white, 10.2 black, 6.8 Asian, 2.3 far eastern, 3.4 other
473	Sanders, 2011, 21865334	55 (95% CI 54, 57)	38.6	77.3 white, 10.2 black, 6.8 Asian, 2.3 far eastern, 3.4 other
474	Sanders, 2011, 21865334	55 (95% CI 54, 57)	38.6	77.3 white, 10.2 black, 6.8 Asian, 2.3 far eastern, 3.4 other
475	Sanders, 2011, 21865334	55 (95% CI 54, 57)	38.6	77.3 white, 10.2 black, 6.8 Asian, 2.3 far eastern, 3.4 other
476	Sanders, 2011, 21865334	55 (95% CI 54, 57)	38.6	77.3 white, 10.2 black, 6.8 Asian, 2.3 far eastern, 3.4 other
477	Sanders, 2011, 21865334	55 (95% CI 54, 57)	38.6	77.3 white, 10.2 black, 6.8 Asian, 2.3 far eastern, 3.4 other
478	Sanders, 2011, 21865334	55 (95% CI 54, 57)	38.6	77.3 white, 10.2 black, 6.8 Asian, 2.3 far eastern, 3.4 other
479	Sanders, 2011, 21865334	55 (95% CI 54, 57)	38.6	77.3 white, 10.2 black, 6.8 Asian, 2.3 far eastern, 3.4 other
480	Sanders, 2011, 21865334	55 (95% CI 54, 57)	38.6	77.3 white, 10.2 black, 6.8 Asian, 2.3 far eastern, 3.4 other
481	Sanders, 2011, 21865334	55 (95% CI 54, 57)	38.6	77.3 white, 10.2 black, 6.8 Asian, 2.3 far eastern, 3.4 other
482	Sanders, 2011, 21865334	55 (95% CI 54, 57)	38.6	77.3 white, 10.2 black, 6.8 Asian, 2.3 far eastern, 3.4 other
483	Shaikh 2014 25185754	53.6 (14.2)	53.5	nd

Row	Study	Blood pressure SBP/DBP mmHg
467	Sanders, 2011, 21865334	120 (95% CI 117, 124)/77 (95% CI 75, 79)
468	Sanders, 2011, 21865334	120 (95% CI 117, 124)/77 (95% CI 75, 79)
469	Sanders, 2011, 21865334	120 (95% CI 117, 124)/77 (95% CI 75, 79)
470	Sanders, 2011, 21865334	120 (95% CI 117, 124)/77 (95% CI 75, 79)
471	Sanders, 2011, 21865334	120 (95% CI 117, 124)/77 (95% CI 75, 79)
472	Sanders, 2011, 21865334	120 (95% CI 117, 124)/77 (95% CI 75, 79)
473	Sanders, 2011, 21865334	120 (95% CI 117, 124)/77 (95% CI 75, 79)
474	Sanders, 2011, 21865334	120 (95% CI 117, 124)/77 (95% CI 75, 79)
475	Sanders, 2011, 21865334	120 (95% CI 117, 124)/77 (95% CI 75, 79)
476	Sanders, 2011, 21865334	120 (95% CI 117, 124)/77 (95% CI 75, 79)
477	Sanders, 2011, 21865334	120 (95% CI 117, 124)/77 (95% CI 75, 79)
478	Sanders, 2011, 21865334	120 (95% CI 117, 124)/77 (95% CI 75, 79)
479	Sanders, 2011, 21865334	120 (95% CI 117, 124)/77 (95% CI 75, 79)
480	Sanders, 2011, 21865334	120 (95% CI 117, 124)/77 (95% CI 75, 79)
481	Sanders, 2011, 21865334	120 (95% CI 117, 124)/77 (95% CI 75, 79)
482	Sanders, 2011, 21865334	120 (95% CI 117, 124)/77 (95% CI 75, 79)
483	Shaikh 2014 25185754	nd

Row	Study	Lipids: Total cholesterol/LDL/HDL/Triglycerides mean (SD) mg/dL [mmol/L]
467	Sanders, 2011, 21865334	nd
468	Sanders, 2011, 21865334	nd
469	Sanders, 2011, 21865334	nd
470	Sanders, 2011, 21865334	nd
471	Sanders, 2011, 21865334	nd
472	Sanders, 2011, 21865334	nd
473	Sanders, 2011, 21865334	nd
474	Sanders, 2011, 21865334	nd
475	Sanders, 2011, 21865334	nd
476	Sanders, 2011, 21865334	nd
477	Sanders, 2011, 21865334	nd
478	Sanders, 2011, 21865334	nd
479	Sanders, 2011, 21865334	nd
480	Sanders, 2011, 21865334	nd
481	Sanders, 2011, 21865334	nd
482	Sanders, 2011, 21865334	nd
483	Shaikh 2014 25185754	[4.83 (1.02)/2.92 (0.84)/1.09 (0.27)/2.25 (1.03)]

Row	Study	BMI mean (SD) Kg/m2/Weight mean (SD) Kg	Baseline n-3 intake	n-3 source (Baseline)
467	Sanders, 2011, 21865334	26 (95% CI 25, 27) (women); 27 (95% CI 26, 28) (men)	nd	nd
468	Sanders, 2011, 21865334	26 (95% CI 25, 27) (women); 27 (95% CI 26, 28) (men)	nd	nd
469	Sanders, 2011, 21865334	26 (95% CI 25, 27) (women); 27 (95% CI 26, 28) (men)	nd	nd
470	Sanders, 2011, 21865334	26 (95% CI 25, 27) (women); 27 (95% CI 26, 28) (men)	nd	nd
471	Sanders, 2011, 21865334	26 (95% CI 25, 27) (women); 27 (95% CI 26, 28) (men)	nd	nd
472	Sanders, 2011, 21865334	26 (95% CI 25, 27) (women); 27 (95% CI 26, 28) (men)	nd	nd
473	Sanders, 2011, 21865334	26 (95% CI 25, 27) (women); 27 (95% CI 26, 28) (men)	nd	nd
474	Sanders, 2011, 21865334	26 (95% CI 25, 27) (women); 27 (95% CI 26, 28) (men)	nd	nd
475	Sanders, 2011, 21865334	26 (95% CI 25, 27) (women); 27 (95% CI 26, 28) (men)	nd	nd
476	Sanders, 2011, 21865334	26 (95% CI 25, 27) (women); 27 (95% CI 26, 28) (men)	nd	nd
477	Sanders, 2011, 21865334	26 (95% CI 25, 27) (women); 27 (95% CI 26, 28) (men)	nd	nd
478	Sanders, 2011, 21865334	26 (95% CI 25, 27) (women); 27 (95% CI 26, 28) (men)	nd	nd
479	Sanders, 2011, 21865334	26 (95% CI 25, 27) (women); 27 (95% CI 26, 28) (men)	nd	nd
480	Sanders, 2011, 21865334	26 (95% CI 25, 27) (women); 27 (95% CI 26, 28) (men)	nd	nd
481	Sanders, 2011, 21865334	26 (95% CI 25, 27) (women); 27 (95% CI 26, 28) (men)	nd	nd
482	Sanders, 2011, 21865334	26 (95% CI 25, 27) (women); 27 (95% CI 26, 28) (men)	nd	nd
483	Shaikh 2014 25185754	31.9 (6.6)	nd	nd

Row	Study	n-3 type(s)	n-3 measure	Study design	Outcome
467	Sanders, 2011, 21865334	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Parallel	SBP
468	Sanders, 2011, 21865334	ALA+EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	SBP
469	Sanders, 2011, 21865334	ALA+EPA+DHA+ vitamin C vs Placebo + vitamin C	g/d	Trial: Randomized Parallel	SBP
470	Sanders, 2011, 21865334	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	SBP
471	Sanders, 2011, 21865334	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	DBP
472	Sanders, 2011, 21865334	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Parallel	DBP
473	Sanders, 2011, 21865334	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Parallel	DBP
474	Sanders, 2011, 21865334	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	DBP
475	Sanders, 2011, 21865334	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	DBP
476	Sanders, 2011, 21865334	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	DBP
477	Sanders, 2011, 21865334	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	MAP
478	Sanders, 2011, 21865334	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Parallel	MAP
479	Sanders, 2011, 21865334	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Parallel	MAP
480	Sanders, 2011, 21865334	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	MAP
481	Sanders, 2011, 21865334	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	MAP
482	Sanders, 2011, 21865334	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	MAP
483	Shaikh 2014 25185754	EPA+DHA 3.6 vs Placebo	g/d	Trial: Randomized Parallel	HDL-c

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Reported effect Size	Dose/intake difference	Dose-corrected effect size
467	Sanders, 2011, 21865334	0 (-4, 4)	0.45	
468	Sanders, 2011, 21865334	0.5 (-3.5, 4.5)	1.8	
469	Sanders, 2011, 21865334	-0.3 (-4.3, 3.7)	1.8	
470	Sanders, 2011, 21865334	−0.8 (−4.8, 3.2)	0.9	
471	Sanders, 2011, 21865334	0.6 (-1.4, 2.6)	1.8	
472	Sanders, 2011, 21865334	0.6 (-1.5, 2.7)	0.9	
473	Sanders, 2011, 21865334	1.2 (-0.9, 3.3)	0.45	
474	Sanders, 2011, 21865334	0 (-2.0, 2.0)	1.8	
475	Sanders, 2011, 21865334	-0.6 (-2.5, 1.3)	1.8	
476	Sanders, 2011, 21865334	−0.6 (−2.7, 1.5)	0.9	
477	Sanders, 2011, 21865334	2 (-1.4, 5.4)	1.8	
478	Sanders, 2011, 21865334	1 (-2.4, 4.4)	0.9	
479	Sanders, 2011, 21865334	-1 (-4.5, 2.5)	0.45	
480	Sanders, 2011, 21865334	1 (-2.2, 4.2)	1.8	
481	Sanders, 2011, 21865334	3 (-0.4, 6.4)	1.8	
482	Sanders, 2011, 21865334	1.0 (−2.7, 4.7)	0.9	
483	Shaikh 2014 25185754	2.32 (-3.31, 7.95)	3.6	0.64

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Outcome classification
467	Sanders, 2011, 21865334	Secondary
468	Sanders, 2011, 21865334	Secondary
469	Sanders, 2011, 21865334	Secondary
470	Sanders, 2011, 21865334	Secondary
471	Sanders, 2011, 21865334	Secondary
472	Sanders, 2011, 21865334	Secondary
473	Sanders, 2011, 21865334	Secondary
474	Sanders, 2011, 21865334	Secondary
475	Sanders, 2011, 21865334	Secondary
476	Sanders, 2011, 21865334	Secondary
477	Sanders, 2011, 21865334	Secondary
478	Sanders, 2011, 21865334	Secondary
479	Sanders, 2011, 21865334	Secondary
480	Sanders, 2011, 21865334	Secondary
481	Sanders, 2011, 21865334	Secondary
482	Sanders, 2011, 21865334	Secondary
483	Shaikh 2014 25185754	Secondary

Row	Study	Study years (start date)	Country	Population
484	Shaikh 2014 25185754	nd	Canada	Primary Prevention, Increased CVD Risk
485	Shaikh 2014 25185754	nd	Canada	Primary Prevention, Healthy
486	Shaikh 2014 25185754	nd	Canada	Primary Prevention, Increased CVD Risk
487	Shaikh 2014 25185754	nd	Canada	Primary Prevention, Healthy
488	Shaikh 2014 25185754	nd	Canada	Primary Prevention, Increased CVD Risk
489	Shidfar, 2003, 12847992	2001 (approx)	Iran	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
490	Shidfar, 2003, 12847992	2001 (approx)	Iran	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
491	Shidfar, 2003, 12847992	2001 (approx)	Iran	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
492	Shidfar, 2003, 12847992	2001 (approx)	Iran	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
493	Shidfar, 2003, 12847992	2001 (approx)	Iran	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
494	Shidfar, 2003, 12847992	2001 (approx)	Iran	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
495	Shidfar, 2003, 12847992	2001 (approx)	Iran	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
496	Shidfar, 2003, 12847992	2001 (approx)	Iran	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
497	Sirtori, 1997, 9174486	nd	Italy	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)

Row	Study	Risk type	Sample size (total)
484	Shaikh 2014 25185754	TG: 2.26-5.65 mmol/L	110
485	Shaikh 2014 25185754	na	110
486	Shaikh 2014 25185754	TG: 2.26-5.65 mmol/L	110
487	Shaikh 2014 25185754	na	110
488	Shaikh 2014 25185754	TG: 2.26-5.65 mmol/L	110
489	Shidfar, 2003, 12847992	Dyslipidemia (serum total cholesterol and triglyceride > 200 mg/dl)	68
490	Shidfar, 2003, 12847992	Dyslipidemia (serum total cholesterol and triglyceride > 200 mg/dl)	68
491	Shidfar, 2003, 12847992	Dyslipidemia (serum total cholesterol and triglyceride > 200 mg/dl)	68
492	Shidfar, 2003, 12847992	Dyslipidemia (serum total cholesterol and triglyceride > 200 mg/dl)	68
493	Shidfar, 2003, 12847992	Dyslipidemia (serum total cholesterol and triglyceride > 200 mg/dl)	68
494	Shidfar, 2003, 12847992	Dyslipidemia (serum total cholesterol and triglyceride > 200 mg/dl)	68
495	Shidfar, 2003, 12847992	Dyslipidemia (serum total cholesterol and triglyceride > 200 mg/dl)	68
496	Shidfar, 2003, 12847992	Dyslipidemia (serum total cholesterol and triglyceride > 200 mg/dl)	68
497	Sirtori, 1997, 9174486	Diabetes and/or metabolic syndrome ; Hypertension (Patients treated with antihypertensive drugs or who on more than one occasion in the past year had had a systolic blood pressure (SBP) >= 160 mm Hg, a diastolic blood pressure (DBP) >= 95 mm Hg, or both, independent of drug treatment, were considered to have arterial hypertension.); Dyslipidemia (Patients with significant and stable triacylglycerol elevations (> 2.26 mmolIL, or 200 mg/dL) were selected. These were defined as type IIB if serum total cholesterol was > 7.21 mmol/L (270 mg/dL) and type IV if cholesterol was >= 7.21 mmol/L (270 mg/dL). Patients with total cholesterol concentrations > 7.76 mmolIL (300 mg/dL) with triacylglycerol concentrations >= 4.52 mmolIL (400 mg/dL) were excluded for ethical reasons.); Other (Impaired glucose tolerance)	935

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Age mean (SD) [median] years	Sex (% male)	Race
484	Shaikh 2014 25185754	53.6 (14.2)	53.5	nd
485	Shaikh 2014 25185754	53.6 (14.2)	53.5	nd
486	Shaikh 2014 25185754	53.6 (14.2)	53.5	nd
487	Shaikh 2014 25185754	53.6 (14.2)	53.5	nd
488	Shaikh 2014 25185754	53.6 (14.2)	53.5	nd
489	Shidfar, 2003, 12847992	54.4 (12.2)	36.8	nd
490	Shidfar, 2003, 12847992	54.4 (12.2)	36.8	nd
491	Shidfar, 2003, 12847992	54.4 (12.2)	36.8	nd
492	Shidfar, 2003, 12847992	54.4 (12.2)	36.8	nd
493	Shidfar, 2003, 12847992	54.4 (12.2)	36.8	nd
494	Shidfar, 2003, 12847992	54.4 (12.2)	36.8	nd
495	Shidfar, 2003, 12847992	54.4 (12.2)	36.8	nd
496	Shidfar, 2003, 12847992	54.4 (12.2)	36.8	nd
497	Sirtori, 1997, 9174486	58.8 (8.99)	62.2	nd

Row	Study	Blood pressure SBP/DBP mmHg
484	Shaikh 2014 25185754	nd
485	Shaikh 2014 25185754	nd
486	Shaikh 2014 25185754	nd
487	Shaikh 2014 25185754	nd
488	Shaikh 2014 25185754	nd
489	Shidfar, 2003, 12847992	nd
490	Shidfar, 2003, 12847992	nd
491	Shidfar, 2003, 12847992	nd
492	Shidfar, 2003, 12847992	nd
493	Shidfar, 2003, 12847992	nd
494	Shidfar, 2003, 12847992	nd
495	Shidfar, 2003, 12847992	nd
496	Shidfar, 2003, 12847992	nd
497	Sirtori, 1997, 9174486	nd

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Lipids: Total cholesterol/LDL/HDL/Triglycerides mean (SD) mg/dL [mmol/L]
484	Shaikh 2014 25185754	[4.83 (1.02)/2.92 (0.84)/1.09 (0.27)/2.25 (1.03)]
485	Shaikh 2014 25185754	[4.83 (1.02)/2.92 (0.84)/1.09 (0.27)/2.25 (1.03)]
486	Shaikh 2014 25185754	[4.83 (1.02)/2.92 (0.84)/1.09 (0.27)/2.25 (1.03)]
487	Shaikh 2014 25185754	[4.83 (1.02)/2.92 (0.84)/1.09 (0.27)/2.25 (1.03)]
488	Shaikh 2014 25185754	[4.83 (1.02)/2.92 (0.84)/1.09 (0.27)/2.25 (1.03)]
489	Shidfar, 2003, 12847992	250.7 (46.3)/167.4 (38.2)/39.2 (9.3)/311.5 (100.2)
490	Shidfar, 2003, 12847992	250.7 (46.3)/167.4 (38.2)/39.2 (9.3)/311.5 (100.2)
491	Shidfar, 2003, 12847992	250.7 (46.3)/167.4 (38.2)/39.2 (9.3)/311.5 (100.2)
492	Shidfar, 2003, 12847992	250.7 (46.3)/167.4 (38.2)/39.2 (9.3)/311.5 (100.2)
493	Shidfar, 2003, 12847992	250.7 (46.3)/167.4 (38.2)/39.2 (9.3)/311.5 (100.2)
494	Shidfar, 2003, 12847992	250.7 (46.3)/167.4 (38.2)/39.2 (9.3)/311.5 (100.2)
495	Shidfar, 2003, 12847992	250.7 (46.3)/167.4 (38.2)/39.2 (9.3)/311.5 (100.2)
496	Shidfar, 2003, 12847992	250.7 (46.3)/167.4 (38.2)/39.2 (9.3)/311.5 (100.2)
497	Sirtori, 1997, 9174486	nd

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	BMI mean (SD) Kg/m2/Weight mean (SD) Kg	Baseline n-3 intake	n-3 source (Baseline)
484	Shaikh 2014 25185754	31.9 (6.6)	nd	nd
485	Shaikh 2014 25185754	31.9 (6.6)	nd	nd
486	Shaikh 2014 25185754	31.9 (6.6)	nd	nd
487	Shaikh 2014 25185754	31.9 (6.6)	nd	nd
488	Shaikh 2014 25185754	31.9 (6.6)	nd	nd
489	Shidfar, 2003, 12847992	27.6 (3)/72 (10.8)	nd	nd
490	Shidfar, 2003, 12847992	27.6 (3)/72 (10.8)	nd	nd
491	Shidfar, 2003, 12847992	27.6 (3)/72 (10.8)	nd	nd
492	Shidfar, 2003, 12847992	27.6 (3)/72 (10.8)	nd	nd
493	Shidfar, 2003, 12847992	27.6 (3)/72 (10.8)	nd	nd
494	Shidfar, 2003, 12847992	27.6 (3)/72 (10.8)	nd	nd
495	Shidfar, 2003, 12847992	27.6 (3)/72 (10.8)	nd	nd
496	Shidfar, 2003, 12847992	27.6 (3)/72 (10.8)	nd	nd
497	Sirtori, 1997, 9174486	weight 73.7 (10.08)	nd	nd

Row	Study	n-3 type(s)	n-3 measure	Study design	Outcome
484	Shaikh 2014 25185754	EPA+DHA 3.6 vs Placebo	g/d	Trial: Randomized Parallel	HDL-c
485	Shaikh 2014 25185754	EPA+DHA 3.6 vs Placebo	g/d	Trial: Randomized Parallel	LDL-c
486	Shaikh 2014 25185754	EPA+DHA 3.6 vs Placebo	g/d	Trial: Randomized Parallel	LDL-c
487	Shaikh 2014 25185754	EPA+DHA 3.6 vs Placebo	g/d	Trial: Randomized Parallel	Tg
488	Shaikh 2014 25185754	EPA+DHA 3.6 vs Placebo	g/d	Trial: Randomized Parallel	Tg
489	Shidfar, 2003, 12847992	ALA+EPA+DHA vs Placebo	g/d	Trial: Randomized Factorial Design	LDL:HDL-c ratio
490	Shidfar, 2003, 12847992	ALA+EPA+DHA+ vitamin C vs Placebo + vitamin C	g/d	Trial: Randomized Factorial Design	LDL:HDL-c ratio
491	Shidfar, 2003, 12847992	ALA+EPA+DHA vs Placebo	g/d	Trial: Randomized Factorial Design	HDL-c
492	Shidfar, 2003, 12847992	ALA+EPA+DHA+ vitamin C vs Placebo + vitamin C	g/d	Trial: Randomized Factorial Design	HDL-c
493	Shidfar, 2003, 12847992	ALA+EPA+DHA vs Placebo	g/d	Trial: Randomized Factorial Design	LDL-c
494	Shidfar, 2003, 12847992	ALA+EPA+DHA+ vitamin C vs Placebo + vitamin C	g/d	Trial: Randomized Factorial Design	LDL-c
495	Shidfar, 2003, 12847992	ALA+EPA+DHA vs Placebo	g/d	Trial: Randomized Factorial Design	Tg
496	Shidfar, 2003, 12847992	ALA+EPA+DHA+ vitamin C vs Placebo + vitamin C	g/d	Trial: Randomized Factorial Design	Tg
497	Sirtori, 1997, 9174486	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	HDL-c

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Reported effect Size	Dose/intake difference	Dose-corrected effect size
484	Shaikh 2014 25185754	1.93 (0.53, 3.33)	3.6	0.54
485	Shaikh 2014 25185754	12.74 (-3.32, 28.8)	3.6	3.54
486	Shaikh 2014 25185754	13.9 (-2.16, 29.96)	3.6	3.86
487	Shaikh 2014 25185754	-28.32 (-63.05, 6.41)	3.6	-7.87
488	Shaikh 2014 25185754	-95.58 (-149.39, -41.76)	3.6	-26.55
489	Shidfar, 2003, 12847992	-0.3 (-1.5, 0.9)	1	-0.3
490	Shidfar, 2003, 12847992	0.2 (-1.1, 1.5)	1	0.2
491	Shidfar, 2003, 12847992	−0.3 (−6.8, 6.2)	1	-4
492	Shidfar, 2003, 12847992	−14.9 (−20.2, −9.6)	1	10.3
493	Shidfar, 2003, 12847992	-4.00 (-34.70, 26.70)	1	-4
494	Shidfar, 2003, 12847992	10.30 (-18.79, 39.39)	1	10.3
495	Shidfar, 2003, 12847992	-109.10 (-176.85, -41.35)	1	-109.1
496	Shidfar, 2003, 12847992	15.20 (-43.85, 74.25)	1	15.2
497	Sirtori, 1997, 9174486	0.39 (0.30, 0.47)	2.57	0.151751

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Outcome classification
484	Shaikh 2014 25185754	Secondary
485	Shaikh 2014 25185754	Secondary
486	Shaikh 2014 25185754	Secondary
487	Shaikh 2014 25185754	Secondary
488	Shaikh 2014 25185754	Secondary
489	Shidfar, 2003, 12847992	Primary (stated)
490	Shidfar, 2003, 12847992	Primary (stated)
491	Shidfar, 2003, 12847992	Secondary
492	Shidfar, 2003, 12847992	Secondary
493	Shidfar, 2003, 12847992	Secondary
494	Shidfar, 2003, 12847992	Secondary
495	Shidfar, 2003, 12847992	Primary (stated)
496	Shidfar, 2003, 12847992	Primary (stated)
497	Sirtori, 1997, 9174486	Primary (power analysis)

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Study years (start date)	Country	Population
498	Sirtori, 1997, 9174486	nd	Italy	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
499	Sirtori, 1997, 9174486	nd	Italy	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
500	Soares, 2014, 24652053	2011	Brazil	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
501	Soares, 2014, 24652053	2011	Brazil	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
502	Soares, 2014, 24652053	2011	Brazil	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
503	Soares, 2014, 24652053	2011	Brazil	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
504	Soares, 2014, 24652053	2011	Brazil	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)

Row	Study	Risk type	Sample size (total)
498	Sirtori, 1997, 9174486	Diabetes and/or metabolic syndrome* ; Hypertension (Patients treated with antihypertensive drugs or who on more than one occasion in the past year had had a systolic blood pressure (SBP) 160 mm Hg, a diastolic blood pressure (DBP) 95 mm Hg, or both, independent of drug treatment, were considered to have arterial hypertension.); Dyslipidemia (Patients with significant and stable triacylglycerol elevations (> 2.26 mmollL, or 200 mg/dL) were selected. These were defined as type IIB if serum total cholesterol was > 7.21 mmol/L (270 mg/dL) and type IV if cholesterol was 7.21 mmol/L (270 mg/dL). Patients with total cholesterol concentrations > 7.76 mmollL (300 mg/dL) with triacylglycerol concentrations 4.52 mmolIL (400 mg/dL) were excluded for ethical reasons.); Other (Impaired glucose tolerance)	935
499	Sirtori, 1997, 9174486	Diabetes and/or metabolic syndrome ; Hypertension (Patients treated with antihypertensive drugs or who on more than one occasion in the past year had had a systolic blood pressure (SBP) >= 160 mm Hg, a diastolic blood pressure (DBP) >= 95 mm Hg, or both, independent of drug treatment, were considered to have arterial hypertension.); Dyslipidemia (Patients with significant and stable triacylglycerol elevations (> 2.26 mmollL, or 200 mg/dL) were selected. These were defined as type IIB if serum total cholesterol was > 7.21 mmol/L (270 mg/dL) and type IV if cholesterol was >= 7.21 mmol/L (270 mg/dL). Patients with total cholesterol concentrations > 7.76 mmollL (300 mg/dL) with triacylglycerol concentrations >= 4.52 mmolIL (400 mg/dL) were excluded for ethical reasons.); Other (Impaired glucose tolerance)	935
500	Soares, 2014, 24652053	Diabetes and/or metabolic syndrome* ; Hypertension (systolic arterial pressure (SAP) of 130 mmHg and a diastolic arterial pressure of 85 mmHg); Dyslipidemia (a triglyceride level of 150 mg/dL, and a high-density lipoprotein cholesterol (HDL-C) level of < 40 mg/dL for men and < 50 mg/dL for women); Obesity/Overweight (abdominal circumference (AC) of > 88 cm for women and > 102 cm for men)	70
501	Soares, 2014, 24652053	Diabetes and/or metabolic syndrome* ; Hypertension (systolic arterial pressure (SAP) of 130 mmHg and a diastolic arterial pressure of 85 mmHg); Dyslipidemia (a triglyceride level of 150 mg/dL, and a high-density lipoprotein cholesterol (HDL-C) level of < 40 mg/dL for men and < 50 mg/dL for women); Obesity/Overweight (abdominal circumference (AC) of > 88 cm for women and > 102 cm for men)	70
502	Soares, 2014, 24652053	Diabetes and/or metabolic syndrome ; Hypertension (systolic arterial pressure (SAP) of >= 130 mmHg and a diastolic arterial pressure of >= 85 mmHg); Dyslipidemia (a triglyceride level of >= 150 mg/dL, and a high-density lipoprotein cholesterol (HDL-C) level of < 40 mg/dL for men and < 50 mg/dL for women); Obesity/Overweight (abdominal circumference (AC) of > 88 cm for women and > 102 cm for men)	70
503	Soares, 2014, 24652053	Diabetes and/or metabolic syndrome ; Hypertension (systolic arterial pressure (SAP) of >= 130 mmHg and a diastolic arterial pressure of >= 85 mmHg); Dyslipidemia (a triglyceride level of >= 150 mg/dL, and a high-density lipoprotein cholesterol (HDL-C) level of < 40 mg/dL for men and < 50 mg/dL for women); Obesity/Overweight (abdominal circumference (AC) of > 88 cm for women and > 102 cm for men)	70
504	Soares, 2014, 24652053	Diabetes and/or metabolic syndrome ; Hypertension (systolic arterial pressure (SAP) of >= 130 mmHg and a diastolic arterial pressure of >= 85 mmHg); Dyslipidemia (a triglyceride level of >= 150 mg/dL, and a high-density lipoprotein cholesterol (HDL-C) level of < 40 mg/dL for men and < 50 mg/dL for women); Obesity/Overweight (abdominal circumference (AC) of > 88 cm for women and > 102 cm for men)	70

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Age mean (SD) [median] years	Sex (% male)	Race
498	Sirtori, 1997, 9174486	58.8 (8.99)	62.2	nd
499	Sirtori, 1997, 9174486	58.8 (8.99)	62.2	nd
500	Soares, 2014, 24652053	51.6 (13.4)	28.6	nd
501	Soares, 2014, 24652053	51.6 (13.4)	28.6	nd
502	Soares, 2014, 24652053	51.6 (13.4)	28.6	nd
503	Soares, 2014, 24652053	51.6 (13.4)	28.6	nd
504	Soares, 2014, 24652053	51.6 (13.4)	28.6	nd

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Blood pressure SBP/DBP mmHg
498	Sirtori, 1997, 9174486	nd
499	Sirtori, 1997, 9174486	nd
500	Soares, 2014, 24652053	134.4 (35.1)/85.3 (21.2)
501	Soares, 2014, 24652053	134.4 (35.1)/85.3 (21.2)
502	Soares, 2014, 24652053	134.4 (35.1)/85.3 (21.2)
503	Soares, 2014, 24652053	134.4 (35.1)/85.3 (21.2)
504	Soares, 2014, 24652053	134.4 (35.1)/85.3 (21.2)

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Lipids: Total cholesterol/LDL/HDL/Triglycerides mean (SD) mg/dL [mmol/L]
498	Sirtori, 1997, 9174486	nd
499	Sirtori, 1997, 9174486	nd
500	Soares, 2014, 24652053	nd/nd/47.3 (14.1)/199.6 (126.3)
501	Soares, 2014, 24652053	nd/nd/47.3 (14.1)/199.6 (126.3)
502	Soares, 2014, 24652053	nd/nd/47.3 (14.1)/199.6 (126.3)
503	Soares, 2014, 24652053	nd/nd/47.3 (14.1)/199.6 (126.3)
504	Soares, 2014, 24652053	nd/nd/47.3 (14.1)/199.6 (126.3)

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	BMI mean (SD) Kg/m2/Weight mean (SD) Kg	Baseline n-3 intake	n-3 source (Baseline)
498	Sirtori, 1997, 9174486	weight 73.7 (10.08)	nd	nd
499	Sirtori, 1997, 9174486	weight 73.7 (10.08)	nd	nd
500	Soares, 2014, 24652053	32.8 (8.1)	nd	nd
501	Soares, 2014, 24652053	32.8 (8.1)	nd	nd
502	Soares, 2014, 24652053	32.8 (8.1)	nd	nd
503	Soares, 2014, 24652053	32.8 (8.1)	nd	nd
504	Soares, 2014, 24652053	32.8 (8.1)	nd	nd

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	n-3 type(s)	n-3 measure	Study design	Outcome
498	Sirtori, 1997, 9174486	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	LDL-c
499	Sirtori, 1997, 9174486	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Tg
500	Soares, 2014, 24652053	EPA+DHA vs EPA	g/d	Trial: Randomized Factorial Design	HDL-c
501	Soares, 2014, 24652053	EPA+DHA vs Placebo	g/d	Trial: Randomized Factorial Design	HDL-c
502	Soares, 2014, 24652053	EPA+DHA vs Placebo	g/d	Trial: Randomized Factorial Design	HDL-c
503	Soares, 2014, 24652053	EPA+DHA vs Placebo	g/d	Trial: Randomized Factorial Design	HDL-c
504	Soares, 2014, 24652053	EPA+DHA vs Placebo	g/d	Trial: Randomized Factorial Design	SBP

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Reported effect Size	Dose/intake difference	Dose-corrected effect size
498	Sirtori, 1997, 9174486	6.56 (6.30, 6.83)	2.57	2.552529
499	Sirtori, 1997, 9174486	-37.17 (-37.84, -36.50)	2.57	-14.46303
500	Soares, 2014, 24652053	1.70 (-3.87, 7.26)	2.4	0.7083333
501	Soares, 2014, 24652053	9.30 (1.17, 17.43)	2.4	3.875
502	Soares, 2014, 24652053	-0.90 (-2.89, 1.09)	2.4	-0.375
503	Soares, 2014, 24652053	7.60 (5.36, 9.84)	2.4	3.166667
504	Soares, 2014, 24652053	0.6 (-1.5, 2.7)	3	0.2

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Outcome classification
498	Sirtori, 1997, 9174486	Primary (implied)
499	Sirtori, 1997, 9174486	Primary (implied)
500	Soares, 2014, 24652053	Secondary
501	Soares, 2014, 24652053	Secondary
502	Soares, 2014, 24652053	Secondary
503	Soares, 2014, 24652053	Secondary
504	Soares, 2014, 24652053	Secondary

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Study years (start date)	Country	Population
505	Soares, 2014, 24652053	2011	Brazil	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
506	Tardivo 2015 25394692	nd	Brazil	Primary Prevention, Healthy
507	Tardivo 2015 25394692	nd	Brazil	Primary Prevention, Healthy
508	Tardivo 2015 25394692	nd	Brazil	Primary Prevention, Healthy
509	Tardivo 2015 25394692	nd	Brazil	Primary Prevention, Healthy
510	Tardivo 2015 25394692	nd	Brazil	Primary Prevention, Healthy
511	Tatsuno, 2013, 24314359	2009	Japan	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
512	Tatsuno, 2013, 24314359	2009	Japan	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
513	Tatsuno, 2013, 24314359	2009	Japan	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
514	Tatsuno, 2013, 24314359	2009	Japan	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
515	Tatsuno, 2013, 24314359	2009	Japan	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
516	Tatsuno, 2013, 24314359	2009	Japan	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
517	Tatsuno, 2013, 24314359	2009	Japan	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
518	Tatsuno, 2013, 24314359	2009	Japan	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
519	Tatsuno, 2013, 24314359	2009	Japan	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
520	Tatsuno, 2013, 24314359	2009	Japan	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
521	Tatsuno, 2013, 24314359	2009	Japan	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)

Row	Study	Risk type	Sample size (total)
505	Soares, 2014, 24652053	Diabetes and/or metabolic syndrome ; Hypertension (systolic arterial pressure (SAP) of >= 130 mmHg and a diastolic arterial pressure of >= 85 mmHg); Dyslipidemia (a triglyceride level of >= 150 mg/dL, and a high-density lipoprotein cholesterol (HDL-C) level of < 40 mg/dL for men and < 50 mg/dL for women); Obesity/Overweight (abdominal circumference (AC) of > 88 cm for women and > 102 cm for men)	70
506	Tardivo 2015 25394692	na	87
507	Tardivo 2015 25394692	na	87
508	Tardivo 2015 25394692	na	87
509	Tardivo 2015 25394692	na	87
510	Tardivo 2015 25394692	na	87
511	Tatsuno, 2013, 24314359	Dyslipidemia (fasting triglyceride level >=150 mg/dL and <750 mg/dL at weeks 4 and 2 during the screening period)	611
512	Tatsuno, 2013, 24314359	Dyslipidemia (fasting triglyceride level >=150 mg/dL and <750 mg/dL at weeks 4 and 2 during the screening period)	611
513	Tatsuno, 2013, 24314359	Dyslipidemia (fasting triglyceride level >=150 mg/dL and <750 mg/dL at weeks 4 and 2 during the screening period)	611
514	Tatsuno, 2013, 24314359	Dyslipidemia (fasting triglyceride level >=150 mg/dL and <750 mg/dL at weeks 4 and 2 during the screening period)	611
515	Tatsuno, 2013, 24314359	Dyslipidemia (fasting triglyceride level >=150 mg/dL and <750 mg/dL at weeks 4 and 2 during the screening period)	611
516	Tatsuno, 2013, 24314359	Dyslipidemia (fasting triglyceride level >=150 mg/dL and <750 mg/dL at weeks 4 and 2 during the screening period)	611
517	Tatsuno, 2013, 24314359	Dyslipidemia (fasting triglyceride level >=150 mg/dL and <750 mg/dL at weeks 4 and 2 during the screening period)	611
518	Tatsuno, 2013, 24314359	Dyslipidemia (fasting triglyceride level >=150 mg/dL and <750 mg/dL at weeks 4 and 2 during the screening period)	611
519	Tatsuno, 2013, 24314359	Dyslipidemia (fasting triglyceride level >=150 mg/dL and <750 mg/dL at weeks 4 and 2 during the screening period)	611
520	Tatsuno, 2013, 24314359	Dyslipidemia (fasting triglyceride level >=150 mg/dL and <750 mg/dL at weeks 4 and 2 during the screening period)	611
521	Tatsuno, 2013, 24314359	Dyslipidemia (fasting triglyceride level >=150 mg/dL and <750 mg/dL at weeks 4 and 2 during the screening period)	611

Row	Study	Age mean (SD) [median] years	Sex (% male)	Race
505	Soares, 2014, 24652053	51.6 (13.4)	28.6	nd
506	Tardivo 2015 25394692	55.1 (6.9)	0	100 Hispanic
507	Tardivo 2015 25394692	55.1 (6.9)	0	100 Hispanic
508	Tardivo 2015 25394692	55.1 (6.9)	0	100 Hispanic
509	Tardivo 2015 25394692	55.1 (6.9)	0	100 Hispanic
510	Tardivo 2015 25394692	55.1 (6.9)	0	100 Hispanic
511	Tatsuno, 2013, 24314359	55.6 (10.5)	80.5	nd
512	Tatsuno, 2013, 24314359	55.6 (10.5)	80.5	nd
513	Tatsuno, 2013, 24314359	55.6 (10.5)	80.5	nd
514	Tatsuno, 2013, 24314359	55.6 (10.5)	80.5	nd
515	Tatsuno, 2013, 24314359	55.6 (10.5)	80.5	nd
516	Tatsuno, 2013, 24314359	55.6 (10.5)	80.5	nd
517	Tatsuno, 2013, 24314359	55.6 (10.5)	80.5	nd
518	Tatsuno, 2013, 24314359	55.6 (10.5)	80.5	nd
519	Tatsuno, 2013, 24314359	55.6 (10.5)	80.5	nd
520	Tatsuno, 2013, 24314359	55.6 (10.5)	80.5	nd
521	Tatsuno, 2013, 24314359	55.6 (10.5)	80.5	nd

Row	Study	Blood pressure SBP/DBP mmHg
505	Soares, 2014, 24652053	134.4 (35.1)/85.3 (21.2)
506	Tardivo 2015 25394692	137.2 (13.4)/85.8 (7.9)
507	Tardivo 2015 25394692	137.2 (13.4)/85.8 (7.9)
508	Tardivo 2015 25394692	137.2 (13.4)/85.8 (7.9)
509	Tardivo 2015 25394692	137.2 (13.4)/85.8 (7.9)
510	Tardivo 2015 25394692	137.2 (13.4)/85.8 (7.9)
511	Tatsuno, 2013, 24314359	nd
512	Tatsuno, 2013, 24314359	nd
513	Tatsuno, 2013, 24314359	nd
514	Tatsuno, 2013, 24314359	nd
515	Tatsuno, 2013, 24314359	nd
516	Tatsuno, 2013, 24314359	nd
517	Tatsuno, 2013, 24314359	nd
518	Tatsuno, 2013, 24314359	nd
519	Tatsuno, 2013, 24314359	nd
520	Tatsuno, 2013, 24314359	nd
521	Tatsuno, 2013, 24314359	nd

Row	Study	Lipids: Total cholesterol/LDL/HDL/Triglycerides mean (SD) mg/dL [mmol/L]
505	Soares, 2014, 24652053	nd/nd/47.3 (14.1)/199.6 (126.3)
506	Tardivo 2015 25394692	220.3 (36.4)/134.6(32.3)/45.3 (7.3)/190.6 (61.6)
507	Tardivo 2015 25394692	220.3 (36.4)/134.6(32.3)/45.3 (7.3)/190.6 (61.6)
508	Tardivo 2015 25394692	220.3 (36.4)/134.6(32.3)/45.3 (7.3)/190.6 (61.6)
509	Tardivo 2015 25394692	220.3 (36.4)/134.6(32.3)/45.3 (7.3)/190.6 (61.6)
510	Tardivo 2015 25394692	220.3 (36.4)/134.6(32.3)/45.3 (7.3)/190.6 (61.6)
511	Tatsuno, 2013, 24314359	nd/130.1 (30.5)/ /271.8 (91.53)
512	Tatsuno, 2013, 24314359	nd/130.1 (30.5)/ /271.8 (91.53)
513	Tatsuno, 2013, 24314359	nd/130.1 (30.5)/ /271.8 (91.53)
514	Tatsuno, 2013, 24314359	nd/130.1 (30.5)/ /271.8 (91.53)
515	Tatsuno, 2013, 24314359	nd/130.1 (30.5)/ /271.8 (91.53)
516	Tatsuno, 2013, 24314359	nd/130.1 (30.5)/ /271.8 (91.53)
517	Tatsuno, 2013, 24314359	nd/130.1 (30.5)/ /271.8 (91.53)
518	Tatsuno, 2013, 24314359	nd/130.1 (30.5)/ /271.8 (91.53)
519	Tatsuno, 2013, 24314359	nd/130.1 (30.5)/ /271.8 (91.53)
520	Tatsuno, 2013, 24314359	nd/130.1 (30.5)/ /271.8 (91.53)
521	Tatsuno, 2013, 24314359	nd/130.1 (30.5)/ /271.8 (91.53)

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	BMI mean (SD) Kg/m2/Weight mean (SD) Kg	Baseline n-3 intake	n-3 source (Baseline)
505	Soares, 2014, 24652053	32.8 (8.1)	nd	nd
506	Tardivo 2015 25394692	32.4 (4.7)	nd	nd
507	Tardivo 2015 25394692	32.4 (4.7)	nd	nd
508	Tardivo 2015 25394692	32.4 (4.7)	nd	nd
509	Tardivo 2015 25394692	32.4 (4.7)	nd	nd
510	Tardivo 2015 25394692	32.4 (4.7)	nd	nd
511	Tatsuno, 2013, 24314359	26.3 (3.6)	ALA: 195 (nd) µg/mL, EPA: 73 (nd) µg/mL, DHA: 184 (nd) µg/mL	plasma
512	Tatsuno, 2013, 24314359	26.3 (3.6)	ALA: 195 (nd) µg/mL, EPA: 73 (nd) µg/mL, DHA: 184 (nd) µg/mL	plasma
513	Tatsuno, 2013, 24314359	26.3 (3.6)	ALA: 195 (nd) µg/mL, EPA: 73 (nd) µg/mL, DHA: 184 (nd) µg/mL	plasma
514	Tatsuno, 2013, 24314359	26.3 (3.6)	ALA: 195 (nd) µg/mL, EPA: 73 (nd) µg/mL, DHA: 184 (nd) µg/mL	plasma
515	Tatsuno, 2013, 24314359	26.3 (3.6)	ALA: 195 (nd) µg/mL, EPA: 73 (nd) µg/mL, DHA: 184 (nd) µg/mL	plasma
516	Tatsuno, 2013, 24314359	26.3 (3.6)	ALA: 195 (nd) µg/mL, EPA: 73 (nd) µg/mL, DHA: 184 (nd) µg/mL	plasma
517	Tatsuno, 2013, 24314359	26.3 (3.6)	ALA: 195 (nd) µg/mL, EPA: 73 (nd) µg/mL, DHA: 184 (nd) µg/mL	plasma
518	Tatsuno, 2013, 24314359	26.3 (3.6)	ALA: 195 (nd) µg/mL, EPA: 73 (nd) µg/mL, DHA: 184 (nd) µg/mL	plasma
519	Tatsuno, 2013, 24314359	26.3 (3.6)	ALA: 195 (nd) µg/mL, EPA: 73 (nd) µg/mL, DHA: 184 (nd) µg/mL	plasma
520	Tatsuno, 2013, 24314359	26.3 (3.6)	ALA: 195 (nd) µg/mL, EPA: 73 (nd) µg/mL, DHA: 184 (nd) µg/mL	plasma
521	Tatsuno, 2013, 24314359	26.3 (3.6)	ALA: 195 (nd) µg/mL, EPA: 73 (nd) µg/mL, DHA: 184 (nd) µg/mL	plasma

Row	Study	n-3 type(s)	n-3 measure	Study design	Outcome
505	Soares, 2014, 24652053	EPA+DHA vs EPA	µg/mL	Trial: Randomized Factorial Design	SBP
506	Tardivo 2015 25394692	EPA+DHA (0.9) vs Placebo	g/d	Trial: Randomized Parallel	HDL-c
507	Tardivo 2015 25394692	EPA+DHA (0.9) vs Placebo	g/d	Trial: Randomized Parallel	LDL-c
508	Tardivo 2015 25394692	EPA+DHA (0.9) vs Placebo	g/d	Trial: Randomized Parallel	Tg
509	Tardivo 2015 25394692	EPA+DHA (0.9) vs Placebo	g/d	Trial: Randomized Parallel	SBP
510	Tardivo 2015 25394692	EPA+DHA (0.9) vs Placebo	g/d	Trial: Randomized Parallel	DBP
511	Tatsuno, 2013, 24314359	EPA+DHA vs EPA	g/d	Trial: Randomized Parallel	LDL:HDL-c ratio
512	Tatsuno, 2013, 24314359	EPA+DHA vs EPA	g/d	Trial: Randomized Parallel	LDL:HDL-c ratio
513	Tatsuno, 2013, 24314359	EPA+DHA vs EPA	g/d	Trial: Randomized Parallel	LDL:HDL-c ratio
514	Tatsuno, 2013, 24314359	EPA+DHA vs EPA	g/d	Trial: Randomized Parallel	LDL:HDL-c ratio
515	Tatsuno, 2013, 24314359	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Parallel	LDL:HDL-c ratio
516	Tatsuno, 2013, 24314359	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Parallel	Total:HDL-c ratio
517	Tatsuno, 2013, 24314359	EPA+DHA vs EPA	g/d	Trial: Randomized Parallel	Total:HDL-c ratio
518	Tatsuno, 2013, 24314359	EPA+DHA vs EPA	g/d	Trial: Randomized Parallel	Total:HDL-c ratio
519	Tatsuno, 2013, 24314359	EPA+DHA vs EPA	g/d	Trial: Randomized Parallel	HDL-c
520	Tatsuno, 2013, 24314359	EPA+DHA vs EPA	g/d	Trial: Randomized Parallel	HDL-c
521	Tatsuno, 2013, 24314359	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Parallel	HDL-c

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Reported effect Size	Dose/intake difference	Dose-corrected effect size
505	Soares, 2014, 24652053	3.8 (1.2, 6.4)	3	1.266667
506	Tardivo 2015 25394692	0 (-3.48, 3.48)	0.9	0
507	Tardivo 2015 25394692	-5.7 (-20.72, 9.32)	0.9	-6.33
508	Tardivo 2015 25394692	-26 (-50.91, -1.09)	0.9	-28.89
509	Tardivo 2015 25394692	-13.9 (-20.92, -6.88)	0.9	-15.44
510	Tardivo 2015 25394692	-5.7 (-8.52, -2.88)	0.9	-6.33
511	Tatsuno, 2013, 24314359	1.8 (-2.4, 5.9)	NA	
512	Tatsuno, 2013, 24314359	-0.9 (-4.5, 2.8)	NA	
513	Tatsuno, 2013, 24314359	1.8% (−2.4, 5.9)	NA	
514	Tatsuno, 2013, 24314359	−0.9% (−4.5, 2.8)	NA	
515	Tatsuno, 2013, 24314359	2.6% (−1.5, 6.7)	1.68	
516	Tatsuno, 2013, 24314359	−0.5% (−3.9, 2.9)	NA	
517	Tatsuno, 2013, 24314359	-1.4 (-4.9, 2.1)	NA	
518	Tatsuno, 2013, 24314359	-0.9 (-3.9, 2.2)	NA	
519	Tatsuno, 2013, 24314359	0.30 (-1.72, 2.32)	NA	
520	Tatsuno, 2013, 24314359	1.30 (-0.74, 3.34)	NA	
521	Tatsuno, 2013, 24314359	1.00 (-0.98, 2.98)	1.68	0.5952381

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Outcome classification
505	Soares, 2014, 24652053	Secondary
506	Tardivo 2015 25394692	Secondary
507	Tardivo 2015 25394692	Secondary
508	Tardivo 2015 25394692	Secondary
509	Tardivo 2015 25394692	Secondary
510	Tardivo 2015 25394692	Secondary
511	Tatsuno, 2013, 24314359	Secondary
512	Tatsuno, 2013, 24314359	Secondary
513	Tatsuno, 2013, 24314359	Secondary
514	Tatsuno, 2013, 24314359	Secondary
515	Tatsuno, 2013, 24314359	Secondary
516	Tatsuno, 2013, 24314359	Secondary
517	Tatsuno, 2013, 24314359	Secondary
518	Tatsuno, 2013, 24314359	Secondary
519	Tatsuno, 2013, 24314359	Secondary
520	Tatsuno, 2013, 24314359	Secondary
521	Tatsuno, 2013, 24314359	Secondary

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Study years (start date)	Country	Population
522	Tatsuno, 2013, 24314359	2009	Japan	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
523	Tatsuno, 2013, 24314359	2009	Japan	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
524	Tatsuno, 2013, 24314359	2009	Japan	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
525	Tatsuno, 2013, 24314359	2009	Japan	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
526	Tatsuno, 2013, 24314359	2009	Japan	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
527	Tatsuno, 2013, 24314359	2009	Japan	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
528	Tatsuno, 2013, 24314359	2009	Japan	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
529	Tatsuno, 2013, 24314359	2009	Japan	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
530	Tatsuno, 2013, 24314359	2009	Japan	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
531	Tatsuno, 2013, 24314359	2009	Japan	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
532	Tatsuno, 2013, 24314359	2009	Japan	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
533	Tatsuno, 2013, 24314359	2009	Japan	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
534	Tavazzi, 2008, 18757090	2002	Italy	Secondary Prevention (history of CVD event)
535	Tavazzi, 2008, 18757090	2002	Italy	Secondary Prevention (history of CVD event)
536	Tavazzi, 2008, 18757090	2002	Italy	Secondary Prevention (history of CVD event)

Row	Study	Risk type	Sample size (total)
522	Tatsuno, 2013, 24314359	Dyslipidemia (fasting triglyceride level >=150 mg/dL and <750 mg/dL at weeks 4 and 2 during the screening period)	611
523	Tatsuno, 2013, 24314359	Dyslipidemia (fasting triglyceride level >=150 mg/dL and <750 mg/dL at weeks 4 and 2 during the screening period)	611
524	Tatsuno, 2013, 24314359	Dyslipidemia (fasting triglyceride level >=150 mg/dL and <750 mg/dL at weeks 4 and 2 during the screening period)	611
525	Tatsuno, 2013, 24314359	Dyslipidemia (fasting triglyceride level >=150 mg/dL and <750 mg/dL at weeks 4 and 2 during the screening period)	611
526	Tatsuno, 2013, 24314359	Dyslipidemia (fasting triglyceride level >=150 mg/dL and <750 mg/dL at weeks 4 and 2 during the screening period)	611
527	Tatsuno, 2013, 24314359	Dyslipidemia (fasting triglyceride level >=150 mg/dL and <750 mg/dL at weeks 4 and 2 during the screening period)	611
528	Tatsuno, 2013, 24314359	Dyslipidemia (fasting triglyceride level >=150 mg/dL and <750 mg/dL at weeks 4 and 2 during the screening period)	611
529	Tatsuno, 2013, 24314359	Dyslipidemia (fasting triglyceride level >=150 mg/dL and <750 mg/dL at weeks 4 and 2 during the screening period)	611
530	Tatsuno, 2013, 24314359	Dyslipidemia (fasting triglyceride level >=150 mg/dL and <750 mg/dL at weeks 4 and 2 during the screening period)	611
531	Tatsuno, 2013, 24314359	Dyslipidemia (fasting triglyceride level >=150 mg/dL and <750 mg/dL at weeks 4 and 2 during the screening period)	611
532	Tatsuno, 2013, 24314359	Dyslipidemia (fasting triglyceride level >=150 mg/dL and <750 mg/dL at weeks 4 and 2 during the screening period)	611
533	Tatsuno, 2013, 24314359	Dyslipidemia (fasting triglyceride level >=150 mg/dL and <750 mg/dL at weeks 4 and 2 during the screening period)	611
534	Tavazzi, 2008, 18757090	Cardiac disease (symptomatic heart failure of any cause and with any level of left ventricular ejection fraction (LVEF))	6975
535	Tavazzi, 2008, 18757090	Cardiac disease (symptomatic heart failure of any cause and with any level of left ventricular ejection fraction (LVEF))	6975
536	Tavazzi, 2008, 18757090	Cardiac disease (symptomatic heart failure of any cause and with any level of left ventricular ejection fraction (LVEF))	6975

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Age mean (SD) [median] years	Sex (% male)	Race
522	Tatsuno, 2013, 24314359	55.6 (10.5)	80.5	nd
523	Tatsuno, 2013, 24314359	55.6 (10.5)	80.5	nd
524	Tatsuno, 2013, 24314359	55.6 (10.5)	80.5	nd
525	Tatsuno, 2013, 24314359	55.6 (10.5)	80.5	nd
526	Tatsuno, 2013, 24314359	55.6 (10.5)	80.5	nd
527	Tatsuno, 2013, 24314359	55.6 (10.5)	80.5	nd
528	Tatsuno, 2013, 24314359	55.6 (10.5)	80.5	nd
529	Tatsuno, 2013, 24314359	55.6 (10.5)	80.5	nd
530	Tatsuno, 2013, 24314359	55.6 (10.5)	80.5	nd
531	Tatsuno, 2013, 24314359	55.6 (10.5)	80.5	nd
532	Tatsuno, 2013, 24314359	55.6 (10.5)	80.5	nd
533	Tatsuno, 2013, 24314359	55.6 (10.5)	80.5	nd
534	Tavazzi, 2008, 18757090	67 (11)	78.8	nd
535	Tavazzi, 2008, 18757090	67 (11)	78.8	nd
536	Tavazzi, 2008, 18757090	67 (11)	78.8	nd

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Blood pressure SBP/DBP mmHg
522	Tatsuno, 2013, 24314359	nd
523	Tatsuno, 2013, 24314359	nd
524	Tatsuno, 2013, 24314359	nd
525	Tatsuno, 2013, 24314359	nd
526	Tatsuno, 2013, 24314359	nd
527	Tatsuno, 2013, 24314359	nd
528	Tatsuno, 2013, 24314359	nd
529	Tatsuno, 2013, 24314359	nd
530	Tatsuno, 2013, 24314359	nd
531	Tatsuno, 2013, 24314359	nd
532	Tatsuno, 2013, 24314359	nd
533	Tatsuno, 2013, 24314359	nd
534	Tavazzi, 2008, 18757090	126 (18)/77 (10)
535	Tavazzi, 2008, 18757090	126 (18)/77 (10)
536	Tavazzi, 2008, 18757090	126 (18)/77 (10)

Row	Study	Lipids: Total cholesterol/LDL/HDL/Triglycerides mean (SD) mg/dL [mmol/L]
522	Tatsuno, 2013, 24314359	nd/130.1 (30.5)/ /271.8 (91.53)
523	Tatsuno, 2013, 24314359	nd/130.1 (30.5)/ /271.8 (91.53)
524	Tatsuno, 2013, 24314359	nd/130.1 (30.5)/ /271.8 (91.53)
525	Tatsuno, 2013, 24314359	nd/130.1 (30.5)/ /271.8 (91.53)
526	Tatsuno, 2013, 24314359	nd/130.1 (30.5)/ /271.8 (91.53)
527	Tatsuno, 2013, 24314359	nd/130.1 (30.5)/ /271.8 (91.53)
528	Tatsuno, 2013, 24314359	nd/130.1 (30.5)/ /271.8 (91.53)
529	Tatsuno, 2013, 24314359	nd/130.1 (30.5)/ /271.8 (91.53)
530	Tatsuno, 2013, 24314359	nd/130.1 (30.5)/ /271.8 (91.53)
531	Tatsuno, 2013, 24314359	nd/130.1 (30.5)/ /271.8 (91.53)
532	Tatsuno, 2013, 24314359	nd/130.1 (30.5)/ /271.8 (91.53)
533	Tatsuno, 2013, 24314359	nd/130.1 (30.5)/ /271.8 (91.53)
534	Tavazzi, 2008, 18757090	nd[median 1.42 (1.05, 1.98)]
535	Tavazzi, 2008, 18757090	nd[median 1.42 (1.05, 1.98)]
536	Tavazzi, 2008, 18757090	nd[median 1.42 (1.05, 1.98)]

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	BMI mean (SD) Kg/m2/Weight mean (SD) Kg	Baseline n-3 intake	n-3 source (Baseline)
522	Tatsuno, 2013, 24314359	26.3 (3.6)	ALA: 195 (nd) µg/mL, EPA: 73 (nd) µg/mL, DHA: 184 (nd) µg/mL	plasma
523	Tatsuno, 2013, 24314359	26.3 (3.6)	ALA: 195 (nd) µg/mL, EPA: 73 (nd) µg/mL, DHA: 184 (nd) µg/mL	plasma
524	Tatsuno, 2013, 24314359	26.3 (3.6)	ALA: 195 (nd) µg/mL, EPA: 73 (nd) µg/mL, DHA: 184 (nd) µg/mL	plasma
525	Tatsuno, 2013, 24314359	26.3 (3.6)	ALA: 195 (nd) µg/mL, EPA: 73 (nd) µg/mL, DHA: 184 (nd) µg/mL	plasma
526	Tatsuno, 2013, 24314359	26.3 (3.6)	ALA: 195 (nd) µg/mL, EPA: 73 (nd) µg/mL, DHA: 184 (nd) µg/mL	plasma
527	Tatsuno, 2013, 24314359	26.3 (3.6)	ALA: 195 (nd) µg/mL, EPA: 73 (nd) µg/mL, DHA: 184 (nd) µg/mL	plasma
528	Tatsuno, 2013, 24314359	26.3 (3.6)	ALA: 195 (nd) µg/mL, EPA: 73 (nd) µg/mL, DHA: 184 (nd) µg/mL	plasma
529	Tatsuno, 2013, 24314359	26.3 (3.6)	ALA: 195 (nd) µg/mL, EPA: 73 (nd) µg/mL, DHA: 184 (nd) µg/mL	plasma
530	Tatsuno, 2013, 24314359	26.3 (3.6)	ALA: 195 (nd) µg/mL, EPA: 73 (nd) µg/mL, DHA: 184 (nd) µg/mL	plasma
531	Tatsuno, 2013, 24314359	26.3 (3.6)	ALA: 195 (nd) µg/mL, EPA: 73 (nd) µg/mL, DHA: 184 (nd) µg/mL	plasma
532	Tatsuno, 2013, 24314359	26.3 (3.6)	ALA: 195 (nd) µg/mL, EPA: 73 (nd) µg/mL, DHA: 184 (nd) µg/mL	plasma
533	Tatsuno, 2013, 24314359	26.3 (3.6)	ALA: 195 (nd) µg/mL, EPA: 73 (nd) µg/mL, DHA: 184 (nd) µg/mL	plasma
534	Tavazzi, 2008, 18757090	27 (5)	EPA: 0.85 (0.77) mol%, DPA: 0.78 (0.32) mol%, DHA: 3.4 (1.2) mol%	plasma
535	Tavazzi, 2008, 18757090	27 (5)	EPA: 0.85 (0.77) mol%, DPA: 0.78 (0.32) mol%, DHA: 3.4 (1.2) mol%	plasma
536	Tavazzi, 2008, 18757090	27 (5)	EPA: 0.85 (0.77) mol%, DPA: 0.78 (0.32) mol%, DHA: 3.4 (1.2) mol%	plasma

Row	Study	n-3 type(s)	n-3 measure	Study design	Outcome
522	Tatsuno, 2013, 24314359	EPA+DHA vs EPA	g/d	Trial: Randomized Parallel	LDL-c
523	Tatsuno, 2013, 24314359	EPA+DHA vs EPA	g/d	Trial: Randomized Parallel	LDL-c
524	Tatsuno, 2013, 24314359	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Parallel	LDL-c
525	Tatsuno, 2013, 24314359	EPA+DHA vs EPA	g/d	Trial: Randomized Parallel	Tg
526	Tatsuno, 2013, 24314359	EPA+DHA vs EPA	g/d	Trial: Randomized Parallel	Tg
527	Tatsuno, 2013, 24314359	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Parallel	Tg
528	Tatsuno, 2013, 24314359	EPA+DHA vs EPA	g/d	Trial: Randomized Parallel	SBP
529	Tatsuno, 2013, 24314359	EPA+DHA vs EPA	g/d	Trial: Randomized Parallel	SBP
530	Tatsuno, 2013, 24314359	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Parallel	SBP
531	Tatsuno, 2013, 24314359	EPA+DHA vs EPA+DHA	g/d	Trial: Randomized Parallel	DBP
532	Tatsuno, 2013, 24314359	EPA+DHA vs EPA	g/d	Trial: Randomized Parallel	DBP
533	Tatsuno, 2013, 24314359	EPA+DHA vs EPA	g/d	Trial: Randomized Parallel	DBP
534	Tavazzi, 2008, 18757090	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Atrial fibrillation
535	Tavazzi, 2008, 18757090	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Death, all cause
536	Tavazzi, 2008, 18757090	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Death, CVD (total)

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Reported effect Size	Dose/intake difference	Dose-corrected effect size
522	Tatsuno, 2013, 24314359	3.40 (-2.58, 9.38)	NA	
523	Tatsuno, 2013, 24314359	4.70 (-1.08, 10.48)	NA	
524	Tatsuno, 2013, 24314359	1.30 (-4.40, 7.00)	1.68	0.7738096
525	Tatsuno, 2013, 24314359	-24.80 (-42.22, -7.38)	NA	
526	Tatsuno, 2013, 24314359	-35.00 (-53.35, -16.65)	NA	
527	Tatsuno, 2013, 24314359	-37.20 (-53.86, -20.54)	1.68	-22.14286
528	Tatsuno, 2013, 24314359	2.6 (nd)	NA	
529	Tatsuno, 2013, 24314359	1.0 (nd)	NA	
530	Tatsuno, 2013, 24314359	1.6 (nd)	1.68	0.952381
531	Tatsuno, 2013, 24314359	0.4 (nd)	1.68	0.2380952
532	Tatsuno, 2013, 24314359	−0.8 (nd)	NA	
533	Tatsuno, 2013, 24314359	−1.2 (nd)	NA	
534	Tavazzi, 2008, 18757090	HR 1.10 (0.96, 1.25)	0.866	1.116343
535	Tavazzi, 2008, 18757090	Adj HR 0.91 (0.833, 0.998)	0.866	0.8968167
536	Tavazzi, 2008, 18757090	Adjusted HR 0.90 (0.81-0.99)b	0.866	0.8854464

Row	Study	Outcome classification
522	Tatsuno, 2013, 24314359	Secondary
523	Tatsuno, 2013, 24314359	Secondary
524	Tatsuno, 2013, 24314359	Secondary
525	Tatsuno, 2013, 24314359	Secondary
526	Tatsuno, 2013, 24314359	Secondary
527	Tatsuno, 2013, 24314359	Secondary
528	Tatsuno, 2013, 24314359	Secondary
529	Tatsuno, 2013, 24314359	Secondary
530	Tatsuno, 2013, 24314359	Secondary
531	Tatsuno, 2013, 24314359	Secondary
532	Tatsuno, 2013, 24314359	Secondary
533	Tatsuno, 2013, 24314359	Secondary
534	Tavazzi, 2008, 18757090	Secondary
535	Tavazzi, 2008, 18757090	Primary (stated)
536	Tavazzi, 2008, 18757090	Secondary

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Study years (start date)	Country	Population
537	Tavazzi, 2008, 18757090	2002	Italy	Secondary Prevention (history of CVD event)
538	Tavazzi, 2008, 18757090	2002	Italy	Secondary Prevention (history of CVD event)
539	Tavazzi, 2008, 18757090	2002	Italy	Secondary Prevention (history of CVD event)
540	Tavazzi, 2008, 18757090	2002	Italy	Secondary Prevention (history of CVD event)
541	Tavazzi, 2008, 18757090	2002	Italy	Secondary Prevention (history of CVD event)
542	Tavazzi, 2008, 18757090	2002	Italy	Secondary Prevention (history of CVD event)
543	Tavazzi, 2008, 18757090	2002	Italy	Secondary Prevention (history of CVD event)
544	Tavazzi, 2008, 18757090	2002	Italy	Secondary Prevention (history of CVD event)
545	Tavazzi, 2008, 18757090	2002	Italy	Secondary Prevention (history of CVD event)
546	Tierney, 2011, 20938439	2004	Netherlands, Norway, Sweden, UK, Ireland, France, Poland, Spain	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
547	Tierney, 2011, 20938439	2004	Netherlands, Norway, Sweden, UK, Ireland, France, Poland, Spain	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)

Row	Study	Risk type	Sample size (total)
537	Tavazzi, 2008, 18757090	Cardiac disease (symptomatic heart failure of any cause and with any level of left ventricular ejection fraction (LVEF))	6975
538	Tavazzi, 2008, 18757090	Cardiac disease (symptomatic heart failure of any cause and with any level of left ventricular ejection fraction (LVEF))	6975
539	Tavazzi, 2008, 18757090	Cardiac disease (symptomatic heart failure of any cause and with any level of left ventricular ejection fraction (LVEF))	6975
540	Tavazzi, 2008, 18757090	Cardiac disease (symptomatic heart failure of any cause and with any level of left ventricular ejection fraction (LVEF))	6975
541	Tavazzi, 2008, 18757090	Cardiac disease (symptomatic heart failure of any cause and with any level of left ventricular ejection fraction (LVEF))	6975
542	Tavazzi, 2008, 18757090	Cardiac disease (symptomatic heart failure of any cause and with any level of left ventricular ejection fraction (LVEF))	6975
543	Tavazzi, 2008, 18757090	Cardiac disease (symptomatic heart failure of any cause and with any level of left ventricular ejection fraction (LVEF))	6975
544	Tavazzi, 2008, 18757090	Cardiac disease (symptomatic heart failure of any cause and with any level of left ventricular ejection fraction (LVEF))	6975
545	Tavazzi, 2008, 18757090	Cardiac disease (symptomatic heart failure of any cause and with any level of left ventricular ejection fraction (LVEF))	6975
546	Tierney, 2011, 20938439	Diabetes and/or metabolic syndrome	206
547	Tierney, 2011, 20938439	Diabetes and/or metabolic syndrome	206

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Age mean (SD) [median] years	Sex (% male)	Race
537	Tavazzi, 2008, 18757090	67 (11)	78.8	nd
538	Tavazzi, 2008, 18757090	67 (11)	78.8	nd
539	Tavazzi, 2008, 18757090	67 (11)	78.8	nd
540	Tavazzi, 2008, 18757090	67 (11)	78.8	nd
541	Tavazzi, 2008, 18757090	67 (11)	78.8	nd
542	Tavazzi, 2008, 18757090	67 (11)	78.8	nd
543	Tavazzi, 2008, 18757090	67 (11)	78.8	nd
544	Tavazzi, 2008, 18757090	67 (11)	78.8	nd
545	Tavazzi, 2008, 18757090	67 (11)	78.8	nd
546	Tierney, 2011, 20938439	54.7 (SE 0.91)	80	nd
547	Tierney, 2011, 20938439	54.7 (SE 0.91)	80	nd

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Blood pressure SBP/DBP mmHg
537	Tavazzi, 2008, 18757090	126 (18)/77 (10)
538	Tavazzi, 2008, 18757090	126 (18)/77 (10)
539	Tavazzi, 2008, 18757090	126 (18)/77 (10)
540	Tavazzi, 2008, 18757090	126 (18)/77 (10)
541	Tavazzi, 2008, 18757090	126 (18)/77 (10)
542	Tavazzi, 2008, 18757090	126 (18)/77 (10)
543	Tavazzi, 2008, 18757090	126 (18)/77 (10)
544	Tavazzi, 2008, 18757090	126 (18)/77 (10)
545	Tavazzi, 2008, 18757090	126 (18)/77 (10)
546	Tierney, 2011, 20938439	139.53 (SE 1.46)/85.50 (SE 0.87)
547	Tierney, 2011, 20938439	139.53 (SE 1.46)/85.50 (SE 0.87)

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Lipids: Total cholesterol/LDL/HDL/Triglycerides mean (SD) mg/dL [mmol/L]
537	Tavazzi, 2008, 18757090	nd[median 1.42 (1.05, 1.98)]
538	Tavazzi, 2008, 18757090	nd[median 1.42 (1.05, 1.98)]
539	Tavazzi, 2008, 18757090	nd[median 1.42 (1.05, 1.98)]
540	Tavazzi, 2008, 18757090	nd[median 1.42 (1.05, 1.98)]
541	Tavazzi, 2008, 18757090	nd[median 1.42 (1.05, 1.98)]
542	Tavazzi, 2008, 18757090	nd[median 1.42 (1.05, 1.98)]
543	Tavazzi, 2008, 18757090	nd[median 1.42 (1.05, 1.98)]
544	Tavazzi, 2008, 18757090	nd[median 1.42 (1.05, 1.98)]
545	Tavazzi, 2008, 18757090	nd[median 1.42 (1.05, 1.98)]
546	Tierney, 2011, 20938439	[5.22 (SE 0.10)]/[3.17 (SE 0.11)]/[1.09 (SE 0.03)]/[1.67 (SE 0.10)]
547	Tierney, 2011, 20938439	[5.22 (SE 0.10)]/[3.17 (SE 0.11)]/[1.09 (SE 0.03)]/[1.67 (SE 0.10)]

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	BMI mean (SD) Kg/m2/Weight mean (SD) Kg	Baseline n-3 intake	n-3 source (Baseline)
537	Tavazzi, 2008, 18757090	27 (5)	EPA: 0.85 (0.77) mol%, DPA: 0.78 (0.32) mol%, DHA: 3.4 (1.2) mol%	plasma
538	Tavazzi, 2008, 18757090	27 (5)	EPA: 0.85 (0.77) mol%, DPA: 0.78 (0.32) mol%, DHA: 3.4 (1.2) mol%	plasma
539	Tavazzi, 2008, 18757090	27 (5)	EPA: 0.85 (0.77) mol%, DPA: 0.78 (0.32) mol%, DHA: 3.4 (1.2) mol%	plasma
540	Tavazzi, 2008, 18757090	27 (5)	EPA: 0.85 (0.77) mol%, DPA: 0.78 (0.32) mol%, DHA: 3.4 (1.2) mol%	plasma
541	Tavazzi, 2008, 18757090	27 (5)	EPA: 0.85 (0.77) mol%, DPA: 0.78 (0.32) mol%, DHA: 3.4 (1.2) mol%	plasma
542	Tavazzi, 2008, 18757090	27 (5)	EPA: 0.85 (0.77) mol%, DPA: 0.78 (0.32) mol%, DHA: 3.4 (1.2) mol%	plasma
543	Tavazzi, 2008, 18757090	27 (5)	EPA: 0.85 (0.77) mol%, DPA: 0.78 (0.32) mol%, DHA: 3.4 (1.2) mol%	plasma
544	Tavazzi, 2008, 18757090	27 (5)	EPA: 0.85 (0.77) mol%, DPA: 0.78 (0.32) mol%, DHA: 3.4 (1.2) mol%	plasma
545	Tavazzi, 2008, 18757090	27 (5)	EPA: 0.85 (0.77) mol%, DPA: 0.78 (0.32) mol%, DHA: 3.4 (1.2) mol%	plasma
546	Tierney, 2011, 20938439	32.51 (SE 0.42)/91.96 (SE 1.38)	nd	nd
547	Tierney, 2011, 20938439	32.51 (SE 0.42)/91.96 (SE 1.38)	nd	nd

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	n-3 type(s)	n-3 measure	Study design	Outcome
537	Tavazzi, 2008, 18757090	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Death, stroke
538	Tavazzi, 2008, 18757090	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	MACE
539	Tavazzi, 2008, 18757090	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Myocardial infarction
540	Tavazzi, 2008, 18757090	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Stroke
541	Tavazzi, 2008, 18757090	ALA+DHA+EPA vs Placebo	g/d	Trial: Randomized Parallel	Sudden cardiac death
542	Tavazzi, 2008, 18757090	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	HDL-c
543	Tavazzi, 2008, 18757090	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	LDL-c
544	Tavazzi, 2008, 18757090	ALA+EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	SBP
545	Tavazzi, 2008, 18757090	ALA+EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	DBP
546	Tierney, 2011, 20938439	ALA+EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	HDL-c
547	Tierney, 2011, 20938439	ALA+EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	LDL-c

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Reported effect Size	Dose/intake difference	Dose-corrected effect size
537	Tavazzi, 2008, 18757090	OR 1.13 (0.75, 1.71)	0.866	1.151573
538	Tavazzi, 2008, 18757090	HR 0.92 (0.85, 0.999)	0.866	0.9082064
539	Tavazzi, 2008, 18757090	Adj HR 0.82 (0.63-1.06)	0.866	0.7952028
540	Tavazzi, 2008, 18757090	HR 1.16 (0.89, 1.51)	0.866	1.186948
541	Tavazzi, 2008, 18757090	OR 0.94 (0.79, 1.1)	0.866	0.9310431
542	Tavazzi, 2008, 18757090	"no differences"	0.866	
543	Tavazzi, 2008, 18757090	"no differences"	0.866	
544	Tavazzi, 2008, 18757090	nd		
545	Tavazzi, 2008, 18757090	nd		
546	Tierney, 2011, 20938439	0.77 (-2.439, 3.983)	1.2	0.6416667
547	Tierney, 2011, 20938439	-5.41 (-17.72, 6.91)	1.2	-4.508333

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Outcome classification
537	Tavazzi, 2008, 18757090	Secondary
538	Tavazzi, 2008, 18757090	Secondary
539	Tavazzi, 2008, 18757090	Secondary
540	Tavazzi, 2008, 18757090	Secondary
541	Tavazzi, 2008, 18757090	Secondary
542	Tavazzi, 2008, 18757090	Secondary
543	Tavazzi, 2008, 18757090	Secondary
544	Tavazzi, 2008, 18757090	Secondary
545	Tavazzi, 2008, 18757090	Secondary
546	Tierney, 2011, 20938439	Secondary
547	Tierney, 2011, 20938439	Secondary

Row	Study	Study years (start date)	Country	Population
548	Tierney, 2011, 20938439	2004	Netherlands, Norway, Sweden, UK, Ireland, France, Poland, Spain	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
549	Tierney, 2011, 20938439	2004	Netherlands, Norway, Sweden, UK, Ireland, France, Poland, Spain	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
550	Tierney, 2011, 20938439	2004	Netherlands, Norway, Sweden, UK, Ireland, France, Poland, Spain	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
551	Vazquez 2014 24462043	2011	Spain	Primary Prevention
552	Vazquez 2014 24462043	2011	Spain	Primary Prevention
553	Vazquez 2014 24462043	2011	Spain	Primary Prevention
554	Vazquez 2014 24462043	2011	Spain	Primary Prevention
555	Vazquez 2014 24462043	2011	Spain	Primary Prevention
556	Vecka, 2012, 23183517	2010 (approx)	Czech Republic	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
557	Vecka, 2012, 23183517	2010 (approx)	Czech Republic	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
558	Vecka, 2012, 23183517	2010 (approx)	Czech Republic	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
559	von Schacky, 1999, 10189324	1992	Canada	Secondary Prevention (history of CVD event)
560	von Schacky, 1999, 10189324	1992	Canada	Secondary Prevention (history of CVD event)
561	von Schacky, 1999, 10189324	1992	Canada	Secondary Prevention (history of CVD event)
562	von Schacky, 1999, 10189324	1992	Canada	Secondary Prevention (history of CVD event)
563	von Schacky, 1999, 10189324	1992	Canada	Secondary Prevention (history of CVD event)
564	Yokoyama, 2007, 17398308	1996	Japan	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
565	Yokoyama, 2007, 17398308	1996	Japan	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)

Row	Study	Risk type	Sample size (total)
548	Tierney, 2011, 20938439	Diabetes and/or metabolic syndrome	206
549	Tierney, 2011, 20938439	Diabetes and/or metabolic syndrome	206
550	Tierney, 2011, 20938439	Diabetes and/or metabolic syndrome	206
551	Vazquez 2014 24462043	Healthy	273
552	Vazquez 2014 24462043	Healthy	273
553	Vazquez 2014 24462043	Healthy	273
554	Vazquez 2014 24462043	Healthy	273
555	Vazquez 2014 24462043	Healthy	273
556	Vecka, 2012, 23183517	Diabetes and/or metabolic syndrome	60
557	Vecka, 2012, 23183517	Diabetes and/or metabolic syndrome	60
558	Vecka, 2012, 23183517	Diabetes and/or metabolic syndrome	60
559	von Schacky, 1999, 10189324	nd	223
560	von Schacky, 1999, 10189324	nd	223
561	von Schacky, 1999, 10189324	nd	223
562	von Schacky, 1999, 10189324	nd	223
563	von Schacky, 1999, 10189324	nd	223
564	Yokoyama, 2007, 17398308	Dyslipidemia (total cholesterol concentration of 6.5 mmol/L or greater, which corresponded to a LDL cholesterol of 4.4 mmol/L or greater)	9319
565	Yokoyama, 2007, 17398308	Dyslipidemia (total cholesterol concentration of 6.5 mmol/L or greater, which corresponded to a LDL cholesterol of 4.4 mmol/L or greater)	9319

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Age mean (SD) [median] years	Sex (% male)	Race
548	Tierney, 2011, 20938439	54.7 (SE 0.91)	80	nd
549	Tierney, 2011, 20938439	54.7 (SE 0.91)	80	nd
550	Tierney, 2011, 20938439	54.7 (SE 0.91)	80	nd
551	Vazquez 2014 24462043	57.3 (10.2)	52.4	nd
552	Vazquez 2014 24462043	57.3 (10.2)	52.4	nd
553	Vazquez 2014 24462043	57.3 (10.2)	52.4	nd
554	Vazquez 2014 24462043	57.3 (10.2)	52.4	nd
555	Vazquez 2014 24462043	57.3 (10.2)	52.4	nd
556	Vecka, 2012, 23183517	52.4	65	nd
557	Vecka, 2012, 23183517	52.4	65	nd
558	Vecka, 2012, 23183517	52.4	65	nd
559	von Schacky, 1999, 10189324	58.9 (8.1)	78.6	nd
560	von Schacky, 1999, 10189324	58.9 (8.1)	78.6	nd
561	von Schacky, 1999, 10189324	58.9 (8.1)	78.6	nd
562	von Schacky, 1999, 10189324	58.9 (8.1)	78.6	nd
563	von Schacky, 1999, 10189324	58.9 (8.1)	78.6	nd
564	Yokoyama, 2007, 17398308	61 (9)	31	nd
565	Yokoyama, 2007, 17398308	61 (9)	31	nd

Row	Study	Blood pressure SBP/DBP mmHg
548	Tierney, 2011, 20938439	139.53 (SE 1.46)/85.50 (SE 0.87)
549	Tierney, 2011, 20938439	139.53 (SE 1.46)/85.50 (SE 0.87)
550	Tierney, 2011, 20938439	139.53 (SE 1.46)/85.50 (SE 0.87)
551	Vazquez 2014 24462043	140.5 (18.6)/83.9 (10.3)
552	Vazquez 2014 24462043	140.5 (18.6)/83.9 (10.3)
553	Vazquez 2014 24462043	140.5 (18.6)/83.9 (10.3)
554	Vazquez 2014 24462043	140.5 (18.6)/83.9 (10.3)
555	Vazquez 2014 24462043	140.5 (18.6)/83.9 (10.3)
556	Vecka, 2012, 23183517	nd
557	Vecka, 2012, 23183517	nd
558	Vecka, 2012, 23183517	nd
559	von Schacky, 1999, 10189324	129.6 (17.8)/79.8 (9.6)
560	von Schacky, 1999, 10189324	129.6 (17.8)/79.8 (9.6)
561	von Schacky, 1999, 10189324	129.6 (17.8)/79.8 (9.6)
562	von Schacky, 1999, 10189324	129.6 (17.8)/79.8 (9.6)
563	von Schacky, 1999, 10189324	129.6 (17.8)/79.8 (9.6)
564	Yokoyama, 2007, 17398308	135 (21)/79 (13)
565	Yokoyama, 2007, 17398308	135 (21)/79 (13)

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Lipids: Total cholesterol/LDL/HDL/Triglycerides mean (SD) mg/dL [mmol/L]
548	Tierney, 2011, 20938439	[5.22 (SE 0.10)]/[3.17 (SE 0.11)]/[1.09 (SE 0.03)]/[1.67 (SE 0.10)]
549	Tierney, 2011, 20938439	[5.22 (SE 0.10)]/[3.17 (SE 0.11)]/[1.09 (SE 0.03)]/[1.67 (SE 0.10)]
550	Tierney, 2011, 20938439	[5.22 (SE 0.10)]/[3.17 (SE 0.11)]/[1.09 (SE 0.03)]/[1.67 (SE 0.10)]
551	Vazquez 2014 24462043	197.6 (41.3)/119.8 (39.0)/46.2 (12.9)/170.6 (94.3)
552	Vazquez 2014 24462043	197.6 (41.3)/119.8 (39.0)/46.2 (12.9)/170.6 (94.3)
553	Vazquez 2014 24462043	197.6 (41.3)/119.8 (39.0)/46.2 (12.9)/170.6 (94.3)
554	Vazquez 2014 24462043	197.6 (41.3)/119.8 (39.0)/46.2 (12.9)/170.6 (94.3)
555	Vazquez 2014 24462043	197.6 (41.3)/119.8 (39.0)/46.2 (12.9)/170.6 (94.3)
556	Vecka, 2012, 23183517	/[3.22]/[1.19]/[3.23]
557	Vecka, 2012, 23183517	/[3.22]/[1.19]/[3.23]
558	Vecka, 2012, 23183517	/[3.22]/[1.19]/[3.23]
559	von Schacky, 1999, 10189324	[6.10 (1.13)]/[4.00 (0.91)]/[1.30 (0.36)]/[2.16 (1.10)]
560	von Schacky, 1999, 10189324	[6.10 (1.13)]/[4.00 (0.91)]/[1.30 (0.36)]/[2.16 (1.10)]
561	von Schacky, 1999, 10189324	[6.10 (1.13)]/[4.00 (0.91)]/[1.30 (0.36)]/[2.16 (1.10)]
562	von Schacky, 1999, 10189324	[6.10 (1.13)]/[4.00 (0.91)]/[1.30 (0.36)]/[2.16 (1.10)]
563	von Schacky, 1999, 10189324	[6.10 (1.13)]/[4.00 (0.91)]/[1.30 (0.36)]/[2.16 (1.10)]
564	Yokoyama, 2007, 17398308	[7.11 (0.68)]/[4.70 (0.75)]/[1.51 (0.44)]/[median 1.74 (1.25,2.49)]
565	Yokoyama, 2007, 17398308	[7.11 (0.68)]/[4.70 (0.75)]/[1.51 (0.44)]/[median 1.74 (1.25,2.49)]

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	BMI mean (SD) Kg/m2/Weight mean (SD) Kg	Baseline n-3 intake	n-3 source (Baseline)
548	Tierney, 2011, 20938439	32.51 (SE 0.42)/91.96 (SE 1.38)	nd	nd
549	Tierney, 2011, 20938439	32.51 (SE 0.42)/91.96 (SE 1.38)	nd	nd
550	Tierney, 2011, 20938439	32.51 (SE 0.42)/91.96 (SE 1.38)	nd	nd
551	Vazquez 2014 24462043	32.6 (4.4)	nd	nd
552	Vazquez 2014 24462043	32.6 (4.4)	nd	nd
553	Vazquez 2014 24462043	32.6 (4.4)	nd	nd
554	Vazquez 2014 24462043	32.6 (4.4)	nd	nd
555	Vazquez 2014 24462043	32.6 (4.4)	nd	nd
556	Vecka, 2012, 23183517	weight 89.6	nd	nd
557	Vecka, 2012, 23183517	weight 89.6	nd	nd
558	Vecka, 2012, 23183517	weight 89.6	nd	nd
559	von Schacky, 1999, 10189324	weight 78.3 (11.1)	nd	nd
560	von Schacky, 1999, 10189324	weight 78.3 (11.1)	nd	nd
561	von Schacky, 1999, 10189324	weight 78.3 (11.1)	nd	nd
562	von Schacky, 1999, 10189324	weight 78.3 (11.1)	nd	nd
563	von Schacky, 1999, 10189324	weight 78.3 (11.1)	nd	nd
564	Yokoyama, 2007, 17398308	24 (3)	nd	nd
565	Yokoyama, 2007, 17398308	24 (3)	nd	nd

Row	Study	n-3 type(s)	n-3 measure	Study design	Outcome
548	Tierney, 2011, 20938439	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Tg
549	Tierney, 2011, 20938439	ALA+EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	SBP
550	Tierney, 2011, 20938439	ALA+EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	DBP
551	Vazquez 2014 24462043	EPA+DHA 0.64 vs Placebo	g/d	Trial: Randomized Cross-over	HDL-c
552	Vazquez 2014 24462043	EPA+DHA 0.64 vs Placebo	g/d	Trial: Randomized Cross-over	LDL-c
553	Vazquez 2014 24462043	EPA+DHA 0.64 vs Placebo	g/d	Trial: Randomized Cross-over	Tg
554	Vazquez 2014 24462043	EPA+DHA 0.64 vs Placebo	g/d	Trial: Randomized Cross-over	SBP
555	Vazquez 2014 24462043	EPA+DHA 0.64 vs Placebo	g/d	Trial: Randomized Cross-over	DBP
556	Vecka, 2012, 23183517	EPA+DHA vs Placebo	g/d	Non-randomized cross-over study	HDL-c
557	Vecka, 2012, 23183517	EPA+DHA vs Placebo	g/d	Non-randomized cross-over study	LDL-c
558	Vecka, 2012, 23183517	EPA+DHA vs Placebo	g/d	Non-randomized cross-over study	Tg
559	von Schacky, 1999, 10189324	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	HDL-c
560	von Schacky, 1999, 10189324	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	LDL-c
561	von Schacky, 1999, 10189324	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	Tg
562	von Schacky, 1999, 10189324	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	SBP
563	von Schacky, 1999, 10189324	EPA+DHA vs Placebo	g/d	Trial: Randomized Parallel	DBP
564	Yokoyama, 2007, 17398308	EPA vs Placebo	g/d	Trial: Randomized Parallel	Angina, unstable
565	Yokoyama, 2007, 17398308	EPA vs Placebo	g/d	Trial: Randomized Parallel	Death, all cause

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Reported effect Size	Dose/intake difference	Dose-corrected effect size
548	Tierney, 2011, 20938439	-19.47 (-44.12, 5.18)	1.2	-16.225
549	Tierney, 2011, 20938439	0.1 (, -4, 4.2)	1.2	0.0833333
550	Tierney, 2011, 20938439	0.7 (−1.7, 3.1)	1.2	0.0833333
551	Vazquez 2014 24462043	-0.69 (-2.16, 0.78)	0.64	-1.08
552	Vazquez 2014 24462043	-3.01 (-7.15, 1.13)	0.64	-4.7
553	Vazquez 2014 24462043	-3.96 (-15.08, 7.16)	0.64	-6.19
554	Vazquez 2014 24462043	-0.28 (-2.63, 2.07)	0.64	-0.44
555	Vazquez 2014 24462043	-1.32 (-2.5, -0.14)	0.64	-2.06
556	Vecka, 2012, 23183517	1.9 (−25.4, 29.2) [difference of final values]	2.58	0.9363636
557	Vecka, 2012, 23183517	10.4 (9.8, 11.1) [difference of final values]	2.58	
558	Vecka, 2012, 23183517	−82.3 (−852.6, 688) [difference of final values]	2.58	-31.89923
559	von Schacky, 1999, 10189324	3.1 (−1.0, 7.2	3.3	
560	von Schacky, 1999, 10189324	5.79 (-5.66, 17.24)	3.3	1.754545
561	von Schacky, 1999, 10189324	-49.56 (-81.42, -17.70)	3.3	-15.01818
562	von Schacky, 1999, 10189324	-0.1 (-5.0, 4.8)	3.3	-0.030303
563	von Schacky, 1999, 10189324	0.2 (−2.8, 3.2)	3.3	
564	Yokoyama, 2007, 17398308	HR 0.76 (0.62, 0.95)	0.9	0.7371751
565	Yokoyama, 2007, 17398308	HR 1.09 (0.92, 1.28)	1.8	

Row	Study	Outcome classification
548	Tierney, 2011, 20938439	Secondary
549	Tierney, 2011, 20938439	Secondary
550	Tierney, 2011, 20938439	Secondary
551	Vazquez 2014 24462043	Secondary
552	Vazquez 2014 24462043	Secondary
553	Vazquez 2014 24462043	Primary (stated)
554	Vazquez 2014 24462043	Primary (stated); Secondary in registry record (NCT01758601)
555	Vazquez 2014 24462043	Primary (stated)
556	Vecka, 2012, 23183517	No data; unclear
557	Vecka, 2012, 23183517	No data; unclear
558	Vecka, 2012, 23183517	No data; unclear
559	von Schacky, 1999, 10189324	Secondary
560	von Schacky, 1999, 10189324	Secondary
561	von Schacky, 1999, 10189324	Secondary
562	von Schacky, 1999, 10189324	Secondary
563	von Schacky, 1999, 10189324	Secondary
564	Yokoyama, 2007, 17398308	Secondary; Primary in registry record (NCT00231738)
565	Yokoyama, 2007, 17398308	Secondary

Row	Study	Study years (start date)	Country	Population
566	Yokoyama, 2007, 17398308	1996	Japan	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
567	Yokoyama, 2007, 17398308	1996	Japan	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
568	Yokoyama, 2007, 17398308	1996	Japan	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
569	Yokoyama, 2007, 17398308	1996	Japan	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
570	Yokoyama, 2007, 17398308	1996	Japan	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
571	Yokoyama, 2007, 17398308	1996	Japan	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
572	Yokoyama, 2007, 17398308	1996	Japan	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
573	Yokoyama, 2007, 17398308	1996	Japan	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
574	Yokoyama, 2007, 17398308	1996	Japan	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
575	Yokoyama, 2007, 17398308	1996	Japan	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
576	Yokoyama, 2007, 17398308	1996	Japan	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
577	Yokoyama, 2007, 17398308	1996	Japan	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)
578	Yokoyama, 2007, 17398308	1996	Japan	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Risk type	Sample size (total)
566	Yokoyama, 2007, 17398308	Dyslipidemia (total cholesterol concentration of 6.5 mmol/L or greater, which corresponded to a LDL cholesterol of 4.4 mmol/L or greater)	9319
567	Yokoyama, 2007, 17398308	Dyslipidemia (total cholesterol concentration of 6.5 mmol/L or greater, which corresponded to a LDL cholesterol of 4.4 mmol/L or greater)	9319
568	Yokoyama, 2007, 17398308	Dyslipidemia (total cholesterol concentration of 6.5 mmol/L or greater, which corresponded to a LDL cholesterol of 4.4 mmol/L or greater)	9319
569	Yokoyama, 2007, 17398308	Dyslipidemia (total cholesterol concentration of 6.5 mmol/L or greater, which corresponded to a LDL cholesterol of 4.4 mmol/L or greater)	9319
570	Yokoyama, 2007, 17398308	Dyslipidemia (total cholesterol concentration of 6.5 mmol/L or greater, which corresponded to a LDL cholesterol of 4.4 mmol/L or greater)	9319
571	Yokoyama, 2007, 17398308	Dyslipidemia (total cholesterol concentration of 6.5 mmol/L or greater, which corresponded to a LDL cholesterol of 4.4 mmol/L or greater)	9319
572	Yokoyama, 2007, 17398308	Dyslipidemia (total cholesterol concentration of 6.5 mmol/L or greater, which corresponded to a LDL cholesterol of 4.4 mmol/L or greater)	9319
573	Yokoyama, 2007, 17398308	Dyslipidemia (total cholesterol concentration of 6.5 mmol/L or greater, which corresponded to a LDL cholesterol of 4.4 mmol/L or greater)	9319
574	Yokoyama, 2007, 17398308	Dyslipidemia (total cholesterol concentration of 6.5 mmol/L or greater, which corresponded to a LDL cholesterol of 4.4 mmol/L or greater)	9319
575	Yokoyama, 2007, 17398308	Dyslipidemia (total cholesterol concentration of 6.5 mmol/L or greater, which corresponded to a LDL cholesterol of 4.4 mmol/L or greater)	9319
576	Yokoyama, 2007, 17398308	Dyslipidemia (total cholesterol concentration of 6.5 mmol/L or greater, which corresponded to a LDL cholesterol of 4.4 mmol/L or greater)	9319
577	Yokoyama, 2007, 17398308	Dyslipidemia (total cholesterol concentration of 6.5 mmol/L or greater, which corresponded to a LDL cholesterol of 4.4 mmol/L or greater)	9319
578	Yokoyama, 2007, 17398308	Dyslipidemia (total cholesterol concentration of 6.5 mmol/L or greater, which corresponded to a LDL cholesterol of 4.4 mmol/L or greater)	9319

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Age mean (SD) [median] years	Sex (% male)	Race
566	Yokoyama, 2007, 17398308	61 (9)	31	nd
567	Yokoyama, 2007, 17398308	61 (9)	31	nd
568	Yokoyama, 2007, 17398308	61 (9)	31	nd
569	Yokoyama, 2007, 17398308	61 (9)	31	nd
570	Yokoyama, 2007, 17398308	61 (9)	31	nd
571	Yokoyama, 2007, 17398308	61 (9)	31	nd
572	Yokoyama, 2007, 17398308	61 (9)	31	nd
573	Yokoyama, 2007, 17398308	61 (9)	31	nd
574	Yokoyama, 2007, 17398308	61 (9)	31	nd
575	Yokoyama, 2007, 17398308	61 (9)	31	nd
576	Yokoyama, 2007, 17398308	61 (9)	31	nd
577	Yokoyama, 2007, 17398308	61 (9)	31	nd
578	Yokoyama, 2007, 17398308	61 (9)	31	nd

Row	Study	Blood pressure SBP/DBP mmHg
566	Yokoyama, 2007, 17398308	135 (21)/79 (13)
567	Yokoyama, 2007, 17398308	135 (21)/79 (13)
568	Yokoyama, 2007, 17398308	135 (21)/79 (13)
569	Yokoyama, 2007, 17398308	135 (21)/79 (13)
570	Yokoyama, 2007, 17398308	135 (21)/79 (13)
571	Yokoyama, 2007, 17398308	135 (21)/79 (13)
572	Yokoyama, 2007, 17398308	135 (21)/79 (13)
573	Yokoyama, 2007, 17398308	135 (21)/79 (13)
574	Yokoyama, 2007, 17398308	135 (21)/79 (13)
575	Yokoyama, 2007, 17398308	135 (21)/79 (13)
576	Yokoyama, 2007, 17398308	135 (21)/79 (13)
577	Yokoyama, 2007, 17398308	135 (21)/79 (13)
578	Yokoyama, 2007, 17398308	135 (21)/79 (13)

Row	Study	Lipids: Total cholesterol/LDL/HDL/Triglycerides mean (SD) mg/dL [mmol/L]
566	Yokoyama, 2007, 17398308	[7.11 (0.68)]/[4.70 (0.75)]/[1.51 (0.44)]/[median 1.74 (1.25,2.49)]
567	Yokoyama, 2007, 17398308	[7.11 (0.68)]/[4.70 (0.75)]/[1.51 (0.44)]/[median 1.74 (1.25,2.49)]
568	Yokoyama, 2007, 17398308	[7.11 (0.68)]/[4.70 (0.75)]/[1.51 (0.44)]/[median 1.74 (1.25,2.49)]
569	Yokoyama, 2007, 17398308	[7.11 (0.68)]/[4.70 (0.75)]/[1.51 (0.44)]/[median 1.74 (1.25,2.49)]
570	Yokoyama, 2007, 17398308	[7.11 (0.68)]/[4.70 (0.75)]/[1.51 (0.44)]/[median 1.74 (1.25,2.49)]
571	Yokoyama, 2007, 17398308	[7.11 (0.68)]/[4.70 (0.75)]/[1.51 (0.44)]/[median 1.74 (1.25,2.49)]
572	Yokoyama, 2007, 17398308	[7.11 (0.68)]/[4.70 (0.75)]/[1.51 (0.44)]/[median 1.74 (1.25,2.49)]
573	Yokoyama, 2007, 17398308	[7.11 (0.68)]/[4.70 (0.75)]/[1.51 (0.44)]/[median 1.74 (1.25,2.49)]
574	Yokoyama, 2007, 17398308	[7.11 (0.68)]/[4.70 (0.75)]/[1.51 (0.44)]/[median 1.74 (1.25,2.49)]
575	Yokoyama, 2007, 17398308	[7.11 (0.68)]/[4.70 (0.75)]/[1.51 (0.44)]/[median 1.74 (1.25,2.49)]
576	Yokoyama, 2007, 17398308	[7.11 (0.68)]/[4.70 (0.75)]/[1.51 (0.44)]/[median 1.74 (1.25,2.49)]
577	Yokoyama, 2007, 17398308	[7.11 (0.68)]/[4.70 (0.75)]/[1.51 (0.44)]/[median 1.74 (1.25,2.49)]
578	Yokoyama, 2007, 17398308	[7.11 (0.68)]/[4.70 (0.75)]/[1.51 (0.44)]/[median 1.74 (1.25,2.49)]

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	BMI mean (SD) Kg/m2/Weight mean (SD) Kg	Baseline n-3 intake	n-3 source (Baseline)
566	Yokoyama, 2007, 17398308	24 (3)	nd	nd
567	Yokoyama, 2007, 17398308	24 (3)	nd	nd
568	Yokoyama, 2007, 17398308	24 (3)	nd	nd
569	Yokoyama, 2007, 17398308	24 (3)	nd	nd
570	Yokoyama, 2007, 17398308	24 (3)	nd	nd
571	Yokoyama, 2007, 17398308	24 (3)	nd	nd
572	Yokoyama, 2007, 17398308	24 (3)	nd	nd
573	Yokoyama, 2007, 17398308	24 (3)	nd	nd
574	Yokoyama, 2007, 17398308	24 (3)	nd	nd
575	Yokoyama, 2007, 17398308	24 (3)	nd	nd
576	Yokoyama, 2007, 17398308	24 (3)	nd	nd
577	Yokoyama, 2007, 17398308	24 (3)	nd	nd
578	Yokoyama, 2007, 17398308	24 (3)	nd	nd

Row	Study	n-3 type(s)	n-3 measure	Study design	Outcome
566	Yokoyama, 2007, 17398308	EPA vs Placebo	g/d	Trial: Randomized Parallel	Death, cardiac
567	Yokoyama, 2007, 17398308	EPA vs Placebo	g/d	Trial: Randomized Parallel	Death, CHD
568	Yokoyama, 2007, 17398308	EPA vs Placebo	g/d	Trial: Randomized Parallel	MACE
569	Yokoyama, 2007, 17398308	EPA vs Placebo	g/d	Trial: Randomized Parallel	Myocardial infarction
570	Yokoyama, 2007, 17398308	EPA vs Placebo	g/d	Trial: Randomized Parallel	Myocardial infarction
571	Yokoyama, 2007, 17398308	EPA vs Placebo	g/d	Trial: Randomized Parallel	Revascularization
572	Yokoyama, 2007, 17398308	EPA vs Placebo	g/d	Trial: Randomized Parallel	Stroke
573	Yokoyama, 2007, 17398308	EPA vs Placebo	g/d	Trial: Randomized Parallel	Sudden cardiac death
574	Yokoyama, 2007, 17398308	EPA vs Placebo	g/d	Trial: Randomized Parallel	HDL-c
575	Yokoyama, 2007, 17398308	EPA vs Placebo	g/d	Trial: Randomized Parallel	LDL-c
576	Yokoyama, 2007, 17398308	EPA vs Placebo	g/d	Trial: Randomized Parallel	Tg
577	Yokoyama, 2007, 17398308	EPA vs Placebo	g/d	Trial: Randomized Parallel	SBP
578	Yokoyama, 2007, 17398308	EPA vs Placebo	g/d	Trial: Randomized Parallel	DBP

Appendix G.1.
Causality Table: Comparative Studies

Row	Study	Reported effect Size	Dose/intake difference	Dose-corrected effect size
566	Yokoyama, 2007, 17398308	HR 0.87 (0.46, 1.64)	1.8	0.9255494
567	Yokoyama, 2007, 17398308	HR 1.10 (0.47, 2.60)	1.8	1.054377
568	Yokoyama, 2007, 17398308	HR 0.81 (0.69, 0.95)	1.8	0.8895254
569	Yokoyama, 2007, 17398308	HR 0.79 (0.52, 1.19)	1.8	0.8772556
570	Yokoyama, 2007, 17398308	HR 0.75 (0.47, 1.19)	1.8	0.8522943
571	Yokoyama, 2007, 17398308	HR 0.86 (0.71, 1.05)	1.8	0.9196239
572	Yokoyama, 2007, 17398308	HR 1.08 (0.95, 1.22)	1.8	
573	Yokoyama, 2007, 17398308	OR 1.24 (0.36, 4.28)	1.8	1.12694
574	Yokoyama, 2007, 17398308	−0.4 (−0.9, 0.1)	1.8	
575	Yokoyama, 2007, 17398308	0 (−0.9, 0.9)	1.8	
576	Yokoyama, 2007, 17398308	−8.9 (−11.0, −6.7)	1.8	
577	Yokoyama, 2007, 17398308	0 (−0.9, 0.9)	1.8	
578	Yokoyama, 2007, 17398308	0 (−0.4, 0.4)	1.8	

Row	Study	Outcome classification
566	Yokoyama, 2007, 17398308	Secondary
567	Yokoyama, 2007, 17398308	Primary (stated)
568	Yokoyama, 2007, 17398308	Secondary
569	Yokoyama, 2007, 17398308	Secondary; Primary in registry record (NCT00231738)
570	Yokoyama, 2007, 17398308	Secondary; Primary in registry record (NCT00231738)
571	Yokoyama, 2007, 17398308	Secondary; Primary in registry record (NCT00231738)
572	Yokoyama, 2007, 17398308	Secondary
573	Yokoyama, 2007, 17398308	Secondary; Primary in registry record (NCT00231738)
574	Yokoyama, 2007, 17398308	Secondary
575	Yokoyama, 2007, 17398308	Secondary
576	Yokoyama, 2007, 17398308	Secondary
577	Yokoyama, 2007, 17398308	Secondary
578	Yokoyama, 2007, 17398308	Secondary

Appendix F

Observational results: acute coronary syndrome

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population type	Population	Subgroup	Cases Total/N Total (Rate)	Followup	n3 FA	n3 measure
2	Joensen 2011 21859970	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Men	779/1708 (1.2 per 1000 pt-y)	7.6 y	DHA	Adipose tissue
3	Joensen 2011 21859970	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Men	779/1708 (1.2 per 1000 pt-y)	7.6 y	DHA	Adipose tissue
4	Joensen 2011 21859970	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Men	779/1708 (1.2 per 1000 pt-y)	7.6 y	DHA	Adipose tissue
5	Joensen 2011 21859970	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Men	779/1708 (1.2 per 1000 pt-y)	7.6 y	DHA	Adipose tissue
6	Joensen 2011 21859970	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Men	779/1708 (1.2 per 1000 pt-y)	7.6 y	DHA	Adipose tissue
7	Joensen 2011 21859970	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Men	779/1708 (1.2 per 1000 pt-y)	7.6 y	DHA	Adipose tissue
8	Joensen 2011 21859970	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Women	233/1084 (1.2 per 1000 pt-y)	7.6 y	DHA	Adipose tissue
9	Joensen 2011 21859970	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Women	233/1084 (1.2 per 1000 pt-y)	7.6 y	DHA	Adipose tissue
10	Joensen 2011 21859970	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Women	233/1084 (1.2 per 1000 pt-y)	7.6 y	DHA	Adipose tissue
11	Joensen 2011 21859970	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Women	233/1084 (1.2 per 1000 pt-y)	7.6 y	DHA	Adipose tissue
12	Joensen 2011 21859970	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Women	233/1084 (1.2 per 1000 pt-y)	7.6 y	DHA	Adipose tissue
13	Joensen 2011 21859970	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Women	233/1084 (1.2 per 1000 pt-y)	7.6 y	DHA	Adipose tissue
14	Joensen 2009 19825219	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Men	852/24786 (4.4 per 1000 pt-y)	7.6 y	DHA	Intake
15	Joensen 2009 19825219	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Men	852/24786 (4.4 per 1000 pt-y)	7.6 y	DHA	Intake
16	Joensen 2009 19825219	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Men	852/24786 (4.4 per 1000 pt-y)	7.6 y	DHA	Intake
17	Joensen 2009 19825219	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Men	852/24786 (4.4 per 1000 pt-y)	7.6 y	DHA	Intake
18	Joensen 2009 19825219	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Men	852/24786 (4.4 per 1000 pt-y)	7.6 y	DHA	Intake
19	Joensen 2009 19825219	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Women	272/29017 (1.2 per 1000 pt-y)	7.6 y	DHA	Intake
20	Joensen 2009 19825219	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Women	272/29017 (1.2 per 1000 pt-y)	7.6 y	DHA	Intake
21	Joensen 2009 19825219	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Women	272/29017 (1.2 per 1000 pt-y)	7.6 y	DHA	Intake
22	Joensen 2009 19825219	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Women	272/29017 (1.2 per 1000 pt-y)	7.6 y	DHA	Intake
23	Joensen 2009 19825219	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Women	272/29017 (1.2 per 1000 pt-y)	7.6 y	DHA	Intake
24	Joensen 2011 21859970	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Men	779/1708 (1.2 per 1000 pt-y)	7.6 y	DPA	Adipose tissue
25	Joensen 2011 21859970	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Men	779/1708 (1.2 per 1000 pt-y)	7.6 y	DPA	Adipose tissue
26	Joensen 2011 21859970	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Men	779/1708 (1.2 per 1000 pt-y)	7.6 y	DPA	Adipose tissue
27	Joensen 2011 21859970	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Men	779/1708 (1.2 per 1000 pt-y)	7.6 y	DPA	Adipose tissue

Appendix F
Observational results: acute coronary syndrome

Row	Study PMID	Supplement	Adjustments	Quantile	n3 units	Quantile low	Quantile median
2	Joensen 2011 21859970	NA	smoking, body mass index, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, education, and alcohol consumption. Analyses in women were also adjusted for hormone replacement therapy.	Qt1	% FA	nd	nd
3	Joensen 2011 21859970	NA	smoking, body mass index, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, education, and alcohol consumption. Analyses in women were also adjusted for hormone replacement therapy.	Qt2	% FA	0.15	nd
4	Joensen 2011 21859970	NA	smoking, body mass index, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, education, and alcohol consumption. Analyses in women were also adjusted for hormone replacement therapy.	Qt3	% FA	0.2	nd
5	Joensen 2011 21859970	NA	smoking, body mass index, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, education, and alcohol consumption. Analyses in women were also adjusted for hormone replacement therapy.	Qt4	% FA	0.25	nd
6	Joensen 2011 21859970	NA	smoking, body mass index, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, education, and alcohol consumption. Analyses in women were also adjusted for hormone replacement therapy.	Qt5	% FA	>0.31	nd
7	Joensen 2011 21859970	NA	smoking, body mass index, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, education, and alcohol consumption. Analyses in women were also adjusted for hormone replacement therapy.	All	% FA	nd	nd
8	Joensen 2011 21859970	NA	smoking, body mass index, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, education, and alcohol consumption. Analyses in women were also adjusted for hormone replacement therapy.	Qt1	% FA	nd	nd
9	Joensen 2011 21859970	NA	smoking, body mass index, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, education, and alcohol consumption. Analyses in women were also adjusted for hormone replacement therapy.	Qt2	% FA	0.19	nd
10	Joensen 2011 21859970	NA	smoking, body mass index, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, education, and alcohol consumption. Analyses in women were also adjusted for hormone replacement therapy.	Qt3	% FA	0.26	nd
11	Joensen 2011 21859970	NA	smoking, body mass index, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, education, and alcohol consumption. Analyses in women were also adjusted for hormone replacement therapy.	Qt4	% FA	0.32	nd
12	Joensen 2011 21859970	NA	smoking, body mass index, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, education, and alcohol consumption. Analyses in women were also adjusted for hormone replacement therapy.	Qt5	% FA	>0.38	nd
13	Joensen 2011 21859970	NA	smoking, body mass index, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, education, and alcohol consumption. Analyses in women were also adjusted for hormone replacement therapy.	All	% FA	nd	nd
14	Joensen 2009 19825219	No	smoking, BMI, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, alcohol consumption, total intake of fruit, vegetables, saturated fat, monounsaturated fat and n-6 PUFA.	Qt1	g/d	nd	nd
15	Joensen 2009 19825219	No	smoking, BMI, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, alcohol consumption, total intake of fruit, vegetables, saturated fat, monounsaturated fat and n-6 PUFA.	Qt2	g/d	0.23	nd
16	Joensen 2009 19825219	No	smoking, BMI, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, alcohol consumption, total intake of fruit, vegetables, saturated fat, monounsaturated fat and n-6 PUFA.	Qt3	g/d	0.35	0.43
17	Joensen 2009 19825219	No	smoking, BMI, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, alcohol consumption, total intake of fruit, vegetables, saturated fat, monounsaturated fat and n-6 PUFA.	Qt4	g/d	0.48	nd
18	Joensen 2009 19825219	No	smoking, BMI, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, alcohol consumption, total intake of fruit, vegetables, saturated fat, monounsaturated fat and n-6 PUFA.	Qt5	g/d	>0.65	nd
19	Joensen 2009 19825219	No	smoking, BMI, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, alcohol consumption, total intake of fruit, vegetables, saturated fat, monounsaturated fat and n-6 PUFA.	Qt1	g/d	nd	nd
20	Joensen 2009 19825219	No	smoking, BMI, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, alcohol consumption, total intake of fruit, vegetables, saturated fat, monounsaturated fat and n-6 PUFA.	Qt2	g/d	0.2	nd
21	Joensen 2009 19825219	No	smoking, BMI, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, alcohol consumption, total intake of fruit, vegetables, saturated fat, monounsaturated fat and n-6 PUFA.	Qt3	g/d	0.32	0.37
22	Joensen 2009 19825219	No	smoking, BMI, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, alcohol consumption, total intake of fruit, vegetables, saturated fat, monounsaturated fat and n-6 PUFA.	Qt4	g/d	0.43	nd
23	Joensen 2009 19825219	No	smoking, BMI, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, alcohol consumption, total intake of fruit, vegetables, saturated fat, monounsaturated fat and n-6 PUFA.	Qt5	g/d	>0.59	nd
24	Joensen 2011 21859970	NA	smoking, body mass index, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, education, and alcohol consumption. Analyses in women were also adjusted for hormone replacement therapy.	Qt1	% FA	nd	nd
25	Joensen 2011 21859970	NA	smoking, body mass index, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, education, and alcohol consumption. Analyses in women were also adjusted for hormone replacement therapy.	Qt2	% FA	0.19	nd
26	Joensen 2011 21859970	NA	smoking, body mass index, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, education, and alcohol consumption. Analyses in women were also adjusted for hormone replacement therapy.	Qt3	% FA	0.23	nd
27	Joensen 2011 21859970	NA	smoking, body mass index, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, education, and alcohol consumption. Analyses in women were also adjusted for hormone replacement therapy.	Qt4	% FA	0.26	nd

Appendix F
Observational results: acute coronary syndrome

Row	Study PMID	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
2	Joensen 2011 21859970	0.15	HR	163	nd	nd	Reference group				nd
3	Joensen 2011 21859970	0.2	HR	173	nd	nd	0.77	0.54	1.09		
4	Joensen 2011 21859970	0.25	HR	152	nd	nd	0.7	0.48	1.01		
5	Joensen 2011 21859970	0.31	HR	142	nd	nd	0.76	0.52	1.11		
6	Joensen 2011 21859970	nd	HR	149	nd	nd	0.51	0.36	0.73		
7	Joensen 2011 21859970	nd	HR	nd	nd	nd	0.85	0.76	0.94	per 0.1%	0.003
8	Joensen 2011 21859970	0.19	HR	49	nd	nd	Reference group				nd
9	Joensen 2011 21859970	0.26	HR	49	nd	nd	0.61	0.34	1.09		
10	Joensen 2011 21859970	0.32	HR	55	nd	nd	1.58	0.9	2.79		
11	Joensen 2011 21859970	0.38	HR	34	nd	nd	0.8	0.41	1.57		
12	Joensen 2011 21859970	nd	HR	46	nd	nd	1.14	0.63	2.07		
13	Joensen 2011 21859970	nd	HR	nd	nd	nd	1	0.88	1.14	per 0.1%	0.98
14	Joensen 2009 19825219	0.23	HR	nd	nd	nd	Reference group				nd
15	Joensen 2009 19825219	0.35	HR	nd	nd	nd	0.84	0.68	1.04		
16	Joensen 2009 19825219	0.48	HR	nd	nd	nd	0.84	0.68	1.05		
17	Joensen 2009 19825219	0.65	HR	nd	nd	nd	0.88	0.7	1.11		
18	Joensen 2009 19825219	nd	HR	nd	nd	nd	0.81	0.63	1.03		
19	Joensen 2009 19825219	0.2	HR	nd	nd	nd	Reference group				nd
20	Joensen 2009 19825219	0.32	HR	nd	nd	nd	0.83	0.56	1.23		
21	Joensen 2009 19825219	0.43	HR	nd	nd	nd	1.1	0.74	1.65		
22	Joensen 2009 19825219	0.59	HR	nd	nd	nd	1.05	0.7	1.6		
23	Joensen 2009 19825219	nd	HR	nd	nd	nd	1	0.64	1.57		
24	Joensen 2011 21859970	0.19	HR	173	nd	nd	Reference group				nd
25	Joensen 2011 21859970	0.23	HR	172	nd	nd	0.91	0.64	1.28		
26	Joensen 2011 21859970	0.26	HR	151	nd	nd	1.04	0.72	1.5		
27	Joensen 2011 21859970	0.3	HR	128	nd	nd	0.73	0.5	1.06		

Appendix F
Observational results: acute coronary syndrome

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population type	Population	Subgroup	Cases Total/N Total (Rate)	Followup	n3 FA	n3 measure
28	Joensen 2011 21859970	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Men	779/1708 (1.2 per 1000 pt-y)	7.6 y	DPA	Adipose tissue
29	Joensen 2011 21859970	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Men	779/1708 (1.2 per 1000 pt-y)	7.6 y	DPA	Adipose tissue
30	Joensen 2011 21859970	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Women	233/1084 (1.2 per 1000 pt-y)	7.6 y	DPA	Adipose tissue
31	Joensen 2011 21859970	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Women	233/1084 (1.2 per 1000 pt-y)	7.6 y	DPA	Adipose tissue
32	Joensen 2011 21859970	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Women	233/1084 (1.2 per 1000 pt-y)	7.6 y	DPA	Adipose tissue
33	Joensen 2011 21859970	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Women	233/1084 (1.2 per 1000 pt-y)	7.6 y	DPA	Adipose tissue
34	Joensen 2011 21859970	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Women	233/1084 (1.2 per 1000 pt-y)	7.6 y	DPA	Adipose tissue
35	Joensen 2011 21859970	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Women	233/1084 (1.2 per 1000 pt-y)	7.6 y	DPA	Adipose tissue
36	Joensen 2009 19825219	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Men	852/24786 (4.4 per 1000 pt-y)	7.6 y	DPA	Intake
37	Joensen 2009 19825219	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Men	852/24786 (4.4 per 1000 pt-y)	7.6 y	DPA	Intake
38	Joensen 2009 19825219	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Men	852/24786 (4.4 per 1000 pt-y)	7.6 y	DPA	Intake
39	Joensen 2009 19825219	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Men	852/24786 (4.4 per 1000 pt-y)	7.6 y	DPA	Intake
40	Joensen 2009 19825219	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Men	852/24786 (4.4 per 1000 pt-y)	7.6 y	DPA	Intake
41	Joensen 2009 19825219	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Women	272/29017 (1.2 per 1000 pt-y)	7.6 y	DPA	Intake
42	Joensen 2009 19825219	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Women	272/29017 (1.2 per 1000 pt-y)	7.6 y	DPA	Intake
43	Joensen 2009 19825219	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Women	272/29017 (1.2 per 1000 pt-y)	7.6 y	DPA	Intake
44	Joensen 2009 19825219	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Women	272/29017 (1.2 per 1000 pt-y)	7.6 y	DPA	Intake
45	Joensen 2009 19825219	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Women	272/29017 (1.2 per 1000 pt-y)	7.6 y	DPA	Intake
46	Joensen 2011 21859970	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Men	779/1708 (1.2 per 1000 pt-y)	7.6 y	EPA	Adipose tissue
47	Joensen 2011 21859970	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Men	779/1708 (1.2 per 1000 pt-y)	7.6 y	EPA	Adipose tissue
48	Joensen 2011 21859970	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Men	779/1708 (1.2 per 1000 pt-y)	7.6 y	EPA	Adipose tissue
49	Joensen 2011 21859970	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Men	779/1708 (1.2 per 1000 pt-y)	7.6 y	EPA	Adipose tissue
50	Joensen 2011 21859970	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Men	779/1708 (1.2 per 1000 pt-y)	7.6 y	EPA	Adipose tissue
51	Joensen 2011 21859970	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Men	779/1708 (1.2 per 1000 pt-y)	7.6 y	EPA	Adipose tissue
52	Joensen 2011 21859970	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Women	233/1084 (1.2 per 1000 pt-y)	7.6 y	EPA	Adipose tissue
53	Joensen 2011 21859970	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Women	233/1084 (1.2 per 1000 pt-y)	7.6 y	EPA	Adipose tissue

Appendix F
Observational results: acute coronary syndrome

Row	Study PMID	Supplement	Adjustments	Quantile	n3 units	Quantile low	Quantile median
28	Joensen 2011 21859970	NA	smoking, body mass index, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, education, and alcohol consumption. Analyses in women were also adjusted for hormone replacement therapy.	Qt5	% FA	>0.30	nd
29	Joensen 2011 21859970	NA	smoking, body mass index, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, education, and alcohol consumption. Analyses in women were also adjusted for hormone replacement therapy.	All	% FA	nd	nd
30	Joensen 2011 21859970	NA	smoking, body mass index, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, education, and alcohol consumption. Analyses in women were also adjusted for hormone replacement therapy.	Qt1	% FA	nd	nd
31	Joensen 2011 21859970	NA	smoking, body mass index, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, education, and alcohol consumption. Analyses in women were also adjusted for hormone replacement therapy.	Qt2	% FA	0.22	nd
32	Joensen 2011 21859970	NA	smoking, body mass index, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, education, and alcohol consumption. Analyses in women were also adjusted for hormone replacement therapy.	Qt3	% FA	0.27	nd
33	Joensen 2011 21859970	NA	smoking, body mass index, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, education, and alcohol consumption. Analyses in women were also adjusted for hormone replacement therapy.	Qt4	% FA	0.31	nd
34	Joensen 2011 21859970	NA	smoking, body mass index, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, education, and alcohol consumption. Analyses in women were also adjusted for hormone replacement therapy.	Qt5	% FA	>0.37	nd
35	Joensen 2011 21859970	NA	smoking, body mass index, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, education, and alcohol consumption. Analyses in women were also adjusted for hormone replacement therapy.	All	% FA	nd	nd
36	Joensen 2009 19825219	No	smoking, BMI, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, alcohol consumption, total intake of fruit, vegetables, saturated fat, monounsaturated fat and n-6 PUFA.	Qt1	g/d	nd	nd
37	Joensen 2009 19825219	No	smoking, BMI, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, alcohol consumption, total intake of fruit, vegetables, saturated fat, monounsaturated fat and n-6 PUFA.	Qt2	g/d	0.05	nd
38	Joensen 2009 19825219	No	smoking, BMI, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, alcohol consumption, total intake of fruit, vegetables, saturated fat, monounsaturated fat and n-6 PUFA.	Qt3	g/d	0.07	0.08
39	Joensen 2009 19825219	No	smoking, BMI, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, alcohol consumption, total intake of fruit, vegetables, saturated fat, monounsaturated fat and n-6 PUFA.	Qt4	g/d	0.09	nd
40	Joensen 2009 19825219	No	smoking, BMI, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, alcohol consumption, total intake of fruit, vegetables, saturated fat, monounsaturated fat and n-6 PUFA.	Qt5	g/d	>0.11	nd
41	Joensen 2009 19825219	No	smoking, BMI, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, alcohol consumption, total intake of fruit, vegetables, saturated fat, monounsaturated fat and n-6 PUFA.	Qt1	g/d	nd	nd
42	Joensen 2009 19825219	No	smoking, BMI, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, alcohol consumption, total intake of fruit, vegetables, saturated fat, monounsaturated fat and n-6 PUFA.	Qt2	g/d	0.04	nd
43	Joensen 2009 19825219	No	smoking, BMI, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, alcohol consumption, total intake of fruit, vegetables, saturated fat, monounsaturated fat and n-6 PUFA.	Qt3	g/d	0.06	0.06
44	Joensen 2009 19825219	No	smoking, BMI, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, alcohol consumption, total intake of fruit, vegetables, saturated fat, monounsaturated fat and n-6 PUFA.	Qt4	g/d	0.07	nd
45	Joensen 2009 19825219	No	smoking, BMI, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, alcohol consumption, total intake of fruit, vegetables, saturated fat, monounsaturated fat and n-6 PUFA.	Qt5	g/d	>0.09	nd
46	Joensen 2011 21859970	NA	smoking, body mass index, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, education, and alcohol consumption. Analyses in women were also adjusted for hormone replacement therapy.	Qt1	% FA	nd	nd
47	Joensen 2011 21859970	NA	smoking, body mass index, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, education, and alcohol consumption. Analyses in women were also adjusted for hormone replacement therapy.	Qt2	% FA	0.06	nd
48	Joensen 2011 21859970	NA	smoking, body mass index, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, education, and alcohol consumption. Analyses in women were also adjusted for hormone replacement therapy.	Qt3	% FA	0.08	nd
49	Joensen 2011 21859970	NA	smoking, body mass index, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, education, and alcohol consumption. Analyses in women were also adjusted for hormone replacement therapy.	Qt4	% FA	0.1	nd
50	Joensen 2011 21859970	NA	smoking, body mass index, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, education, and alcohol consumption. Analyses in women were also adjusted for hormone replacement therapy.	Qt5	% FA	>0.13	nd
51	Joensen 2011 21859970	NA	smoking, body mass index, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, education, and alcohol consumption. Analyses in women were also adjusted for hormone replacement therapy.	All	% FA	nd	nd
52	Joensen 2011 21859970	NA	smoking, body mass index, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, education, and alcohol consumption. Analyses in women were also adjusted for hormone replacement therapy.	Qt1	% FA	nd	nd
53	Joensen 2011 21859970	NA	smoking, body mass index, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, education, and alcohol consumption. Analyses in women were also adjusted for hormone replacement therapy.	Qt2	% FA	0.07	nd

Appendix F
Observational results: acute coronary syndrome

Row	Study PMID	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
28	Joensen 2011 21859970	nd	HR	155	nd	nd	0.72	0.5	1.04		
29	Joensen 2011 21859970	nd	HR	nd	nd	nd	0.84	0.71	1	per 0.1%	0.046
30	Joensen 2011 21859970	0.22	HR	48	nd	nd	Reference group				nd
31	Joensen 2011 21859970	0.27	HR	53	nd	nd	1.13	0.65	1.96		
32	Joensen 2011 21859970	0.31	HR	44	nd	nd	0.92	0.5	1.68		
33	Joensen 2011 21859970	0.37	HR	46	nd	nd	1.27	0.7	2.31		
34	Joensen 2011 21859970	nd	HR	52	nd	nd	0.81	0.43	1.51		
35	Joensen 2011 21859970	nd	HR	nd	nd	nd	0.94	0.76	1.16	per 0.1%	0.56
36	Joensen 2009 19825219	0.05	HR	nd	nd	nd	Reference group				nd
37	Joensen 2009 19825219	0.07	HR	nd	nd	nd	0.98	0.78	1.22		
38	Joensen 2009 19825219	0.09	HR	nd	nd	nd	0.94	0.74	1.18		
39	Joensen 2009 19825219	0.11	HR	nd	nd	nd	0.9	0.71	1.15		
40	Joensen 2009 19825219	nd	HR	nd	nd	nd	0.89	0.68	1.16		
41	Joensen 2009 19825219	0.04	HR	nd	nd	nd	Reference group				nd
42	Joensen 2009 19825219	0.06	HR	nd	nd	nd	0.73	0.49	1.1		
43	Joensen 2009 19825219	0.07	HR	nd	nd	nd	1.12	0.74	1.71		
44	Joensen 2009 19825219	0.09	HR	nd	nd	nd	0.93	0.6	1.45		
45	Joensen 2009 19825219	nd	HR	nd	nd	nd	0.98	0.6	1.6		
46	Joensen 2011 21859970	0.06	HR	172	nd	nd	Reference group				nd
47	Joensen 2011 21859970	0.08	HR	194	nd	nd	1.2	0.86	1.68		
48	Joensen 2011 21859970	0.1	HR	147	nd	nd	0.76	0.53	1.08		
49	Joensen 2011 21859970	0.13	HR	140	nd	nd	0.88	0.62	1.27		
50	Joensen 2011 21859970	nd	HR	126	nd	nd	0.77	0.53	1.11		
51	Joensen 2011 21859970	nd	HR	nd	nd	nd	0.82	0.63	1.08	per 0.1%	0.17
52	Joensen 2011 21859970	0.07	HR	64	nd	nd	Reference group				nd
53	Joensen 2011 21859970	0.09	HR	53	nd	nd	1.26	0.74	2.13		

Appendix F
Observational results: acute coronary syndrome

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population type	Population	Subgroup	Cases Total/N Total (Rate)	Followup	n3 FA	n3 measure
54	Joensen 2011 21859970	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Women	233/1084 (1.2 per 1000 pt-y)	7.6 y	EPA	Adipose tissue
55	Joensen 2011 21859970	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Women	233/1084 (1.2 per 1000 pt-y)	7.6 y	EPA	Adipose tissue
56	Joensen 2011 21859970	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Women	233/1084 (1.2 per 1000 pt-y)	7.6 y	EPA	Adipose tissue
57	Joensen 2011 21859970	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Women	233/1084 (1.2 per 1000 pt-y)	7.6 y	EPA	Adipose tissue
58	Joensen 2009 19825219	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Men	852/24786 (4.4 per 1000 pt-y)	7.6 y	EPA	Intake
59	Joensen 2009 19825219	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Men	852/24786 (4.4 per 1000 pt-y)	7.6 y	EPA	Intake
60	Joensen 2009 19825219	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Men	852/24786 (4.4 per 1000 pt-y)	7.6 y	EPA	Intake
61	Joensen 2009 19825219	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Men	852/24786 (4.4 per 1000 pt-y)	7.6 y	EPA	Intake
62	Joensen 2009 19825219	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Men	852/24786 (4.4 per 1000 pt-y)	7.6 y	EPA	Intake
63	Joensen 2009 19825219	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Women	272/29017 (1.2 per 1000 pt-y)	7.6 y	EPA	Intake
64	Joensen 2009 19825219	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Women	272/29017 (1.2 per 1000 pt-y)	7.6 y	EPA	Intake
65	Joensen 2009 19825219	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Women	272/29017 (1.2 per 1000 pt-y)	7.6 y	EPA	Intake
66	Joensen 2009 19825219	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Women	272/29017 (1.2 per 1000 pt-y)	7.6 y	EPA	Intake
67	Joensen 2009 19825219	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Women	272/29017 (1.2 per 1000 pt-y)	7.6 y	EPA	Intake
68	Joensen 2011 21859970	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Men	779/1708 (1.2 per 1000 pt-y)	7.6 y	EPA+DHA+DPA	Adipose tissue
69	Joensen 2011 21859970	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Men	779/1708 (1.2 per 1000 pt-y)	7.6 y	EPA+DHA+DPA	Adipose tissue
70	Joensen 2011 21859970	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Men	779/1708 (1.2 per 1000 pt-y)	7.6 y	EPA+DHA+DPA	Adipose tissue
71	Joensen 2011 21859970	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Men	779/1708 (1.2 per 1000 pt-y)	7.6 y	EPA+DHA+DPA	Adipose tissue
72	Joensen 2011 21859970	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Men	779/1708 (1.2 per 1000 pt-y)	7.6 y	EPA+DHA+DPA	Adipose tissue
73	Joensen 2011 21859970	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Men	779/1708 (1.2 per 1000 pt-y)	7.6 y	EPA+DHA+DPA	Adipose tissue
74	Joensen 2011 21859970	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Women	233/1084 (1.2 per 1000 pt-y)	7.6 y	EPA+DHA+DPA	Adipose tissue
75	Joensen 2011 21859970	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Women	233/1084 (1.2 per 1000 pt-y)	7.6 y	EPA+DHA+DPA	Adipose tissue
76	Joensen 2011 21859970	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Women	233/1084 (1.2 per 1000 pt-y)	7.6 y	EPA+DHA+DPA	Adipose tissue
77	Joensen 2011 21859970	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Women	233/1084 (1.2 per 1000 pt-y)	7.6 y	EPA+DHA+DPA	Adipose tissue
78	Joensen 2011 21859970	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Women	233/1084 (1.2 per 1000 pt-y)	7.6 y	EPA+DHA+DPA	Adipose tissue
79	Joensen 2011 21859970	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Women	233/1084 (1.2 per 1000 pt-y)	7.6 y	EPA+DHA+DPA	Adipose tissue

Appendix F
Observational results: acute coronary syndrome

Row	Study PMID	Supplement	Adjustments	Quantile	n3 units	Quantile low	Quantile median
54	Joensen 2011 21859970	NA	smoking, body mass index, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, education, and alcohol consumption. Analyses in women were also adjusted for hormone replacement therapy.	Qt3	% FA	0.09	nd
55	Joensen 2011 21859970	NA	smoking, body mass index, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, education, and alcohol consumption. Analyses in women were also adjusted for hormone replacement therapy.	Qt4	% FA	0.1	nd
56	Joensen 2011 21859970	NA	smoking, body mass index, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, education, and alcohol consumption. Analyses in women were also adjusted for hormone replacement therapy.	Qt5	% FA	>0.14	nd
57	Joensen 2011 21859970	NA	smoking, body mass index, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, education, and alcohol consumption. Analyses in women were also adjusted for hormone replacement therapy.	All	% FA	nd	nd
58	Joensen 2009 19825219	No	smoking, BMI, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, alcohol consumption, total intake of fruit, vegetables, saturated fat, monounsaturated fat and n-6 PUFA.	Qt1	g/d	nd	nd
59	Joensen 2009 19825219	No	smoking, BMI, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, alcohol consumption, total intake of fruit, vegetables, saturated fat, monounsaturated fat and n-6 PUFA.	Qt2	g/d	0.09	nd
60	Joensen 2009 19825219	No	smoking, BMI, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, alcohol consumption, total intake of fruit, vegetables, saturated fat, monounsaturated fat and n-6 PUFA.	Qt3	g/d	0.14	0.18
61	Joensen 2009 19825219	No	smoking, BMI, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, alcohol consumption, total intake of fruit, vegetables, saturated fat, monounsaturated fat and n-6 PUFA.	Qt4	g/d	0.2	nd
62	Joensen 2009 19825219	No	smoking, BMI, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, alcohol consumption, total intake of fruit, vegetables, saturated fat, monounsaturated fat and n-6 PUFA.	Qt5	g/d	>0.28	nd
63	Joensen 2009 19825219	No	smoking, BMI, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, alcohol consumption, total intake of fruit, vegetables, saturated fat, monounsaturated fat and n-6 PUFA.	Qt1	g/d	nd	nd
64	Joensen 2009 19825219	No	smoking, BMI, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, alcohol consumption, total intake of fruit, vegetables, saturated fat, monounsaturated fat and n-6 PUFA.	Qt2	g/d	0.08	nd
65	Joensen 2009 19825219	No	smoking, BMI, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, alcohol consumption, total intake of fruit, vegetables, saturated fat, monounsaturated fat and n-6 PUFA.	Qt3	g/d	0.13	nd
66	Joensen 2009 19825219	No	smoking, BMI, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, alcohol consumption, total intake of fruit, vegetables, saturated fat, monounsaturated fat and n-6 PUFA.	Qt4	g/d	0.19	0.15
67	Joensen 2009 19825219	No	smoking, BMI, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, alcohol consumption, total intake of fruit, vegetables, saturated fat, monounsaturated fat and n-6 PUFA.	Qt5	g/d	>0.24	nd
68	Joensen 2011 21859970	NA	smoking, body mass index, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, education, and alcohol consumption. Analyses in women were also adjusted for hormone replacement therapy.	Qt1	% FA	nd	nd
69	Joensen 2011 21859970	NA	smoking, body mass index, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, education, and alcohol consumption. Analyses in women were also adjusted for hormone replacement therapy.	Qt2	% FA	0.42	nd
70	Joensen 2011 21859970	NA	smoking, body mass index, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, education, and alcohol consumption. Analyses in women were also adjusted for hormone replacement therapy.	Qt3	% FA	0.51	nd
71	Joensen 2011 21859970	NA	smoking, body mass index, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, education, and alcohol consumption. Analyses in women were also adjusted for hormone replacement therapy.	Qt4	% FA	0.61	nd
72	Joensen 2011 21859970	NA	smoking, body mass index, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, education, and alcohol consumption. Analyses in women were also adjusted for hormone replacement therapy.	Qt5	% FA	>0.74	nd
73	Joensen 2011 21859970	NA	smoking, body mass index, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, education, and alcohol consumption. Analyses in women were also adjusted for hormone replacement therapy.	All	% FA	nd	nd
74	Joensen 2011 21859970	NA	smoking, body mass index, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, education, and alcohol consumption. Analyses in women were also adjusted for hormone replacement therapy.	Qt1	% FA	nd	nd
75	Joensen 2011 21859970	NA	smoking, body mass index, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, education, and alcohol consumption. Analyses in women were also adjusted for hormone replacement therapy.	Qt2	% FA	0.49	nd
76	Joensen 2011 21859970	NA	smoking, body mass index, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, education, and alcohol consumption. Analyses in women were also adjusted for hormone replacement therapy.	Qt3	% FA	0.64	nd
77	Joensen 2011 21859970	NA	smoking, body mass index, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, education, and alcohol consumption. Analyses in women were also adjusted for hormone replacement therapy.	Qt4	% FA	0.73	nd
78	Joensen 2011 21859970	NA	smoking, body mass index, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, education, and alcohol consumption. Analyses in women were also adjusted for hormone replacement therapy.	Qt5	% FA	>0.86	nd
79	Joensen 2011 21859970	NA	smoking, body mass index, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, education, and alcohol consumption. Analyses in women were also adjusted for hormone replacement therapy.	All	% FA	nd	nd

Appendix F
Observational results: acute coronary syndrome

Row	Study PMID	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
54	Joensen 2011 21859970	0.1	HR	28	nd	nd	2.23	1.19	4.17		
55	Joensen 2011 21859970	0.14	HR	48	nd	nd	1.21	0.69	2.13		
56	Joensen 2011 21859970	nd	HR	40	nd	nd	1.11	0.63	1.97		
57	Joensen 2011 21859970	nd	HR	nd	nd	nd	0.85	0.59	1.23	per 0.1%	0.39
58	Joensen 2009 19825219	0.09	HR	nd	nd	nd	Reference group				nd
59	Joensen 2009 19825219	0.14	HR	nd	nd	nd	0.87	0.7	1.08		
60	Joensen 2009 19825219	0.2	HR	nd	nd	nd	0.86	0.69	1.08		
61	Joensen 2009 19825219	0.28	HR	nd	nd	nd	0.86	0.69	1.08		
62	Joensen 2009 19825219	nd	HR	nd	nd	nd	0.84	0.66	1.06		
63	Joensen 2009 19825219	0.08	HR	nd	nd	nd	Reference group				nd
64	Joensen 2009 19825219	0.13	HR	nd	nd	nd	0.92	0.62	1.36		
65	Joensen 2009 19825219	0.19	HR	nd	nd	nd	1.11	0.75	1.66		
66	Joensen 2009 19825219	0.24	HR	nd	nd	nd	1.57	1.04	2.38		
67	Joensen 2009 19825219	nd	HR	nd	nd	nd	0.93	0.6	1.42		
68	Joensen 2011 21859970	0.42	HR	159	nd	nd	Reference group				nd
69	Joensen 2011 21859970	0.51	HR	165	nd	nd	0.91	0.63	1.31		
70	Joensen 2011 21859970	0.61	HR	154	nd	nd	0.84	0.57	1.22		
71	Joensen 2011 21859970	0.74	HR	150	nd	nd	0.75	0.52	1.1		
72	Joensen 2011 21859970	nd	HR	151	nd	nd	0.65	0.45	0.95		
73	Joensen 2011 21859970	nd	HR	nd	nd	nd	0.93	0.88	0.98	per 0.1%	0.01
74	Joensen 2011 21859970	0.49	HR	47	nd	nd	Reference group				nd
75	Joensen 2011 21859970	0.64	HR	51	nd	nd	0.51	0.28	0.94		
76	Joensen 2011 21859970	0.73	HR	45	nd	nd	1.22	0.68	2.19		
77	Joensen 2011 21859970	0.86	HR	44	nd	nd	0.98	0.52	1.86		
78	Joensen 2011 21859970	nd	HR	46	nd	nd	0.78	0.42	1.46		
79	Joensen 2011 21859970	nd	HR	nd	nd	nd	0.99	0.92	1.06	per 0.1%	0.39

Appendix F
Observational results: acute coronary syndrome

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population type	Population	Subgroup	Cases Total/N Total (Rate)	Followup	n3 FA	n3 measure
80	Joensen 2009 19825219	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Men	852/24786 (4.4 per 1000 pt-y)	7.6 y	EPA+DHA+DPA	Intake
81	Joensen 2009 19825219	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Men	852/24786 (4.4 per 1000 pt-y)	7.6 y	EPA+DHA+DPA	Intake
82	Joensen 2009 19825219	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Men	852/24786 (4.4 per 1000 pt-y)	7.6 y	EPA+DHA+DPA	Intake
83	Joensen 2009 19825219	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Men	852/24786 (4.4 per 1000 pt-y)	7.6 y	EPA+DHA+DPA	Intake
84	Joensen 2009 19825219	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Men	852/24786 (4.4 per 1000 pt-y)	7.6 y	EPA+DHA+DPA	Intake
85	Joensen 2009 19825219	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Women	272/29017 (1.2 per 1000 pt-y)	7.6 y	EPA+DHA+DPA	Intake
86	Joensen 2009 19825219	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Women	272/29017 (1.2 per 1000 pt-y)	7.6 y	EPA+DHA+DPA	Intake
87	Joensen 2009 19825219	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Women	272/29017 (1.2 per 1000 pt-y)	7.6 y	EPA+DHA+DPA	Intake
88	Joensen 2009 19825219	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Women	272/29017 (1.2 per 1000 pt-y)	7.6 y	EPA+DHA+DPA	Intake
89	Joensen 2009 19825219	Diet, Cancer, Health (Danish)	ACS	MI or UA	Healthy	Healthy 50-64 yo	Women	272/29017 (1.2 per 1000 pt-y)	7.6 y	EPA+DHA+DPA	Intake

Appendix F
Observational results: acute coronary syndrome

Row	Study PMID	Supplement	Adjustments	Quantile	n3 units	Quantile low	Quantile median
80	Joensen 2009 19825219	No	smoking, BMI, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, alcohol consumption, total intake of fruit, vegetables, saturated fat, monounsaturated fat and n-6 PUFA.	Qt1	g/d	nd	nd
81	Joensen 2009 19825219	No	smoking, BMI, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, alcohol consumption, total intake of fruit, vegetables, saturated fat, monounsaturated fat and n-6 PUFA.	Qt2	g/d	0.39	nd
82	Joensen 2009 19825219	No	smoking, BMI, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, alcohol consumption, total intake of fruit, vegetables, saturated fat, monounsaturated fat and n-6 PUFA.	Qt3	g/d	0.58	0.7
83	Joensen 2009 19825219	No	smoking, BMI, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, alcohol consumption, total intake of fruit, vegetables, saturated fat, monounsaturated fat and n-6 PUFA.	Qt4	g/d	0.79	nd
84	Joensen 2009 19825219	No	smoking, BMI, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, alcohol consumption, total intake of fruit, vegetables, saturated fat, monounsaturated fat and n-6 PUFA.	Qt5	g/d	>1.08	nd
85	Joensen 2009 19825219	No	smoking, BMI, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, alcohol consumption, total intake of fruit, vegetables, saturated fat, monounsaturated fat and n-6 PUFA.	Qt1	g/d	nd	nd
86	Joensen 2009 19825219	No	smoking, BMI, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, alcohol consumption, total intake of fruit, vegetables, saturated fat, monounsaturated fat and n-6 PUFA.	Qt2	g/d	0.38	nd
87	Joensen 2009 19825219	No	smoking, BMI, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, alcohol consumption, total intake of fruit, vegetables, saturated fat, monounsaturated fat and n-6 PUFA.	Qt3	g/d	0.57	0.57
88	Joensen 2009 19825219	No	smoking, BMI, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, alcohol consumption, total intake of fruit, vegetables, saturated fat, monounsaturated fat and n-6 PUFA.	Qt4	g/d	0.76	nd
89	Joensen 2009 19825219	No	smoking, BMI, time of moderate to vigorous physical activity, history of diabetes mellitus, systolic blood pressure, total cholesterol, alcohol consumption, total intake of fruit, vegetables, saturated fat, monounsaturated fat and n-6 PUFA.	Qt5	g/d	>1.03	nd

Appendix F
Observational results: acute coronary syndrome

Row	Study PMID	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
80	Joensen 2009 19825219	0.39	HR	nd	nd	nd	Reference group				nd
81	Joensen 2009 19825219	0.58	HR	nd	nd	nd	0.83	0.67	1.03		
82	Joensen 2009 19825219	0.79	HR	nd	nd	nd	0.81	0.65	1.01		
83	Joensen 2009 19825219	1.08	HR	nd	nd	nd	0.9	0.71	1.13		
84	Joensen 2009 19825219	nd	HR	nd	nd	nd	0.81	0.64	1.04		
85	Joensen 2009 19825219	0.38	HR	nd	nd	nd	Reference group				nd
86	Joensen 2009 19825219	0.57	HR	nd	nd	nd	0.85	0.57	1.26		
87	Joensen 2009 19825219	0.76	HR	nd	nd	nd	1.09	0.73	1.63		
88	Joensen 2009 19825219	1.03	HR	nd	nd	nd	1.31	0.86	1.98		
89	Joensen 2009 19825219	nd	HR	nd	nd	nd	0.97	0.62	1.52		

Appendix F
Observational results: atrial fibrillation

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure
2	Fretts 2013 23525429	Cardiovascular Health Study	AFib	incident AF	Healthy	Healthy age >= 65y	none	1089/4337 (25.1)	12y	ALA	Intake
3	Fretts 2013 23525429	Cardiovascular Health Study	AFib	incident AF	Healthy	Healthy age >= 65y	none	1089/4337 (25.1)	12y	ALA	Intake
4	Fretts 2013 23525429	Cardiovascular Health Study	AFib	incident AF	Healthy	Healthy age >= 65y	none	1089/4337 (25.1)	12y	ALA	Intake
5	Fretts 2013 23525429	Cardiovascular Health Study	AFib	incident AF	Healthy	Healthy age >= 65y	none	1089/4337 (25.1)	12y	ALA	Intake
6	Fretts 2013 23525429	Cardiovascular Health Study	AFib	incident AF	Healthy	Healthy age >= 65y	none	707/2899 (23.2)	16y	ALA	Plasma
7	Fretts 2013 23525429	Cardiovascular Health Study	AFib	incident AF	Healthy	Healthy age >= 65y	none	707/2899 (23.2)	16y	ALA	Plasma
8	Fretts 2013 23525429	Cardiovascular Health Study	AFib	incident AF	Healthy	Healthy age >= 65y	none	707/2899 (23.2)	16y	ALA	Plasma
9	Fretts 2013 23525429	Cardiovascular Health Study	AFib	incident AF	Healthy	Healthy age >= 65y	none	707/2899 (23.2)	16y	ALA	Plasma
10	Wu 2012 22282329	Cardiovascular Health Study	AFib	incident AF	Healthy	Healthy age >= 65y	none	789/3326 (24)	14y	All n-3	Plasma
11	Wu 2012 22282329	Cardiovascular Health Study	AFib	incident AF	Healthy	Healthy age >= 65y	none	789/3326 (24)	14y	All n-3	Plasma
12	Wu 2012 22282329	Cardiovascular Health Study	AFib	incident AF	Healthy	Healthy age >= 65y	none	789/3326 (24)	14y	All n-3	Plasma
13	Wu 2012 22282329	Cardiovascular Health Study	AFib	incident AF	Healthy	Healthy age >= 65y	none	789/3326 (24)	14y	All n-3	Plasma
14	Wu 2012 22282329	Cardiovascular Health Study	AFib	incident AF	Healthy	Healthy age >= 65y	none	789/3326 (24)	14y	DHA	Plasma
15	Wu 2012 22282329	Cardiovascular Health Study	AFib	incident AF	Healthy	Healthy age >= 65y	none	789/3326 (24)	14y	DHA	Plasma
16	Wu 2012 22282329	Cardiovascular Health Study	AFib	incident AF	Healthy	Healthy age >= 65y	none	789/3326 (24)	14y	DHA	Plasma
17	Wu 2012 22282329	Cardiovascular Health Study	AFib	incident AF	Healthy	Healthy age >= 65y	none	789/3326 (24)	14y	DHA	Plasma
18	Wu 2012 22282329	Cardiovascular Health Study	AFib	incident AF	Healthy	Healthy age >= 65y	none	789/3326 (24)	14y	DPA	Plasma
19	Wu 2012 22282329	Cardiovascular Health Study	AFib	incident AF	Healthy	Healthy age >= 65y	none	789/3326 (24)	14y	DPA	Plasma
20	Wu 2012 22282329	Cardiovascular Health Study	AFib	incident AF	Healthy	Healthy age >= 65y	none	789/3326 (24)	14y	DPA	Plasma
21	Wu 2012 22282329	Cardiovascular Health Study	AFib	incident AF	Healthy	Healthy age >= 65y	none	789/3326 (24)	14y	DPA	Plasma
22	Wu 2012 22282329	Cardiovascular Health Study	AFib	incident AF	Healthy	Healthy age >= 65y	none	789/3326 (24)	14y	EPA	Plasma
23	Wu 2012 22282329	Cardiovascular Health Study	AFib	incident AF	Healthy	Healthy age >= 65y	none	789/3326 (24)	14y	EPA	Plasma
24	Wu 2012 22282329	Cardiovascular Health Study	AFib	incident AF	Healthy	Healthy age >= 65y	none	789/3326 (24)	14y	EPA	Plasma
25	Wu 2012 22282329	Cardiovascular Health Study	AFib	incident AF	Healthy	Healthy age >= 65y	none	789/3326 (24)	14y	EPA	Plasma
26	Berry 2010 20211329	Women's Health Initiative	AFib	atrial fibrillation	Healthy	Women 50-79, Healthy	Women	378/44720 (0.85)	10 y	EPA+DHA	Intake
27	Berry 2010 20211329	Women's Health Initiative	AFib	atrial fibrillation	Healthy	Women 50-79, Healthy	Women	378/44720 (0.85)	10 y	EPA+DHA	Intake

Appendix F
Observational results: atrial fibrillation

Row	Study PMID	Supplement	Adjustments	Quantile	n3 units	Quantile low	Quantile median
2	Fretts 2013 23525429	no	age and sex, enrollment site, race, education, smoking, diabetes, history of heart failure, history of stroke, physical activity, BMI, waist circumference, treated HTN, and alcohol consumption.	Qr1	% fat intake	0.80	1.50
3	Fretts 2013 23525429	no	age and sex, enrollment site, race, education, smoking, diabetes, history of heart failure, history of stroke, physical activity, BMI, waist circumference, treated HTN, and alcohol consumption.	Qr2	% fat intake	1.80	1.90
4	Fretts 2013 23525429	no	age and sex, enrollment site, race, education, smoking, diabetes, history of heart failure, history of stroke, physical activity, BMI, waist circumference, treated HTN, and alcohol consumption.	Qr3	% fat intake	2.10	2.20
5	Fretts 2013 23525429	no	age and sex, enrollment site, race, education, smoking, diabetes, history of heart failure, history of stroke, physical activity, BMI, waist circumference, treated HTN, and alcohol consumption.	Qr4	% fat intake	2.50	2.80
6	Fretts 2013 23525429	no	age and sex, enrollment site, race, education, smoking, diabetes, history of heart failure, history of stroke, physical activity, BMI, waist circumference, treated HTN, and alcohol consumption.	Qr1	% FA	0.05	0.10
7	Fretts 2013 23525429	no	age and sex, enrollment site, race, education, smoking, diabetes, history of heart failure, history of stroke, physical activity, BMI, waist circumference, treated HTN, and alcohol consumption.	Qr2	% FA	0.11	0.13
8	Fretts 2013 23525429	no	age and sex, enrollment site, race, education, smoking, diabetes, history of heart failure, history of stroke, physical activity, BMI, waist circumference, treated HTN, and alcohol consumption.	Qr3	% FA	0.14	0.16
9	Fretts 2013 23525429	no	age and sex, enrollment site, race, education, smoking, diabetes, history of heart failure, history of stroke, physical activity, BMI, waist circumference, treated HTN, and alcohol consumption.	Qr4	% FA	0.18	0.21
10	Wu 2012 22282329	no	age, gender, race, education, enrollment site, BMI, persistent treated HTN, prevalent diabetes, prevalent MI, prevalent valvular disease, smoking, leasure time activity, alcohol intake, saturated fat intake, fruit and vegetable intake, and total calories	Qr1	% FA	nd	NR
11	Wu 2012 22282329	no	age, gender, race, education, enrollment site, BMI, persistent treated HTN, prevalent diabetes, prevalent MI, prevalent valvular disease, smoking, leasure time activity, alcohol intake, saturated fat intake, fruit and vegetable intake, and total calories	Qr2	% FA	nd	NR
12	Wu 2012 22282329	no	age, gender, race, education, enrollment site, BMI, persistent treated HTN, prevalent diabetes, prevalent MI, prevalent valvular disease, smoking, leasure time activity, alcohol intake, saturated fat intake, fruit and vegetable intake, and total calories	Qr3	% FA	nd	NR
13	Wu 2012 22282329	no	age, gender, race, education, enrollment site, BMI, persistent treated HTN, prevalent diabetes, prevalent MI, prevalent valvular disease, smoking, leasure time activity, alcohol intake, saturated fat intake, fruit and vegetable intake, and total calories	Qr4	% FA	nd	NR
14	Wu 2012 22282329	no	age, gender, race, education, enrollment site, BMI, persistent treated HTN, prevalent diabetes, prevalent MI, prevalent valvular disease, smoking, leasure time activity, alcohol intake, saturated fat intake, fruit and vegetable intake, and total calories	Qr1	% FA	0.78	1.98 (mean)
15	Wu 2012 22282329	no	age, gender, race, education, enrollment site, BMI, persistent treated HTN, prevalent diabetes, prevalent MI, prevalent valvular disease, smoking, leasure time activity, alcohol intake, saturated fat intake, fruit and vegetable intake, and total calories	Qr2	% FA	2.36	2.61 (mean)
16	Wu 2012 22282329	no	age, gender, race, education, enrollment site, BMI, persistent treated HTN, prevalent diabetes, prevalent MI, prevalent valvular disease, smoking, leasure time activity, alcohol intake, saturated fat intake, fruit and vegetable intake, and total calories	Qr3	% FA	2.89	3.19 (mean)
17	Wu 2012 22282329	no	age, gender, race, education, enrollment site, BMI, persistent treated HTN, prevalent diabetes, prevalent MI, prevalent valvular disease, smoking, leasure time activity, alcohol intake, saturated fat intake, fruit and vegetable intake, and total calories	Qr4	% FA	3.55	4.37 (mean)
18	Wu 2012 22282329	no	age, gender, race, education, enrollment site, BMI, persistent treated HTN, prevalent diabetes, prevalent MI, prevalent valvular disease, smoking, leasure time activity, alcohol intake, saturated fat intake, fruit and vegetable intake, and total calories	Qr1	% FA	0.11	0.63 (mean)
19	Wu 2012 22282329	no	age, gender, race, education, enrollment site, BMI, persistent treated HTN, prevalent diabetes, prevalent MI, prevalent valvular disease, smoking, leasure time activity, alcohol intake, saturated fat intake, fruit and vegetable intake, and total calories	Qr2	% FA	0.73	0.77 (mean)
20	Wu 2012 22282329	no	age, gender, race, education, enrollment site, BMI, persistent treated HTN, prevalent diabetes, prevalent MI, prevalent valvular disease, smoking, leasure time activity, alcohol intake, saturated fat intake, fruit and vegetable intake, and total calories	Qr3	% FA	0.83	0.87 (mean)
21	Wu 2012 22282329	no	age, gender, race, education, enrollment site, BMI, persistent treated HTN, prevalent diabetes, prevalent MI, prevalent valvular disease, smoking, leasure time activity, alcohol intake, saturated fat intake, fruit and vegetable intake, and total calories	Qr4	% FA	0.94	1.05 (mean)
22	Wu 2012 22282329	no	age, gender, race, education, enrollment site, BMI, persistent treated HTN, prevalent diabetes, prevalent MI, prevalent valvular disease, smoking, leasure time activity, alcohol intake, saturated fat intake, fruit and vegetable intake, and total calories	Qr1	% FA	0.11	0.3 (mean)
23	Wu 2012 22282329	no	age, gender, race, education, enrollment site, BMI, persistent treated HTN, prevalent diabetes, prevalent MI, prevalent valvular disease, smoking, leasure time activity, alcohol intake, saturated fat intake, fruit and vegetable intake, and total calories	Qr2	% FA	0.40	0.45 (mean)
24	Wu 2012 22282329	no	age, gender, race, education, enrollment site, BMI, persistent treated HTN, prevalent diabetes, prevalent MI, prevalent valvular disease, smoking, leasure time activity, alcohol intake, saturated fat intake, fruit and vegetable intake, and total calories	Qr3	% FA	0.52	0.58 (mean)
25	Wu 2012 22282329	no	age, gender, race, education, enrollment site, BMI, persistent treated HTN, prevalent diabetes, prevalent MI, prevalent valvular disease, smoking, leasure time activity, alcohol intake, saturated fat intake, fruit and vegetable intake, and total calories	Qr4	% FA	0.68	0.99 (mean)
26	Berry 2010 20211329	No	age, BMI, ethnicity, education, treated diabetes, SBP, treated hypertension, prior CVD, smoking, alcohol use, total energy intake, fruit/vegetables intakes, fiber intake	Qr1	g/d	0.00	nd
27	Berry 2010 20211329	No	age, BMI, ethnicity, education, treated diabetes, SBP, treated hypertension, prior CVD, smoking, alcohol use, total energy intake, fruit/vegetables intakes, fiber intake	Qr2	g/d	0.05	nd

Appendix F
Observational results: atrial fibrillation

Row	Study PMID	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
2	Fretts 2013 23525429	1.70	HR	272	nd	11118	Reference group			P trend	0.48
3	Fretts 2013 23525429	2.00	HR	277	nd	13362	0.87	0.74	1.04		
4	Fretts 2013 23525429	2.40	HR	271	nd	13683	0.90	0.75	1.07		
5	Fretts 2013 23525429	4.80	HR	269	nd	11900	1.06	0.89	1.27		
6	Fretts 2013 23525429	0.11	HR	178	nd	7616	Reference group			P trend	0.48
7	Fretts 2013 23525429	0.14	HR	182	nd	7156	1.11	0.90	1.37		
8	Fretts 2013 23525429	0.18	HR	177	nd	7170	1.09	0.88	1.35		
9	Fretts 2013 23525429	0.47	HR	170	nd	7921	0.92	0.74	1.15		
10	Wu 2012 22282329	nd	RR	220	nd	7510	Reference group			P trend	0.00
11	Wu 2012 22282329	nd	RR	210	nd	7788	0.93	0.77	1.12		
12	Wu 2012 22282329	nd	RR	204	nd	7676	0.97	0.80	1.18		
13	Wu 2012 22282329	nd	RR	155	nd	8159	0.71	0.57	0.89		
14	Wu 2012 22282329	2.35	RR	214	834	7771	Reference group			P trend	0.01
15	Wu 2012 22282329	2.88	RR	219	829	7476	1.08	0.89	1.30		
16	Wu 2012 22282329	3.54	RR	201	832	7852	0.98	0.80	1.19		
17	Wu 2012 22282329	8.17	RR	155	831	8070	0.77	0.62	0.96		
18	Wu 2012 22282329	0.72	RR	204	832	7616	Reference group			P trend	0.24
19	Wu 2012 22282329	0.82	RR	200	831	7828	0.97	0.79	1.18		
20	Wu 2012 22282329	0.93	RR	212	843	7842	1.06	0.87	1.29		
21	Wu 2012 22282329	1.63	RR	173	820	7882	0.86	0.70	1.06		
22	Wu 2012 22282329	0.39	RR	209	834	7227	Reference group			P trend	0.30
23	Wu 2012 22282329	0.51	RR	188	834	7778	0.88	0.72	1.07		
24	Wu 2012 22282329	0.67	RR	210	827	8004	1.01	0.83	1.23		
25	Wu 2012 22282329	8.52	RR	182	831	8160	0.86	0.69	1.06		
26	Berry 2010 20211329	<0.049	OR	nd	nd	nd	Reference group			P trend	0.58
27	Berry 2010 20211329	0.09	OR	nd	nd	nd	1.00	0.73	1.37		

Appendix F
Observational results: atrial fibrillation

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure
28	Berry 2010 20211329	Women's Health Initiative	AFib	atrial fibrillation	Healthy	Women 50-79, Healthy	Women	378/44720 (0.85)	10 y	EPA+DHA	Intake
29	Berry 2010 20211329	Women's Health Initiative	AFib	atrial fibrillation	Healthy	Women 50-79, Healthy	Women	378/44720 (0.85)	10 y	EPA+DHA	Intake
30	Brouwer 2006 16569549	Rotterdam	AFib	Atrial fibrillation is the most common sustained cardiac arrhythmia	Healthy	ppl who had no AF at baseline	none	312/5184 (6.01)	6.4 y	EPA+DHA	Intake
31	Brouwer 2006 16569549	Rotterdam	AFib	Atrial fibrillation is the most common sustained cardiac arrhythmia	Healthy	ppl who had no AF at baseline	none	312/5184 (6.01)	6.4 y	EPA+DHA	Intake
32	Brouwer 2006 16569549	Rotterdam	AFib	Atrial fibrillation is the most common sustained cardiac arrhythmia	Healthy	ppl who had no AF at baseline	none	312/5184 (6.01)	6.4 y	EPA+DHA	Intake
33	Brouwer 2006 16569549	Rotterdam	AFib	Atrial fibrillation is the most common sustained cardiac arrhythmia	Healthy	Subjects without previous MI	none	241/4584 (5.25)	6.4 y	EPA+DHA	Intake
34	Brouwer 2006 16569549	Rotterdam	AFib	Atrial fibrillation is the most common sustained cardiac arrhythmia	Healthy	Subjects without previous MI	none	241/4584 (5.25)	6.4 y	EPA+DHA	Intake
35	Brouwer 2006 16569549	Rotterdam	AFib	Atrial fibrillation is the most common sustained cardiac arrhythmia	Healthy	Subjects without previous MI	none	241/4584 (5.25)	6.4 y	EPA+DHA	Intake
36	Frost 2005 15640459	Diet, Cancer, Health (Danish)	AFib	atrial fibrillation or flutter	Healthy	Healthy 50-64 yo	Women	556/47949 (1.7%, 29.1/10000 (men); 0.7%, 12.4/10000 (women))	8.1 yr	EPA+DHA+DPA	Intake
37	Frost 2005 15640459	Diet, Cancer, Health (Danish)	AFib	atrial fibrillation or flutter	Healthy	Healthy 50-64 yo	Women	556/47949 (1.7%, 29.1/10000 (men); 0.7%, 12.4/10000 (women))	8.1 yr	EPA+DHA+DPA	Intake
38	Frost 2005 15640459	Diet, Cancer, Health (Danish)	AFib	atrial fibrillation or flutter	Healthy	Healthy 50-64 yo	Women	556/47949 (1.7%, 29.1/10000 (men); 0.7%, 12.4/10000 (women))	8.1 yr	EPA+DHA+DPA	Intake
39	Frost 2005 15640459	Diet, Cancer, Health (Danish)	AFib	atrial fibrillation or flutter	Healthy	Healthy 50-64 yo	Women	556/47949 (1.7%, 29.1/10000 (men); 0.7%, 12.4/10000 (women))	8.1 yr	EPA+DHA+DPA	Intake
40	Frost 2005 15640459	Diet, Cancer, Health (Danish)	AFib	atrial fibrillation or flutter	Healthy	Healthy 50-64 yo	Women	556/47949 (1.7%, 29.1/10000 (men); 0.7%, 12.4/10000 (women))	8.1 yr	EPA+DHA+DPA	Intake
42	**Subgroup analyses**										
43	Fretts 2013 23525429	Cardiovascular Health Study	AFib	incident AF	Healthy	Healthy age >= 65y	women	nd	12y	ALA	Intake
44	Fretts 2013 23525429	Cardiovascular Health Study	AFib	incident AF	Healthy	Healthy age >= 65y	women	nd	12y	ALA	Intake
45	Fretts 2013 23525429	Cardiovascular Health Study	AFib	incident AF	Healthy	Healthy age >= 65y	women	nd	12y	ALA	Intake
46	Fretts 2013 23525429	Cardiovascular Health Study	AFib	incident AF	Healthy	Healthy age >= 65y	women	nd	12y	ALA	Intake
47	Fretts 2013 23525429	Cardiovascular Health Study	AFib	incident AF	Healthy	Healthy age >= 65y	men	nd	12y	ALA	Intake
48	Fretts 2013 23525429	Cardiovascular Health Study	AFib	incident AF	Healthy	Healthy age >= 65y	men	nd	12y	ALA	Intake
49	Fretts 2013 23525429	Cardiovascular Health Study	AFib	incident AF	Healthy	Healthy age >= 65y	men	nd	12y	ALA	Intake
50	Fretts 2013 23525429	Cardiovascular Health Study	AFib	incident AF	Healthy	Healthy age >= 65y	men	nd	12y	ALA	Intake

Appendix F
Observational results: atrial fibrillation

Row	Study PMID	Supplement	Adjustments	Quantile	n3 units	Quantile low	Quantile median
28	Berry 2010 20211329	No	age, BMI, ethnicity, education, treated diabetes, SBP, treated hypertension, prior CVD, smoking, alcohol use, total energy intake, fruit/vegetables intakes, fiber intake	Qr3	g/d	0.09	nd
29	Berry 2010 20211329	No	age, BMI, ethnicity, education, treated diabetes, SBP, treated hypertension, prior CVD, smoking, alcohol use, total energy intake, fruit/vegetables intakes, fiber intake	Qr4	g/d	>0.157	nd
30	Brouwer 2006 16569549	Yes	age, sex, energy intake, diabetes mellitus, alcohol intake, systolic blood pressure, HDL and total cholesterol levels, intake of saturated fatty acids, smoking status, and previous myocardial infarction	Qr1	mg/d	nd	19.40
31	Brouwer 2006 16569549	Yes	age, sex, energy intake, diabetes mellitus, alcohol intake, systolic blood pressure, HDL and total cholesterol levels, intake of saturated fatty acids, smoking status, and previous myocardial infarction	Qr2	mg/d	43.20	87.80
32	Brouwer 2006 16569549	Yes	age, sex, energy intake, diabetes mellitus, alcohol intake, systolic blood pressure, HDL and total cholesterol levels, intake of saturated fatty acids, smoking status, and previous myocardial infarction	Qr3	mg/d	143.50	330.00
33	Brouwer 2006 16569549	Yes	age, sex, energy intake, diabetes mellitus, alcohol intake, systolic blood pressure, HDL and total cholesterol levels, intake of saturated fatty acids, smoking status, and previous myocardial infarction	Qr1	mg/d	nd	nd
34	Brouwer 2006 16569549	Yes	age, sex, energy intake, diabetes mellitus, alcohol intake, systolic blood pressure, HDL and total cholesterol levels, intake of saturated fatty acids, smoking status, and previous myocardial infarction	Qr2	mg/d	nd	nd
35	Brouwer 2006 16569549	Yes	age, sex, energy intake, diabetes mellitus, alcohol intake, systolic blood pressure, HDL and total cholesterol levels, intake of saturated fatty acids, smoking status, and previous myocardial infarction	Qr3	mg/d	nd	nd
36	Frost 2005 15640459	No	age, sex, height, BMI, smoking, consumption of alcohol, total energy intake, systolic blood pressure, treatment for hypertension, total serum cholestrol, and level of education	Qt1	g/d	nd	0.16 (SD=0.08)
37	Frost 2005 15640459	No	age, sex, height, BMI, smoking, consumption of alcohol, total energy intake, systolic blood pressure, treatment for hypertension, total serum cholestrol, and level of education	Qt2	g/d	nd	0.36 (SD=0.06)
38	Frost 2005 15640459	No	age, sex, height, BMI, smoking, consumption of alcohol, total energy intake, systolic blood pressure, treatment for hypertension, total serum cholestrol, and level of education	Qt3	g/d	nd	0.52 (SD=0.07)
39	Frost 2005 15640459	No	age, sex, height, BMI, smoking, consumption of alcohol, total energy intake, systolic blood pressure, treatment for hypertension, total serum cholestrol, and level of education	Qt4	g/d	nd	0.74 (SD=0.10
40	Frost 2005 15640459	No	age, sex, height, BMI, smoking, consumption of alcohol, total energy intake, systolic blood pressure, treatment for hypertension, total serum cholestrol, and level of education	Qt5	g/d	nd	1.29 (SD=0.47)
42	**Subgroup analyses**						
43	Fretts 2013 23525429	no	age and sex, enrollment site, race, education, smoking, diabetes, history of heart failure, history of stroke, physical activity, BMI, waist circumference, treated HTN, and alcohol consumption.	Qr1	% fat intake	0.80	1.50
44	Fretts 2013 23525429	no	age and sex, enrollment site, race, education, smoking, diabetes, history of heart failure, history of stroke, physical activity, BMI, waist circumference, treated HTN, and alcohol consumption.	Qr2	% fat intake	1.80	1.90
45	Fretts 2013 23525429	no	age and sex, enrollment site, race, education, smoking, diabetes, history of heart failure, history of stroke, physical activity, BMI, waist circumference, treated HTN, and alcohol consumption.	Qr3	% fat intake	2.10	2.20
46	Fretts 2013 23525429	no	age and sex, enrollment site, race, education, smoking, diabetes, history of heart failure, history of stroke, physical activity, BMI, waist circumference, treated HTN, and alcohol consumption.	Qr4	% fat intake	2.50	2.80
47	Fretts 2013 23525429	no	age and sex, enrollment site, race, education, smoking, diabetes, history of heart failure, history of stroke, physical activity, BMI, waist circumference, treated HTN, and alcohol consumption.	Qr1	% fat intake	0.80	1.50
48	Fretts 2013 23525429	no	age and sex, enrollment site, race, education, smoking, diabetes, history of heart failure, history of stroke, physical activity, BMI, waist circumference, treated HTN, and alcohol consumption.	Qr2	% fat intake	1.80	1.90
49	Fretts 2013 23525429	no	age and sex, enrollment site, race, education, smoking, diabetes, history of heart failure, history of stroke, physical activity, BMI, waist circumference, treated HTN, and alcohol consumption.	Qr3	% fat intake	2.10	2.20
50	Fretts 2013 23525429	no	age and sex, enrollment site, race, education, smoking, diabetes, history of heart failure, history of stroke, physical activity, BMI, waist circumference, treated HTN, and alcohol consumption.	Qr4	% fat intake	2.50	2.80

Row	Study PMID	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
28	Berry 2010 20211329	0.16	OR	nd	nd	nd	1.07	0.78	1.47		
29	Berry 2010 20211329	nd	OR	nd	nd	nd	1.02	0.73	1.44		
30	Brouwer 2006 16569549	43.20	RR	96	1728	11202	Reference group				nd
31	Brouwer 2006 16569549	143.50	RR	111	1728	11108	1.22	0.92	1.61		
32	Brouwer 2006 16569549	nd	RR	105	1728	11013	1.18	0.88	1.57		
33	Brouwer 2006 16569549	nd	RR	76	nd	9835	Reference group				nd
34	Brouwer 2006 16569549	nd	RR	86	nd	9657	1.23	0.90	1.69		
35	Brouwer 2006 16569549	nd	RR	79	nd	9712	1.15	0.83	1.60		
36	Frost 2005 15640459	nd	HR	100	9589	nd	Reference group			P trend	0.01
37	Frost 2005 15640459	nd	HR	92	9590	nd	0.86	0.65	1.15		
38	Frost 2005 15640459	nd	HR	110	9591	nd	1.08	0.82	1.42		
39	Frost 2005 15640459	nd	HR	110	9590	nd	1.01	0.77	1.34		
40	Frost 2005 15640459	nd	HR	144	9589	nd	1.34	1.02	1.76		
42	**Subgroup analyses**										
43	Fretts 2013 23525429	1.70	HR	133	nd	5561	Reference group			P trend	0.90
44	Fretts 2013 23525429	2.00	HR	146	nd	8137	0.78	0.62	1.08		
45	Fretts 2013 23525429	2.40	HR	174	nd	9826	0.75	0.60	1.07		
46	Fretts 2013 23525429	4.80	HR	179	nd	8898	1.00	0.79	1.26		
47	Fretts 2013 23525429	1.70	HR	112	nd	5558	Reference group			P trend	0.59
48	Fretts 2013 23525429	2.00	HR	143	nd	5525	0.94	0.65	1.35		
49	Fretts 2013 23525429	2.40	HR	106	nd	3856	0.98	0.68	1.42		
50	Fretts 2013 23525429	4.80	HR	96	nd	3002	0.87	0.59	1.30		

Appendix F
Observational results: atrial fibrillation

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure
51	Fretts 2013 23525429	Cardiovascular Health Study	AFib	incident AF	Healthy	Healthy age >= 65y	women	412/1844 (22.3)	16y	ALA	Plasma
52	Fretts 2013 23525429	Cardiovascular Health Study	AFib	incident AF	Healthy	Healthy age >= 65y	women	412/1844 (22.3)	16y	ALA	Plasma
53	Fretts 2013 23525429	Cardiovascular Health Study	AFib	incident AF	Healthy	Healthy age >= 65y	women	412/1844 (22.3)	16y	ALA	Plasma
54	Fretts 2013 23525429	Cardiovascular Health Study	AFib	incident AF	Healthy	Healthy age >= 65y	women	412/1844 (22.3)	16y	ALA	Plasma
55	Fretts 2013 23525429	Cardiovascular Health Study	AFib	incident AF	Healthy	Healthy age >= 65y	men	295/1055 (28)	16y	ALA	Plasma
56	Fretts 2013 23525429	Cardiovascular Health Study	AFib	incident AF	Healthy	Healthy age >= 65y	men	295/1055 (28)	16y	ALA	Plasma
57	Fretts 2013 23525429	Cardiovascular Health Study	AFib	incident AF	Healthy	Healthy age >= 65y	men	295/1055 (28)	16y	ALA	Plasma
58	Fretts 2013 23525429	Cardiovascular Health Study	AFib	incident AF	Healthy	Healthy age >= 65y	men	295/1055 (28)	16y	ALA	Plasma

Appendix F
Observational results: atrial fibrillation

Row	Study PMID	Supplement	Adjustments	Quantile	n3 units	Quantile low	Quantile median
51	Fretts 2013 23525429	no	age and sex, enrollment site, race, education, smoking, diabetes, history of heart failure, history of stroke, physical activity, BMI, waist circumference, treated HTN, and alcohol consumption.	Qr1	% FA	0.05	0.10
52	Fretts 2013 23525429	no	age and sex, enrollment site, race, education, smoking, diabetes, history of heart failure, history of stroke, physical activity, BMI, waist circumference, treated HTN, and alcohol consumption.	Qr2	% FA	0.11	0.13
53	Fretts 2013 23525429	no	age and sex, enrollment site, race, education, smoking, diabetes, history of heart failure, history of stroke, physical activity, BMI, waist circumference, treated HTN, and alcohol consumption.	Qr3	% FA	0.14	0.16
54	Fretts 2013 23525429	no	age and sex, enrollment site, race, education, smoking, diabetes, history of heart failure, history of stroke, physical activity, BMI, waist circumference, treated HTN, and alcohol consumption.	Qr4	% FA	0.18	0.21
55	Fretts 2013 23525429	no	age and sex, enrollment site, race, education, smoking, diabetes, history of heart failure, history of stroke, physical activity, BMI, waist circumference, treated HTN, and alcohol consumption.	Qr1	% FA	0.05	0.10
56	Fretts 2013 23525429	no	age and sex, enrollment site, race, education, smoking, diabetes, history of heart failure, history of stroke, physical activity, BMI, waist circumference, treated HTN, and alcohol consumption.	Qr2	% FA	0.11	0.13
57	Fretts 2013 23525429	no	age and sex, enrollment site, race, education, smoking, diabetes, history of heart failure, history of stroke, physical activity, BMI, waist circumference, treated HTN, and alcohol consumption.	Qr3	% FA	0.14	0.16
58	Fretts 2013 23525429	no	age and sex, enrollment site, race, education, smoking, diabetes, history of heart failure, history of stroke, physical activity, BMI, waist circumference, treated HTN, and alcohol consumption.	Qr4	% FA	0.18	0.21

Appendix F
Observational results: atrial fibrillation

Row	Study PMID	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
51	Fretts 2013 23525429	0.11	HR	100	nd	4972	Reference group			P trend	0.53
52	Fretts 2013 23525429	0.14	HR	110	nd	4886	1.08	0.82	1.43		
53	Fretts 2013 23525429	0.18	HR	99	nd	4992	0.95	0.71	1.27		
54	Fretts 2013 23525429	0.47	HR	103	nd	5180	0.95	0.71	1.26		
55	Fretts 2013 23525429	0.11	HR	82	nd	2800	Reference group			P trend	0.42
56	Fretts 2013 23525429	0.14	HR	76	nd	2232	1.10	0.80	1.51		
57	Fretts 2013 23525429	0.18	HR	70	nd	2261	1.07	0.77	1.48		
58	Fretts 2013 23525429	0.47	HR	67	nd	2540	0.81	0.58	1.31		

Appendix F
Observational results: sudden coronary death

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure
2	Albert 2005 16301356	Nurses' Health Study	SCD	nd	Healthy	Healthy 34-59 yo female nurses	All	206/76763 (0.27)	18 y	ALA	Intake
3	Albert 2005 16301356	Nurses' Health Study	SCD	nd	Healthy	Healthy 34-59 yo female nurses	All	206/76763 (0.27)	18 y	ALA	Intake
4	Albert 2005 16301356	Nurses' Health Study	SCD	nd	Healthy	Healthy 34-59 yo female nurses	All	206/76763 (0.27)	18 y	ALA	Intake
5	Albert 2005 16301356	Nurses' Health Study	SCD	nd	Healthy	Healthy 34-59 yo female nurses	All	206/76763 (0.27)	18 y	ALA	Intake
6	Albert 2005 16301356	Nurses' Health Study	SCD	nd	Healthy	Healthy 34-59 yo female nurses	All	206/76763 (0.27)	18 y	ALA	Intake
7	Fretts 2014 25159901	Cardiovascular Health Study	SCD	Arrythmic death	Healthy	Healthy age >= 65y	All	135/2583 (5.2)	12y	ALA	Intake
8	Fretts 2014 25159901	Cardiovascular Health Study	SCD	Arrythmic death	Healthy	Healthy age >= 65y	All	135/2583 (5.2)	12y	ALA	Intake
9	Fretts 2014 25159901	Cardiovascular Health Study	SCD	Arrythmic death	Healthy	Healthy age >= 65y	All	135/2583 (5.2)	12y	ALA	Intake
10	Fretts 2014 25159901	Cardiovascular Health Study	SCD	Arrythmic death	Healthy	Healthy age >= 65y	All	135/2583 (5.2)	12y	ALA	Intake
11	Fretts 2014 25159901	Cardiovascular Health Study	SCD	Arrythmic death	Healthy	Healthy age >= 65y	All	135/2583 (5.2)	12y	ALA	Intake
12	Fretts 2014 25159901	Cardiovascular Health Study	SCD	Arrythmic death	Healthy	Healthy age >= 65y	All	170/2709 (6.3)	16y	ALA	Plasma
13	Fretts 2014 25159901	Cardiovascular Health Study	SCD	Arrythmic death	Healthy	Healthy age >= 65y	All	170/2709 (6.3)	16y	ALA	Plasma
14	Fretts 2014 25159901	Cardiovascular Health Study	SCD	Arrythmic death	Healthy	Healthy age >= 65y	All	170/2709 (6.3)	16y	ALA	Plasma
15	Fretts 2014 25159901	Cardiovascular Health Study	SCD	Arrythmic death	Healthy	Healthy age >= 65y	All	170/2709 (6.3)	16y	ALA	Plasma
16	Fretts 2014 25159901	Cardiovascular Health Study	SCD	Arrythmic death	Healthy	Healthy age >= 65y	All	170/2709 (6.3)	16y	ALA	Plasma
17	Mozaffarian 2013 23546563	Cardiovascular Health Study	SCD	Arrythmic death	Healthy	Healthy age >= 65y	All	194/3941 (4.92)	16y	All n-3	Plasma
18	Mozaffarian 2013 23546563	Cardiovascular Health Study	SCD	Arrythmic death	Healthy	Healthy age >= 65y	All	194/3941 (4.92)	16y	All n-3	Plasma
19	Mozaffarian 2013 23546563	Cardiovascular Health Study	SCD	Arrythmic death	Healthy	Healthy age >= 65y	All	194/3941 (4.92)	16y	All n-3	Plasma
20	Mozaffarian 2013 23546563	Cardiovascular Health Study	SCD	Arrythmic death	Healthy	Healthy age >= 65y	All	194/3941 (4.92)	16y	All n-3	Plasma
21	Mozaffarian 2013 23546563	Cardiovascular Health Study	SCD	Arrythmic death	Healthy	Healthy age >= 65y	All	194/3941 (4.92)	16y	All n-3	Plasma

Appendix F
Observational results: sudden coronary death

Row	Study PMID	Supplement	Adjustments
2	Albert 2005 16301356	no	age, time periods, smoking status (never, past, curent), BMI (<22, 22-22.9, 23-24.9, 25-28.9, 29+ kg/m2), alcohol intake (0, <5, 5-14, 15+), menopausal status and postmenopausal hormone use, vigorous to moderate activity (<1, 1-1.9, 2-3.9, 4-6.9, 7+ hours/week), number of times aspirin was used per week (<1, 1-2, 3-6, 7-14, 15+), multivitamin use (yes vs. no), vitamin E supplement use (yes vs. no), history of HTN (yes vs. no), hypercholesterolemia (yes vs. no), diabetes (yes vs. no), family history of MI (no, before age 60 y, after age 60 y), history of prior CVD (yes vs. no)
3	Albert 2005 16301356	no	age, time periods, smoking status (never, past, curent), BMI (<22, 22-22.9, 23-24.9, 25-28.9, 29+ kg/m2), alcohol intake (0, <5, 5-14, 15+), menopausal status and postmenopausal hormone use, vigorous to moderate activity (<1, 1-1.9, 2-3.9, 4-6.9, 7+ hours/week), number of times aspirin was used per week (<1, 1-2, 3-6, 7-14, 15+), multivitamin use (yes vs. no), vitamin E supplement use (yes vs. no), history of HTN (yes vs. no), hypercholesterolemia (yes vs. no), diabetes (yes vs. no), family history of MI (no, before age 60 y, after age 60 y), history of prior CVD (yes vs. no)
4	Albert 2005 16301356	no	age, time periods, smoking status (never, past, curent), BMI (<22, 22-22.9, 23-24.9, 25-28.9, 29+ kg/m2), alcohol intake (0, <5, 5-14, 15+), menopausal status and postmenopausal hormone use, vigorous to moderate activity (<1, 1-1.9, 2-3.9, 4-6.9, 7+ hours/week), number of times aspirin was used per week (<1, 1-2, 3-6, 7-14, 15+), multivitamin use (yes vs. no), vitamin E supplement use (yes vs. no), history of HTN (yes vs. no), hypercholesterolemia (yes vs. no), diabetes (yes vs. no), family history of MI (no, before age 60 y, after age 60 y), history of prior CVD (yes vs. no)
5	Albert 2005 16301356	no	age, time periods, smoking status (never, past, curent), BMI (<22, 22-22.9, 23-24.9, 25-28.9, 29+ kg/m2), alcohol intake (0, <5, 5-14, 15+), menopausal status and postmenopausal hormone use, vigorous to moderate activity (<1, 1-1.9, 2-3.9, 4-6.9, 7+ hours/week), number of times aspirin was used per week (<1, 1-2, 3-6, 7-14, 15+), multivitamin use (yes vs. no), vitamin E supplement use (yes vs. no), history of HTN (yes vs. no), hypercholesterolemia (yes vs. no), diabetes (yes vs. no), family history of MI (no, before age 60 y, after age 60 y), history of prior CVD (yes vs. no)
6	Albert 2005 16301356	no	age, time periods, smoking status (never, past, curent), BMI (<22, 22-22.9, 23-24.9, 25-28.9, 29+ kg/m2), alcohol intake (0, <5, 5-14, 15+), menopausal status and postmenopausal hormone use, vigorous to moderate activity (<1, 1-1.9, 2-3.9, 4-6.9, 7+ hours/week), number of times aspirin was used per week (<1, 1-2, 3-6, 7-14, 15+), multivitamin use (yes vs. no), vitamin E supplement use (yes vs. no), history of HTN (yes vs. no), hypercholesterolemia (yes vs. no), diabetes (yes vs. no), family history of MI (no, before age 60 y, after age 60 y), history of prior CVD (yes vs. no)
7	Fretts 2014 25159901	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.
8	Fretts 2014 25159901	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.
9	Fretts 2014 25159901	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.
10	Fretts 2014 25159901	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.
11	Fretts 2014 25159901	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.
12	Fretts 2014 25159901	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.
13	Fretts 2014 25159901	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.
14	Fretts 2014 25159901	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.
15	Fretts 2014 25159901	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.
16	Fretts 2014 25159901	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.
17	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).
18	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).
19	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).
20	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).
21	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).

Appendix F
Observational results: sudden coronary death

Row	Study PMID	Quantile	n3 units	Quantile low	Quantile median	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
2	Albert 2005 16301356	Qt1	% kcal	nd	0.37	nd	RR	54		265219	Reference group			P trend	0.02
3	Albert 2005 16301356	Qt2	nd	nd	0.45	nd	RR	44		264770	0.85	0.57	1.27		
4	Albert 2005 16301356	Qt3	nd	nd	0.52	nd	RR	40		264962	0.76	0.5	1.16		
5	Albert 2005 16301356	Qt4	nd	nd	0.6	nd	RR	32		264647	0.63	0.4	0.98		
6	Albert 2005 16301356	Qt5	nd	nd	0.74	nd	RR	36		264520	0.63	0.41	0.98		
7	Fretts 2014 25159901	Qt1	% fat intake	0.39	1.33	1.45	HR	30	nd	4875	Reference group			P trend	0.42
8	Fretts 2014 25159901	Qt2	% fat intake	1.45	1.56	1.65	HR	28	nd	4987	0.93	0.55	1.58		
9	Fretts 2014 25159901	Qt3	% fat intake	1.65	1.76	1.87	HR	23	nd	5096	0.8	0.46	1.38		
10	Fretts 2014 25159901	Qt4	% fat intake	1.87	2	2.17	HR	34	nd	5291	1.1	0.66	1.84		
11	Fretts 2014 25159901	Qt5	% fat intake	2.17	2.44	4.88	HR	20	nd	5600	0.68	0.38	1.23		
12	Fretts 2014 25159901	Qt1	% FA	0.05	0.09	0.11	HR	35	nd	6483	Reference group			P trend	0.99
13	Fretts 2014 25159901	Qt2	% FA	0.11	0.12	0.13	HR	30	nd	6025	1.02	0.62	1.67		
14	Fretts 2014 25159901	Qt3	% FA	0.13	0.14	0.15	HR	38	nd	6315	1.23	0.76	1.99		
15	Fretts 2014 25159901	Qt4	% FA	0.15	0.17	0.19	HR	34	nd	6352	1.05	0.64	1.71		
16	Fretts 2014 25159901	Qt5	% FA	0.19	0.22	0.47	HR	33	nd	6936	0.98	0.6	1.62		
17	Mozaffarian 2013 23546563	Qt1	% FA	nd	3.17	nd	HR	nd	nd	nd	Reference group			P trend	0.008
18	Mozaffarian 2013 23546563	Qt2	% FA	nd	3.72	nd	HR	nd	nd	nd	0.79	0.5	1.24		
19	Mozaffarian 2013 23546563	Qt3	% FA	nd	4.21	nd	HR	nd	nd	nd	1.07	0.7	1.63		
20	Mozaffarian 2013 23546563	Qt4	% FA	nd	4.8	nd	HR	nd	nd	nd	0.68	0.42	1.1		
21	Mozaffarian 2013 23546563	Qt5	% FA	nd	6.04	nd	HR	nd	nd	nd	0.52	0.31	0.86		

Appendix F
Observational results: sudden coronary death

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure
22	Mozaffarian 2013 23546563	Cardiovascular Health Study	SCD	Arrythmic death	Healthy	Healthy age >= 65y	All	194/3941 (4.92)	16y	DHA	Plasma
23	Mozaffarian 2013 23546563	Cardiovascular Health Study	SCD	Arrythmic death	Healthy	Healthy age >= 65y	All	194/3941 (4.92)	16y	DHA	Plasma
24	Mozaffarian 2013 23546563	Cardiovascular Health Study	SCD	Arrythmic death	Healthy	Healthy age >= 65y	All	194/3941 (4.92)	16y	DHA	Plasma
25	Mozaffarian 2013 23546563	Cardiovascular Health Study	SCD	Arrythmic death	Healthy	Healthy age >= 65y	All	194/3941 (4.92)	16y	DHA	Plasma
26	Mozaffarian 2013 23546563	Cardiovascular Health Study	SCD	Arrythmic death	Healthy	Healthy age >= 65y	All	194/3941 (4.92)	16y	DHA	Plasma
27	Mozaffarian 2013 23546563	Cardiovascular Health Study	SCD	Arrythmic death	Healthy	Healthy age >= 65y	All	194/3941 (4.92)	16y	DPA	Plasma
28	Mozaffarian 2013 23546563	Cardiovascular Health Study	SCD	Arrythmic death	Healthy	Healthy age >= 65y	All	194/3941 (4.92)	16y	DPA	Plasma
29	Mozaffarian 2013 23546563	Cardiovascular Health Study	SCD	Arrythmic death	Healthy	Healthy age >= 65y	All	194/3941 (4.92)	16y	DPA	Plasma
30	Mozaffarian 2013 23546563	Cardiovascular Health Study	SCD	Arrythmic death	Healthy	Healthy age >= 65y	All	194/3941 (4.92)	16y	DPA	Plasma
31	Mozaffarian 2013 23546563	Cardiovascular Health Study	SCD	Arrythmic death	Healthy	Healthy age >= 65y	All	194/3941 (4.92)	16y	DPA	Plasma
32	Mozaffarian 2013 23546563	Cardiovascular Health Study	SCD	Arrythmic death	Healthy	Healthy age >= 65y	All	194/3941 (4.92)	16y	EPA	Plasma
33	Mozaffarian 2013 23546563	Cardiovascular Health Study	SCD	Arrythmic death	Healthy	Healthy age >= 65y	All	194/3941 (4.92)	16y	EPA	Plasma
34	Mozaffarian 2013 23546563	Cardiovascular Health Study	SCD	Arrythmic death	Healthy	Healthy age >= 65y	All	194/3941 (4.92)	16y	EPA	Plasma
35	Mozaffarian 2013 23546563	Cardiovascular Health Study	SCD	Arrythmic death	Healthy	Healthy age >= 65y	All	194/3941 (4.92)	16y	EPA	Plasma
36	Mozaffarian 2013 23546563	Cardiovascular Health Study	SCD	Arrythmic death	Healthy	Healthy age >= 65y	All	194/3941 (4.92)	16y	EPA	Plasma
37	Iso 2006 16401768	Japan Public Health Center-Based Study - Cohort I	SCD	nd	Healthy	Healthy 40-59	All	37/41578 (0.09)	11.5 y	EPA+DHA	Intake
38	Iso 2006 16401768	Japan Public Health Center-Based Study - Cohort I	SCD	nd	Healthy	Healthy 40-59	All	37/41578 (0.09)	11.5 y	EPA+DHA	Intake

Appendix F
Observational results: sudden coronary death

Row	Study PMID	Supplement	Adjustments
22	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).
23	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).
24	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).
25	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).
26	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).
27	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).
28	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).
29	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).
30	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).
31	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).
32	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).
33	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).
34	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).
35	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).
36	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).
37	Iso 2006 16401768	No	age; sex; cigarette smoking; alcohol intake; body mass index; histories of hypertension and diabetes; medication use for hypercholesterolemia; education level; sports at leisure time; quintiles of dietary intake of fruits, vegetables, saturated fat, monounsaturated fat, n6 polyunsaturated fat, cholesterol, and total energy; and PHC.
38	Iso 2006 16401768	No	age; sex; cigarette smoking; alcohol intake; body mass index; histories of hypertension and diabetes; medication use for hypercholesterolemia; education level; sports at leisure time; quintiles of dietary intake of fruits, vegetables, saturated fat, monounsaturated fat, n6 polyunsaturated fat, cholesterol, and total energy; and PHC.

Appendix F
Observational results: sudden coronary death

Row	Study PMID	Quantile	n3 units	Quantile low	Quantile median	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
22	Mozaffarian 2013 23546563	Qt1	% FA	nd	1.95	nd	HR	nd	nd	nd	Reference group			P trend	0.028
23	Mozaffarian 2013 23546563	Qt2	% FA	nd	2.44	nd	HR	nd	nd	nd	0.97	0.62	1.51		
24	Mozaffarian 2013 23546563	Qt3	% FA	nd	2.87	nd	HR	nd	nd	nd	0.85	0.54	1.33		
25	Mozaffarian 2013 23546563	Qt4	% FA	nd	3.36	nd	HR	nd	nd	nd	0.92	0.59	1.44		
26	Mozaffarian 2013 23546563	Qt5	% FA	nd	4.34	nd	HR	nd	nd	nd	0.55	0.33	0.93		
27	Mozaffarian 2013 23546563	Qt1	% FA	nd	0.63	nd	HR	nd	nd	nd	Reference group			P trend	0.39
28	Mozaffarian 2013 23546563	Qt2	% FA	nd	0.75	nd	HR	nd	nd	nd	0.79	0.49	1.27		
29	Mozaffarian 2013 23546563	Qt3	% FA	nd	0.82	nd	HR	nd	nd	nd	1.32	0.85	2.04		
30	Mozaffarian 2013 23546563	Qt4	% FA	nd	0.91	nd	HR	nd	nd	nd	0.83	0.52	1.34		
31	Mozaffarian 2013 23546563	Qt5	% FA	nd	1.04	nd	HR	nd	nd	nd	0.79	0.49	1.3		
32	Mozaffarian 2013 23546563	Qt1	% FA	nd	0.3	nd	HR	nd	nd	nd	Reference group			P trend	0.22
33	Mozaffarian 2013 23546563	Qt2	% FA	nd	0.41	nd	HR	nd	nd	nd	0.96	0.62	1.5		
34	Mozaffarian 2013 23546563	Qt3	% FA	nd	0.51	nd	HR	nd	nd	nd	0.83	0.53	1.31		
35	Mozaffarian 2013 23546563	Qt4	% FA	nd	0.64	nd	HR	nd	nd	nd	0.82	0.52	1.29		
36	Mozaffarian 2013 23546563	Qt5	% FA	nd	0.92	nd	HR	nd	nd	nd	0.76	0.47	1.23		
37	Iso 2006 16401768	Qt1	g/d	nd	0.3 (mean)	nd	HR	7	nd	102711	Reference group			P trend	0.12
38	Iso 2006 16401768	Qt2	g/d	nd	0.6 (mean)	nd	HR	0	nd	95861	ND				

Appendix F
Observational results: sudden coronary death

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure
39	Iso 2006 16401768	Japan Public Health Center-Based Study - Cohort I	SCD	nd	Healthy	Healthy 40-59	All	37/41578 (0.09)	11.5 y	EPA+DHA	Intake
40	Iso 2006 16401768	Japan Public Health Center-Based Study - Cohort I	SCD	nd	Healthy	Healthy 40-59	All	37/41578 (0.09)	11.5 y	EPA+DHA	Intake
41	Iso 2006 16401768	Japan Public Health Center-Based Study - Cohort I	SCD	nd	Healthy	Healthy 40-59	All	37/41578 (0.09)	11.5 y	EPA+DHA	Intake
42	Albert 1998 942039	Physician's Health Study	SCD	sudden cardiac death	Healthy	US male physicians	All	133/20551 (0.65)	11 y	All n-3	Intake
43	Albert 1998 942039	Physician's Health Study	SCD	sudden cardiac death	Healthy	US male physicians	All	133/20551 (0.65)	11 y	All n-3	Intake
44	Albert 1998 942039	Physician's Health Study	SCD	sudden cardiac death	Healthy	US male physicians	All	133/20551 (0.65)	11 y	All n-3	Intake
45	Albert 1998 942039	Physician's Health Study	SCD	sudden cardiac death	Healthy	US male physicians	All	133/20551 (0.65)	11 y	All n-3	Intake
46	Albert 1998 942039	Physician's Health Study	SCD	sudden cardiac death	Healthy	US male physicians	All	133/20551 (0.65)	11 y	All n-3	Intake
48	**Subgroup analyses**										
49	Albert 2005 16301356	Nurses' Health Study	SCD	nd	CVD	CVD (women)	CVD	47/nd (0.3)	18 y	ALA	Intake
50	Albert 2005 16301356	Nurses' Health Study	SCD	nd	CVD	CVD (women)	CVD	47/nd (0.3)	18 y	ALA	Intake
51	Albert 2005 16301356	Nurses' Health Study	SCD	nd	CVD	CVD (women)	CVD	47/nd (0.3)	18 y	ALA	Intake
52	Albert 2005 16301356	Nurses' Health Study	SCD	nd	CVD	CVD (women)	CVD	47/nd (0.3)	18 y	ALA	Intake
53	Albert 2005 16301356	Nurses' Health Study	SCD	nd	CVD	CVD (women)	CVD	47/nd (0.3)	18 y	ALA	Intake
54	Albert 2005 16301356	Nurses' Health Study	SCD	nd	Healthy	Healthy 34-59 yo female nurses	No CVD	159/nd (0.3)	18 y	ALA	Intake
55	Albert 2005 16301356	Nurses' Health Study	SCD	nd	Healthy	Healthy 34-59 yo female nurses	No CVD	159/nd (0.3)	18 y	ALA	Intake
56	Albert 2005 16301356	Nurses' Health Study	SCD	nd	Healthy	Healthy 34-59 yo female nurses	No CVD	159/nd (0.3)	18 y	ALA	Intake
57	Albert 2005 16301356	Nurses' Health Study	SCD	nd	Healthy	Healthy 34-59 yo female nurses	No CVD	159/nd (0.3)	18 y	ALA	Intake

Observational results: sudden coronary death

Row	Study PMID	Supplement	Adjustments
39	Iso 2006 16401768	No	age; sex; cigarette smoking; alcohol intake; body mass index; histories of hypertension and diabetes; medication use for hypercholesterolemia; education level; sports at leisure time; quintiles of dietary intake of fruits, vegetables, saturated fat, monounsaturated fat, n6 polyunsaturated fat, cholesterol, and total energy; and PHC.
40	Iso 2006 16401768	No	age; sex; cigarette smoking; alcohol intake; body mass index; histories of hypertension and diabetes; medication use for hypercholesterolemia; education level; sports at leisure time; quintiles of dietary intake of fruits, vegetables, saturated fat, monounsaturated fat, n6 polyunsaturated fat, cholesterol, and total energy; and PHC.
41	Iso 2006 16401768	No	age; sex; cigarette smoking; alcohol intake; body mass index; histories of hypertension and diabetes; medication use for hypercholesterolemia; education level; sports at leisure time; quintiles of dietary intake of fruits, vegetables, saturated fat, monounsaturated fat, n6 polyunsaturated fat, cholesterol, and total energy; and PHC.
42	Albert 1998 942039	explicitly excluded fish oil supplements	age, aspirin and bea carotene treatment assignment, evidence of CVD prior to 12-month questionnaire, BMI, smoking status, history of diabetes, history of hypertension, history of hypercholesterolemia, alcohol consumption, and vitamin E, vitamin C, and multivitamin use.
43	Albert 1998 942039	explicitly excluded fish oil supplements	age, aspirin and bea carotene treatment assignment, evidence of CVD prior to 12-month questionnaire, BMI, smoking status, history of diabetes, history of hypertension, history of hypercholesterolemia, alcohol consumption, and vitamin E, vitamin C, and multivitamin use.
44	Albert 1998 942039	explicitly excluded fish oil supplements	age, aspirin and bea carotene treatment assignment, evidence of CVD prior to 12-month questionnaire, BMI, smoking status, history of diabetes, history of hypertension, history of hypercholesterolemia, alcohol consumption, and vitamin E, vitamin C, and multivitamin use.
45	Albert 1998 942039	explicitly excluded fish oil supplements	age, aspirin and bea carotene treatment assignment, evidence of CVD prior to 12-month questionnaire, BMI, smoking status, history of diabetes, history of hypertension, history of hypercholesterolemia, alcohol consumption, and vitamin E, vitamin C, and multivitamin use.
46	Albert 1998 942039	explicitly excluded fish oil supplements	age, aspirin and bea carotene treatment assignment, evidence of CVD prior to 12-month questionnaire, BMI, smoking status, history of diabetes, history of hypertension, history of hypercholesterolemia, alcohol consumption, and vitamin E, vitamin C, and multivitamin use.
48	**Subgroup analyses**		
49	Albert 2005 16301356	no	age, time periods, smoking status (never, past, curent), BMI (<22, 22-22.9, 23-24.9, 25-28.9, 29+ kg/m2), alcohol intake (0, <5, 5-14, 15+), menopausal status and postmenopausal hormone use, vigorous to moderate activity (<1, 1-1.9, 2-3.9, 4-6.9, 7+ hours/week), number of times aspirin was used per week (<1, 1-2, 3-6, 7-14, 15+), multivitamin use (yes vs. no), vitamin E supplement use (yes vs. no), history of HTN (yes vs. no), hypercholesterolemia (yes vs. no), diabetes (yes vs. no), family history of MI (no, before age 60 y, after age 60 y), history of prior CVD (yes vs. no)
50	Albert 2005 16301356	no	age, time periods, smoking status (never, past, curent), BMI (<22, 22-22.9, 23-24.9, 25-28.9, 29+ kg/m2), alcohol intake (0, <5, 5-14, 15+), menopausal status and postmenopausal hormone use, vigorous to moderate activity (<1, 1-1.9, 2-3.9, 4-6.9, 7+ hours/week), number of times aspirin was used per week (<1, 1-2, 3-6, 7-14, 15+), multivitamin use (yes vs. no), vitamin E supplement use (yes vs. no), history of HTN (yes vs. no), hypercholesterolemia (yes vs. no), diabetes (yes vs. no), family history of MI (no, before age 60 y, after age 60 y), history of prior CVD (yes vs. no)
51	Albert 2005 16301356	no	age, time periods, smoking status (never, past, curent), BMI (<22, 22-22.9, 23-24.9, 25-28.9, 29+ kg/m2), alcohol intake (0, <5, 5-14, 15+), menopausal status and postmenopausal hormone use, vigorous to moderate activity (<1, 1-1.9, 2-3.9, 4-6.9, 7+ hours/week), number of times aspirin was used per week (<1, 1-2, 3-6, 7-14, 15+), multivitamin use (yes vs. no), vitamin E supplement use (yes vs. no), history of HTN (yes vs. no), hypercholesterolemia (yes vs. no), diabetes (yes vs. no), family history of MI (no, before age 60 y, after age 60 y), history of prior CVD (yes vs. no)
52	Albert 2005 16301356	no	age, time periods, smoking status (never, past, curent), BMI (<22, 22-22.9, 23-24.9, 25-28.9, 29+ kg/m2), alcohol intake (0, <5, 5-14, 15+), menopausal status and postmenopausal hormone use, vigorous to moderate activity (<1, 1-1.9, 2-3.9, 4-6.9, 7+ hours/week), number of times aspirin was used per week (<1, 1-2, 3-6, 7-14, 15+), multivitamin use (yes vs. no), vitamin E supplement use (yes vs. no), history of HTN (yes vs. no), hypercholesterolemia (yes vs. no), diabetes (yes vs. no), family history of MI (no, before age 60 y, after age 60 y), history of prior CVD (yes vs. no)
53	Albert 2005 16301356	no	age, time periods, smoking status (never, past, curent), BMI (<22, 22-22.9, 23-24.9, 25-28.9, 29+ kg/m2), alcohol intake (0, <5, 5-14, 15+), menopausal status and postmenopausal hormone use, vigorous to moderate activity (<1, 1-1.9, 2-3.9, 4-6.9, 7+ hours/week), number of times aspirin was used per week (<1, 1-2, 3-6, 7-14, 15+), multivitamin use (yes vs. no), vitamin E supplement use (yes vs. no), history of HTN (yes vs. no), hypercholesterolemia (yes vs. no), diabetes (yes vs. no), family history of MI (no, before age 60 y, after age 60 y), history of prior CVD (yes vs. no)
54	Albert 2005 16301356	no	age, time periods, smoking status (never, past, curent), BMI (<22, 22-22.9, 23-24.9, 25-28.9, 29+ kg/m2), alcohol intake (0, <5, 5-14, 15+), menopausal status and postmenopausal hormone use, vigorous to moderate activity (<1, 1-1.9, 2-3.9, 4-6.9, 7+ hours/week), number of times aspirin was used per week (<1, 1-2, 3-6, 7-14, 15+), multivitamin use (yes vs. no), vitamin E supplement use (yes vs. no), history of HTN (yes vs. no), hypercholesterolemia (yes vs. no), diabetes (yes vs. no), family history of MI (no, before age 60 y, after age 60 y), history of prior CVD (yes vs. no)
55	Albert 2005 16301356	no	age, time periods, smoking status (never, past, curent), BMI (<22, 22-22.9, 23-24.9, 25-28.9, 29+ kg/m2), alcohol intake (0, <5, 5-14, 15+), menopausal status and postmenopausal hormone use, vigorous to moderate activity (<1, 1-1.9, 2-3.9, 4-6.9, 7+ hours/week), number of times aspirin was used per week (<1, 1-2, 3-6, 7-14, 15+), multivitamin use (yes vs. no), vitamin E supplement use (yes vs. no), history of HTN (yes vs. no), hypercholesterolemia (yes vs. no), diabetes (yes vs. no), family history of MI (no, before age 60 y, after age 60 y), history of prior CVD (yes vs. no)
56	Albert 2005 16301356	no	age, time periods, smoking status (never, past, curent), BMI (<22, 22-22.9, 23-24.9, 25-28.9, 29+ kg/m2), alcohol intake (0, <5, 5-14, 15+), menopausal status and postmenopausal hormone use, vigorous to moderate activity (<1, 1-1.9, 2-3.9, 4-6.9, 7+ hours/week), number of times aspirin was used per week (<1, 1-2, 3-6, 7-14, 15+), multivitamin use (yes vs. no), vitamin E supplement use (yes vs. no), history of HTN (yes vs. no), hypercholesterolemia (yes vs. no), diabetes (yes vs. no), family history of MI (no, before age 60 y, after age 60 y), history of prior CVD (yes vs. no)
57	Albert 2005 16301356	no	age, time periods, smoking status (never, past, curent), BMI (<22, 22-22.9, 23-24.9, 25-28.9, 29+ kg/m2), alcohol intake (0, <5, 5-14, 15+), menopausal status and postmenopausal hormone use, vigorous to moderate activity (<1, 1-1.9, 2-3.9, 4-6.9, 7+ hours/week), number of times aspirin was used per week (<1, 1-2, 3-6, 7-14, 15+), multivitamin use (yes vs. no), vitamin E supplement use (yes vs. no), history of HTN (yes vs. no), hypercholesterolemia (yes vs. no), diabetes (yes vs. no), family history of MI (no, before age 60 y, after age 60 y), history of prior CVD (yes vs. no)

Appendix F
Observational results: sudden coronary death

Row	Study PMID	Quantile	n3 units	Quantile low	Quantile median	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
39	Iso 2006 16401768	Qt3	g/d	nd	0.9 (mean)	nd	HR	9	nd	95258	1.04	0.34	3.16		
40	Iso 2006 16401768	Qt4	g/d	nd	1.3 (mean)	nd	HR	9	nd	91435	1.03	0.32	3.37		
41	Iso 2006 16401768	Qt5	g/d	nd	2.1 (mean)	nd	HR	12	nd	92062	1.24	0.39	3.98		
42	Albert 1998 942039	T1	g/mo	<0.3	nd	nd	RR	9	nd	7715	1				0.21
43	Albert 1998 942039	T2	g/mo	0.3	nd	2.7	RR	40	nd	65223	0.58	0.28	1.21		
44	Albert 1998 942039	T3	g/mo	2.7	nd	4.9	RR	19	nd	56083	0.34	0.15	0.75		
45	Albert 1998 942039	T4	g/mo	4.9	nd	7.4	RR	37	nd	61936	0.6	0.29	1.27		
46	Albert 1998 942039	T5	g/mo	nd	nd	>=7.4	RR	28	nd	62820	0.43	0.2	0.93		
48	**Subgroup analyses**														
49	Albert 2005 16301356	Qt1	% kcal	nd	0.35	nd	RR	13	nd	13007	Reference group			P trend	0.33
50	Albert 2005 16301356	Qt2	% kcal	nd	0.43	nd	RR	9	nd	12965	0.68	0.28	1.64		
51	Albert 2005 16301356	Qt3	% kcal	nd	0.49	nd	RR	6	nd	12936	0.38	0.14	1.06		
52	Albert 2005 16301356	Qt4	% kcal	nd	0.58	nd	RR	10	nd	12907	0.76	0.3	1.88		
53	Albert 2005 16301356	Qt5	% kcal	nd	0.72	nd	RR	9	nd	12841	0.53	0.19	1.45		
54	Albert 2005 16301356	Qt1	% kcal	nd	0.37	nd	RR	40	nd	252241	Reference group			P trend	0.03
55	Albert 2005 16301356	Qt2	% kcal	nd	0.45	nd	RR	34	nd	251981	0.89	0.56	1.41		
56	Albert 2005 16301356	Qt3	% kcal	nd	0.52	nd	RR	34	nd	251869	0.86	0.54	1.39		
57	Albert 2005 16301356	Qt4	% kcal	nd	0.6	nd	RR	24	nd	251644	0.6	0.35	1.03		

Appendix F

Observational results: sudden coronary death

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure
58	Albert 2005 16301356	Nurses' Health Study	SCD	nd	Healthy	Healthy 34-59 yo female nurses	No CVD	159/nd (0.3)	18 y	ALA	Intake
59	Mozaffarian_2005_15630029	Health Professional Follow-up Study	SCD	nd	Healthy	Healthy 40-75 y/o men	men	218/45722 (0.48)	14y	EPA+DHA	Intake
60	Mozaffarian_2005_15630029	Health Professional Follow-up Study	SCD	nd	Healthy	Healthy 40-75 y/o men	men	218/45722 (0.48)	14y	EPA+DHA	Intake
61	Mozaffarian_2005_15630029	Health Professional Follow-up Study	SCD	nd	Healthy	Healthy 40-75 y/o men	men	218/45722 (0.48)	14y	EPA+DHA	Intake
62	Mozaffarian_2005_15630029	Health Professional Follow-up Study	SCD	nd	Healthy	Healthy 40-75 y/o men	men	218/45722 (0.48)	14y	EPA+DHA	Intake
63	Mozaffarian_2005_15630029	Health Professional Follow-up Study	SCD	nd	Healthy	Healthy 40-75 y/o men	men	218/45722 (0.48)	14y	EPA+DHA	Intake
64	Mozaffarian_2005_15630029	Health Professional Follow-up Study	SCD	nd	Healthy	Healthy 40-75 y/o men	men	218/45722 (0.48)	14y	EPA+DHA	Intake
65	Mozaffarian_2005_15630029	Health Professional Follow-up Study	SCD	nd	Healthy	Healthy 40-75 y/o men	men	218/45722 (0.48)	14y	ALA	Intake
66	Mozaffarian_2005_15630029	Health Professional Follow-up Study	SCD	nd	Healthy	Healthy 40-75 y/o men	men	218/45722 (0.48)	14y	ALA	Intake
67	Mozaffarian_2005_15630029	Health Professional Follow-up Study	SCD	nd	Healthy	Healthy 40-75 y/o men	men	218/45722 (0.48)	14y	ALA	Intake
68	Mozaffarian_2005_15630029	Health Professional Follow-up Study	SCD	nd	Healthy	Healthy 40-75 y/o men	men	218/45722 (0.48)	14y	ALA	Intake
69	Mozaffarian_2005_15630029	Health Professional Follow-up Study	SCD	nd	Healthy	Healthy 40-75 y/o men	men	218/45722 (0.48)	14y	ALA	Intake

Appendix F
Observational results: sudden coronary death

Row	Study PMID	Supplement	Adjustments
58	Albert 2005 16301356	no	age, time periods, smoking status (never, past, curent), BMI (<22, 22-22.9, 23-24.9, 25-28.9, 29+ kg/m2), alcohol intake (0, <5, 5-14, 15+), menopausal status and postmenopausal hormone use, vigorous to moderate activity (<1, 1-1.9, 2-3.9, 4-6.9, 7+ hours/week), number of times aspirin was used per week (<1, 1-2, 3-6, 7-14, 15+), multivitamin use (yes vs. no), vitamin E supplement use (yes vs. no), history of HTN (yes vs. no), hypercholesterolemia (yes vs. no), diabetes (yes vs. no), family history of MI (no, before age 60 y, after age 60 y), history of prior CVD (yes vs. no)
59	Mozaffarian_2005_15630029	no	age (5-year categories); body mass index (quintiles); smoking (5 categories); physical activity (quintiles); history of diabetes, hypertension, or hypercholesterolemia; aspirin use; alcohol use (quintiles); and intake of protein, saturated fat, dietary fiber, monounsaturated fat, trans fatty acids, total calories, and ALA (each in quintiles).
60	Mozaffarian_2005_15630029	no	age (5-year categories); body mass index (quintiles); smoking (5 categories); physical activity (quintiles); history of diabetes, hypertension, or hypercholesterolemia; aspirin use; alcohol use (quintiles); and intake of protein, saturated fat, dietary fiber, monounsaturated fat, trans fatty acids, total calories, and ALA (each in quintiles).
61	Mozaffarian_2005_15630029	no	age (5-year categories); body mass index (quintiles); smoking (5 categories); physical activity (quintiles); history of diabetes, hypertension, or hypercholesterolemia; aspirin use; alcohol use (quintiles); and intake of protein, saturated fat, dietary fiber, monounsaturated fat, trans fatty acids, total calories, and ALA (each in quintiles).
62	Mozaffarian_2005_15630029	no	age (5-year categories); body mass index (quintiles); smoking (5 categories); physical activity (quintiles); history of diabetes, hypertension, or hypercholesterolemia; aspirin use; alcohol use (quintiles); and intake of protein, saturated fat, dietary fiber, monounsaturated fat, trans fatty acids, total calories, and ALA (each in quintiles).
63	Mozaffarian_2005_15630029	no	age (5-year categories); body mass index (quintiles); smoking (5 categories); physical activity (quintiles); history of diabetes, hypertension, or hypercholesterolemia; aspirin use; alcohol use (quintiles); and intake of protein, saturated fat, dietary fiber, monounsaturated fat, trans fatty acids, total calories, and ALA (each in quintiles).
64	Mozaffarian_2005_15630029	no	age (5-year categories); body mass index (quintiles); smoking (5 categories); physical activity (quintiles); history of diabetes, hypertension, or hypercholesterolemia; aspirin use; alcohol use (quintiles); and intake of protein, saturated fat, dietary fiber, monounsaturated fat, trans fatty acids, total calories, and ALA (each in quintiles).
65	Mozaffarian_2005_15630029	no	age (5-year categories); body mass index (quintiles); smoking (5 categories); physical activity (quintiles); history of diabetes, hypertension, or hypercholesterolemia; aspirin use; alcohol use (quintiles); and intake of protein, saturated fat, dietary fiber, monounsaturated fat, trans fatty acids, total calories, and ALA (each in quintiles).
66	Mozaffarian_2005_15630029	no	age (5-year categories); body mass index (quintiles); smoking (5 categories); physical activity (quintiles); history of diabetes, hypertension, or hypercholesterolemia; aspirin use; alcohol use (quintiles); and intake of protein, saturated fat, dietary fiber, monounsaturated fat, trans fatty acids, total calories, and ALA (each in quintiles).
67	Mozaffarian_2005_15630029	no	age (5-year categories); body mass index (quintiles); smoking (5 categories); physical activity (quintiles); history of diabetes, hypertension, or hypercholesterolemia; aspirin use; alcohol use (quintiles); and intake of protein, saturated fat, dietary fiber, monounsaturated fat, trans fatty acids, total calories, and ALA (each in quintiles).
68	Mozaffarian_2005_15630029	no	age (5-year categories); body mass index (quintiles); smoking (5 categories); physical activity (quintiles); history of diabetes, hypertension, or hypercholesterolemia; aspirin use; alcohol use (quintiles); and intake of protein, saturated fat, dietary fiber, monounsaturated fat, trans fatty acids, total calories, and ALA (each in quintiles).
69	Mozaffarian_2005_15630029	no	age (5-year categories); body mass index (quintiles); smoking (5 categories); physical activity (quintiles); history of diabetes, hypertension, or hypercholesterolemia; aspirin use; alcohol use (quintiles); and intake of protein, saturated fat, dietary fiber, monounsaturated fat, trans fatty acids, total calories, and ALA (each in quintiles).

Appendix F
Observational results: sudden coronary death

Row	Study PMID	Quantile	n3 units	Quantile low	Quantile median	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
58	Albert 2005 16301356	Qt5	% kcal	nd	0.74	nd	RR	27	nd	251727	0.59	0.34	1.02		
59	Mozaffarian_2005_15630029	<Median	mg/d	nd	n-6<11.2 g/d	250	HR	127	23111	nd	Ref				
60	Mozaffarian_2005_15630029	>Median	mg/d	250	n-6>11.2 g/d	nd	HR	91	22611	nd	0.65	0.47	0.88		
61	Mozaffarian_2005_15630029	<Median	mg/d	nd	n-6<11.2 g/d	250	RR	62	10982	nd	Ref			P low vs high n-6 intake	0.13
62	Mozaffarian_2005_15630029	<Median	mg/d	nd	n-6>11.2 g/d	250	RR	65	12129	nd	0.76	0.52	1.11		
63	Mozaffarian_2005_15630029	>Median	mg/d	250	n-6<11.2 g/d	nd	RR	46	11880	nd	0.52	0.34	0.79		
64	Mozaffarian_2005_15630029	>Median	mg/d	250	n-6>11.2 g/d	nd	RR	45	10731	nd	0.6	0.39	0.93		
65	Mozaffarian_2005_15630029	All	mg/d	nd	per 1 g/d increase	nd	HR				1.15	0.69	1.93		
66	Mozaffarian_2005_15630029	<Median	mg/d	nd	n-6<11.2 g/d	1080	RR	66	14462	nd	Ref			P low vs high n-6 intake	0.38
67	Mozaffarian_2005_15630029	<Median	mg/d	nd	n-6>11.2 g/d	1080	RR	36	8385	nd	0.88	0.56	1.36		
68	Mozaffarian_2005_15630029	>Median	mg/d	1080	n-6<11.2 g/d	nd	RR	42	8400	nd	0.95	0.64	1.43		
69	Mozaffarian_2005_15630029	>Median	mg/d	1080	n-6>11.2 g/d	nd	RR	74	14475	nd	0.93	0.64	1.35		

Appendix F
Observational results: hypertension

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure	Supplement
2	Wang 2010 20713915	Women's Health Study	HTN	incident HTN	Healthy	healthy 39-89	All	13633/28100 (48.5)	12.9y	All n-3	Intake	no
3	Wang 2010 20713915	Women's Health Study	HTN	incident HTN	Healthy	healthy 39-89	All	13633/28100 (48.5)	12.9y	All n-3	Intake	no
4	Wang 2010 20713915	Women's Health Study	HTN	incident HTN	Healthy	healthy 39-89	All	13633/28100 (48.5)	12.9y	All n-3	Intake	no
5	Wang 2010 20713915	Women's Health Study	HTN	incident HTN	Healthy	healthy 39-89	All	13633/28100 (48.5)	12.9y	All n-3	Intake	no
6	Wang 2010 20713915	Women's Health Study	HTN	incident HTN	Healthy	healthy 39-89	All	13633/28100 (48.5)	12.9y	All n-3	Intake	no
7	Wang 2011 21734059	Women's Health Study	HTN	incident HTN	Healthy	Healthy	All	516/1032 (50)	12.9y	All n-3	Erythrocyte PUFA	no
8	Wang 2011 21734059	Women's Health Study	HTN	incident HTN	Healthy	Healthy	All	516/1032 (50)	12.9y	All n-3	Erythrocyte PUFA	no
9	Wang 2011 21734059	Women's Health Study	HTN	incident HTN	Healthy	Healthy	All	516/1032 (50)	12.9y	All n-3	Erythrocyte PUFA	no
10	Wang 2011 21734059	Women's Health Study	HTN	incident HTN	Healthy	Healthy	All	516/1032 (50)	12.9y	All n-3	Erythrocyte PUFA	no
11	Xun 2011 21205024	CARDIA	HTN	incident HTN	Healthy	healthy	All: 18-30 y	999/4508 (22.1)	20 y	EPA+DHA+DPA	Intake	no
12	Xun 2011 21205024	CARDIA	HTN	incident HTN	Healthy	healthy	All: 18-30 y	999/4508 (22.1)	20 y	EPA+DHA+DPA	Intake	no
13	Xun 2011 21205024	CARDIA	HTN	incident HTN	Healthy	healthy	All: 18-30 y	999/4508 (22.1)	20 y	EPA+DHA+DPA	Intake	no
14	Xun 2011 21205024	CARDIA	HTN	incident HTN	Healthy	healthy	All: 18-30 y	999/4508 (22.1)	20 y	EPA+DHA+DPA	Intake	no
15	Xun 2011 21205024	CARDIA	HTN	incident HTN	Healthy	healthy	All: 18-30 y	999/4508 (22.1)	20 y	EPA	Intake	no
16	Xun 2011 21205024	CARDIA	HTN	incident HTN	Healthy	healthy	All: 18-30 y	999/4508 (22.1)	20 y	EPA	Intake	no
17	Xun 2011 21205024	CARDIA	HTN	incident HTN	Healthy	healthy	All: 18-30 y	999/4508 (22.1)	20 y	EPA	Intake	no
18	Xun 2011 21205024	CARDIA	HTN	incident HTN	Healthy	healthy	All: 18-30 y	999/4508 (22.1)	20 y	EPA	Intake	no

Appendix F
Observational results: hypertension

Row	Study PMID	Adjustments	Quantile	n3 units
2	Wang 2010 20713915	age (continuous), race (white or nonwhite), total energy intake (continuous), treatment (vitamin E, aspirin, └-carotene, or placebo), smoking (never, former, or current), alcohol intake (continuous), physical activity (continuous), postmenopausal status (yes, no, or uncertain), postmenopausal hormone use (never, former, or current), dietary sodium, potassium, calcium, and fiber (all in quintiles), BMI (continuous), history of diabetes mellitus (yes or no), and history of hypercholesterolemia (yes or no).	Qt1	g/d
3	Wang 2010 20713915	age (continuous), race (white or nonwhite), total energy intake (continuous), treatment (vitamin E, aspirin, └-carotene, or placebo), smoking (never, former, or current), alcohol intake (continuous), physical activity (continuous), postmenopausal status (yes, no, or uncertain), postmenopausal hormone use (never, former, or current), dietary sodium, potassium, calcium, and fiber (all in quintiles), BMI (continuous), history of diabetes mellitus (yes or no), and history of hypercholesterolemia (yes or no).	Qt2	g/d
4	Wang 2010 20713915	age (continuous), race (white or nonwhite), total energy intake (continuous), treatment (vitamin E, aspirin, └-carotene, or placebo), smoking (never, former, or current), alcohol intake (continuous), physical activity (continuous), postmenopausal status (yes, no, or uncertain), postmenopausal hormone use (never, former, or current), dietary sodium, potassium, calcium, and fiber (all in quintiles), BMI (continuous), history of diabetes mellitus (yes or no), and history of hypercholesterolemia (yes or no).	Qt3	g/d
5	Wang 2010 20713915	age (continuous), race (white or nonwhite), total energy intake (continuous), treatment (vitamin E, aspirin, └-carotene, or placebo), smoking (never, former, or current), alcohol intake (continuous), physical activity (continuous), postmenopausal status (yes, no, or uncertain), postmenopausal hormone use (never, former, or current), dietary sodium, potassium, calcium, and fiber (all in quintiles), BMI (continuous), history of diabetes mellitus (yes or no), and history of hypercholesterolemia (yes or no).	Qt4	g/d
6	Wang 2010 20713915	age (continuous), race (white or nonwhite), total energy intake (continuous), treatment (vitamin E, aspirin, └-carotene, or placebo), smoking (never, former, or current), alcohol intake (continuous), physical activity (continuous), postmenopausal status (yes, no, or uncertain), postmenopausal hormone use (never, former, or current), dietary sodium, potassium, calcium, and fiber (all in quintiles), BMI (continuous), history of diabetes mellitus (yes or no), and history of hypercholesterolemia (yes or no).	Qt5	g/d
7	Wang 2011 21734059	age, race, total energy intake (continuous), smoking status (current, past, never), alcohol use (rarely/never, 10–45 g ethanol/mo, 10–90 g ethanol/wk, >13 g ethanol/d), exercise (rarely/never,1, 1–3, $4 times/wk), menopause status (premenopausal, postmenopausal, unknown), and postmenopausal hormone use (current, past, never), BMI (continuous), history of diabetes (yes, no), and history of hypercholesterolemia (yes, no).	Qr1	% FA
8	Wang 2011 21734059	age, race, total energy intake (continuous), smoking status (current, past, never), alcohol use (rarely/never, 10–45 g ethanol/mo, 10–90 g ethanol/wk, >13 g ethanol/d), exercise (rarely/never,1, 1–3, $4 times/wk), menopause status (premenopausal, postmenopausal, unknown), and postmenopausal hormone use (current, past, never), BMI (continuous), history of diabetes (yes, no), and history of hypercholesterolemia (yes, no).	Qr2	% FA
9	Wang 2011 21734059	age, race, total energy intake (continuous), smoking status (current, past, never), alcohol use (rarely/never, 10–45 g ethanol/mo, 10–90 g ethanol/wk, >13 g ethanol/d), exercise (rarely/never,1, 1–3, $4 times/wk), menopause status (premenopausal, postmenopausal, unknown), and postmenopausal hormone use (current, past, never), BMI (continuous), history of diabetes (yes, no), and history of hypercholesterolemia (yes, no).	Qr3	% FA
10	Wang 2011 21734059	age, race, total energy intake (continuous), smoking status (current, past, never), alcohol use (rarely/never, 10–45 g ethanol/mo, 10–90 g ethanol/wk, >13 g ethanol/d), exercise (rarely/never,1, 1–3, $4 times/wk), menopause status (premenopausal, postmenopausal, unknown), and postmenopausal hormone use (current, past, never), BMI (continuous), history of diabetes (yes, no), and history of hypercholesterolemia (yes, no).	Qr4	% FA
11	Xun 2011 21205024	age, gender, ethnicity (African American, Caucasian) and study center, body mass index (continuous), physical activity (quartiles), education (<12, 12, 13–15, 16, >16 years), smoking status (non, former and current smokers), alcohol consumption (0, 0.1–4.9, 5.0–9.9, 10.0–14.9, 15.0–29.9, = 30 ml/d), family history of hypertension (yes or no), and dietary intakes (quartiles) of total energy, sodium, a-linolenic acid and linolenic-acid	Qr1	g/d
12	Xun 2011 21205024	age, gender, ethnicity (African American, Caucasian) and study center, body mass index (continuous), physical activity (quartiles), education (<12, 12, 13–15, 16, >16 years), smoking status (non, former and current smokers), alcohol consumption (0, 0.1–4.9, 5.0–9.9, 10.0–14.9, 15.0–29.9, = 30 ml/d), family history of hypertension (yes or no), and dietary intakes (quartiles) of total energy, sodium, a-linolenic acid and linolenic-acid	Qr2	g/d
13	Xun 2011 21205024	age, gender, ethnicity (African American, Caucasian) and study center, body mass index (continuous), physical activity (quartiles), education (<12, 12, 13–15, 16, >16 years), smoking status (non, former and current smokers), alcohol consumption (0, 0.1–4.9, 5.0–9.9, 10.0–14.9, 15.0–29.9, = 30 ml/d), family history of hypertension (yes or no), and dietary intakes (quartiles) of total energy, sodium, a-linolenic acid and linolenic-acid	Qr3	g/d
14	Xun 2011 21205024	age, gender, ethnicity (African American, Caucasian) and study center, body mass index (continuous), physical activity (quartiles), education (<12, 12, 13–15, 16, >16 years), smoking status (non, former and current smokers), alcohol consumption (0, 0.1–4.9, 5.0–9.9, 10.0–14.9, 15.0–29.9, = 30 ml/d), family history of hypertension (yes or no), and dietary intakes (quartiles) of total energy, sodium, a-linolenic acid and linolenic-acid	Qr4	g/d
15	Xun 2011 21205024	age, gender, ethnicity (African American, Caucasian) and study center, body mass index (continuous), physical activity (quartiles), education (<12, 12, 13–15, 16, >16 years), smoking status (non, former and current smokers), alcohol consumption (0, 0.1–4.9, 5.0–9.9, 10.0–14.9, 15.0–29.9, = 30 ml/d), family history of hypertension (yes or no), and dietary intakes (quartiles) of total energy, sodium, a-linolenic acid and linolenic-acid	Qr1	g/d
16	Xun 2011 21205024	age, gender, ethnicity (African American, Caucasian) and study center, body mass index (continuous), physical activity (quartiles), education (<12, 12, 13–15, 16, >16 years), smoking status (non, former and current smokers), alcohol consumption (0, 0.1–4.9, 5.0–9.9, 10.0–14.9, 15.0–29.9, = 30 ml/d), family history of hypertension (yes or no), and dietary intakes (quartiles) of total energy, sodium, a-linolenic acid and linolenic-acid	Qr2	g/d
17	Xun 2011 21205024	age, gender, ethnicity (African American, Caucasian) and study center, body mass index (continuous), physical activity (quartiles), education (<12, 12, 13–15, 16, >16 years), smoking status (non, former and current smokers), alcohol consumption (0, 0.1–4.9, 5.0–9.9, 10.0–14.9, 15.0–29.9, = 30 ml/d), family history of hypertension (yes or no), and dietary intakes (quartiles) of total energy, sodium, a-linolenic acid and linolenic-acid	Qr3	g/d
18	Xun 2011 21205024	age, gender, ethnicity (African American, Caucasian) and study center, body mass index (continuous), physical activity (quartiles), education (<12, 12, 13–15, 16, >16 years), smoking status (non, former and current smokers), alcohol consumption (0, 0.1–4.9, 5.0–9.9, 10.0–14.9, 15.0–29.9, = 30 ml/d), family history of hypertension (yes or no), and dietary intakes (quartiles) of total energy, sodium, a-linolenic acid and linolenic-acid	Qr4	g/d

Appendix F
Observational results: hypertension

Row	Study PMID	Quantile low	Quantile median	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
2	Wang 2010 20713915	nd	7.34	nd	RR	2627	5632	nd	Reference group			P trend	0.53
3	Wang 2010 20713915	nd	9.09	nd	RR	2619	nd	nd	0.99	0.94	1.04		
4	Wang 2010 20713915	nd	10.4	nd	RR	2783	nd	nd	1	0.95	1.06		
5	Wang 2010 20713915	nd	12	nd	RR	2786	nd	nd	0.99	0.94	1.05		
6	Wang 2010 20713915	nd	14.5	nd	RR	2818	5609	nd	1.01	0.96	1.07		
7	Wang 2011 21734059	nd	4.7	nd	RR	nd	nd	nd	Reference group			P trend	0.19
8	Wang 2011 21734059	nd	5.7	nd	RR	nd	nd	nd	0.84	0.55	1.27		
9	Wang 2011 21734059	nd	6.4	nd	RR	nd	nd	nd	0.67	0.43	1.04		
10	Wang 2011 21734059	nd	7.8	nd	RR	nd	nd	nd	0.75	0.47	1.2		
11	Xun 2011 21205024	nd	nd	0.06	HR	247	1165	nd	Reference group			P trend	<0.01
12	Xun 2011 21205024	0.06	nd	0.113	HR	259	1085	nd	0.94	0.79	1.13		
13	Xun 2011 21205024	0.114	nd	0.2	HR	270	1125	nd	0.85	0.71	1.02		
14	Xun 2011 21205024	0.201	nd	nd	HR	223	1133	nd	0.65	0.53	0.79		
15	Xun 2011 21205024	nd	nd	0.06	HR	277	1278	nd	Reference group			P trend	0.02
16	Xun 2011 21205024	0.06	nd	0.113	HR	231	1001	nd	0.94	0.79	1.12		
17	Xun 2011 21205024	0.114	nd	0.2	HR	246	1059	nd	0.87	0.73	1.05		
18	Xun 2011 21205024	0.201	nd	nd	HR	245	1170	nd	0.8	0.66	0.96		

Appendix F
Observational results: hypertension

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure	Supplement
19	Xun 2011 21205024	CARDIA	HTN	incident HTN	Healthy	healthy	All: 18-30 y	999/4508 (22.1)	20 y	DHA	Intake	no
20	Xun 2011 21205024	CARDIA	HTN	incident HTN	Healthy	healthy	All: 18-30 y	999/4508 (22.1)	20 y	DHA	Intake	no
21	Xun 2011 21205024	CARDIA	HTN	incident HTN	Healthy	healthy	All: 18-30 y	999/4508 (22.1)	20 y	DHA	Intake	no
22	Xun 2011 21205024	CARDIA	HTN	incident HTN	Healthy	healthy	All: 18-30 y	999/4508 (22.1)	20 y	DHA	Intake	no
24	**Subgroup analyses**											
25	Wang 2010 20713915	Women's Health Study	HTN	incident HTN	Healthy	healthy	age 39-54	13633/28100 (48.5)	12.9	ALA	Intake	no
26	Wang 2010 20713915	Women's Health Study	HTN	incident HTN	Healthy	healthy	age 39-54	13633/28100 (48.5)	12.9	ALA	Intake	no
27	Wang 2010 20713915	Women's Health Study	HTN	incident HTN	Healthy	healthy	age 39-54	13633/28100 (48.5)	12.9	ALA	Intake	no
28	Wang 2010 20713915	Women's Health Study	HTN	incident HTN	Healthy	healthy	age 39-54	13633/28100 (48.5)	12.9	ALA	Intake	no
29	Wang 2010 20713915	Women's Health Study	HTN	incident HTN	Healthy	healthy	age 39-54	13633/28100 (48.5)	12.9	ALA	Intake	no
30	Wang 2010 20713915	Women's Health Study	HTN	incident HTN	Healthy	healthy	age 55-89	13633/28100 (48.5)	12.9	ALA	Intake	no
31	Wang 2010 20713915	Women's Health Study	HTN	incident HTN	Healthy	healthy	age 55-89	13633/28100 (48.5)	12.9	ALA	Intake	no
32	Wang 2010 20713915	Women's Health Study	HTN	incident HTN	Healthy	healthy	age 55-89	13633/28100 (48.5)	12.9	ALA	Intake	no
33	Wang 2010 20713915	Women's Health Study	HTN	incident HTN	Healthy	healthy	age 55-89	13633/28100 (48.5)	12.9	ALA	Intake	no
34	Wang 2010 20713915	Women's Health Study	HTN	incident HTN	Healthy	healthy	age 55-89	13633/28100 (48.5)	12.9	ALA	Intake	no
35	Wang 2010 20713915	Women's Health Study	HTN	incident HTN	Healthy	healthy	age 39-54	13633/28100 (48.5)	12.9	EPA	Intake	no
36	Wang 2010 20713915	Women's Health Study	HTN	incident HTN	Healthy	healthy	age 39-54	13633/28100 (48.5)	12.9	EPA	Intake	no

Appendix F
Observational results: hypertension

Row	Study PMID	Adjustments	Quantile	n3 units
19	Xun 2011 21205024	age, gender, ethnicity (African American, Caucasian) and study center, body mass index (continuous), physical activity (quartiles), education (<12, 12, 13–15, 16, >16 years), smoking status (non, former and current smokers), alcohol consumption (0, 0.1–4.9, 5.0–9.9, 10.0–14.9, 15.0–29.9, = 30 ml/d), family history of hypertension (yes or no), and dietary intakes (quartiles) of total energy, sodium, a-linolenic acid and linolenic-acid	Qr1	g/d
20	Xun 2011 21205024	age, gender, ethnicity (African American, Caucasian) and study center, body mass index (continuous), physical activity (quartiles), education (<12, 12, 13–15, 16, >16 years), smoking status (non, former and current smokers), alcohol consumption (0, 0.1–4.9, 5.0–9.9, 10.0–14.9, 15.0–29.9, = 30 ml/d), family history of hypertension (yes or no), and dietary intakes (quartiles) of total energy, sodium, a-linolenic acid and linolenic-acid	Qr2	g/d
21	Xun 2011 21205024	age, gender, ethnicity (African American, Caucasian) and study center, body mass index (continuous), physical activity (quartiles), education (<12, 12, 13–15, 16, >16 years), smoking status (non, former and current smokers), alcohol consumption (0, 0.1–4.9, 5.0–9.9, 10.0–14.9, 15.0–29.9, = 30 ml/d), family history of hypertension (yes or no), and dietary intakes (quartiles) of total energy, sodium, a-linolenic acid and linolenic-acid	Qr3	g/d
22	Xun 2011 21205024	age, gender, ethnicity (African American, Caucasian) and study center, body mass index (continuous), physical activity (quartiles), education (<12, 12, 13–15, 16, >16 years), smoking status (non, former and current smokers), alcohol consumption (0, 0.1–4.9, 5.0–9.9, 10.0–14.9, 15.0–29.9, = 30 ml/d), family history of hypertension (yes or no), and dietary intakes (quartiles) of total energy, sodium, a-linolenic acid and linolenic-acid	Qr4	g/d
24	**Subgroup analyses**			
25	Wang 2010 20713915	age (continuous), race (white or nonwhite), total energy intake (continuous), treatment (vitamin E, aspirin, └-carotene, or placebo), smoking (never, former, or current), alcohol intake (continuous), physical activity (continuous), postmenopausal status (yes, no, or uncertain), postmenopausal hormone use (never, former, or current), dietary sodium, potassium, calcium, and fiber (all in quintiles), BMI (continuous), history of diabetes mellitus (yes or no), and history of hypercholesterolemia (yes or no).	Qt1	g/d
26	Wang 2010 20713915	age (continuous), race (white or nonwhite), total energy intake (continuous), treatment (vitamin E, aspirin, └-carotene, or placebo), smoking (never, former, or current), alcohol intake (continuous), physical activity (continuous), postmenopausal status (yes, no, or uncertain), postmenopausal hormone use (never, former, or current), dietary sodium, potassium, calcium, and fiber (all in quintiles), BMI (continuous), history of diabetes mellitus (yes or no), and history of hypercholesterolemia (yes or no).	Qt2	g/d
27	Wang 2010 20713915	age (continuous), race (white or nonwhite), total energy intake (continuous), treatment (vitamin E, aspirin, └-carotene, or placebo), smoking (never, former, or current), alcohol intake (continuous), physical activity (continuous), postmenopausal status (yes, no, or uncertain), postmenopausal hormone use (never, former, or current), dietary sodium, potassium, calcium, and fiber (all in quintiles), BMI (continuous), history of diabetes mellitus (yes or no), and history of hypercholesterolemia (yes or no).	Qt3	g/d
28	Wang 2010 20713915	age (continuous), race (white or nonwhite), total energy intake (continuous), treatment (vitamin E, aspirin, └-carotene, or placebo), smoking (never, former, or current), alcohol intake (continuous), physical activity (continuous), postmenopausal status (yes, no, or uncertain), postmenopausal hormone use (never, former, or current), dietary sodium, potassium, calcium, and fiber (all in quintiles), BMI (continuous), history of diabetes mellitus (yes or no), and history of hypercholesterolemia (yes or no).	Qt4	g/d
29	Wang 2010 20713915	age (continuous), race (white or nonwhite), total energy intake (continuous), treatment (vitamin E, aspirin, └-carotene, or placebo), smoking (never, former, or current), alcohol intake (continuous), physical activity (continuous), postmenopausal status (yes, no, or uncertain), postmenopausal hormone use (never, former, or current), dietary sodium, potassium, calcium, and fiber (all in quintiles), BMI (continuous), history of diabetes mellitus (yes or no), and history of hypercholesterolemia (yes or no).	Qt5	g/d
30	Wang 2010 20713915	age (continuous), race (white or nonwhite), total energy intake (continuous), treatment (vitamin E, aspirin, └-carotene, or placebo), smoking (never, former, or current), alcohol intake (continuous), physical activity (continuous), postmenopausal status (yes, no, or uncertain), postmenopausal hormone use (never, former, or current), dietary sodium, potassium, calcium, and fiber (all in quintiles), BMI (continuous), history of diabetes mellitus (yes or no), and history of hypercholesterolemia (yes or no).	Qt1	g/d
31	Wang 2010 20713915	age (continuous), race (white or nonwhite), total energy intake (continuous), treatment (vitamin E, aspirin, └-carotene, or placebo), smoking (never, former, or current), alcohol intake (continuous), physical activity (continuous), postmenopausal status (yes, no, or uncertain), postmenopausal hormone use (never, former, or current), dietary sodium, potassium, calcium, and fiber (all in quintiles), BMI (continuous), history of diabetes mellitus (yes or no), and history of hypercholesterolemia (yes or no).	Qt2	g/d
32	Wang 2010 20713915	age (continuous), race (white or nonwhite), total energy intake (continuous), treatment (vitamin E, aspirin, └-carotene, or placebo), smoking (never, former, or current), alcohol intake (continuous), physical activity (continuous), postmenopausal status (yes, no, or uncertain), postmenopausal hormone use (never, former, or current), dietary sodium, potassium, calcium, and fiber (all in quintiles), BMI (continuous), history of diabetes mellitus (yes or no), and history of hypercholesterolemia (yes or no).	Qt3	g/d
33	Wang 2010 20713915	age (continuous), race (white or nonwhite), total energy intake (continuous), treatment (vitamin E, aspirin, └-carotene, or placebo), smoking (never, former, or current), alcohol intake (continuous), physical activity (continuous), postmenopausal status (yes, no, or uncertain), postmenopausal hormone use (never, former, or current), dietary sodium, potassium, calcium, and fiber (all in quintiles), BMI (continuous), history of diabetes mellitus (yes or no), and history of hypercholesterolemia (yes or no).	Qt4	g/d
34	Wang 2010 20713915	age (continuous), race (white or nonwhite), total energy intake (continuous), treatment (vitamin E, aspirin, └-carotene, or placebo), smoking (never, former, or current), alcohol intake (continuous), physical activity (continuous), postmenopausal status (yes, no, or uncertain), postmenopausal hormone use (never, former, or current), dietary sodium, potassium, calcium, and fiber (all in quintiles), BMI (continuous), history of diabetes mellitus (yes or no), and history of hypercholesterolemia (yes or no).	Qt5	g/d
35	Wang 2010 20713915	age (continuous), race (white or nonwhite), total energy intake (continuous), treatment (vitamin E, aspirin, └-carotene, or placebo), smoking (never, former, or current), alcohol intake (continuous), physical activity (continuous), postmenopausal status (yes, no, or uncertain), postmenopausal hormone use (never, former, or current), dietary sodium, potassium, calcium, and fiber (all in quintiles), BMI (continuous), history of diabetes mellitus (yes or no), and history of hypercholesterolemia (yes or no).	Qt1	g/d
36	Wang 2010 20713915	age (continuous), race (white or nonwhite), total energy intake (continuous), treatment (vitamin E, aspirin, └-carotene, or placebo), smoking (never, former, or current), alcohol intake (continuous), physical activity (continuous), postmenopausal status (yes, no, or uncertain), postmenopausal hormone use (never, former, or current), dietary sodium, potassium, calcium, and fiber (all in quintiles), BMI (continuous), history of diabetes mellitus (yes or no), and history of hypercholesterolemia (yes or no).	Qt2	g/d

Appendix F
Observational results: hypertension

Row	Study PMID	Quantile low	Quantile median	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
19	Xun 2011 21205024	nd	nd	0.06	HR	261	1134	nd	Reference group			P trend	<0.01
20	Xun 2011 21205024	0.06	nd	0.113	HR	241	1043	nd	0.72	0.6	0.86		
21	Xun 2011 21205024	0.114	nd	0.2	HR	292	1207	nd	0.71	0.59	0.84		
22	Xun 2011 21205024	0.201	nd	nd	HR	205	1124	nd	0.45	0.37	0.55		
24	**Subgroup analyses**												
25	Wang 2010 20713915	nd	7.34	nd	RR	nd	5632	nd	Reference group			P trend	0.2
26	Wang 2010 20713915	nd	9.09	nd	RR	nd	nd	nd	nd				
27	Wang 2010 20713915	nd	10.4	nd	RR	nd	nd	nd	nd				
28	Wang 2010 20713915	nd	12	nd	RR	nd	nd	nd	nd				
29	Wang 2010 20713915	nd	14.5	nd	RR	nd	5609	nd	1.08	1	1.16		
30	Wang 2010 20713915	nd	7.34	nd	RR	nd	5632	nd	Reference group			P trend	0.63
31	Wang 2010 20713915	nd	9.09	nd	RR	nd	nd	nd	nd				
32	Wang 2010 20713915	nd	10.4	nd	RR	nd	nd	nd	nd				
33	Wang 2010 20713915	nd	12	nd	RR	nd	nd	nd	nd				
34	Wang 2010 20713915	nd	14.5	nd	RR	nd	5609	nd	0.98	0.9	1.07		
35	Wang 2010 20713915	nd	7.34	nd	RR	nd	5632	nd	Reference group			P trend	0.43
36	Wang 2010 20713915	nd	9.09	nd	RR	nd	nd	nd	nd				

Appendix F
Observational results: hypertension

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure	Supplement
37	Wang 2010 20713915	Women's Health Study	HTN	incident HTN	Healthy	healthy	age 39-54	13633/28100 (48.5)	12.9	EPA	Intake	no
38	Wang 2010 20713915	Women's Health Study	HTN	incident HTN	Healthy	healthy	age 39-54	13633/28100 (48.5)	12.9	EPA	Intake	no
39	Wang 2010 20713915	Women's Health Study	HTN	incident HTN	Healthy	healthy	age 39-54	13633/28100 (48.5)	12.9	EPA	Intake	no
40	Wang 2010 20713915	Women's Health Study	HTN	incident HTN	Healthy	healthy	age 55-89	13633/28100 (48.5)	12.9	EPA	Intake	no
41	Wang 2010 20713915	Women's Health Study	HTN	incident HTN	Healthy	healthy	age 55-89	13633/28100 (48.5)	12.9	EPA	Intake	no
42	Wang 2010 20713915	Women's Health Study	HTN	incident HTN	Healthy	healthy	age 55-89	13633/28100 (48.5)	12.9	EPA	Intake	no
43	Wang 2010 20713915	Women's Health Study	HTN	incident HTN	Healthy	healthy	age 55-89	13633/28100 (48.5)	12.9	EPA	Intake	no
44	Wang 2010 20713915	Women's Health Study	HTN	incident HTN	Healthy	healthy	age 55-89	13633/28100 (48.5)	12.9	EPA	Intake	no
45	Wang 2010 20713915	Women's Health Study	HTN	incident HTN	Healthy	healthy	age 39-54	13633/28100 (48.5)	12.9	DHA	Intake	no
46	Wang 2010 20713915	Women's Health Study	HTN	incident HTN	Healthy	healthy	age 39-54	13633/28100 (48.5)	12.9	DHA	Intake	no
47	Wang 2010 20713915	Women's Health Study	HTN	incident HTN	Healthy	healthy	age 39-54	13633/28100 (48.5)	12.9	DHA	Intake	no
48	Wang 2010 20713915	Women's Health Study	HTN	incident HTN	Healthy	healthy	age 39-54	13633/28100 (48.5)	12.9	DHA	Intake	no
49	Wang 2010 20713915	Women's Health Study	HTN	incident HTN	Healthy	healthy	age 39-54	13633/28100 (48.5)	12.9	DHA	Intake	no
50	Wang 2010 20713915	Women's Health Study	HTN	incident HTN	Healthy	healthy	age 55-89	13633/28100 (48.5)	12.9	DHA	Intake	no
51	Wang 2010 20713915	Women's Health Study	HTN	incident HTN	Healthy	healthy	age 55-89	13633/28100 (48.5)	12.9	DHA	Intake	no
52	Wang 2010 20713915	Women's Health Study	HTN	incident HTN	Healthy	healthy	age 55-89	13633/28100 (48.5)	12.9	DHA	Intake	no
53	Wang 2010 20713915	Women's Health Study	HTN	incident HTN	Healthy	healthy	age 55-89	13633/28100 (48.5)	12.9	DHA	Intake	no

Appendix F
Observational results: hypertension

Row	Study PMID	Adjustments	Quantile	n3 units
37	Wang 2010 20713915	age (continuous), race (white or nonwhite), total energy intake (continuous), treatment (vitamin E, aspirin, └-carotene, or placebo), smoking (never, former, or current), alcohol intake (continuous), physical activity (continuous), postmenopausal status (yes, no, or uncertain), postmenopausal hormone use (never, former, or current), dietary sodium, potassium, calcium, and fiber (all in quintiles), BMI (continuous), history of diabetes mellitus (yes or no), and history of hypercholesterolemia (yes or no).	Qt3	g/d
38	Wang 2010 20713915	age (continuous), race (white or nonwhite), total energy intake (continuous), treatment (vitamin E, aspirin, └-carotene, or placebo), smoking (never, former, or current), alcohol intake (continuous), physical activity (continuous), postmenopausal status (yes, no, or uncertain), postmenopausal hormone use (never, former, or current), dietary sodium, potassium, calcium, and fiber (all in quintiles), BMI (continuous), history of diabetes mellitus (yes or no), and history of hypercholesterolemia (yes or no).	Qt4	g/d
39	Wang 2010 20713915	age (continuous), race (white or nonwhite), total energy intake (continuous), treatment (vitamin E, aspirin, └-carotene, or placebo), smoking (never, former, or current), alcohol intake (continuous), physical activity (continuous), postmenopausal status (yes, no, or uncertain), postmenopausal hormone use (never, former, or current), dietary sodium, potassium, calcium, and fiber (all in quintiles), BMI (continuous), history of diabetes mellitus (yes or no), and history of hypercholesterolemia (yes or no).	Qt5	g/d
40	Wang 2010 20713915	age (continuous), race (white or nonwhite), total energy intake (continuous), treatment (vitamin E, aspirin, └-carotene, or placebo), smoking (never, former, or current), alcohol intake (continuous), physical activity (continuous), postmenopausal status (yes, no, or uncertain), postmenopausal hormone use (never, former, or current), dietary sodium, potassium, calcium, and fiber (all in quintiles), BMI (continuous), history of diabetes mellitus (yes or no), and history of hypercholesterolemia (yes or no).	Qt1	g/d
41	Wang 2010 20713915	age (continuous), race (white or nonwhite), total energy intake (continuous), treatment (vitamin E, aspirin, └-carotene, or placebo), smoking (never, former, or current), alcohol intake (continuous), physical activity (continuous), postmenopausal status (yes, no, or uncertain), postmenopausal hormone use (never, former, or current), dietary sodium, potassium, calcium, and fiber (all in quintiles), BMI (continuous), history of diabetes mellitus (yes or no), and history of hypercholesterolemia (yes or no).	Qt2	g/d
42	Wang 2010 20713915	age (continuous), race (white or nonwhite), total energy intake (continuous), treatment (vitamin E, aspirin, └-carotene, or placebo), smoking (never, former, or current), alcohol intake (continuous), physical activity (continuous), postmenopausal status (yes, no, or uncertain), postmenopausal hormone use (never, former, or current), dietary sodium, potassium, calcium, and fiber (all in quintiles), BMI (continuous), history of diabetes mellitus (yes or no), and history of hypercholesterolemia (yes or no).	Qt3	g/d
43	Wang 2010 20713915	age (continuous), race (white or nonwhite), total energy intake (continuous), treatment (vitamin E, aspirin, └-carotene, or placebo), smoking (never, former, or current), alcohol intake (continuous), physical activity (continuous), postmenopausal status (yes, no, or uncertain), postmenopausal hormone use (never, former, or current), dietary sodium, potassium, calcium, and fiber (all in quintiles), BMI (continuous), history of diabetes mellitus (yes or no), and history of hypercholesterolemia (yes or no).	Qt4	g/d
44	Wang 2010 20713915	age (continuous), race (white or nonwhite), total energy intake (continuous), treatment (vitamin E, aspirin, └-carotene, or placebo), smoking (never, former, or current), alcohol intake (continuous), physical activity (continuous), postmenopausal status (yes, no, or uncertain), postmenopausal hormone use (never, former, or current), dietary sodium, potassium, calcium, and fiber (all in quintiles), BMI (continuous), history of diabetes mellitus (yes or no), and history of hypercholesterolemia (yes or no).	Qt5	g/d
45	Wang 2010 20713915	age (continuous), race (white or nonwhite), total energy intake (continuous), treatment (vitamin E, aspirin, └-carotene, or placebo), smoking (never, former, or current), alcohol intake (continuous), physical activity (continuous), postmenopausal status (yes, no, or uncertain), postmenopausal hormone use (never, former, or current), dietary sodium, potassium, calcium, and fiber (all in quintiles), BMI (continuous), history of diabetes mellitus (yes or no), and history of hypercholesterolemia (yes or no).	Qt1	g/d
46	Wang 2010 20713915	age (continuous), race (white or nonwhite), total energy intake (continuous), treatment (vitamin E, aspirin, └-carotene, or placebo), smoking (never, former, or current), alcohol intake (continuous), physical activity (continuous), postmenopausal status (yes, no, or uncertain), postmenopausal hormone use (never, former, or current), dietary sodium, potassium, calcium, and fiber (all in quintiles), BMI (continuous), history of diabetes mellitus (yes or no), and history of hypercholesterolemia (yes or no).	Qt2	g/d
47	Wang 2010 20713915	age (continuous), race (white or nonwhite), total energy intake (continuous), treatment (vitamin E, aspirin, └-carotene, or placebo), smoking (never, former, or current), alcohol intake (continuous), physical activity (continuous), postmenopausal status (yes, no, or uncertain), postmenopausal hormone use (never, former, or current), dietary sodium, potassium, calcium, and fiber (all in quintiles), BMI (continuous), history of diabetes mellitus (yes or no), and history of hypercholesterolemia (yes or no).	Qt3	g/d
48	Wang 2010 20713915	age (continuous), race (white or nonwhite), total energy intake (continuous), treatment (vitamin E, aspirin, └-carotene, or placebo), smoking (never, former, or current), alcohol intake (continuous), physical activity (continuous), postmenopausal status (yes, no, or uncertain), postmenopausal hormone use (never, former, or current), dietary sodium, potassium, calcium, and fiber (all in quintiles), BMI (continuous), history of diabetes mellitus (yes or no), and history of hypercholesterolemia (yes or no).	Qt4	g/d
49	Wang 2010 20713915	age (continuous), race (white or nonwhite), total energy intake (continuous), treatment (vitamin E, aspirin, └-carotene, or placebo), smoking (never, former, or current), alcohol intake (continuous), physical activity (continuous), postmenopausal status (yes, no, or uncertain), postmenopausal hormone use (never, former, or current), dietary sodium, potassium, calcium, and fiber (all in quintiles), BMI (continuous), history of diabetes mellitus (yes or no), and history of hypercholesterolemia (yes or no).	Qt5	g/d
50	Wang 2010 20713915	age (continuous), race (white or nonwhite), total energy intake (continuous), treatment (vitamin E, aspirin, └-carotene, or placebo), smoking (never, former, or current), alcohol intake (continuous), physical activity (continuous), postmenopausal status (yes, no, or uncertain), postmenopausal hormone use (never, former, or current), dietary sodium, potassium, calcium, and fiber (all in quintiles), BMI (continuous), history of diabetes mellitus (yes or no), and history of hypercholesterolemia (yes or no).	Qt1	g/d
51	Wang 2010 20713915	age (continuous), race (white or nonwhite), total energy intake (continuous), treatment (vitamin E, aspirin, └-carotene, or placebo), smoking (never, former, or current), alcohol intake (continuous), physical activity (continuous), postmenopausal status (yes, no, or uncertain), postmenopausal hormone use (never, former, or current), dietary sodium, potassium, calcium, and fiber (all in quintiles), BMI (continuous), history of diabetes mellitus (yes or no), and history of hypercholesterolemia (yes or no).	Qt2	g/d
52	Wang 2010 20713915	age (continuous), race (white or nonwhite), total energy intake (continuous), treatment (vitamin E, aspirin, └-carotene, or placebo), smoking (never, former, or current), alcohol intake (continuous), physical activity (continuous), postmenopausal status (yes, no, or uncertain), postmenopausal hormone use (never, former, or current), dietary sodium, potassium, calcium, and fiber (all in quintiles), BMI (continuous), history of diabetes mellitus (yes or no), and history of hypercholesterolemia (yes or no).	Qt3	g/d
53	Wang 2010 20713915	age (continuous), race (white or nonwhite), total energy intake (continuous), treatment (vitamin E, aspirin, └-carotene, or placebo), smoking (never, former, or current), alcohol intake (continuous), physical activity (continuous), postmenopausal status (yes, no, or uncertain), postmenopausal hormone use (never, former, or current), dietary sodium, potassium, calcium, and fiber (all in quintiles), BMI (continuous), history of diabetes mellitus (yes or no), and history of hypercholesterolemia (yes or no).	Qt4	g/d

Appendix F
Observational results: hypertension

Row	Study PMID	Quantile low	Quantile median	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
37	Wang 2010 20713915	nd	10.4	nd	RR	nd	nd	nd	nd				
38	Wang 2010 20713915	nd	12	nd	RR	nd	nd	nd	nd				
39	Wang 2010 20713915	nd	14.5	nd	RR	nd	5609	nd	1.05	0.98	1.13		
40	Wang 2010 20713915	nd	7.34	nd	RR	nd	5632	nd	Reference group			P trend	0.18
41	Wang 2010 20713915	nd	9.09	nd	RR	nd	nd	nd	nd				
42	Wang 2010 20713915	nd	10.4	nd	RR	nd	nd	nd	nd				
43	Wang 2010 20713915	nd	12	nd	RR	nd	nd	nd	nd				
44	Wang 2010 20713915	nd	14.5	nd	RR	nd	5609	nd	1.02	0.93	1.11		
45	Wang 2010 20713915	nd	7.34	nd	RR	nd	5632	nd	Reference group			P trend	0.05
46	Wang 2010 20713915	nd	9.09	nd	RR	nd	nd	nd	nd				
47	Wang 2010 20713915	nd	10.4	nd	RR	nd	nd	nd	nd				
48	Wang 2010 20713915	nd	12	nd	RR	nd	nd	nd	nd				
49	Wang 2010 20713915	nd	14.5	nd	RR	nd	5609	nd	1.08	1.01	1.16		
50	Wang 2010 20713915	nd	7.34	nd	RR	nd	5632	nd	Reference group			P trend	0.33
51	Wang 2010 20713915	nd	9.09	nd	RR	nd	nd	nd	nd				
52	Wang 2010 20713915	nd	10.4	nd	RR	nd	nd	nd	nd				
53	Wang 2010 20713915	nd	12	nd	RR	nd	nd	nd	nd				

Appendix F
Observational results: hypertension

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure	Supplement
54	Wang 2010 20713915	Women's Health Study	HTN	incident HTN	Healthy	healthy	age 55-89	13633/28100 (48.5)	12.9	DHA	Intake	no
55	Wang 2011 21734059	Women's Health Study	HTN	incident HTN	Healthy	Healthy	age 39-54	177/356 (49.7)	12.9y	All n-3	Erythrocyte PUFA	no
56	Wang 2011 21734059	Women's Health Study	HTN	incident HTN	Healthy	Healthy	age 39-54	339/676 (50.1)	12.9y	All n-3	Erythrocyte PUFA	no
57	Wang 2011 21734059	Women's Health Study	HTN	incident HTN	Healthy	Healthy	age 39-54	339/676 (50.1)	12.9y	All n-3	Erythrocyte PUFA	no
58	Wang 2011 21734059	Women's Health Study	HTN	incident HTN	Healthy	Healthy	age 39-54	339/676 (50.1)	12.9y	All n-3	Erythrocyte PUFA	no
59	Wang 2011 21734059	Women's Health Study	HTN	incident HTN	Healthy	Healthy	age 55-89	177/356 (49.7)	12.9y	All n-3	Erythrocyte PUFA	no
60	Wang 2011 21734059	Women's Health Study	HTN	incident HTN	Healthy	Healthy	age 55-89	177/356 (49.7)	12.9y	All n-3	Erythrocyte PUFA	no
61	Wang 2011 21734059	Women's Health Study	HTN	incident HTN	Healthy	Healthy	age 55-89	177/356 (49.7)	12.9y	All n-3	Erythrocyte PUFA	no
62	Wang 2011 21734059	Women's Health Study	HTN	incident HTN	Healthy	Healthy	age 55-89	177/356 (49.7)	12.9y	All n-3	Erythrocyte PUFA	no
63	Wang 2011 21734059	Women's Health Study	HTN	incident HTN	Healthy	Healthy	age 39-54	339/676 (50.1)	12.9y	ALA	Erythrocyte PUFA	no
64	Wang 2011 21734059	Women's Health Study	HTN	incident HTN	Healthy	Healthy	age 39-54	339/676 (50.1)	12.9y	ALA	Erythrocyte PUFA	no
65	Wang 2011 21734059	Women's Health Study	HTN	incident HTN	Healthy	Healthy	age 55-89	177/356 (49.7)	12.9y	ALA	Erythrocyte PUFA	no
66	Wang 2011 21734059	Women's Health Study	HTN	incident HTN	Healthy	Healthy	age 55-89	177/356 (49.7)	12.9y	ALA	Erythrocyte PUFA	no
67	Wang 2011 21734059	Women's Health Study	HTN	incident HTN	Healthy	Healthy	age 39-54	339/676 (50.1)	12.9y	EPA	Erythrocyte PUFA	no
68	Wang 2011 21734059	Women's Health Study	HTN	incident HTN	Healthy	Healthy	age 39-54	339/676 (50.1)	12.9y	EPA	Erythrocyte PUFA	no
69	Wang 2011 21734059	Women's Health Study	HTN	incident HTN	Healthy	Healthy	age 55-89	177/356 (49.7)	12.9y	EPA	Erythrocyte PUFA	no
70	Wang 2011 21734059	Women's Health Study	HTN	incident HTN	Healthy	Healthy	age 55-89	177/356 (49.7)	12.9y	EPA	Erythrocyte PUFA	no

Appendix F
Observational results: hypertension

Row	Study PMID	Adjustments	Quantile	n3 units
54	Wang 2010 20713915	age (continuous), race (white or nonwhite), total energy intake (continuous), treatment (vitamin E, aspirin, └-carotene, or placebo), smoking (never, former, or current), alcohol intake (continuous), physical activity (continuous), postmenopausal status (yes, no, or uncertain), postmenopausal hormone use (never, former, or current), dietary sodium, potassium, calcium, and fiber (all in quintiles), BMI (continuous), history of diabetes mellitus (yes or no), and history of hypercholesterolemia (yes or no).	Qt5	g/d
55	Wang 2011 21734059	age, race, total energy intake (continuous), smoking status (current, past, never), alcohol use (rarely/never, 10–45 g ethanol/mo, 10–90 g ethanol/wk, >13 g ethanol/d), exercise (rarely/never,1, 1–3, $4 times/wk), menopause status (premenopausal, postmenopausal, unknown), and postmenopausal hormone use (current, past, never), BMI (continuous), history of diabetes (yes, no), and history of hypercholesterolemia (yes, no).	Qr1	% FA
56	Wang 2011 21734059	age, race, total energy intake (continuous), smoking status (current, past, never), alcohol use (rarely/never, 10–45 g ethanol/mo, 10–90 g ethanol/wk, >13 g ethanol/d), exercise (rarely/never,1, 1–3, $4 times/wk), menopause status (premenopausal, postmenopausal, unknown), and postmenopausal hormone use (current, past, never), BMI (continuous), history of diabetes (yes, no), and history of hypercholesterolemia (yes, no).	Qr2	% FA
57	Wang 2011 21734059	age, race, total energy intake (continuous), smoking status (current, past, never), alcohol use (rarely/never, 10–45 g ethanol/mo, 10–90 g ethanol/wk, >13 g ethanol/d), exercise (rarely/never,1, 1–3, $4 times/wk), menopause status (premenopausal, postmenopausal, unknown), and postmenopausal hormone use (current, past, never), BMI (continuous), history of diabetes (yes, no), and history of hypercholesterolemia (yes, no).	Qr3	% FA
58	Wang 2011 21734059	age, race, total energy intake (continuous), smoking status (current, past, never), alcohol use (rarely/never, 10–45 g ethanol/mo, 10–90 g ethanol/wk, >13 g ethanol/d), exercise (rarely/never,1, 1–3, $4 times/wk), menopause status (premenopausal, postmenopausal, unknown), and postmenopausal hormone use (current, past, never), BMI (continuous), history of diabetes (yes, no), and history of hypercholesterolemia (yes, no).	Qr4	% FA
59	Wang 2011 21734059	age, race, total energy intake (continuous), smoking status (current, past, never), alcohol use (rarely/never, 10–45 g ethanol/mo, 10–90 g ethanol/wk, >13 g ethanol/d), exercise (rarely/never,1, 1–3, $4 times/wk), menopause status (premenopausal, postmenopausal, unknown), and postmenopausal hormone use (current, past, never), BMI (continuous), history of diabetes (yes, no), and history of hypercholesterolemia (yes, no).	Qr1	% FA
60	Wang 2011 21734059	age, race, total energy intake (continuous), smoking status (current, past, never), alcohol use (rarely/never, 10–45 g ethanol/mo, 10–90 g ethanol/wk, >13 g ethanol/d), exercise (rarely/never,1, 1–3, $4 times/wk), menopause status (premenopausal, postmenopausal, unknown), and postmenopausal hormone use (current, past, never), BMI (continuous), history of diabetes (yes, no), and history of hypercholesterolemia (yes, no).	Qr2	% FA
61	Wang 2011 21734059	age, race, total energy intake (continuous), smoking status (current, past, never), alcohol use (rarely/never, 10–45 g ethanol/mo, 10–90 g ethanol/wk, >13 g ethanol/d), exercise (rarely/never,1, 1–3, $4 times/wk), menopause status (premenopausal, postmenopausal, unknown), and postmenopausal hormone use (current, past, never), BMI (continuous), history of diabetes (yes, no), and history of hypercholesterolemia (yes, no).	Qr3	% FA
62	Wang 2011 21734059	age, race, total energy intake (continuous), smoking status (current, past, never), alcohol use (rarely/never, 10–45 g ethanol/mo, 10–90 g ethanol/wk, >13 g ethanol/d), exercise (rarely/never,1, 1–3, $4 times/wk), menopause status (premenopausal, postmenopausal, unknown), and postmenopausal hormone use (current, past, never), BMI (continuous), history of diabetes (yes, no), and history of hypercholesterolemia (yes, no).	Qr4	% FA
63	Wang 2011 21734059	age, race, total energy intake (continuous), smoking status (current, past, never), alcohol use (rarely/never, 10–45 g ethanol/mo, 10–90 g ethanol/wk, >13 g ethanol/d), exercise (rarely/never,1, 1–3, $4 times/wk), menopause status (premenopausal, postmenopausal, unknown), and postmenopausal hormone use (current, past, never), BMI (continuous), history of diabetes (yes, no), and history of hypercholesterolemia (yes, no).	Qr1	% FA
64	Wang 2011 21734059	age, race, total energy intake (continuous), smoking status (current, past, never), alcohol use (rarely/never, 10–45 g ethanol/mo, 10–90 g ethanol/wk, >13 g ethanol/d), exercise (rarely/never,1, 1–3, $4 times/wk), menopause status (premenopausal, postmenopausal, unknown), and postmenopausal hormone use (current, past, never), BMI (continuous), history of diabetes (yes, no), and history of hypercholesterolemia (yes, no).	Qr4	% FA
65	Wang 2011 21734059	age, race, total energy intake (continuous), smoking status (current, past, never), alcohol use (rarely/never, 10–45 g ethanol/mo, 10–90 g ethanol/wk, >13 g ethanol/d), exercise (rarely/never,1, 1–3, $4 times/wk), menopause status (premenopausal, postmenopausal, unknown), and postmenopausal hormone use (current, past, never), BMI (continuous), history of diabetes (yes, no), and history of hypercholesterolemia (yes, no).	Qr1	% FA
66	Wang 2011 21734059	age, race, total energy intake (continuous), smoking status (current, past, never), alcohol use (rarely/never, 10–45 g ethanol/mo, 10–90 g ethanol/wk, >13 g ethanol/d), exercise (rarely/never,1, 1–3, $4 times/wk), menopause status (premenopausal, postmenopausal, unknown), and postmenopausal hormone use (current, past, never), BMI (continuous), history of diabetes (yes, no), and history of hypercholesterolemia (yes, no).	Qr4	% FA
67	Wang 2011 21734059	age, race, total energy intake (continuous), smoking status (current, past, never), alcohol use (rarely/never, 10–45 g ethanol/mo, 10–90 g ethanol/wk, >13 g ethanol/d), exercise (rarely/never,1, 1–3, $4 times/wk), menopause status (premenopausal, postmenopausal, unknown), and postmenopausal hormone use (current, past, never), BMI (continuous), history of diabetes (yes, no), and history of hypercholesterolemia (yes, no).	Qr1	% FA
68	Wang 2011 21734059	age, race, total energy intake (continuous), smoking status (current, past, never), alcohol use (rarely/never, 10–45 g ethanol/mo, 10–90 g ethanol/wk, >13 g ethanol/d), exercise (rarely/never,1, 1–3, $4 times/wk), menopause status (premenopausal, postmenopausal, unknown), and postmenopausal hormone use (current, past, never), BMI (continuous), history of diabetes (yes, no), and history of hypercholesterolemia (yes, no).	Qr4	% FA
69	Wang 2011 21734059	age, race, total energy intake (continuous), smoking status (current, past, never), alcohol use (rarely/never, 10–45 g ethanol/mo, 10–90 g ethanol/wk, >13 g ethanol/d), exercise (rarely/never,1, 1–3, $4 times/wk), menopause status (premenopausal, postmenopausal, unknown), and postmenopausal hormone use (current, past, never), BMI (continuous), history of diabetes (yes, no), and history of hypercholesterolemia (yes, no).	Qr1	% FA
70	Wang 2011 21734059	age, race, total energy intake (continuous), smoking status (current, past, never), alcohol use (rarely/never, 10–45 g ethanol/mo, 10–90 g ethanol/wk, >13 g ethanol/d), exercise (rarely/never,1, 1–3, $4 times/wk), menopause status (premenopausal, postmenopausal, unknown), and postmenopausal hormone use (current, past, never), BMI (continuous), history of diabetes (yes, no), and history of hypercholesterolemia (yes, no).	Qr4	% FA

Appendix F
Observational results: hypertension

Row	Study PMID	Quantile low	Quantile median	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
54	Wang 2010 20713915	nd	14.5	nd	RR	nd	5609	nd	1.06	0.97	1.15		
55	Wang 2011 21734059	nd	4.7	nd	RR	nd	nd	nd	Reference group			P trend	0.05
56	Wang 2011 21734059	nd	5.7	nd	RR	nd	nd	nd	0.71	0.42	1.2		
57	Wang 2011 21734059	nd	6.4	nd	RR	nd	nd	nd	0.47	0.26	0.85		
58	Wang 2011 21734059	nd	7.8	nd	RR	nd	nd	nd	0.59	0.32	1.06		
59	Wang 2011 21734059	nd	4.7	nd	RR	nd	nd	nd	Reference group			P trend	0.93
60	Wang 2011 21734059	nd	5.7	nd	RR	nd	nd	nd	1.16	0.49	2.73		
61	Wang 2011 21734059	nd	6.4	nd	RR	nd	nd	nd	1.05	0.47	2.36		
62	Wang 2011 21734059	nd	7.8	nd	RR	nd	nd	nd	1.07	0.43	2.66		
63	Wang 2011 21734059	nd	nd	nd	RR	nd	nd	nd	Reference group				
64	Wang 2011 21734059	nd	nd	nd	RR	nd	nd	nd	0.59	0.32	1.09	P trend	0.2
65	Wang 2011 21734059	nd	nd	nd	RR	nd	nd	nd	Reference group				
66	Wang 2011 21734059	nd	nd	nd	RR	nd	nd	nd	1.49	0.64	3.48	P trend	0.41
67	Wang 2011 21734059	nd	nd	nd	RR	nd	nd	nd	Reference group				
68	Wang 2011 21734059	nd	nd	nd	RR	nd	nd	nd	0.84	0.47	1.49	P trend	0.32
69	Wang 2011 21734059	nd	nd	nd	RR	nd	nd	nd	Reference group				
70	Wang 2011 21734059	nd	nd	nd	RR	nd	nd	nd	0.32	0.1	1.07	P trend	0.02

Appendix F
Observational results: hypertension

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure	Supplement
71	Wang 2011 21734059	Women's Health Study	HTN	incident HTN	Healthy	Healthy	age 39-54	339/676 (50.1)	12.9y	DPA	Erythrocyte PUFA	no
72	Wang 2011 21734059	Women's Health Study	HTN	incident HTN	Healthy	Healthy	age 39-54	339/676 (50.1)	12.9y	DPA	Erythrocyte PUFA	no
73	Wang 2011 21734059	Women's Health Study	HTN	incident HTN	Healthy	Healthy	age 55-89	177/356 (49.7)	12.9y	DPA	Erythrocyte PUFA	no
74	Wang 2011 21734059	Women's Health Study	HTN	incident HTN	Healthy	Healthy	age 55-89	177/356 (49.7)	12.9y	DPA	Erythrocyte PUFA	no
75	Wang 2011 21734059	Women's Health Study	HTN	incident HTN	Healthy	Healthy	age 39-54	339/676 (50.1)	12.9y	DHA	Erythrocyte PUFA	no
76	Wang 2011 21734059	Women's Health Study	HTN	incident HTN	Healthy	Healthy	age 39-54	339/676 (50.1)	12.9y	DHA	Erythrocyte PUFA	no
77	Wang 2011 21734059	Women's Health Study	HTN	incident HTN	Healthy	Healthy	age 55-89	177/356 (49.7)	12.9y	DHA	Erythrocyte PUFA	no
78	Wang 2011 21734059	Women's Health Study	HTN	incident HTN	Healthy	Healthy	age 55-89	177/356 (49.7)	12.9y	DHA	Erythrocyte PUFA	no

Appendix F
Observational results: hypertension

Row	Study PMID	Adjustments	Quantile	n3 units
71	Wang 2011 21734059	age, race, total energy intake (continuous), smoking status (current, past, never), alcohol use (rarely/never, 10–45 g ethanol/mo, 10–90 g ethanol/wk, >13 g ethanol/d), exercise (rarely/never,1, 1–3, $4 times/wk), menopause status (premenopausal, postmenopausal, unknown), and postmenopausal hormone use (current, past, never), BMI (continuous), history of diabetes (yes, no), and history of hypercholesterolemia (yes, no).	Qr1	% FA
72	Wang 2011 21734059	age, race, total energy intake (continuous), smoking status (current, past, never), alcohol use (rarely/never, 10–45 g ethanol/mo, 10–90 g ethanol/wk, >13 g ethanol/d), exercise (rarely/never,1, 1–3, $4 times/wk), menopause status (premenopausal, postmenopausal, unknown), and postmenopausal hormone use (current, past, never), BMI (continuous), history of diabetes (yes, no), and history of hypercholesterolemia (yes, no).	Qr4	% FA
73	Wang 2011 21734059	age, race, total energy intake (continuous), smoking status (current, past, never), alcohol use (rarely/never, 10–45 g ethanol/mo, 10–90 g ethanol/wk, >13 g ethanol/d), exercise (rarely/never,1, 1–3, $4 times/wk), menopause status (premenopausal, postmenopausal, unknown), and postmenopausal hormone use (current, past, never), BMI (continuous), history of diabetes (yes, no), and history of hypercholesterolemia (yes, no).	Qr1	% FA
74	Wang 2011 21734059	age, race, total energy intake (continuous), smoking status (current, past, never), alcohol use (rarely/never, 10–45 g ethanol/mo, 10–90 g ethanol/wk, >13 g ethanol/d), exercise (rarely/never,1, 1–3, $4 times/wk), menopause status (premenopausal, postmenopausal, unknown), and postmenopausal hormone use (current, past, never), BMI (continuous), history of diabetes (yes, no), and history of hypercholesterolemia (yes, no).	Qr4	% FA
75	Wang 2011 21734059	age, race, total energy intake (continuous), smoking status (current, past, never), alcohol use (rarely/never, 10–45 g ethanol/mo, 10–90 g ethanol/wk, >13 g ethanol/d), exercise (rarely/never,1, 1–3, $4 times/wk), menopause status (premenopausal, postmenopausal, unknown), and postmenopausal hormone use (current, past, never), BMI (continuous), history of diabetes (yes, no), and history of hypercholesterolemia (yes, no).	Qr1	% FA
76	Wang 2011 21734059	age, race, total energy intake (continuous), smoking status (current, past, never), alcohol use (rarely/never, 10–45 g ethanol/mo, 10–90 g ethanol/wk, >13 g ethanol/d), exercise (rarely/never,1, 1–3, $4 times/wk), menopause status (premenopausal, postmenopausal, unknown), and postmenopausal hormone use (current, past, never), BMI (continuous), history of diabetes (yes, no), and history of hypercholesterolemia (yes, no).	Qr4	% FA
77	Wang 2011 21734059	age, race, total energy intake (continuous), smoking status (current, past, never), alcohol use (rarely/never, 10–45 g ethanol/mo, 10–90 g ethanol/wk, >13 g ethanol/d), exercise (rarely/never,1, 1–3, $4 times/wk), menopause status (premenopausal, postmenopausal, unknown), and postmenopausal hormone use (current, past, never), BMI (continuous), history of diabetes (yes, no), and history of hypercholesterolemia (yes, no).	Qr1	% FA
78	Wang 2011 21734059	age, race, total energy intake (continuous), smoking status (current, past, never), alcohol use (rarely/never, 10–45 g ethanol/mo, 10–90 g ethanol/wk, >13 g ethanol/d), exercise (rarely/never,1, 1–3, $4 times/wk), menopause status (premenopausal, postmenopausal, unknown), and postmenopausal hormone use (current, past, never), BMI (continuous), history of diabetes (yes, no), and history of hypercholesterolemia (yes, no).	Qr4	% FA

Appendix F
Observational results: hypertension

Row	Study PMID	Quantile low	Quantile median	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
71	Wang 2011 21734059	nd	nd	nd	RR	nd	nd	nd	Reference group				
72	Wang 2011 21734059	nd	nd	nd	RR	nd	nd	nd	0.5	0.29	0.85	P trend	0.02
73	Wang 2011 21734059	nd	nd	nd	RR	nd	nd	nd	Reference group				
74	Wang 2011 21734059	nd	nd	nd	RR	nd	nd	nd	0.82	0.33	2.06	P trend	0.66
75	Wang 2011 21734059	nd	nd	nd	RR	nd	nd	nd	Reference group				
76	Wang 2011 21734059	nd	nd	nd	RR	nd	nd	nd	0.57	0.31	1.04	P trend	0.03
77	Wang 2011 21734059	nd	nd	nd	RR	nd	nd	nd	Reference group				
78	Wang 2011 21734059	nd	nd	nd	RR	nd	nd	nd	1.23	0.46	3.26	P trend	0.9

Appendix F
Observational results: coronary heart disease

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA
2	Amiano 2014 24360762	Spanish EPIC	CHD	Fatal and nonfatal CHD events	Healthy	Men healthy, ages 20-69	Men	481/15444 (3.11)	10.4 y	EPA+DHA
3	Amiano 2014 24360762	Spanish EPIC	CHD	Fatal and nonfatal CHD events	Healthy	Men healthy, ages 20-69	Men	481/15444 (3.11)	10.4 y	EPA+DHA
4	Amiano 2014 24360762	Spanish EPIC	CHD	Fatal and nonfatal CHD events	Healthy	Men healthy, ages 20-69	Men	481/15444 (3.11)	10.4 y	EPA+DHA
5	Amiano 2014 24360762	Spanish EPIC	CHD	Fatal and nonfatal CHD events	Healthy	Men healthy, ages 20-69	Men	481/15444 (3.11)	10.4 y	EPA+DHA
6	Amiano 2014 24360762	Spanish EPIC	CHD	Fatal and nonfatal CHD events	Healthy	Women healthy, ages 20-69	Women	128/25647 (0.5)	10.4 y	EPA+DHA
7	Amiano 2014 24360762	Spanish EPIC	CHD	Fatal and nonfatal CHD events	Healthy	Women healthy, ages 20-69	Women	128/25647 (0.5)	10.4 y	EPA+DHA
8	Amiano 2014 24360762	Spanish EPIC	CHD	Fatal and nonfatal CHD events	Healthy	Women healthy, ages 20-69	Women	128/25647 (0.5)	10.4 y	EPA+DHA
9	Amiano 2014 24360762	Spanish EPIC	CHD	Fatal and nonfatal CHD events	Healthy	Women healthy, ages 20-69	Women	128/25647 (0.5)	10.4 y	EPA+DHA
10	Amiano 2014 24360762	Spanish EPIC	CHD	Fatal and nonfatal CHD events	Healthy	Men healthy, ages 20-69	Men	481/15444 (3.11)	10.4 y	EPA
11	Amiano 2014 24360762	Spanish EPIC	CHD	Fatal and nonfatal CHD events	Healthy	Men healthy, ages 20-69	Men	481/15444 (3.11)	10.4 y	EPA
12	Amiano 2014 24360762	Spanish EPIC	CHD	Fatal and nonfatal CHD events	Healthy	Men healthy, ages 20-69	Men	481/15444 (3.11)	10.4 y	EPA
13	Amiano 2014 24360762	Spanish EPIC	CHD	Fatal and nonfatal CHD events	Healthy	Men healthy, ages 20-69	Men	481/15444 (3.11)	10.4 y	EPA
14	Amiano 2014 24360762	Spanish EPIC	CHD	Fatal and nonfatal CHD events	Healthy	Women healthy, ages 20-69	Women	128/25647 (0.5)	10.4 y	EPA
15	Amiano 2014 24360762	Spanish EPIC	CHD	Fatal and nonfatal CHD events	Healthy	Women healthy, ages 20-69	Women	128/25647 (0.5)	10.4 y	EPA
16	Amiano 2014 24360762	Spanish EPIC	CHD	Fatal and nonfatal CHD events	Healthy	Women healthy, ages 20-69	Women	128/25647 (0.5)	10.4 y	EPA
17	Amiano 2014 24360762	Spanish EPIC	CHD	Fatal and nonfatal CHD events	Healthy	Women healthy, ages 20-69	Women	128/25647 (0.5)	10.4 y	EPA
18	Amiano 2014 24360762	Spanish EPIC	CHD	Fatal and nonfatal CHD events	Healthy	Men healthy, ages 20-69	Men	481/15444 (3.11)	10.4 y	DHA
19	Amiano 2014 24360762	Spanish EPIC	CHD	Fatal and nonfatal CHD events	Healthy	Men healthy, ages 20-69	Men	481/15444 (3.11)	10.4 y	DHA
20	Amiano 2014 24360762	Spanish EPIC	CHD	Fatal and nonfatal CHD events	Healthy	Men healthy, ages 20-69	Men	481/15444 (3.11)	10.4 y	DHA
21	Amiano 2014 24360762	Spanish EPIC	CHD	Fatal and nonfatal CHD events	Healthy	Men healthy, ages 20-69	Men	481/15444 (3.11)	10.4 y	DHA
22	Amiano 2014 24360762	Spanish EPIC	CHD	Fatal and nonfatal CHD events	Healthy	Women healthy, ages 20-69	Women	128/25647 (0.5)	10.4 y	DHA
23	Amiano 2014 24360762	Spanish EPIC	CHD	Fatal and nonfatal CHD events	Healthy	Women healthy, ages 20-69	Women	128/25647 (0.5)	10.4 y	DHA
24	Amiano 2014 24360762	Spanish EPIC	CHD	Fatal and nonfatal CHD events	Healthy	Women healthy, ages 20-69	Women	128/25647 (0.5)	10.4 y	DHA
25	Amiano 2014 24360762	Spanish EPIC	CHD	Fatal and nonfatal CHD events	Healthy	Women healthy, ages 20-69	Women	128/25647 (0.5)	10.4 y	DHA
26	Ascherio 1995 7885425	Health Professional Follow-up Study	CHD	Any CHD	Healthy	Healthy 40-75 yo men without diagnosis of myocardial infarction, angina, stroke, transient ischemic attack, or peripheral arterial disease, or had undergone coronary artery surgery.	Men	1543/44895 (3.44)	6 y	EPA+DHA

Appendix F
Observational results: coronary heart disease

Row	Study PMID	n3 measure	Supplement	Adjustments	Quantile
2	Amiano 2014 24360762	Intake	no	stratified by age and adjusted for centre, height, waist/hip ratio, energy, % of energy from carbohydrate, % of energy from protein, physical activity, educational level, hypertension, hyperlipidaemia and vegetable and fruit intake.	Qr1
3	Amiano 2014 24360762	Intake	no	stratified by age and adjusted for centre, height, waist/hip ratio, energy, % of energy from carbohydrate, % of energy from protein, physical activity, educational level, hypertension, hyperlipidaemia and vegetable and fruit intake.	Qr2
4	Amiano 2014 24360762	Intake	no	stratified by age and adjusted for centre, height, waist/hip ratio, energy, % of energy from carbohydrate, % of energy from protein, physical activity, educational level, hypertension, hyperlipidaemia and vegetable and fruit intake.	Qr3
5	Amiano 2014 24360762	Intake	no	stratified by age and adjusted for centre, height, waist/hip ratio, energy, % of energy from carbohydrate, % of energy from protein, physical activity, educational level, hypertension, hyperlipidaemia and vegetable and fruit intake.	Qr4
6	Amiano 2014 24360762	Intake	no	stratified by age and adjusted for centre, height, waist/hip ratio, energy, % of energy from carbohydrate, % of energy from protein, physical activity, educational level, hypertension, hyperlipidaemia and vegetable and fruit intake.	Qr1
7	Amiano 2014 24360762	Intake	no	stratified by age and adjusted for centre, height, waist/hip ratio, energy, % of energy from carbohydrate, % of energy from protein, physical activity, educational level, hypertension, hyperlipidaemia and vegetable and fruit intake.	Qr2
8	Amiano 2014 24360762	Intake	no	stratified by age and adjusted for centre, height, waist/hip ratio, energy, % of energy from carbohydrate, % of energy from protein, physical activity, educational level, hypertension, hyperlipidaemia and vegetable and fruit intake.	Qr3
9	Amiano 2014 24360762	Intake	no	stratified by age and adjusted for centre, height, waist/hip ratio, energy, % of energy from carbohydrate, % of energy from protein, physical activity, educational level, hypertension, hyperlipidaemia and vegetable and fruit intake.	Qr4
10	Amiano 2014 24360762	Intake	no	stratified by age and adjusted for centre, height, waist/hip ratio, energy, % of energy from carbohydrate, % of energy from protein, physical activity, educational level, hypertension, hyperlipidaemia and vegetable and fruit intake.	Qr1
11	Amiano 2014 24360762	Intake	no	stratified by age and adjusted for centre, height, waist/hip ratio, energy, % of energy from carbohydrate, % of energy from protein, physical activity, educational level, hypertension, hyperlipidaemia and vegetable and fruit intake.	Qr2
12	Amiano 2014 24360762	Intake	no	stratified by age and adjusted for centre, height, waist/hip ratio, energy, % of energy from carbohydrate, % of energy from protein, physical activity, educational level, hypertension, hyperlipidaemia and vegetable and fruit intake.	Qr3
13	Amiano 2014 24360762	Intake	no	stratified by age and adjusted for centre, height, waist/hip ratio, energy, % of energy from carbohydrate, % of energy from protein, physical activity, educational level, hypertension, hyperlipidaemia and vegetable and fruit intake.	Qr4
14	Amiano 2014 24360762	Intake	no	stratified by age and adjusted for centre, height, waist/hip ratio, energy, % of energy from carbohydrate, % of energy from protein, physical activity, educational level, hypertension, hyperlipidaemia and vegetable and fruit intake.	Qr1
15	Amiano 2014 24360762	Intake	no	stratified by age and adjusted for centre, height, waist/hip ratio, energy, % of energy from carbohydrate, % of energy from protein, physical activity, educational level, hypertension, hyperlipidaemia and vegetable and fruit intake.	Qr2
16	Amiano 2014 24360762	Intake	no	stratified by age and adjusted for centre, height, waist/hip ratio, energy, % of energy from carbohydrate, % of energy from protein, physical activity, educational level, hypertension, hyperlipidaemia and vegetable and fruit intake.	Qr3
17	Amiano 2014 24360762	Intake	no	stratified by age and adjusted for centre, height, waist/hip ratio, energy, % of energy from carbohydrate, % of energy from protein, physical activity, educational level, hypertension, hyperlipidaemia and vegetable and fruit intake.	Qr4
18	Amiano 2014 24360762	Intake	no	stratified by age and adjusted for centre, height, waist/hip ratio, energy, % of energy from carbohydrate, % of energy from protein, physical activity, educational level, hypertension, hyperlipidaemia and vegetable and fruit intake.	Qr1
19	Amiano 2014 24360762	Intake	no	stratified by age and adjusted for centre, height, waist/hip ratio, energy, % of energy from carbohydrate, % of energy from protein, physical activity, educational level, hypertension, hyperlipidaemia and vegetable and fruit intake.	Qr2
20	Amiano 2014 24360762	Intake	no	stratified by age and adjusted for centre, height, waist/hip ratio, energy, % of energy from carbohydrate, % of energy from protein, physical activity, educational level, hypertension, hyperlipidaemia and vegetable and fruit intake.	Qr3
21	Amiano 2014 24360762	Intake	no	stratified by age and adjusted for centre, height, waist/hip ratio, energy, % of energy from carbohydrate, % of energy from protein, physical activity, educational level, hypertension, hyperlipidaemia and vegetable and fruit intake.	Qr4
22	Amiano 2014 24360762	Intake	no	stratified by age and adjusted for centre, height, waist/hip ratio, energy, % of energy from carbohydrate, % of energy from protein, physical activity, educational level, hypertension, hyperlipidaemia and vegetable and fruit intake.	Qr1
23	Amiano 2014 24360762	Intake	no	stratified by age and adjusted for centre, height, waist/hip ratio, energy, % of energy from carbohydrate, % of energy from protein, physical activity, educational level, hypertension, hyperlipidaemia and vegetable and fruit intake.	Qr2
24	Amiano 2014 24360762	Intake	no	stratified by age and adjusted for centre, height, waist/hip ratio, energy, % of energy from carbohydrate, % of energy from protein, physical activity, educational level, hypertension, hyperlipidaemia and vegetable and fruit intake.	Qr3
25	Amiano 2014 24360762	Intake	no	stratified by age and adjusted for centre, height, waist/hip ratio, energy, % of energy from carbohydrate, % of energy from protein, physical activity, educational level, hypertension, hyperlipidaemia and vegetable and fruit intake.	Qr4
26	Ascherio 1995 7885425	Intake	No	age, BMI, smoking habits, alcohol consumption, history of hypertension, history of diabetes, history of hypercholesterolemia, family history of myocardial infarction before 60 years of age, profession	Qt1

Appendix F
Observational results: coronary heart disease

Row	Study PMID	n3 units	Quantile low	Quantile median	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
2	Amiano 2014 24360762	g/d	nd	nd	1.19	HR	nd	nd	nd	Reference group			P trend	0.2
3	Amiano 2014 24360762	g/d	1.2	nd	1.57	HR	nd	nd	nd	0.99	0.76	1.3		
4	Amiano 2014 24360762	g/d	1.58	nd	2.04	HR	nd	nd	nd	0.96	0.73	1.26		
5	Amiano 2014 24360762	g/d	2.05	nd	nd	HR	nd	nd	nd	1.23	0.94	1.59		
6	Amiano 2014 24360762	g/d	nd	nd	0.85	HR	nd	nd	nd	Reference group			P trend	0.76
7	Amiano 2014 24360762	g/d	0.86	nd	1.12	HR	nd	nd	nd	0.82	0.49	1.38		
8	Amiano 2014 24360762	g/d	1.13	nd	1.47	HR	nd	nd	nd	0.8	0.48	1.35		
9	Amiano 2014 24360762	g/d	1.48	nd	nd	HR	nd	nd	nd	0.77	0.46	1.3		
10	Amiano 2014 24360762	g/d	nd	nd	0.08	HR	nd	nd	nd	Reference group			P trend	0.57
11	Amiano 2014 24360762	g/d	0.09	nd	0.17	HR	nd	nd	nd	1.15	0.88	1.51		
12	Amiano 2014 24360762	g/d	0.18	nd	0.33	HR	nd	nd	nd	1.05	0.79	1.38		
13	Amiano 2014 24360762	g/d	0.34	nd	nd	HR	nd	nd	nd	1.18	0.9	1.56		
14	Amiano 2014 24360762	g/d	nd	nd	0.05	HR	nd	nd	nd	Reference group			P trend	0.57
15	Amiano 2014 24360762	g/d	0.06	nd	0.1	HR	nd	nd	nd	0.88	0.51	1.52		
16	Amiano 2014 24360762	g/d	0.11	nd	0.21	HR	nd	nd	nd	0.99	0.58	1.68		
17	Amiano 2014 24360762	g/d	0.22	nd	nd	HR	nd	nd	nd	0.71	0.4	1.25		
18	Amiano 2014 24360762	g/d	nd	nd	0.19	HR	nd	nd	nd	Reference group			P trend	0.5
19	Amiano 2014 24360762	g/d	0.2	nd	0.35	HR	nd	nd	nd	0.91	0.69	1.19		
20	Amiano 2014 24360762	g/d	0.36	nd	0.61	HR	nd	nd	nd	0.92	0.7	1.21		
21	Amiano 2014 24360762	g/d	0.62	nd	nd	HR	nd	nd	nd	1.08	0.83	1.42		
22	Amiano 2014 24360762	g/d	nd	nd	0.12	HR	nd	nd	nd	Reference group			P trend	0.82
23	Amiano 2014 24360762	g/d	0.31	nd	0.22	HR	nd	nd	nd	0.91	0.54	1.54		
24	Amiano 2014 24360762	g/d	0.23	nd	0.4	HR	nd	nd	nd	0.79	0.45	1.38		
25	Amiano 2014 24360762	g/d	0.41	nd	nd	HR	nd	nd	nd	0.79	0.44	1.39		
26	Ascherio 1995 7885425	g/d	0.01	nd	0.11	RR	294	9329	50499	Reference group			Q5 vs. Q1	0.09

Appendix F
Observational results: coronary heart disease

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA
27	Ascherio 1995 7885425	Health Professional Follow-up Study	CHD	Any CHD	Healthy	Healthy 40-75 yo men without diagnosis of myocardial infarction, angina, stroke, transient ischemic attack, or peripheral arterial disease, or had undergone coronary artery surgery.	Men	1543/44895 (3.44)	6 y	EPA+DHA
28	Ascherio 1995 7885425	Health Professional Follow-up Study	CHD	Any CHD	Healthy	Healthy 40-75 yo men without diagnosis of myocardial infarction, angina, stroke, transient ischemic attack, or peripheral arterial disease, or had undergone coronary artery surgery.	Men	1543/44895 (3.44)	6 y	EPA+DHA
29	Ascherio 1995 7885425	Health Professional Follow-up Study	CHD	Any CHD	Healthy	Healthy 40-75 yo men without diagnosis of myocardial infarction, angina, stroke, transient ischemic attack, or peripheral arterial disease, or had undergone coronary artery surgery.	Men	1543/44895 (3.44)	6 y	EPA+DHA
30	Ascherio 1995 7885425	Health Professional Follow-up Study	CHD	Any CHD	Healthy	Healthy 40-75 yo men without diagnosis of myocardial infarction, angina, stroke, transient ischemic attack, or peripheral arterial disease, or had undergone coronary artery surgery.	Men	1543/44895 (3.44)	6 y	EPA+DHA
31	Mozaffarian_2005_15630029	Health Professional Follow-up Study	CHD	Total CHD represents combined sudden death, other coronary heart disease deaths, and nonfatal MI.	Healthy	Healthy 40-75 yo men without diagnosis of myocardial infarction, angina, stroke, transient ischemic attack, or peripheral arterial disease, or had undergone coronary artery surgery.	Men	2306/45722 (5.04)	14y	EPA+DHA
32	Mozaffarian_2005_15630029	Health Professional Follow-up Study	CHD	Total CHD represents combined sudden death, other coronary heart disease deaths, and nonfatal MI.	Healthy	Healthy 40-75 yo men without diagnosis of myocardial infarction, angina, stroke, transient ischemic attack, or peripheral arterial disease, or had undergone coronary artery surgery.	Men	2306/45722 (5.04)	14y	EPA+DHA
33	Mozaffarian_2005_15630029	Health Professional Follow-up Study	CHD	Total CHD represents combined sudden death, other coronary heart disease deaths, and nonfatal MI.	Healthy	Healthy 40-75 yo men without diagnosis of myocardial infarction, angina, stroke, transient ischemic attack, or peripheral arterial disease, or had undergone coronary artery surgery.	Men	2306/45722 (5.04)	14y	EPA+DHA
34	Mozaffarian_2005_15630029	Health Professional Follow-up Study	CHD	Total CHD represents combined sudden death, other coronary heart disease deaths, and nonfatal MI.	Healthy	Healthy 40-75 yo men without diagnosis of myocardial infarction, angina, stroke, transient ischemic attack, or peripheral arterial disease, or had undergone coronary artery surgery.	Men	2306/45722 (5.04)	14y	EPA+DHA
35	Mozaffarian_2005_15630029	Health Professional Follow-up Study	CHD	Total CHD represents combined sudden death, other coronary heart disease deaths, and nonfatal MI.	Healthy	Healthy 40-75 yo men without diagnosis of myocardial infarction, angina, stroke, transient ischemic attack, or peripheral arterial disease, or had undergone coronary artery surgery.	Men	2306/45722 (5.04)	14y	ALA
36	Mozaffarian_2005_15630029	Health Professional Follow-up Study	CHD	Total CHD represents combined sudden death, other coronary heart disease deaths, and nonfatal MI.	Healthy	Healthy 40-75 yo men without diagnosis of myocardial infarction, angina, stroke, transient ischemic attack, or peripheral arterial disease, or had undergone coronary artery surgery.	Men	2306/45722 (5.04)	14y	ALA
37	Mozaffarian_2005_15630029	Health Professional Follow-up Study	CHD	Total CHD represents combined sudden death, other coronary heart disease deaths, and nonfatal MI.	Healthy	Healthy 40-75 yo men without diagnosis of myocardial infarction, angina, stroke, transient ischemic attack, or peripheral arterial disease, or had undergone coronary artery surgery.	Men	2306/45722 (5.04)	14y	ALA

Appendix F
Observational results: coronary heart disease

Row	Study PMID	n3 measure	Supplement	Adjustments	Quantile
27	Ascherio 1995 7885425	Intake	No	age, BMI, smoking habits, alcohol consumption, history of hypertension, history of diabetes, history of hypercholesterolemia, family history of myocardial infarction before 60 years of age, profession	Qt2
28	Ascherio 1995 7885425	Intake	No	age, BMI, smoking habits, alcohol consumption, history of hypertension, history of diabetes, history of hypercholesterolemia, family history of myocardial infarction before 60 years of age, profession	Qt3
29	Ascherio 1995 7885425	Intake	No	age, BMI, smoking habits, alcohol consumption, history of hypertension, history of diabetes, history of hypercholesterolemia, family history of myocardial infarction before 60 years of age, profession	Qt4
30	Ascherio 1995 7885425	Intake	No	age, BMI, smoking habits, alcohol consumption, history of hypertension, history of diabetes, history of hypercholesterolemia, family history of myocardial infarction before 60 years of age, profession	Qt5
31	Mozaffarian_2005_15630029	Intake	No	age (5-year categories); body mass index (quintiles); smoking (5 categories); physical activity (quintiles); history of diabetes, hypertension, or hypercholesterolemia; aspirin use; alcohol use (quintiles); and intake of protein, saturated fat, dietary fiber, monounsaturated fat, trans fatty acids, total calories, and ALA (each in quintiles).	<Median
32	Mozaffarian_2005_15630029	Intake	No	age (5-year categories); body mass index (quintiles); smoking (5 categories); physical activity (quintiles); history of diabetes, hypertension, or hypercholesterolemia; aspirin use; alcohol use (quintiles); and intake of protein, saturated fat, dietary fiber, monounsaturated fat, trans fatty acids, total calories, and ALA (each in quintiles).	<Median
33	Mozaffarian_2005_15630029	Intake	No	age (5-year categories); body mass index (quintiles); smoking (5 categories); physical activity (quintiles); history of diabetes, hypertension, or hypercholesterolemia; aspirin use; alcohol use (quintiles); and intake of protein, saturated fat, dietary fiber, monounsaturated fat, trans fatty acids, total calories, and ALA (each in quintiles).	>Median
34	Mozaffarian_2005_15630029	Intake	No	age (5-year categories); body mass index (quintiles); smoking (5 categories); physical activity (quintiles); history of diabetes, hypertension, or hypercholesterolemia; aspirin use; alcohol use (quintiles); and intake of protein, saturated fat, dietary fiber, monounsaturated fat, trans fatty acids, total calories, and ALA (each in quintiles).	>Median
35	Mozaffarian_2005_15630029	Intake	No	age (5-year categories); body mass index (quintiles); smoking (5 categories); physical activity (quintiles); history of diabetes, hypertension, or hypercholesterolemia; aspirin use; alcohol use (quintiles); and intake of protein, saturated fat, dietary fiber, monounsaturated fat, trans fatty acids, total calories, and ALA (each in quintiles).	All
36	Mozaffarian_2005_15630029	Intake	No	age (5-year categories); body mass index (quintiles); smoking (5 categories); physical activity (quintiles); history of diabetes, hypertension, or hypercholesterolemia; aspirin use; alcohol use (quintiles); and intake of protein, saturated fat, dietary fiber, monounsaturated fat, trans fatty acids, total calories, and ALA (each in quintiles).	<Median
37	Mozaffarian_2005_15630029	Intake	No	age (5-year categories); body mass index (quintiles); smoking (5 categories); physical activity (quintiles); history of diabetes, hypertension, or hypercholesterolemia; aspirin use; alcohol use (quintiles); and intake of protein, saturated fat, dietary fiber, monounsaturated fat, trans fatty acids, total calories, and ALA (each in quintiles).	<Median

Appendix F
Observational results: coronary heart disease

Row	Study PMID	n3 units	Quantile low	Quantile median	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
27	Ascherio 1995 7885425	g/d	0.12	nd	0.19	RR	296	9220	49902	0.98	0.83	1.15		
28	Ascherio 1995 7885425	g/d	0.2	nd	0.28	RR	295	9005	48613	0.97	0.83	1.15		
29	Ascherio 1995 7885425	g/d	0.29	nd	0.41	RR	305	8860	47722	0.99	0.84	1.17		
30	Ascherio 1995 7885425	g/d	0.42	nd	6.52	RR	353	8481	45343	1.12	0.96	1.31		
31	Mozaffarian_2005_15630029	mg/d	nd	n-6<11.2 g/d	250	RR	549	10982	nd	Ref			P low vs high n-6 intake	0.99
32	Mozaffarian_2005_15630029	mg/d	nd	n-6>11.2 g/d	250	RR	576	12129	nd	0.97	0.85	1.1	P ratio of intake of different PUFAs	>0.10
33	Mozaffarian_2005_15630029	mg/d	250	n-6<11.2 g/d	nd	RR	617	11880	nd	1.05	0.92	1.19		
34	Mozaffarian_2005_15630029	mg/d	250	n-6>11.2 g/d	nd	RR	564	10731	nd	1.02	0.89	1.16		
35	Mozaffarian_2005_15630029	g/d		per 1 g/d increase		HR				0.84	0.71	1	P ratio of intake of different PUFAs	>0.10
36	Mozaffarian_2005_15630029	mg/d	nd	n-6<11.2 g/d	1080	RR	737	14462	nd	Ref			P low vs high n-6 intake	0.71
37	Mozaffarian_2005_15630029	mg/d	nd	n-6>11.2 g/d	1080	RR	407	8385	nd	0.93	0.82	1.07		

Appendix F
Observational results: coronary heart disease

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA
38	Mozaffarian_2005_15630029	Health Professional Follow-up Study	CHD	Total CHD represents combined sudden death, other coronary heart disease deaths, and nonfatal MI.	Healthy	Healthy 40-75 yo men without diagnosis of myocardial infarction, angina, stroke, transient ischemic attack, or peripheral arterial disease, or had undergone coronary artery surgery.	Men	2306/45722 (5.04)	14y	ALA
39	Mozaffarian_2005_15630029	Health Professional Follow-up Study	CHD	Total CHD represents combined sudden death, other coronary heart disease deaths, and nonfatal MI.	Healthy	Healthy 40-75 yo men without diagnosis of myocardial infarction, angina, stroke, transient ischemic attack, or peripheral arterial disease, or had undergone coronary artery surgery.	Men	2306/45722 (5.04)	14y	ALA
40	Hu 2002 11939867	Nurses' Health Study	CHD	CHD death and nonfatal MI	Healthy	Healthy 34-59 yo female nurses	Women	1513/84688 (1.79)	16 y	EPA+DHA
41	Hu 2002 11939867	Nurses' Health Study	CHD	CHD death and nonfatal MI	Healthy	Healthy 34-59 yo female nurses	Women	1513/84688 (1.79)	16 y	EPA+DHA
42	Hu 2002 11939867	Nurses' Health Study	CHD	CHD death and nonfatal MI	Healthy	Healthy 34-59 yo female nurses	Women	1513/84688 (1.79)	16 y	EPA+DHA
43	Hu 2002 11939867	Nurses' Health Study	CHD	CHD death and nonfatal MI	Healthy	Healthy 34-59 yo female nurses	Women	1513/84688 (1.79)	16 y	EPA+DHA
44	Hu 2002 11939867	Nurses' Health Study	CHD	CHD death and nonfatal MI	Healthy	Healthy 34-59 yo female nurses	Women	1513/84688 (1.79)	16 y	EPA+DHA
45	Iso 2006 16401768	Japan Public Health Center-Based Study - Cohort I	CHD	Fatal and nonfatal CHD events	Healthy	Healthy 40-59	All	258/41578 (0.62)	11.5 y	EPA+DHA
46	Iso 2006 16401768	Japan Public Health Center-Based Study - Cohort I	CHD	Fatal and nonfatal CHD events	Healthy	Healthy 40-59	All	258/41578 (0.62)	11.5 y	EPA+DHA
47	Iso 2006 16401768	Japan Public Health Center-Based Study - Cohort I	CHD	Fatal and nonfatal CHD events	Healthy	Healthy 40-59	All	258/41578 (0.62)	11.5 y	EPA+DHA
48	Iso 2006 16401768	Japan Public Health Center-Based Study - Cohort I	CHD	Fatal and nonfatal CHD events	Healthy	Healthy 40-59	All	258/41578 (0.62)	11.5 y	EPA+DHA
49	Iso 2006 16401768	Japan Public Health Center-Based Study - Cohort I	CHD	Fatal and nonfatal CHD events	Healthy	Healthy 40-59	All	258/41578 (0.62)	11.5 y	EPA+DHA
50	Khaw 2012 22802735	EPIC Norfolk	CHD	incident CHD	Healthy	healthy	All	2434/7364 (33.05)	13 y	All n-3
51	Khaw 2012 22802735	EPIC Norfolk	CHD	incident CHD	Healthy	healthy	All	2434/7364 (33.05)	13 y	All n-3
52	Khaw 2012 22802735	EPIC Norfolk	CHD	incident CHD	Healthy	healthy	All	2434/7364 (33.05)	13 y	All n-3
53	Khaw 2012 22802735	EPIC Norfolk	CHD	incident CHD	Healthy	healthy	All	2434/7364 (33.05)	13 y	All n-3
54	Khaw 2012 22802735	EPIC Norfolk	CHD	incident CHD	Healthy	healthy	All	2434/7364 (33.05)	13 y	All n-3
55	Khaw 2012 22802735	EPIC Norfolk	CHD	incident CHD	Healthy	healthy	All	2434/7364 (33.05)	13 y	All n-3
56	Khaw 2012 22802735	EPIC Norfolk	CHD	incident CHD	Healthy	healthy	All	2434/7364 (33.05)	13 y	ALA

Appendix F
Observational results: coronary heart disease

Row	Study PMID	n3 measure	Supplement	Adjustments	Quantile
38	Mozaffarian_2005_15630029	Intake	No	age (5-year categories); body mass index (quintiles); smoking (5 categories); physical activity (quintiles); history of diabetes, hypertension, or hypercholesterolemia; aspirin use; alcohol use (quintiles); and intake of protein, saturated fat, dietary fiber, monounsaturated fat, trans fatty acids, total calories, and ALA (each in quintiles).	>Median
39	Mozaffarian_2005_15630029	Intake	No	age (5-year categories); body mass index (quintiles); smoking (5 categories); physical activity (quintiles); history of diabetes, hypertension, or hypercholesterolemia; aspirin use; alcohol use (quintiles); and intake of protein, saturated fat, dietary fiber, monounsaturated fat, trans fatty acids, total calories, and ALA (each in quintiles).	>Median
40	Hu 2002 11939867	Intake	no	age, time periods, smoking status (never, past, curent), BMI (<22, 22-22.9, 23-24.9, 25-28.9, 29+ kg/m2), alcohol intake (0, <5, 5-14, 15+), menopausal status and postmenopausal hormone use, vigorous to moderate activity (<1, 1-1.9, 2-3.9, 4-6.9, 7+ hours/week), number of times aspirin was used per week (<1, 1-2, 3-6, 7-14, 15+), multivitamin use (yes vs. no), vitamin E supplement use (yes vs. no), history of HTN (yes vs. no), hypercholesterolemia (yes vs. no), diabetes (yes vs. no)	Qt1
41	Hu 2002 11939867	Intake	no	age, time periods, smoking status (never, past, curent), BMI (<22, 22-22.9, 23-24.9, 25-28.9, 29+ kg/m2), alcohol intake (0, <5, 5-14, 15+), menopausal status and postmenopausal hormone use, vigorous to moderate activity (<1, 1-1.9, 2-3.9, 4-6.9, 7+ hours/week), number of times aspirin was used per week (<1, 1-2, 3-6, 7-14, 15+), multivitamin use (yes vs. no), vitamin E supplement use (yes vs. no), history of HTN (yes vs. no), hypercholesterolemia (yes vs. no), diabetes (yes vs. no)	Qt2
42	Hu 2002 11939867	Intake	no	age, time periods, smoking status (never, past, curent), BMI (<22, 22-22.9, 23-24.9, 25-28.9, 29+ kg/m2), alcohol intake (0, <5, 5-14, 15+), menopausal status and postmenopausal hormone use, vigorous to moderate activity (<1, 1-1.9, 2-3.9, 4-6.9, 7+ hours/week), number of times aspirin was used per week (<1, 1-2, 3-6, 7-14, 15+), multivitamin use (yes vs. no), vitamin E supplement use (yes vs. no), history of HTN (yes vs. no), hypercholesterolemia (yes vs. no), diabetes (yes vs. no)	Qt3
43	Hu 2002 11939867	Intake	no	age, time periods, smoking status (never, past, curent), BMI (<22, 22-22.9, 23-24.9, 25-28.9, 29+ kg/m2), alcohol intake (0, <5, 5-14, 15+), menopausal status and postmenopausal hormone use, vigorous to moderate activity (<1, 1-1.9, 2-3.9, 4-6.9, 7+ hours/week), number of times aspirin was used per week (<1, 1-2, 3-6, 7-14, 15+), multivitamin use (yes vs. no), vitamin E supplement use (yes vs. no), history of HTN (yes vs. no), hypercholesterolemia (yes vs. no), diabetes (yes vs. no)	Qt4
44	Hu 2002 11939867	Intake	no	age, time periods, smoking status (never, past, curent), BMI (<22, 22-22.9, 23-24.9, 25-28.9, 29+ kg/m2), alcohol intake (0, <5, 5-14, 15+), menopausal status and postmenopausal hormone use, vigorous to moderate activity (<1, 1-1.9, 2-3.9, 4-6.9, 7+ hours/week), number of times aspirin was used per week (<1, 1-2, 3-6, 7-14, 15+), multivitamin use (yes vs. no), vitamin E supplement use (yes vs. no), history of HTN (yes vs. no), hypercholesterolemia (yes vs. no), diabetes (yes vs. no)	Qt5
45	Iso 2006 16401768	Intake	No	age; sex; cigarette smoking; alcohol intake; body mass index; histories of hypertension and diabetes; medication use for hypercholesterolemia; education level; sports at leisure time; quintiles of dietary intake of fruits, vegetables, saturated fat, monounsaturated fat, n6 polyunsaturated fat, cholesterol, and total energy; and PHC.	Qt1
46	Iso 2006 16401768	Intake	No	age; sex; cigarette smoking; alcohol intake; body mass index; histories of hypertension and diabetes; medication use for hypercholesterolemia; education level; sports at leisure time; quintiles of dietary intake of fruits, vegetables, saturated fat, monounsaturated fat, n6 polyunsaturated fat, cholesterol, and total energy; and PHC.	Qt2
47	Iso 2006 16401768	Intake	No	age; sex; cigarette smoking; alcohol intake; body mass index; histories of hypertension and diabetes; medication use for hypercholesterolemia; education level; sports at leisure time; quintiles of dietary intake of fruits, vegetables, saturated fat, monounsaturated fat, n6 polyunsaturated fat, cholesterol, and total energy; and PHC.	Qt3
48	Iso 2006 16401768	Intake	No	age; sex; cigarette smoking; alcohol intake; body mass index; histories of hypertension and diabetes; medication use for hypercholesterolemia; education level; sports at leisure time; quintiles of dietary intake of fruits, vegetables, saturated fat, monounsaturated fat, n6 polyunsaturated fat, cholesterol, and total energy; and PHC.	Qt4
49	Iso 2006 16401768	Intake	No	age; sex; cigarette smoking; alcohol intake; body mass index; histories of hypertension and diabetes; medication use for hypercholesterolemia; education level; sports at leisure time; quintiles of dietary intake of fruits, vegetables, saturated fat, monounsaturated fat, n6 polyunsaturated fat, cholesterol, and total energy; and PHC.	Qt5
50	Khaw 2012 22802735	Blood	No	age, sex, PFA, BMI, smoking, alcohol intake, physical activity, plasma vitamin C, social class, education, diabetes, systolic blood pressure, and cholesterol	Qr1
51	Khaw 2012 22802735	Blood	No	age, sex, PFA, BMI, smoking, alcohol intake, physical activity, plasma vitamin C, social class, education, diabetes, systolic blood pressure, and cholesterol	Qr2
52	Khaw 2012 22802735	Blood	No	age, sex, PFA, BMI, smoking, alcohol intake, physical activity, plasma vitamin C, social class, education, diabetes, systolic blood pressure, and cholesterol	Qr3
53	Khaw 2012 22802735	Blood	No	age, sex, PFA, BMI, smoking, alcohol intake, physical activity, plasma vitamin C, social class, education, diabetes, systolic blood pressure, and cholesterol	Qr4
54	Khaw 2012 22802735	Blood	No	age, sex, PFA, BMI, smoking, alcohol intake, physical activity, plasma vitamin C, social class, education, diabetes, systolic blood pressure, and cholesterol	All
55	Khaw 2012 22802735	Blood	No	age, sex, other PFA, BMI, smoking, physical activity, alcohol intake, social class, education, blood pressure	All
56	Khaw 2012 22802735	Blood	No	age, sex, other PFA, BMI, smoking, physical activity, alcohol intake, social class, education, blood pressure	All

Appendix F
Observational results: coronary heart disease

Row	Study PMID	n3 units	Quantile low	Quantile median	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
38	Mozaffarian_2005_15630029	mg/d	1080	n-6<11.2 g/d	nd	RR	429	8400	nd	0.88	0.78	0.99		
39	Mozaffarian_2005_15630029	mg/d	1080	n-6>11.2 g/d	nd	RR	733	14475	nd	0.89	0.79	0.99		
40	Hu 2002 11939867	% kcal	nd	0.03	nd	RR	261	nd	255434	Reference group			P trend	<0.001
41	Hu 2002 11939867	% kcal	nd	0.05	nd	RR	391	nd	270898	0.93	0.78	1.09		
42	Hu 2002 11939867	% kcal	nd	0.08	nd	RR	329	nd	263131	0.78	0.65	0.93		
43	Hu 2002 11939867	% kcal	nd	0.14	nd	RR	267	nd	259454	0.68	0.56	0.82		
44	Hu 2002 11939867	% kcal	nd	0.24	nd	RR	265	nd	258583	0.67	0.55	0.81		
45	Iso 2006 16401768	g/d	nd	0.3 (mean)	nd	HR	83	nd	102711	Reference group			P trend	0.18
46	Iso 2006 16401768	g/d	nd	0.6 (mean)	nd	HR	44	nd	95861	0.7	0.47	1.03		
47	Iso 2006 16401768	g/d	nd	0.9 (mean)	nd	HR	48	nd	95258	0.75	0.5	1.12		
48	Iso 2006 16401768	g/d	nd	1.3 (mean)	nd	HR	45	nd	91435	0.75	0.48	1.18		
49	Iso 2006 16401768	g/d	nd	2.1 (mean)	nd	HR	38	nd	92062	0.58	0.35	0.97		
50	Khaw 2012 22802735	Mol%	nd	mean 259 (men) 277.5 (women)	nd	OR	nd	nd	nd	Reference group				0.98
51	Khaw 2012 22802735	Mol%	nd	mean 329 (men) 340.2 (women)	nd	OR	nd	nd	nd	1.1	0.94	1.3		
52	Khaw 2012 22802735	Mol%	nd	mean 395 (men) 404.5 (women)	nd	OR	nd	nd	nd	0.9	0.77	1.05		
53	Khaw 2012 22802735	Mol%	nd	mean 498 (men) 526.4 (women)	nd	OR	nd	nd	nd	0.97	0.84	1.26		
54	Khaw 2012 22802735	Mol%	nd	per SD increase	nd	OR	nd	nd	nd	1	0.93	1.07	per SD increase	
55	Khaw 2012 22802735	mmol/L	nd	mean 377 (165.7)	nd	OR	nd	nd	nd	1.01	0.92	1.11	per SD increase	0.82
56	Khaw 2012 22802735	mmol/L	nd	mean 11.4 (6.4)	nd	OR	nd	nd	nd	0.98	0.89	1.09	per SD increase	0.7

Appendix F
Observational results: coronary heart disease

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA
57	Khaw 2012 22802735	EPIC Norfolk	CHD	incident CHD	Healthy	healthy	All	2434/7364 (33.05)	13 y	EPA
58	Khaw 2012 22802735	EPIC Norfolk	CHD	incident CHD	Healthy	healthy	All	2434/7364 (33.05)	13 y	DPA
59	Khaw 2012 22802735	EPIC Norfolk	CHD	incident CHD	Healthy	healthy	All	2434/7364 (33.05)	13 y	DHA
60	Fretts 2014 25159901	Cardiovascular Health Study	CHD	Total fatal and nonfatal CHD	Healthy	Healthy age >= 65y	All	426/2709 (15.7)	16y	ALA
61	Fretts 2014 25159901	Cardiovascular Health Study	CHD	Total fatal and nonfatal CHD	Healthy	Healthy age >= 65y	All	378/2583 (14.6)	12y	ALA
62	Fretts 2014 25159901	Cardiovascular Health Study	CHD	Total fatal and nonfatal CHD	Healthy	Healthy age >= 65y	All	378/2583 (14.6)	12y	ALA
63	Fretts 2014 25159901	Cardiovascular Health Study	CHD	Total fatal and nonfatal CHD	Healthy	Healthy age >= 65y	All	378/2583 (14.6)	12y	ALA
64	Fretts 2014 25159901	Cardiovascular Health Study	CHD	Total fatal and nonfatal CHD	Healthy	Healthy age >= 65y	All	426/2709 (15.7)	16y	ALA
65	Fretts 2014 25159901	Cardiovascular Health Study	CHD	Total fatal and nonfatal CHD	Healthy	Healthy age >= 65y	All	426/2709 (15.7)	16y	ALA
66	Fretts 2014 25159901	Cardiovascular Health Study	CHD	Total fatal and nonfatal CHD	Healthy	Healthy age >= 65y	All	426/2709 (15.7)	16y	ALA
67	Fretts 2014 25159901	Cardiovascular Health Study	CHD	Total fatal and nonfatal CHD	Healthy	Healthy age >= 65y	All	426/2709 (15.7)	16y	ALA
68	Fretts 2014 25159901	Cardiovascular Health Study	CHD	Total fatal and nonfatal CHD	Healthy	Healthy age >= 65y	All	378/2583 (14.6)	12y	ALA
69	Fretts 2014 25159901	Cardiovascular Health Study	CHD	Total fatal and nonfatal CHD	Healthy	Healthy age >= 65y	All	378/2583 (14.6)	12y	ALA
70	Mozaffarian 2013 23546563	Cardiovascular Health Study	CHD	Total fatal and nonfatal CHD	Healthy	Healthy age >= 65y	All	630/3941 (16)	16y	DHA
71	Mozaffarian 2013 23546563	Cardiovascular Health Study	CHD	Total fatal and nonfatal CHD	Healthy	Healthy age >= 65y	All	630/3941 (16)	16y	DHA
72	Mozaffarian 2013 23546563	Cardiovascular Health Study	CHD	Total fatal and nonfatal CHD	Healthy	Healthy age >= 65y	All	630/3941 (16)	16y	DHA
73	Mozaffarian 2013 23546563	Cardiovascular Health Study	CHD	Total fatal and nonfatal CHD	Healthy	Healthy age >= 65y	All	630/3941 (16)	16y	DHA
74	Mozaffarian 2013 23546563	Cardiovascular Health Study	CHD	Total fatal and nonfatal CHD	Healthy	Healthy age >= 65y	All	630/3941 (16)	16y	DHA
75	Mozaffarian 2013 23546563	Cardiovascular Health Study	CHD	Total fatal and nonfatal CHD	Healthy	Healthy age >= 65y	All	630/3941 (16)	16y	DPA
76	Mozaffarian 2013 23546563	Cardiovascular Health Study	CHD	Total fatal and nonfatal CHD	Healthy	Healthy age >= 65y	All	630/3941 (16)	16y	DPA
77	Mozaffarian 2013 23546563	Cardiovascular Health Study	CHD	Total fatal and nonfatal CHD	Healthy	Healthy age >= 65y	All	630/3941 (16)	16y	DPA
78	Mozaffarian 2013 23546563	Cardiovascular Health Study	CHD	Total fatal and nonfatal CHD	Healthy	Healthy age >= 65y	All	630/3941 (16)	16y	DPA

Appendix F

Observational results: coronary heart disease

Row	Study PMID	n3 measure	Supplement	Adjustments	Quantile
57	Khaw 2012 22802735	Blood	No	age, sex, other PFA, BMI, smoking, physical activity, alcohol intake, social class, education, blood pressure	All
58	Khaw 2012 22802735	Blood	No	age, sex, other PFA, BMI, smoking, physical activity, alcohol intake, social class, education, blood pressure	All
59	Khaw 2012 22802735	Blood	No	age, sex, other PFA, BMI, smoking, physical activity, alcohol intake, social class, education, blood pressure	All
60	Fretts 2014 25159901	Plasma	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt5
61	Fretts 2014 25159901	Intake	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt1
62	Fretts 2014 25159901	Intake	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt2
63	Fretts 2014 25159901	Intake	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt3
64	Fretts 2014 25159901	Plasma	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt1
65	Fretts 2014 25159901	Plasma	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt2
66	Fretts 2014 25159901	Plasma	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt3
67	Fretts 2014 25159901	Plasma	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt4
68	Fretts 2014 25159901	Intake	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt4
69	Fretts 2014 25159901	Intake	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt5
70	Mozaffarian 2013 23546563	Plasma	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt1
71	Mozaffarian 2013 23546563	Plasma	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt2
72	Mozaffarian 2013 23546563	Plasma	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt3
73	Mozaffarian 2013 23546563	Plasma	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt4
74	Mozaffarian 2013 23546563	Plasma	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt5
75	Mozaffarian 2013 23546563	Plasma	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt1
76	Mozaffarian 2013 23546563	Plasma	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt2
77	Mozaffarian 2013 23546563	Plasma	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt3
78	Mozaffarian 2013 23546563	Plasma	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt4

Appendix F
Observational results: coronary heart disease

Row	Study PMID	n3 units	Quantile low	Quantile median	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
57	Khaw 2012 22802735	mmol/L	nd	mean 63.1 (45.2)	nd	OR	nd	nd	nd	1	0.89	1.11	per SD increase	0.95
58	Khaw 2012 22802735	mmol/L	nd	mean65.1 (28)	nd	OR	nd	nd	nd	0.84	0.72	0.98	per SD increase	0.03
59	Khaw 2012 22802735	mmol/L	nd	mean 237.4 (106.2)	nd	OR	nd	nd	nd	0.96	0.85	1.09	per SD increase	0.56
60	Fretts 2014 25159901	% FA	0.19	0.22	0.47	HR	90	nd	6589	1.22	0.9	1.68		
61	Fretts 2014 25159901	% fat intake	0.39	1.33	1.45	HR	77	nd	4691	Reference group			P trend	0.75
62	Fretts 2014 25159901	% fat intake	1.45	1.56	1.65	HR	71	nd	4785	0.97	0.7	1.34		
63	Fretts 2014 25159901	% fat intake	1.65	1.76	1.87	HR	67	nd	4891	0.88	0.63	1.23		
64	Fretts 2014 25159901	% FA	0.05	0.09	0.11	HR	83	nd	6208	Reference group			P trend	0.16
65	Fretts 2014 25159901	% FA	0.11	0.12	0.13	HR	80	nd	5792	1.1	0.8	1.5		
66	Fretts 2014 25159901	% FA	0.13	0.14	0.15	HR	81	nd	6026	1.1	0.8	1.52		
67	Fretts 2014 25159901	% FA	0.15	0.17	0.19	HR	92	nd	6132	1.21	0.88	1.64		
68	Fretts 2014 25159901	% fat intake	1.87	2	2.17	HR	92	nd	4997	1.25	0.91	1.7		
69	Fretts 2014 25159901	% fat intake	2.17	2.44	4.88	HR	71	nd	5380	0.93	0.67	1.3		
70	Mozaffarian 2013 23546563	% FA	nd	1.95	nd	HR	nd	nd	nd	Reference group			P trend	0.01
71	Mozaffarian 2013 23546563	% FA	nd	2.44	nd	HR	nd	nd	nd	0.94	0.73	1.2		
72	Mozaffarian 2013 23546563	% FA	nd	2.87	nd	HR	nd	nd	nd	1.06	0.83	1.35		
73	Mozaffarian 2013 23546563	% FA	nd	3.36	nd	HR	nd	nd	nd	0.83	0.64	1.08		
74	Mozaffarian 2013 23546563	% FA	nd	4.34	nd	HR	nd	nd	nd	0.72	0.55	0.95		
75	Mozaffarian 2013 23546563	% FA	nd	0.63	nd	HR	nd	nd	nd	Reference group			P trend	0.28
76	Mozaffarian 2013 23546563	% FA	nd	0.75	nd	HR	nd	nd	nd	0.72	0.56	0.93		
77	Mozaffarian 2013 23546563	% FA	nd	0.82	nd	HR	nd	nd	nd	0.88	0.69	1.13		
78	Mozaffarian 2013 23546563	% FA	nd	0.91	nd	HR	nd	nd	nd	0.82	0.64	1.05		

Appendix F
Observational results: coronary heart disease

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA
79	Mozaffarian 2013 23546563	Cardiovascular Health Study	CHD	Total fatal and nonfatal CHD	Healthy	Healthy age >= 65y	All	630/3941 (16)	16y	DPA
80	Mozaffarian 2013 23546563	Cardiovascular Health Study	CHD	Total fatal and nonfatal CHD	Healthy	Healthy age >= 65y	All	630/3941 (16)	16y	EPA
81	Mozaffarian 2013 23546563	Cardiovascular Health Study	CHD	Total fatal and nonfatal CHD	Healthy	Healthy age >= 65y	All	630/3941 (16)	16y	EPA
82	Mozaffarian 2013 23546563	Cardiovascular Health Study	CHD	Total fatal and nonfatal CHD	Healthy	Healthy age >= 65y	All	630/3941 (16)	16y	EPA
83	Mozaffarian 2013 23546563	Cardiovascular Health Study	CHD	Total fatal and nonfatal CHD	Healthy	Healthy age >= 65y	All	630/3941 (16)	16y	EPA
84	Mozaffarian 2013 23546563	Cardiovascular Health Study	CHD	Total fatal and nonfatal CHD	Healthy	Healthy age >= 65y	All	630/3941 (16)	16y	EPA
85	Mozaffarian 2013 23546563	Cardiovascular Health Study	CHD	Total fatal and nonfatal CHD	Healthy	Healthy age >= 65y	All	630/3941 (16)	16y	All n-3
86	Mozaffarian 2013 23546563	Cardiovascular Health Study	CHD	Total fatal and nonfatal CHD	Healthy	Healthy age >= 65y	All	630/3941 (16)	16y	All n-3
87	Mozaffarian 2013 23546563	Cardiovascular Health Study	CHD	Total fatal and nonfatal CHD	Healthy	Healthy age >= 65y	All	630/3941 (16)	16y	All n-3
88	Mozaffarian 2013 23546563	Cardiovascular Health Study	CHD	Total fatal and nonfatal CHD	Healthy	Healthy age >= 65y	All	630/3941 (16)	16y	All n-3
89	Mozaffarian 2013 23546563	Cardiovascular Health Study	CHD	Total fatal and nonfatal CHD	Healthy	Healthy age >= 65y	All	630/3941 (16)	16y	All n-3
90	Pietinen 1997 9149659	Alpha-Tocopherol, Beta-Carotene Cancer Prevention	CHD	includes first nonfatal myocardial infarction and coronary death	Healthy	health smoking men aged 50-69 years	Men	1399/21930 (6.38)	6 y	ALA
91	Pietinen 1997 9149659	Alpha-Tocopherol, Beta-Carotene Cancer Prevention	CHD	includes first nonfatal myocardial infarction and coronary death	Healthy	health smoking men aged 50-69 years	Men	1399/21930 (6.38)	6 y	ALA
92	Pietinen 1997 9149659	Alpha-Tocopherol, Beta-Carotene Cancer Prevention	CHD	includes first nonfatal myocardial infarction and coronary death	Healthy	health smoking men aged 50-69 years	Men	1399/21930 (6.38)	6 y	ALA
93	Pietinen 1997 9149659	Alpha-Tocopherol, Beta-Carotene Cancer Prevention	CHD	includes first nonfatal myocardial infarction and coronary death	Healthy	health smoking men aged 50-69 years	Men	1399/21930 (6.38)	6 y	ALA
94	Pietinen 1997 9149659	Alpha-Tocopherol, Beta-Carotene Cancer Prevention	CHD	includes first nonfatal myocardial infarction and coronary death	Healthy	health smoking men aged 50-69 years	Men	1399/21930 (6.38)	6 y	ALA
95	Pietinen 1997 9149659	Alpha-Tocopherol, Beta-Carotene Cancer Prevention	CHD	includes first nonfatal myocardial infarction and coronary death	Healthy	health smoking men aged 50-69 years	Men	1399/21930 (6.38)	6 y	EPA+DHA+DPA

Appendix F
Observational results: coronary heart disease

Row	Study PMID	n3 measure	Supplement	Adjustments	Quantile
79	Mozaffarian 2013 23546563	Plasma	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt5
80	Mozaffarian 2013 23546563	Plasma	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt1
81	Mozaffarian 2013 23546563	Plasma	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt2
82	Mozaffarian 2013 23546563	Plasma	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt3
83	Mozaffarian 2013 23546563	Plasma	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt4
84	Mozaffarian 2013 23546563	Plasma	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt5
85	Mozaffarian 2013 23546563	Plasma	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt1
86	Mozaffarian 2013 23546563	Plasma	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt2
87	Mozaffarian 2013 23546563	Plasma	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt3
88	Mozaffarian 2013 23546563	Plasma	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt4
89	Mozaffarian 2013 23546563	Plasma	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt5
90	Pietinen 1997 9149659	Intake	no	age, treatment group, smoking, body mass index, blood pressure, intakes of energy, alcohol, and fiber (quintiles), education (<7, 7-11, >11 years), and physical activity (<1, 1-2, >2 times per week).	Qt1
91	Pietinen 1997 9149659	Intake	no	age, treatment group, smoking, body mass index, blood pressure, intakes of energy, alcohol, and fiber (quintiles), education (<7, 7-11, >11 years), and physical activity (<1, 1-2, >2 times per week).	Qt2
92	Pietinen 1997 9149659	Intake	no	age, treatment group, smoking, body mass index, blood pressure, intakes of energy, alcohol, and fiber (quintiles), education (<7, 7-11, >11 years), and physical activity (<1, 1-2, >2 times per week).	Qt3
93	Pietinen 1997 9149659	Intake	no	age, treatment group, smoking, body mass index, blood pressure, intakes of energy, alcohol, and fiber (quintiles), education (<7, 7-11, >11 years), and physical activity (<1, 1-2, >2 times per week).	Qt4
94	Pietinen 1997 9149659	Intake	no	age, treatment group, smoking, body mass index, blood pressure, intakes of energy, alcohol, and fiber (quintiles), education (<7, 7-11, >11 years), and physical activity (<1, 1-2, >2 times per week).	Qt5
95	Pietinen 1997 9149659	Intake	no	age, treatment group, smoking, body mass index, blood pressure, intakes of energy, alcohol, and fiber (quintiles), education (<7, 7-11, >11 years), and physical activity (<1, 1-2, >2 times per week).	Qt1

Appendix F
Observational results: coronary heart disease

Row	Study PMID	n3 units	Quantile low	Quantile median	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
79	Mozaffarian 2013 23546563	% FA	nd	1.04	nd	HR	nd	nd	nd	0.82	0.63	1.05		
80	Mozaffarian 2013 23546563	% FA	nd	0.3	nd	HR	nd	nd	nd	Reference group			P trend	0.032
81	Mozaffarian 2013 23546563	% FA	nd	0.41	nd	HR	nd	nd	nd	1.04	0.82	1.34		
82	Mozaffarian 2013 23546563	% FA	nd	0.51	nd	HR	nd	nd	nd	0.91	0.71	1.18		
83	Mozaffarian 2013 23546563	% FA	nd	0.64	nd	HR	nd	nd	nd	0.98	0.76	1.26		
84	Mozaffarian 2013 23546563	% FA	nd	0.92	nd	HR	nd	nd	nd	0.76	0.58	1		
85	Mozaffarian 2013 23546563	% FA	nd	3.17	nd	HR	nd	nd	nd	Reference group			P trend	0.009
86	Mozaffarian 2013 23546563	% FA	nd	3.72	nd	HR	nd	nd	nd	0.88	0.69	1.13		
87	Mozaffarian 2013 23546563	% FA	nd	4.21	nd	HR	nd	nd	nd	1.06	0.83	1.35		
88	Mozaffarian 2013 23546563	% FA	nd	4.8	nd	HR	nd	nd	nd	0.74	0.57	0.96		
89	Mozaffarian 2013 23546563	% FA	nd	6.04	nd	HR	nd	nd	nd	0.72	0.55	0.95		
90	Pietinen 1997 9149659	g/d	nd	0.9	nd	RR	303	nd	24808	1	nd	nd	Overall Test for trend	0.911
91	Pietinen 1997 9149659	g/d	nd	1.2	nd	RR	277	nd	24345	0.94	0.8	1.11		
92	Pietinen 1997 9149659	g/d	nd	1.5	nd	RR	280	nd	25714	0.99	0.84	1.17		
93	Pietinen 1997 9149659	g/d	nd	1.9	nd	RR	274	nd	25471	1.01	0.86	1.2		
94	Pietinen 1997 9149659	g/d	nd	2.5	nd	RR	265	nd	25632	0.96	0.8	1.14		
95	Pietinen 1997 9149659	g/d	nd	0.2	nd	RR	284	nd	25538	1	nd	nd	Overall Test for trend	0.119

Appendix F
Observational results: coronary heart disease

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA
96	Pietinen 1997 9149659	Alpha-Tocopherol, Beta-Carotene Cancer Prevention	CHD	includes first nonfatal myocardial infarction and coronary death	Healthy	health smoking men aged 50-69 years	Men	1399/21930 (6.38)	6 y	EPA+DHA+DPA
97	Pietinen 1997 9149659	Alpha-Tocopherol, Beta-Carotene Cancer Prevention	CHD	includes first nonfatal myocardial infarction and coronary death	Healthy	health smoking men aged 50-69 years	Men	1399/21930 (6.38)	6 y	EPA+DHA+DPA
98	Pietinen 1997 9149659	Alpha-Tocopherol, Beta-Carotene Cancer Prevention	CHD	includes first nonfatal myocardial infarction and coronary death	Healthy	health smoking men aged 50-69 years	Men	1399/21930 (6.38)	6 y	EPA+DHA+DPA
99	Pietinen 1997 9149659	Alpha-Tocopherol, Beta-Carotene Cancer Prevention	CHD	includes first nonfatal myocardial infarction and coronary death	Healthy	health smoking men aged 50-69 years	Men	1399/21930 (6.38)	6 y	EPA+DHA+DPA
100	Vedtofte 2011 21865326	Glostrup Population Studies	CHD	incident IHD	Healthy	Healthy, ages 30-61	women	159/1643 (10)	23.3 y	ALA
101	Vedtofte 2011 21865326	Glostrup Population Studies	CHD	incident IHD	Healthy	Healthy, ages 30-61	women	159/1643 (10)	23.3 y	ALA
102	Vedtofte 2011 21865326	Glostrup Population Studies	CHD	incident IHD	Healthy	Healthy, ages 30-61	women	159/1643 (10)	23.3 y	ALA
103	Vedtofte 2011 21865326	Glostrup Population Studies	CHD	incident IHD	Healthy	Healthy, ages 30-61	men	312/1634 (19)	23.3 y	ALA
104	Vedtofte 2011 21865326	Glostrup Population Studies	CHD	incident IHD	Healthy	Healthy, ages 30-61	men	312/1634 (19)	23.3 y	ALA
105	Vedtofte 2011 21865326	Glostrup Population Studies	CHD	incident IHD	Healthy	Healthy, ages 30-61	men	312/1634 (19)	23.3 y	ALA
106	Vedtofte 2011 21865326	Glostrup Population Studies	CHD	incident IHD	Healthy	Healthy, ages 30-61	women	159/1643 (10)	23.3 y	EPA+DHA
107	Vedtofte 2011 21865326	Glostrup Population Studies	CHD	incident IHD	Healthy	Healthy, ages 30-61	women	159/1643 (10)	23.3 y	EPA+DHA
108	Vedtofte 2011 21865326	Glostrup Population Studies	CHD	incident IHD	Healthy	Healthy, ages 30-61	women	159/1643 (10)	23.3 y	EPA+DHA
109	Vedtofte 2011 21865326	Glostrup Population Studies	CHD	incident IHD	Healthy	Healthy, ages 30-61	men	312/1634 (19)	23.3 y	EPA+DHA

Appendix F
Observational results: coronary heart disease

Row	Study PMID	n3 measure	Supplement	Adjustments	Quantile
96	Pietinen 1997 9149659	Intake	no	age, treatment group, smoking, body mass index, blood pressure, intakes of energy, alcohol, and fiber (quintiles), education (<7, 7-11, >11 years), and physical activity (<1, 1-2, >2 times per week).	Qt2
97	Pietinen 1997 9149659	Intake	no	age, treatment group, smoking, body mass index, blood pressure, intakes of energy, alcohol, and fiber (quintiles), education (<7, 7-11, >11 years), and physical activity (<1, 1-2, >2 times per week).	Qt3
98	Pietinen 1997 9149659	Intake	no	age, treatment group, smoking, body mass index, blood pressure, intakes of energy, alcohol, and fiber (quintiles), education (<7, 7-11, >11 years), and physical activity (<1, 1-2, >2 times per week).	Qt4
99	Pietinen 1997 9149659	Intake	no	age, treatment group, smoking, body mass index, blood pressure, intakes of energy, alcohol, and fiber (quintiles), education (<7, 7-11, >11 years), and physical activity (<1, 1-2, >2 times per week).	Qt5
100	Vedtofte 2011 21865326	Intake	no	smoking, educational attainment, familial history of acute myocardial infarction, systolic blood pressure, alcohol intake, and other PUFAs as appropriate (n–3 LC-PUFA and LA in analyses of ALA, ALA and LA in analyses of n–3 LC-PUFA, and ALA and n–3 LC-PUFA in analyses of LA), total energy, leisure-time physical activity, and BMI LC-PUFA, long-chain PUFA.	T1
101	Vedtofte 2011 21865326	Intake	no	smoking, educational attainment, familial history of acute myocardial infarction, systolic blood pressure, alcohol intake, and other PUFAs as appropriate (n–3 LC-PUFA and LA in analyses of ALA, ALA and LA in analyses of n–3 LC-PUFA, and ALA and n–3 LC-PUFA in analyses of LA), total energy, leisure-time physical activity, and BMI LC-PUFA, long-chain PUFA.	T2
102	Vedtofte 2011 21865326	Intake	no	smoking, educational attainment, familial history of acute myocardial infarction, systolic blood pressure, alcohol intake, and other PUFAs as appropriate (n–3 LC-PUFA and LA in analyses of ALA, ALA and LA in analyses of n–3 LC-PUFA, and ALA and n–3 LC-PUFA in analyses of LA), total energy, leisure-time physical activity, and BMI LC-PUFA, long-chain PUFA.	T3
103	Vedtofte 2011 21865326	Intake	no	smoking, educational attainment, familial history of acute myocardial infarction, systolic blood pressure, alcohol intake, and other PUFAs as appropriate (n–3 LC-PUFA and LA in analyses of ALA, ALA and LA in analyses of n–3 LC-PUFA, and ALA and n–3 LC-PUFA in analyses of LA), total energy, leisure-time physical activity, and BMI LC-PUFA, long-chain PUFA.	T1
104	Vedtofte 2011 21865326	Intake	no	smoking, educational attainment, familial history of acute myocardial infarction, systolic blood pressure, alcohol intake, and other PUFAs as appropriate (n–3 LC-PUFA and LA in analyses of ALA, ALA and LA in analyses of n–3 LC-PUFA, and ALA and n–3 LC-PUFA in analyses of LA), total energy, leisure-time physical activity, and BMI LC-PUFA, long-chain PUFA.	T2
105	Vedtofte 2011 21865326	Intake	no	smoking, educational attainment, familial history of acute myocardial infarction, systolic blood pressure, alcohol intake, and other PUFAs as appropriate (n–3 LC-PUFA and LA in analyses of ALA, ALA and LA in analyses of n–3 LC-PUFA, and ALA and n–3 LC-PUFA in analyses of LA), total energy, leisure-time physical activity, and BMI LC-PUFA, long-chain PUFA.	T3
106	Vedtofte 2011 21865326	Intake	no	smoking, educational attainment, familial history of acute myocardial infarction, systolic blood pressure, alcohol intake, and other PUFAs as appropriate (n–3 LC-PUFA and LA in analyses of ALA, ALA and LA in analyses of n–3 LC-PUFA, and ALA and n–3 LC-PUFA in analyses of LA), total energy, leisure-time physical activity, and BMI LC-PUFA, long-chain PUFA.	T1
107	Vedtofte 2011 21865326	Intake	no	smoking, educational attainment, familial history of acute myocardial infarction, systolic blood pressure, alcohol intake, and other PUFAs as appropriate (n–3 LC-PUFA and LA in analyses of ALA, ALA and LA in analyses of n–3 LC-PUFA, and ALA and n–3 LC-PUFA in analyses of LA), total energy, leisure-time physical activity, and BMI LC-PUFA, long-chain PUFA.	T2
108	Vedtofte 2011 21865326	Intake	no	smoking, educational attainment, familial history of acute myocardial infarction, systolic blood pressure, alcohol intake, and other PUFAs as appropriate (n–3 LC-PUFA and LA in analyses of ALA, ALA and LA in analyses of n–3 LC-PUFA, and ALA and n–3 LC-PUFA in analyses of LA), total energy, leisure-time physical activity, and BMI LC-PUFA, long-chain PUFA.	T3
109	Vedtofte 2011 21865326	Intake	no	smoking, educational attainment, familial history of acute myocardial infarction, systolic blood pressure, alcohol intake, and other PUFAs as appropriate (n–3 LC-PUFA and LA in analyses of ALA, ALA and LA in analyses of n–3 LC-PUFA, and ALA and n–3 LC-PUFA in analyses of LA), total energy, leisure-time physical activity, and BMI LC-PUFA, long-chain PUFA.	T1

Appendix F
Observational results: coronary heart disease

Row	Study PMID	n3 units	Quantile low	Quantile median	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
96	Pietinen 1997 9149659	g/d	nd	0.3	nd	RR	263	nd	25630	0.94	0.8	1.12		
97	Pietinen 1997 9149659	g/d	nd	0.4	nd	RR	280	nd	25460	1.03	0.87	1.21		
98	Pietinen 1997 9149659	g/d	nd	0.5	nd	RR	274	nd	25390	1.02	0.86	1.2		
99	Pietinen 1997 9149659	g/d	nd	0.8	nd	RR	298	nd	24952	1.15	0.97	1.35		
100	Vedtofte 2011 21865326	g/d	0.27	0.81	1.03	HR	53	527	nd	Reference group			P trend	0.8
101	Vedtofte 2011 21865326	g/d	1.03	1.24	1.49	HR	52	615	nd	0.82	0.53	1.27		
102	Vedtofte 2011 21865326	g/d	1.49	1.83	4.32	HR	54	501	nd	1.04	0.58	1.86		
103	Vedtofte 2011 21865326	g/d	0.39	1.09	1.36	HR	104	531	nd	Reference group			P trend	0.39
104	Vedtofte 2011 21865326	g/d	1.37	1.61	1.91	HR	104	547	nd	0.84	0.62	1.14		
105	Vedtofte 2011 21865326	g/d	1.91	2.27	10.6	HR	104	556	nd	0.83	0.56	1.24		
106	Vedtofte 2011 21865326	g/d	0	0.11	0.2	HR	53	604	nd	Reference group			P trend	0.04
107	Vedtofte 2011 21865326	g/d	0.2	0.3	0.45	HR	52	503	nd	0.8	0.54	1.2		
108	Vedtofte 2011 21865326	g/d	0.45	0.78	11.2	HR	54	536	nd	0.62	0.4	0.97		
109	Vedtofte 2011 21865326	g/d	0	0.16	0.26	HR	105	545	nd	Reference group			P trend	0.15

Appendix F
Observational results: coronary heart disease

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA
110	Vedtofte 2011 21865326	Glostrup Population Studies	CHD	incident IHD	Healthy	Healthy, ages 30-61	men	312/1634 (19)	23.3 y	EPA+DHA
111	Vedtofte 2011 21865326	Glostrup Population Studies	CHD	incident IHD	Healthy	Healthy, ages 30-61	men	312/1634 (19)	23.3 y	EPA+DHA
112	Vedtofte 2014 24964401	Pooling Project of Cohort Studies on Diet and Coronary Disease	CHD	Fatal and non-fatal CHD	Healthy	healthy 49 to 61 y	All	4493/229043 (1.96)	4-10 y	ALA
113	de Goede 2011 21464993	MORGEN	CHD	Fatal CHD, cardiac arrest, and nonfatal MI	Healthy	Healthy 20-65 yo	All	280/19896 (1.41)	10.5 y	ALA
114	de Goede 2011 21464993	MORGEN	CHD	Fatal CHD, cardiac arrest, and nonfatal MI	Healthy	Healthy 20-65 yo	All	280/19896 (1.41)	10.5 y	ALA
115	de Goede 2011 21464993	MORGEN	CHD	Fatal CHD, cardiac arrest, and nonfatal MI	Healthy	Healthy 20-65 yo	All	280/19896 (1.41)	10.5 y	ALA
116	de Goede 2011 21464993	MORGEN	CHD	Fatal CHD, cardiac arrest, and nonfatal MI	Healthy	Healthy 20-65 yo	All	280/19896 (1.41)	10.5 y	ALA
117	de Goede 2011 21464993	MORGEN	CHD	Fatal CHD, cardiac arrest, and nonfatal MI	Healthy	Healthy 20-65 yo	All	280/19896 (1.41)	10.5 y	ALA
118	de Oliveira 2013 24351702	MESA	CHD	MI, resuscitated cardiac arrest, angina followed by revascularization, and CHD death	Healthy	Healthy, multiethnic Adults	All	nd/2837	10 y	EPA
119	de Oliveira 2013 24351702	MESA	CHD	MI, resuscitated cardiac arrest, angina followed by revascularization, and CHD death	Healthy	Healthy, multiethnic Adults	All	nd/2837	10 y	EPA
120	de Oliveira 2013 24351702	MESA	CHD	MI, resuscitated cardiac arrest, angina followed by revascularization, and CHD death	Healthy	Healthy, multiethnic Adults	All	nd/2837	10 y	EPA
121	de Oliveira 2013 24351702	MESA	CHD	MI, resuscitated cardiac arrest, angina followed by revascularization, and CHD death	Healthy	Healthy, multiethnic Adults	All	nd/2837	10 y	EPA
122	de Oliveira 2013 24351702	MESA	CHD	MI, resuscitated cardiac arrest, angina followed by revascularization, and CHD death	Healthy	Healthy, multiethnic Adults	All	nd/2837	10 y	DPA
123	de Oliveira 2013 24351702	MESA	CHD	MI, resuscitated cardiac arrest, angina followed by revascularization, and CHD death	Healthy	Healthy, multiethnic Adults	All	nd/2837	10 y	DPA
124	de Oliveira 2013 24351702	MESA	CHD	MI, resuscitated cardiac arrest, angina followed by revascularization, and CHD death	Healthy	Healthy, multiethnic Adults	All	nd/2837	10 y	DPA

Appendix F
Observational results: coronary heart disease

Row	Study PMID	n3 measure	Supplement	Adjustments	Quantile
110	Vedtofte 2011 21865326	Intake	no	smoking, educational attainment, familial history of acute myocardial infarction, systolic blood pressure, alcohol intake, and other PUFAs as appropriate (n–3 LC-PUFA and LA in analyses of ALA, ALA and LA in analyses of n–3 LC-PUFA, and ALA and n–3 LC-PUFA in analyses of LA), total energy, leisure-time physical activity, and BMI LC-PUFA, long-chain PUFA.	T2
111	Vedtofte 2011 21865326	Intake	no	smoking, educational attainment, familial history of acute myocardial infarction, systolic blood pressure, alcohol intake, and other PUFAs as appropriate (n–3 LC-PUFA and LA in analyses of ALA, ALA and LA in analyses of n–3 LC-PUFA, and ALA and n–3 LC-PUFA in analyses of LA), total energy, leisure-time physical activity, and BMI LC-PUFA, long-chain PUFA.	T3
112	Vedtofte 2014 24964401	Intake	NA (no ALA supplememt)	age at baseline, calendar year, smoking habits, BMI, physical activity, educational level, history of hypertension, alcohol intake, total energy intake (where alcohol is excluded), fiber intake, MUFA, SFA, trans-fatty acid, long-chain n-3 FA, and linoleic acid intake	All
113	de Goede 2011 21464993	Intake	No	age, gender, BMI, total energy intake, cigarette smoking, education level, parental history of MI, alcohol intake, intake of vit C, beta-carotene, fiber, SFA, TFA, PUFA other than ALA	Qt1
114	de Goede 2011 21464993	Intake	No	age, gender, BMI, total energy intake, cigarette smoking, education level, parental history of MI, alcohol intake, intake of vit C, beta-carotene, fiber, SFA, TFA, PUFA other than ALA	Qt2
115	de Goede 2011 21464993	Intake	No	age, gender, BMI, total energy intake, cigarette smoking, education level, parental history of MI, alcohol intake, intake of vit C, beta-carotene, fiber, SFA, TFA, PUFA other than ALA	Qt3
116	de Goede 2011 21464993	Intake	No	age, gender, BMI, total energy intake, cigarette smoking, education level, parental history of MI, alcohol intake, intake of vit C, beta-carotene, fiber, SFA, TFA, PUFA other than ALA	Qt4
117	de Goede 2011 21464993	Intake	No	age, gender, BMI, total energy intake, cigarette smoking, education level, parental history of MI, alcohol intake, intake of vit C, beta-carotene, fiber, SFA, TFA, PUFA other than ALA	Qt5
118	de Oliveira 2013 24351702	Phospholipid	No	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr1
119	de Oliveira 2013 24351702	Phospholipid	No	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr2
120	de Oliveira 2013 24351702	Phospholipid	No	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr3
121	de Oliveira 2013 24351702	Phospholipid	No	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr4
122	de Oliveira 2013 24351702	Phospholipid	No	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr1
123	de Oliveira 2013 24351702	Phospholipid	No	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr2
124	de Oliveira 2013 24351702	Phospholipid	No	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr3

Appendix F
Observational results: coronary heart disease

Row	Study PMID	n3 units	Quantile low	Quantile median	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
110	Vedtofte 2011 21865326	g/d	0.26	0.38	0.56	HR	103	534	nd	0.81	0.61	1.07		
111	Vedtofte 2011 21865326	g/d	0.56	0.96	10.8	HR	104	555	nd	0.74	0.51	1.06		
112	Vedtofte 2014 24964401	g/d	nd	nd	nd	HR				0.88	0.75	1.02	per g/d increase	
113	de Goede 2011 21464993	g/d	nd	1	nd	HR	66	4013	nd	Reference group				NS
114	de Goede 2011 21464993	g/d	nd	1.2	nd	HR	42	4014	nd	0.89	0.61	1.3		
115	de Goede 2011 21464993	g/d	nd	1.3	nd	HR	46	4014	nd	0.9	0.61	1.33		
116	de Goede 2011 21464993	g/d	nd	1.5	nd	HR	54	4014	nd	0.97	0.66	1.44		
117	de Goede 2011 21464993	g/d	nd	1.9	nd	HR	72	4014	nd	1.01	0.66	1.54		
118	de Oliveira 2013 24351702	% FA	nd	0.4	nd	HR	49	732	19778	Reference group			P trend	0.004
119	de Oliveira 2013 24351702	% FA	nd	0.6	nd	HR	38	711	nd	0.82	0.53	1.26		
120	de Oliveira 2013 24351702	% FA	nd	0.86	nd	HR	37	695	nd	0.93	0.59	1.46		
121	de Oliveira 2013 24351702	% FA	nd	1.62	nd	HR	17	699	nd	0.42	0.23	0.75		
122	de Oliveira 2013 24351702	% FA	nd	0.72	nd	HR	41	752	19778	Reference group			P trend	0.29
123	de Oliveira 2013 24351702	% FA	nd	0.88	nd	HR	43	701	nd	1.1	0.71	1.7		
124	de Oliveira 2013 24351702	% FA	nd	1.01	nd	HR	33	747	nd	0.84	0.53	1.35		

Appendix F
Observational results: coronary heart disease

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA
125	de Oliveira 2013 24351702	MESA	CHD	MI, resuscitated cardiac arrest, angina followed by revascularization, and CHD death	Healthy	Healthy, multiethnic Adults	All	nd/2837	10 y	DPA
126	de Oliveira 2013 24351702	MESA	CHD	MI, resuscitated cardiac arrest, angina followed by revascularization, and CHD death	Healthy	Healthy, multiethnic Adults	All	nd/2837	10 y	DHA
127	de Oliveira 2013 24351702	MESA	CHD	MI, resuscitated cardiac arrest, angina followed by revascularization, and CHD death	Healthy	Healthy, multiethnic Adults	All	nd/2837	10 y	DHA
128	de Oliveira 2013 24351702	MESA	CHD	MI, resuscitated cardiac arrest, angina followed by revascularization, and CHD death	Healthy	Healthy, multiethnic Adults	All	nd/2837	10 y	DHA
129	de Oliveira 2013 24351702	MESA	CHD	MI, resuscitated cardiac arrest, angina followed by revascularization, and CHD death	Healthy	Healthy, multiethnic Adults	All	nd/2837	10 y	DHA
130	de Oliveira 2013 24351702	MESA	CHD	MI, resuscitated cardiac arrest, angina followed by revascularization, and CHD death	Healthy	Healthy, multiethnic Adults	All	nd/2837	10 y	EPA+DHA+DPA
131	de Oliveira 2013 24351702	MESA	CHD	MI, resuscitated cardiac arrest, angina followed by revascularization, and CHD death	Healthy	Healthy, multiethnic Adults	All	nd/2837	10 y	EPA+DHA+DPA
132	de Oliveira 2013 24351702	MESA	CHD	MI, resuscitated cardiac arrest, angina followed by revascularization, and CHD death	Healthy	Healthy, multiethnic Adults	All	nd/2837	10 y	EPA+DHA+DPA
133	de Oliveira 2013 24351702	MESA	CHD	MI, resuscitated cardiac arrest, angina followed by revascularization, and CHD death	Healthy	Healthy, multiethnic Adults	All	nd/2837	10 y	EPA+DHA+DPA
134	de Oliveira 2013 24351702	MESA	CHD	MI, resuscitated cardiac arrest, angina followed by revascularization, and CHD death	Healthy	Healthy, multiethnic Adults	All	nd/2372	10 y	EPA
135	de Oliveira 2013 24351702	MESA	CHD	MI, resuscitated cardiac arrest, angina followed by revascularization, and CHD death	Healthy	Healthy, multiethnic Adults	All	nd/2372	10 y	EPA
136	de Oliveira 2013 24351702	MESA	CHD	MI, resuscitated cardiac arrest, angina followed by revascularization, and CHD death	Healthy	Healthy, multiethnic Adults	All	nd/2372	10 y	EPA
137	de Oliveira 2013 24351702	MESA	CHD	MI, resuscitated cardiac arrest, angina followed by revascularization, and CHD death	Healthy	Healthy, multiethnic Adults	All	nd/2372	10 y	EPA

Appendix F
Observational results: coronary heart disease

Row	Study PMID	n3 measure	Supplement	Adjustments	Quantile
125	de Oliveira 2013 24351702	Phospholipid	No	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr4
126	de Oliveira 2013 24351702	Phospholipid	No	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr1
127	de Oliveira 2013 24351702	Phospholipid	No	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr2
128	de Oliveira 2013 24351702	Phospholipid	No	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr3
129	de Oliveira 2013 24351702	Phospholipid	No	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr4
130	de Oliveira 2013 24351702	Phospholipid	No	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr1
131	de Oliveira 2013 24351702	Phospholipid	No	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr2
132	de Oliveira 2013 24351702	Phospholipid	No	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr3
133	de Oliveira 2013 24351702	Phospholipid	No	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr4
134	de Oliveira 2013 24351702	Intake	No	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr1
135	de Oliveira 2013 24351702	Intake	No	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr2
136	de Oliveira 2013 24351702	Intake	No	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr3
137	de Oliveira 2013 24351702	Intake	No	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr4

Appendix F
Observational results: coronary heart disease

Row	Study PMID	n3 units	Quantile low	Quantile median	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
125	de Oliveira 2013 24351702	% FA	nd	1.21	nd	HR	24	637	nd	0.8	0.48	1.35		
126	de Oliveira 2013 24351702	% FA	nd	2.5	nd	HR	48	694	19778	Reference group			P trend	0.0002
127	de Oliveira 2013 24351702	% FA	nd	3.5	nd	HR	45	738	nd	0.87	0.57	1.34		
128	de Oliveira 2013 24351702	% FA	nd	4.5	nd	HR	34	693	nd	0.66	0.4	1.09		
129	de Oliveira 2013 24351702	% FA	nd	6	nd	HR	14	712	nd	0.29	0.15	0.58		
130	de Oliveira 2013 24351702	% FA	nd	3.9	nd	HR	50	736	19778	Reference group			P trend	0.006
131	de Oliveira 2013 24351702	% FA	nd	5	nd	HR	42	688	nd	0.92	0.6	1.41		
132	de Oliveira 2013 24351702	% FA	nd	6.3	nd	HR	30	713	nd	0.66	0.4	1.1		
133	de Oliveira 2013 24351702	% FA	nd	8.7	nd	HR	19	700	nd	0.45	0.25	0.82		
134	de Oliveira 2013 24351702	mg/d	nd	7.3	nd	HR	40	599	19778	Reference group			P trend	0.06
135	de Oliveira 2013 24351702	mg/d	nd	21	nd	HR	33	547	nd	1.12	0.7	1.8		
136	de Oliveira 2013 24351702	mg/d	nd	40	nd	HR	28	585	nd	0.82	0.5	1.37		
137	de Oliveira 2013 24351702	mg/d	nd	85	nd	HR	21	641	nd	0.61	0.34	1.1		

Appendix F
Observational results: coronary heart disease

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA
138	de Oliveira 2013 24351702	MESA	CHD	MI, resuscitated cardiac arrest, angina followed by revascularization, and CHD death	Healthy	Healthy, multiethnic Adults	All	nd/2372	10 y	DPA
139	de Oliveira 2013 24351702	MESA	CHD	MI, resuscitated cardiac arrest, angina followed by revascularization, and CHD death	Healthy	Healthy, multiethnic Adults	All	nd/2372	10 y	DPA
140	de Oliveira 2013 24351702	MESA	CHD	MI, resuscitated cardiac arrest, angina followed by revascularization, and CHD death	Healthy	Healthy, multiethnic Adults	All	nd/2372	10 y	DPA
141	de Oliveira 2013 24351702	MESA	CHD	MI, resuscitated cardiac arrest, angina followed by revascularization, and CHD death	Healthy	Healthy, multiethnic Adults	All	nd/2372	10 y	DPA
142	de Oliveira 2013 24351702	MESA	CHD	MI, resuscitated cardiac arrest, angina followed by revascularization, and CHD death	Healthy	Healthy, multiethnic Adults	All	nd/2372	10 y	DHA
143	de Oliveira 2013 24351702	MESA	CHD	MI, resuscitated cardiac arrest, angina followed by revascularization, and CHD death	Healthy	Healthy, multiethnic Adults	All	nd/2372	10 y	DHA
144	de Oliveira 2013 24351702	MESA	CHD	MI, resuscitated cardiac arrest, angina followed by revascularization, and CHD death	Healthy	Healthy, multiethnic Adults	All	nd/2372	10 y	DHA
145	de Oliveira 2013 24351702	MESA	CHD	MI, resuscitated cardiac arrest, angina followed by revascularization, and CHD death	Healthy	Healthy, multiethnic Adults	All	nd/2372	10 y	DHA
146	de Oliveira 2013 24351702	MESA	CHD	MI, resuscitated cardiac arrest, angina followed by revascularization, and CHD death	Healthy	Healthy, multiethnic Adults	All	nd/2837	10 y	EPA+DHA+DPA
147	de Oliveira 2013 24351702	MESA	CHD	MI, resuscitated cardiac arrest, angina followed by revascularization, and CHD death	Healthy	Healthy, multiethnic Adults	All	nd/2837	10 y	EPA+DHA+DPA
148	de Oliveira 2013 24351702	MESA	CHD	MI, resuscitated cardiac arrest, angina followed by revascularization, and CHD death	Healthy	Healthy, multiethnic Adults	All	nd/2837	10 y	EPA+DHA+DPA
149	de Oliveira 2013 24351702	MESA	CHD	MI, resuscitated cardiac arrest, angina followed by revascularization, and CHD death	Healthy	Healthy, multiethnic Adults	All	nd/2837	10 y	EPA+DHA+DPA
150	de Oliveira 2013 24351702	MESA	CHD	MI, resuscitated cardiac arrest, angina followed by revascularization, and CHD death	Healthy	Healthy, multiethnic Adults	All	nd/2837	10 y	ALA

Appendix F
Observational results: coronary heart disease

Row	Study PMID	n3 measure	Supplement	Adjustments	Quantile
138	de Oliveira 2013 24351702	Intake	No	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr1
139	de Oliveira 2013 24351702	Intake	No	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr2
140	de Oliveira 2013 24351702	Intake	No	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr3
141	de Oliveira 2013 24351702	Intake	No	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr4
142	de Oliveira 2013 24351702	Intake	No	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr1
143	de Oliveira 2013 24351702	Intake	No	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr2
144	de Oliveira 2013 24351702	Intake	No	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr3
145	de Oliveira 2013 24351702	Intake	No	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr4
146	de Oliveira 2013 24351702	Intake	No	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr1
147	de Oliveira 2013 24351702	Intake	No	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr2
148	de Oliveira 2013 24351702	Intake	No	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr3
149	de Oliveira 2013 24351702	Intake	No	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr4
150	de Oliveira 2013 24351702	Phospholipid	No	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr1

Appendix F
Observational results: coronary heart disease

Row	Study PMID	n3 units	Quantile low	Quantile median	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
138	de Oliveira 2013 24351702	mg/d	nd	4.3	nd	HR	40	622	19778	Reference group			P trend	0.02
139	de Oliveira 2013 24351702	mg/d	nd	11	nd	HR	40	618	nd	1.19	0.76	1.86		
140	de Oliveira 2013 24351702	mg/d	nd	19	nd	HR	24	559	nd	0.74	0.5	1.26		
141	de Oliveira 2013 24351702	mg/d	nd	39	nd	HR	18	573	nd	0.54	0.29	0.99		
142	de Oliveira 2013 24351702	mg/d	nd	24	nd	HR	34	606	19778	Reference group			P trend	0.09
143	de Oliveira 2013 24351702	mg/d	nd	49	nd	HR	34	572	nd	1.02	0.63	1.67		
144	de Oliveira 2013 24351702	mg/d	nd	80	nd	HR	36	600	nd	1.12	0.68	1.86		
145	de Oliveira 2013 24351702	mg/d	nd	150	nd	HR	18	594	nd	0.57	0.3	1.09		
146	de Oliveira 2013 24351702	mg/d	nd	38	nd	HR	33	600	19778	Reference group			P trend	0.08
147	de Oliveira 2013 24351702	mg/d	nd	82	nd	HR	39	546	nd	1.39	0.86	2.23		
148	de Oliveira 2013 24351702	mg/d	nd	140	nd	HR	32	651	nd	1	0.6	1.69		
149	de Oliveira 2013 24351702	mg/d	nd	280	nd	HR	18	575	nd	0.64	0.34	1.22		
150	de Oliveira 2013 24351702	% FA	nd	0.11	nd	HR	46	883	19778	Reference group			P trend	0.48

Appendix F
Observational results: coronary heart disease

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA
151	de Oliveira 2013 24351702	MESA	CHD	MI, resuscitated cardiac arrest, angina followed by revascularization, and CHD death	Healthy	Healthy, multiethnic Adults	All	nd/2837	10 y	ALA
152	de Oliveira 2013 24351702	MESA	CHD	MI, resuscitated cardiac arrest, angina followed by revascularization, and CHD death	Healthy	Healthy, multiethnic Adults	All	nd/2837	10 y	ALA
153	de Oliveira 2013 24351702	MESA	CHD	MI, resuscitated cardiac arrest, angina followed by revascularization, and CHD death	Healthy	Healthy, multiethnic Adults	All	nd/2837	10 y	ALA
154	de Oliveira 2013 24351702	MESA	CHD	MI, resuscitated cardiac arrest, angina followed by revascularization, and CHD death	Healthy	Healthy, multiethnic Adults	All	nd/2837	10 y	ALA
155	de Oliveira 2013 24351702	MESA	CHD	MI, resuscitated cardiac arrest, angina followed by revascularization, and CHD death	Healthy	Healthy, multiethnic Adults	All	nd/2837	10 y	ALA
156	de Oliveira 2013 24351702	MESA	CHD	MI, resuscitated cardiac arrest, angina followed by revascularization, and CHD death	Healthy	Healthy, multiethnic Adults	All	nd/2837	10 y	ALA
157	de Oliveira 2013 24351702	MESA	CHD	MI, resuscitated cardiac arrest, angina followed by revascularization, and CHD death	Healthy	Healthy, multiethnic Adults	All	nd/2837	10 y	ALA
159	**Subgroup analyses**									
160	Vedtofte 2014 24964401	Pooling Project of Cohort Studies on Diet and Coronary Disease	CHD	Fatal and non-fatal CHD	Healthy	healthy 49 to 61 y	Women	1156/148675 (0.78)	4-10 y	ALA
161	Vedtofte 2014 24964401	Pooling Project of Cohort Studies on Diet and Coronary Disease	CHD	Fatal and non-fatal CHD	Healthy	healthy 49 to 61 y	Men	3337/80368 (4.15)	4-10 y	ALA

Appendix F
Observational results: coronary heart disease

Row	Study PMID	n3 measure	Supplement	Adjustments	Quantile
151	de Oliveira 2013 24351702	Phospholipid	No	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr2
152	de Oliveira 2013 24351702	Phospholipid	No	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr3
153	de Oliveira 2013 24351702	Phospholipid	No	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr4
154	de Oliveira 2013 24351702	Intake	No	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr1
155	de Oliveira 2013 24351702	Intake	No	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr2
156	de Oliveira 2013 24351702	Intake	No	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr3
157	de Oliveira 2013 24351702	Intake	No	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr4
159	**Subgroup analyses**				
160	Vedtofte 2014 24964401	Intake	NA (no ALA supplememt)	age at baseline, calendar year, smoking habits, BMI, physical activity, educational level, history of hypertension, alcohol intake, total energy intake (where alcohol is excluded), fiber intake, MUFA, SFA, trans-fatty acid, long-chain n-3 FA, and linoleic acid intake	All
161	Vedtofte 2014 24964401	Intake	NA (no ALA supplememt)	age at baseline, calendar year, smoking habits, BMI, physical activity, educational level, history of hypertension, alcohol intake, total energy intake (where alcohol is excluded), fiber intake, MUFA, SFA, trans-fatty acid, long-chain n-3 FA, and linoleic acid intake	All

Appendix F
Observational results: coronary heart disease

Row	Study PMID	n3 units	Quantile low	Quantile median	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
151	de Oliveira 2013 24351702	% FA	nd	0.15	nd	HR	27	569	nd	0.93	0.58	1.51		
152	de Oliveira 2013 24351702	% FA	nd	0.19	nd	HR	37	757	nd	1.02	0.65	1.58		
153	de Oliveira 2013 24351702	% FA	nd	0.25	nd	HR	31	628	nd	1.18	0.74	1.91		
154	de Oliveira 2013 24351702	mg/d	nd	450	nd	HR	34	700	19778	Reference group			P trend	0.24
155	de Oliveira 2013 24351702	mg/d	nd	760	nd	HR	33	592	nd	0.93	0.55	1.56		
156	de Oliveira 2013 24351702	mg/d	nd	1080	nd	HR	33	555	nd	0.99	0.53	1.83		
157	de Oliveira 2013 24351702	mg/d	nd	1690	nd	HR	22	525	nd	0.6	0.25	1.41		
159	**Subgroup analyses**													
160	Vedtofte 2014 24964401	g/d	nd	nd	nd	HR	nd	nd	nd	1.02	0.65	1.59	per g/d increase	
161	Vedtofte 2014 24964401	g/d	nd	nd	nd	HR	nd	nd	nd	0.85	0.72	1.01	per g/d increase	

Appendix F
Observational results: congestive heart failure

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure	Supplement
2	Belin 2011 21610249	Women's Health Initiative	CHF	incident HF	Healthy	Women, 50-79 y, Healthy	All	1858/84493 (2.2)	10 y	EPA+DHA	Intake	No
3	Belin 2011 21610249	Women's Health Initiative	CHF	incident HF	Healthy	Women, 50-79 y, Healthy	All	1858/84493 (2.2)	10 y	EPA+DHA	Intake	No
4	Belin 2011 21610249	Women's Health Initiative	CHF	incident HF	Healthy	Women, 50-79 y, Healthy	All	1858/84493 (2.2)	10 y	EPA+DHA	Intake	No
5	Belin 2011 21610249	Women's Health Initiative	CHF	incident HF	Healthy	Women, 50-79 y, Healthy	All	1858/84493 (2.2)	10 y	EPA+DHA	Intake	No
6	Belin 2011 21610249	Women's Health Initiative	CHF	incident HF	Healthy	Women, 50-79 y, Healthy	All	1858/84493 (2.2)	10 y	ALA	Intake	No
7	Belin 2011 21610249	Women's Health Initiative	CHF	incident HF	Healthy	Women, 50-79 y, Healthy	All	1858/84493 (2.2)	10 y	ALA	Intake	No
8	Belin 2011 21610249	Women's Health Initiative	CHF	incident HF	Healthy	Women, 50-79 y, Healthy	All	1858/84493 (2.2)	10 y	ALA	Intake	No
9	Belin 2011 21610249	Women's Health Initiative	CHF	incident HF	Healthy	Women, 50-79 y, Healthy	All	1858/84493 (2.2)	10 y	ALA	Intake	No
10	Brouwer 2006 16569549	Rotterdam	CHF	shortness of breath, ankle oedema, and pulmonary crepitation	Healthy	ppl who had no heart failure at baseline	All	669/5299 (12.6)	11.4 y	EPA+DHA	Intake	Yes
11	Brouwer 2006 16569549	Rotterdam	CHF	shortness of breath, ankle oedema, and pulmonary crepitation	Healthy	ppl who had no heart failure at baseline	All	669/5299 (12.6)	11.4 y	EPA+DHA	Intake	Yes
12	Brouwer 2006 16569549	Rotterdam	CHF	shortness of breath, ankle oedema, and pulmonary crepitation	Healthy	ppl who had no heart failure at baseline	All	669/5299 (12.6)	11.4 y	EPA+DHA	Intake	Yes
13	Brouwer 2006 16569549	Rotterdam	CHF	shortness of breath, ankle oedema, and pulmonary crepitation	Healthy	ppl who had no heart failure at baseline	All	669/5299 (12.6)	11.4 y	EPA+DHA	Intake	Yes
14	Brouwer 2006 16569549	Rotterdam	CHF	shortness of breath, ankle oedema, and pulmonary crepitation	Healthy	ppl who had no heart failure at baseline	All	669/5299 (12.6)	11.4 y	EPA+DHA	Intake	Yes
15	Hara 2013 23047296	Osaka Acute Coronary Insufficiency Study	CHF	Heart Failure Hospitalization	CVD	AMI patients	All	nd/671	4 y	DHA	Blood	No
16	Hara 2013 23047296	Osaka Acute Coronary Insufficiency Study	CHF	Heart Failure Hospitalization	CVD	AMI patients	All	nd/671	4 y	DHA	Blood	No
17	Hara 2013 23047296	Osaka Acute Coronary Insufficiency Study	CHF	Heart Failure Hospitalization	CVD	AMI patients	All	nd/671	4 y	DHA	Blood	No
18	Hara 2012 23047296	Osaka Acute Coronary Insufficiency Study	CHF	Heart Failure Hospitalization	CVD	AMI Patients	All	nd/671	4 y	EPA	Blood	No
19	Hara 2012 23047296	Osaka Acute Coronary Insufficiency Study	CHF	Heart Failure Hospitalization	CVD	AMI Patients	All	nd/671	4 y	EPA	Blood	No
20	Hara 2012 23047296	Osaka Acute Coronary Insufficiency Study	CHF	Heart Failure Hospitalization	CVD	AMI Patients	All	nd/671	4 y	EPA	Blood	No
21	Levitan 2010 20332801	Swedish Mammography Study	CHF	Heart failure hospitalization or mortality	Healthy	Healthy, ages 49-83	All	651/36234 (1.8)	9 y	ALA	Intake	yes
22	Levitan 2010 20332801	Swedish Mammography Study	CHF	Heart failure hospitalization or mortality	Healthy	Healthy, ages 49-83	All	651/36234 (1.8)	9 y	ALA	Intake	yes

Appendix F
Observational results: congestive heart failure

Row	Study PMID	Adjustments	Quantile	n3 units	Quantile low	Quantile median
2	Belin 2011 21610249	age, ethniity, education, physical activity, smoking, alcohol diabetes, hypertension, AF, MI/CABG/PTCA, BMI, time-dependent MI	Qr1	g/d	0	nd
3	Belin 2011 21610249	age, ethniity, education, physical activity, smoking, alcohol diabetes, hypertension, AF, MI/CABG/PTCA, BMI, time-dependent MI	Qr2	g/d	0.048	nd
4	Belin 2011 21610249	age, ethniity, education, physical activity, smoking, alcohol diabetes, hypertension, AF, MI/CABG/PTCA, BMI, time-dependent MI	Qr3	g/d	0.093	nd
5	Belin 2011 21610249	age, ethniity, education, physical activity, smoking, alcohol diabetes, hypertension, AF, MI/CABG/PTCA, BMI, time-dependent MI	Qr4	g/d	>0.163	nd
6	Belin 2011 21610249	age, ethniity, education, physical activity, smoking, alcohol diabetes, hypertension, AF, MI/CABG/PTCA, BMI, time-dependent MI	Qr1	g/d	0	nd
7	Belin 2011 21610249	age, ethniity, education, physical activity, smoking, alcohol diabetes, hypertension, AF, MI/CABG/PTCA, BMI, time-dependent MI	Qr2	g/d	0.711	nd
8	Belin 2011 21610249	age, ethniity, education, physical activity, smoking, alcohol diabetes, hypertension, AF, MI/CABG/PTCA, BMI, time-dependent MI	Qr3	g/d	1.02	nd
9	Belin 2011 21610249	age, ethniity, education, physical activity, smoking, alcohol diabetes, hypertension, AF, MI/CABG/PTCA, BMI, time-dependent MI	Qr4	g/d	>1.465	nd
10	Brouwer 2006 16569549	age, sex, total energy intake, smoking, BMI, education, and alcohol intake.	Qt1	mg/d	nd	14
11	Brouwer 2006 16569549	age, sex, total energy intake, smoking, BMI, education, and alcohol intake.	Qt2	mg/d	28	42
12	Brouwer 2006 16569549	age, sex, total energy intake, smoking, BMI, education, and alcohol intake.	Qt3	mg/d	62	89
13	Brouwer 2006 16569549	age, sex, total energy intake, smoking, BMI, education, and alcohol intake.	Qt4	mg/d	121	161
14	Brouwer 2006 16569549	age, sex, total energy intake, smoking, BMI, education, and alcohol intake.	Qt5	mg/d	213	313
15	Hara 2013 23047296	Propensity score	T1	mcg/mL	nd	nd
16	Hara 2013 23047296	Propensity score	T2	mcg/mL	61.4	nd
17	Hara 2013 23047296	Propensity score	T3	mcg/mL	83.5	nd
18	Hara 2012 23047296	Propensity score	T1	mcg/mL	nd	nd
19	Hara 2012 23047296	Propensity score	T2	mcg/mL	24.6	nd
20	Hara 2012 23047296	Propensity score	T3	mcg/mL	38.8	nd
21	Levitan 2010 20332801	We adjusted for BMI (linear), physical activity (linear), energy intake (linear), alcohol consumption (linear), fiber consumption (linear), sodium consumption (linear), daily servings of red or processed meat (linear), education (less than high school, high school, university), family history of myocardial infarction at <60 years (yes, no), cigarette smoking (current, past, never), living alone (yes, no), postmenopausal hormone use (yes, no), self-reported history of hypertension (yes, no) and self-reported history of high cholesterol (yes, no).	Qt1	g/d	nd	mean 0.86 (0.09)
22	Levitan 2010 20332801	We adjusted for BMI (linear), physical activity (linear), energy intake (linear), alcohol consumption (linear), fiber consumption (linear), sodium consumption (linear), daily servings of red or processed meat (linear), education (less than high school, high school, university), family history of myocardial infarction at <60 years (yes, no), cigarette smoking (current, past, never), living alone (yes, no), postmenopausal hormone use (yes, no), self-reported history of hypertension (yes, no) and self-reported history of high cholesterol (yes, no).	Qt2	g/d	nd	mean 1.03 (0.04)

Appendix F
Observational results: congestive heart failure

Row	Study PMID	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
2	Belin 2011 21610249	<0.048	HR	510	21013		Reference group			P trend	0.29
3	Belin 2011 21610249	0.092		492	21252		0.95	0.84	1.08		
4	Belin 2011 21610249	0.163		435	21051		0.91	0.8	1.03		
5	Belin 2011 21610249	nd		421	21177		0.95	0.83	1.08		
6	Belin 2011 21610249	<0.711	HR	443	21238		Reference group			P trend	0.773
7	Belin 2011 21610249	1.019		464	21092		1.06	0.93	1.2		
8	Belin 2011 21610249	1.465		468	21155		1.03	0.9	1.17		
9	Belin 2011 21610249	nd		483	21008		1.03	0.9	1.17		
10	Brouwer 2006 16569549	27	RR	155	1060	11715	1			P trend	0.22
11	Brouwer 2006 16569549	61	RR	135	1060	12006	0.95	0.75	1.2		
12	Brouwer 2006 16569549	120	RR	142	1060	12048	0.98	0.77	1.23		
13	Brouwer 2006 16569549	212	RR	120	1060	12234	0.84	0.66	1.07		
14	Brouwer 2006 16569549	nd	RR	117	1060	10097	0.88	0.69	1.12		
15	Hara 2013 23047296	61.4	HR	nd	239	nd	0.581395349	0.289855072	1.162790698	T2-3 vs. T1	0.1224
16	Hara 2013 23047296	83.5		nd	236	nd					
17	Hara 2013 23047296	nd		nd	237	nd					
18	Hara 2012 23047296	24.6	HR	nd	237	nd	0.416666667	0.210526316	0.826446281	T2-3 vs. T1	0.0097
19	Hara 2012 23047296	38.8		nd	237	nd					
20	Hara 2012 23047296	nd		nd	238	nd					
21	Levitan 2010 20332801	nd	RR	168	nd	61959	Reference group			P trend	0.41
22	Levitan 2010 20332801	nd		123	nd	62897	1.1	0.87	1.38		

Appendix F
Observational results: congestive heart failure

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure	Supplement
23	Levitan 2010 20332801	Swedish Mammography Study	CHF	Heart failure hospitalization or mortality	Healthy	Healthy, ages 49-83	All	651/36234 (1.8)	9 y	ALA	Intake	yes
24	Levitan 2010 20332801	Swedish Mammography Study	CHF	Heart failure hospitalization or mortality	Healthy	Healthy, ages 49-83	All	651/36234 (1.8)	9 y	ALA	Intake	yes
25	Levitan 2010 20332801	Swedish Mammography Study	CHF	Heart failure hospitalization or mortality	Healthy	Healthy, ages 49-83	All	651/36234 (1.8)	9 y	ALA	Intake	yes
26	Levitan 2010 20332801	Swedish Mammography Study	CHF	Heart failure hospitalization or mortality	Healthy	Healthy, ages 49-83	All	651/36234 (1.8)	9 y	EPA+DHA	Intake	yes
27	Levitan 2010 20332801	Swedish Mammography Study	CHF	Heart failure hospitalization or mortality	Healthy	Healthy, ages 49-83	All	651/36234 (1.8)	9 y	EPA+DHA	Intake	yes
28	Levitan 2010 20332801	Swedish Mammography Study	CHF	Heart failure hospitalization or mortality	Healthy	Healthy, ages 49-83	All	651/36234 (1.8)	9 y	EPA+DHA	Intake	yes
29	Levitan 2010 20332801	Swedish Mammography Study	CHF	Heart failure hospitalization or mortality	Healthy	Healthy, ages 49-83	All	651/36234 (1.8)	9 y	EPA+DHA	Intake	yes
30	Levitan 2010 20332801	Swedish Mammography Study	CHF	Heart failure hospitalization or mortality	Healthy	Healthy, ages 49-83	All	651/36234 (1.8)	9 y	EPA+DHA	Intake	yes
31	Lemaitre 2012 22743310	Cardiovascular Health Study	CHF	incident CHF	Healthy	Healthy age >= 65y	All	686/2957 (23.2)	16y	ALA	Plasma	no
32	Lemaitre 2012 22743310	Cardiovascular Health Study	CHF	incident CHF	Healthy	Healthy age >= 65y	All	686/2957 (23.2)	16y	ALA	Plasma	no
33	Lemaitre 2012 22743310	Cardiovascular Health Study	CHF	incident CHF	Healthy	Healthy age >= 65y	All	686/2957 (23.2)	16y	ALA	Plasma	no
34	Lemaitre 2012 22743310	Cardiovascular Health Study	CHF	incident CHF	Healthy	Healthy age >= 65y	All	686/2957 (23.2)	16y	ALA	Plasma	no
35	Mozaffarian 2011 21810709	Cardiovascular Health Study	CHF	incident CHF	Healthy	Healthy age >= 65y	All	555/2735 (20.3)	14y	DPA	Plasma	no
36	Mozaffarian 2011 21810709	Cardiovascular Health Study	CHF	incident CHF	Healthy	Healthy age >= 65y	All	555/2735 (20.3)	14y	DPA	Plasma	no
37	Mozaffarian 2011 21810709	Cardiovascular Health Study	CHF	incident CHF	Healthy	Healthy age >= 65y	All	555/2735 (20.3)	14y	DHA	Plasma	no
38	Mozaffarian 2011 21810709	Cardiovascular Health Study	CHF	incident CHF	Healthy	Healthy age >= 65y	All	555/2735 (20.3)	14y	DHA	Plasma	no

Appendix F
Observational results: congestive heart failure

Row	Study PMID	Adjustments	Quantile	n3 units	Quantile low	Quantile median
23	Levitan 2010 20332801	We adjusted for BMI (linear), physical activity (linear), energy intake (linear), alcohol consumption (linear), fiber consumption (linear), sodium consumption (linear), daily servings of red or processed meat (linear), education (less than high school, high school, university), family history of myocardial infarction at <60 years (yes, no), cigarette smoking (current, past, never), living alone (yes, no), postmenopausal hormone use (yes, no), self-reported history of hypertension (yes, no) and self-reported history of high cholesterol (yes, no).	Qt3	g/d	nd	mean 1.15 (0.03)
24	Levitan 2010 20332801	We adjusted for BMI (linear), physical activity (linear), energy intake (linear), alcohol consumption (linear), fiber consumption (linear), sodium consumption (linear), daily servings of red or processed meat (linear), education (less than high school, high school, university), family history of myocardial infarction at <60 years (yes, no), cigarette smoking (current, past, never), living alone (yes, no), postmenopausal hormone use (yes, no), self-reported history of hypertension (yes, no) and self-reported history of high cholesterol (yes, no).	Qt4	g/d	nd	mean 1.28 (0.04)
25	Levitan 2010 20332801	We adjusted for BMI (linear), physical activity (linear), energy intake (linear), alcohol consumption (linear), fiber consumption (linear), sodium consumption (linear), daily servings of red or processed meat (linear), education (less than high school, high school, university), family history of myocardial infarction at <60 years (yes, no), cigarette smoking (current, past, never), living alone (yes, no), postmenopausal hormone use (yes, no), self-reported history of hypertension (yes, no) and self-reported history of high cholesterol (yes, no).	Qt5	g/d	nd	mean 1.56 (0.22)
26	Levitan 2010 20332801	We adjusted for BMI (linear), physical activity (linear), energy intake (linear), alcohol consumption (linear), fiber consumption (linear), sodium consumption (linear), daily servings of red or processed meat (linear), education (less than high school, high school, university), family history of myocardial infarction at <60 years (yes, no), cigarette smoking (current, past, never), living alone (yes, no), postmenopausal hormone use (yes, no), self-reported history of hypertension (yes, no) and self-reported history of high cholesterol (yes, no).	Qt1	g/d	0.01	0.14
27	Levitan 2010 20332801	We adjusted for BMI (linear), physical activity (linear), energy intake (linear), alcohol consumption (linear), fiber consumption (linear), sodium consumption (linear), daily servings of red or processed meat (linear), education (less than high school, high school, university), family history of myocardial infarction at <60 years (yes, no), cigarette smoking (current, past, never), living alone (yes, no), postmenopausal hormone use (yes, no), self-reported history of hypertension (yes, no) and self-reported history of high cholesterol (yes, no).	Qt2	g/d	0.2	0.23
28	Levitan 2010 20332801	We adjusted for BMI (linear), physical activity (linear), energy intake (linear), alcohol consumption (linear), fiber consumption (linear), sodium consumption (linear), daily servings of red or processed meat (linear), education (less than high school, high school, university), family history of myocardial infarction at <60 years (yes, no), cigarette smoking (current, past, never), living alone (yes, no), postmenopausal hormone use (yes, no), self-reported history of hypertension (yes, no) and self-reported history of high cholesterol (yes, no).	Qt3	g/d	0.28	0.3
29	Levitan 2010 20332801	We adjusted for BMI (linear), physical activity (linear), energy intake (linear), alcohol consumption (linear), fiber consumption (linear), sodium consumption (linear), daily servings of red or processed meat (linear), education (less than high school, high school, university), family history of myocardial infarction at <60 years (yes, no), cigarette smoking (current, past, never), living alone (yes, no), postmenopausal hormone use (yes, no), self-reported history of hypertension (yes, no) and self-reported history of high cholesterol (yes, no).	Qt4	g/d	0.34	0.38
30	Levitan 2010 20332801	We adjusted for BMI (linear), physical activity (linear), energy intake (linear), alcohol consumption (linear), fiber consumption (linear), sodium consumption (linear), daily servings of red or processed meat (linear), education (less than high school, high school, university), family history of myocardial infarction at <60 years (yes, no), cigarette smoking (current, past, never), living alone (yes, no), postmenopausal hormone use (yes, no), self-reported history of hypertension (yes, no) and self-reported history of high cholesterol (yes, no).	Qt5	g/d	0.46	0.57
31	Lemaitre 2012 22743310	age (y) and sex, enrollment site (4 sites), race (white, nonwhite), education (,high school, high school, college), smoking (never, former, current), leisure-time physical activity (kcal/wk), BMI (kg/m2), waist circumference (cm), and alcohol consumption (g/d).	Qr1	% FA	0.05	0.09 (mean)
32	Lemaitre 2012 22743310	age (y) and sex, enrollment site (4 sites), race (white, nonwhite), education (,high school, high school, college), smoking (never, former, current), leisure-time physical activity (kcal/wk), BMI (kg/m2), waist circumference (cm), and alcohol consumption (g/d).	Qr2	% FA	0.11	0.13 (mean)
33	Lemaitre 2012 22743310	age (y) and sex, enrollment site (4 sites), race (white, nonwhite), education (,high school, high school, college), smoking (never, former, current), leisure-time physical activity (kcal/wk), BMI (kg/m2), waist circumference (cm), and alcohol consumption (g/d).	Qr3	% FA	0.14	0.16 (mean)
34	Lemaitre 2012 22743310	age (y) and sex, enrollment site (4 sites), race (white, nonwhite), education (,high school, high school, college), smoking (never, former, current), leisure-time physical activity (kcal/wk), BMI (kg/m2), waist circumference (cm), and alcohol consumption (g/d).	Qr4	% FA	0.18	0.22 (mean)
35	Mozaffarian 2011 21810709	Adjusted for age, sex, race (white or nonwhite), education (less than high school, high school, some college, or college graduate), enrollment site, smoking status (never, former, or current), prevalent diabetes (yes or no), prevalent atrial fibrillation (yes or no), leisure-time physical activity, body mass index, waist circumference, and alcohol use (6 categories).	Qr3	% FA	0.82	0.88 (mean)
36	Mozaffarian 2011 21810709	Adjusted for age, sex, race (white or nonwhite), education (less than high school, high school, some college, or college graduate), enrollment site, smoking status (never, former, or current), prevalent diabetes (yes or no), prevalent atrial fibrillation (yes or no), leisure-time physical activity, body mass index, waist circumference, and alcohol use (6 categories).	Qr4	% FA	0.94	1.06 (mean)
37	Mozaffarian 2011 21810709	Adjusted for age, sex, race (white or nonwhite), education (less than high school, high school, some college, or college graduate), enrollment site, smoking status (never, former, or current), prevalent diabetes (yes or no), prevalent atrial fibrillation (yes or no), leisure-time physical activity, body mass index, waist circumference, and alcohol use (6 categories).	Qr1	% FA	1.07	1.98 (mean)
38	Mozaffarian 2011 21810709	Adjusted for age, sex, race (white or nonwhite), education (less than high school, high school, some college, or college graduate), enrollment site, smoking status (never, former, or current), prevalent diabetes (yes or no), prevalent atrial fibrillation (yes or no), leisure-time physical activity, body mass index, waist circumference, and alcohol use (6 categories).	Qr2	% FA	2.34	2.6 (mean)

Appendix F
Observational results: congestive heart failure

Row	Study PMID	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
23	Levitan 2010 20332801	nd		99	nd	63153	0.99	0.77	1.26		
24	Levitan 2010 20332801	nd		120	nd	63064	1.05	0.82	1.33		
25	Levitan 2010 20332801	nd		141	nd	62146	0.91	0.71	1.17		
26	Levitan 2010 20332801	0.19	RR	168	nd	61959	Reference group			P linear trend	0.04
27	Levitan 2010 20332801	0.27		123	nd	62847	0.85	0.67	1.07		
28	Levitan 2010 20332801	0.33		99	nd	63153	0.79	0.61	1.02		
29	Levitan 2010 20332801	0.45		120	nd	63064	0.83	0.65	1.06		
30	Levitan 2010 20332801	7.15		141	nd	62146	0.75	0.58	0.96		
31	Lemaitre 2012 22743310	0.11	HR	191	nd	7838	Reference group			P trend	0.85
32	Lemaitre 2012 22743310	0.14	HR	169	nd	7570	0.97	0.78	1.2		
33	Lemaitre 2012 22743310	0.18	HR	161	nd	7469	0.98	0.79	1.22		
34	Lemaitre 2012 22743310	0.47	HR	165	nd	7864	0.97	0.79	1.21		
35	Mozaffarian 2011 21810709	0.93	HR	131	nd	6732	0.73	0.53	1		
36	Mozaffarian 2011 21810709	1.63	HR	132	nd	6635	0.76	0.56	1.04		
37	Mozaffarian 2011 21810709	2.33	HR	141	nd	6533	Reference group			P trend	0.38
38	Mozaffarian 2011 21810709	2.86	HR	144	nd	6415	0.9	0.66	1.21		

Appendix F
Observational results: congestive heart failure

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure	Supplement
39	Mozaffarian 2011 21810709	Cardiovascular Health Study	CHF	incident CHF	Healthy	Healthy age >= 65y	All	555/2735 (20.3)	14y	DHA	Plasma	no
40	Mozaffarian 2011 21810709	Cardiovascular Health Study	CHF	incident CHF	Healthy	Healthy age >= 65y	All	555/2735 (20.3)	14y	EPA	Plasma	no
41	Mozaffarian 2011 21810709	Cardiovascular Health Study	CHF	incident CHF	Healthy	Healthy age >= 65y	All	555/2735 (20.3)	14y	EPA	Plasma	no
42	Mozaffarian 2011 21810709	Cardiovascular Health Study	CHF	incident CHF	Healthy	Healthy age >= 65y	All	555/2735 (20.3)	14y	EPA	Plasma	no
43	Mozaffarian 2011 21810709	Cardiovascular Health Study	CHF	incident CHF	Healthy	Healthy age >= 65y	All	555/2735 (20.3)	14y	EPA	Plasma	no
44	Mozaffarian 2011 21810709	Cardiovascular Health Study	CHF	incident CHF	Healthy	Healthy age >= 65y	All	555/2735 (20.3)	14y	DPA	Plasma	no
45	Mozaffarian 2011 21810709	Cardiovascular Health Study	CHF	incident CHF	Healthy	Healthy age >= 65y	All	555/2735 (20.3)	14y	DPA	Plasma	no
46	Lemaitre 2012 22743310	Cardiovascular Health Study	CHF	incident CHF	Healthy	Healthy age >= 65y	All	1072/4432 (24.2)	12y	ALA	Intake	no
47	Lemaitre 2012 22743310	Cardiovascular Health Study	CHF	incident CHF	Healthy	Healthy age >= 65y	All	1072/4432 (24.2)	12y	ALA	Intake	no
48	Lemaitre 2012 22743310	Cardiovascular Health Study	CHF	incident CHF	Healthy	Healthy age >= 65y	All	1072/4432 (24.2)	12y	ALA	Intake	no
49	Lemaitre 2012 22743310	Cardiovascular Health Study	CHF	incident CHF	Healthy	Healthy age >= 65y	All	1072/4432 (24.2)	12y	ALA	Intake	no
50	Mozaffarian 2011 21810709	Cardiovascular Health Study	CHF	incident CHF	Healthy	Healthy age >= 65y	All	555/2735 (20.3)	14y	DHA	Plasma	no
51	Mozaffarian 2011 21810709	Cardiovascular Health Study	CHF	incident CHF	Healthy	Healthy age >= 65y	All	555/2735 (20.3)	14y	All n-3	Plasma	no
52	Mozaffarian 2011 21810709	Cardiovascular Health Study	CHF	incident CHF	Healthy	Healthy age >= 65y	All	555/2735 (20.3)	14y	All n-3	Plasma	no
53	Mozaffarian 2011 21810709	Cardiovascular Health Study	CHF	incident CHF	Healthy	Healthy age >= 65y	All	555/2735 (20.3)	14y	All n-3	Plasma	no
54	Mozaffarian 2011 21810709	Cardiovascular Health Study	CHF	incident CHF	Healthy	Healthy age >= 65y	All	555/2735 (20.3)	14y	All n-3	Plasma	no
55	Levitan 2009 19383731	Cohort of Swedish Men	CHF	nd	Healthy	Healthy Swedish Men	All	nd/44601	7 y	EPA+DHA	Intake	No
56	Levitan 2009 19383731	Cohort of Swedish Men	CHF	nd	Healthy	Healthy Swedish Men	All	nd/44601	7 y	EPA+DHA	Intake	No
57	Levitan 2009 19383731	Cohort of Swedish Men	CHF	nd	Healthy	Healthy Swedish Men	All	nd/44601	7 y	EPA+DHA	Intake	No
58	Levitan 2009 19383731	Cohort of Swedish Men	CHF	nd	Healthy	Healthy Swedish Men	All	nd/44601	7 y	EPA+DHA	Intake	No

Appendix F
Observational results: congestive heart failure

Row	Study PMID	Adjustments	Quantile	n3 units	Quantile low	Quantile median
39	Mozaffarian 2011 21810709	Adjusted for age, sex, race (white or nonwhite), education (less than high school, high school, some college, or college graduate), enrollment site, smoking status (never, former, or current), prevalent diabetes (yes or no), prevalent atrial fibrillation (yes or no), leisure-time physical activity, body mass index, waist circumference, and alcohol use (6 categories).	Qr3	% FA	2.87	3.17 (mean)
40	Mozaffarian 2011 21810709	Adjusted for age, sex, race (white or nonwhite), education (less than high school, high school, some college, or college graduate), enrollment site, smoking status (never, former, or current), prevalent diabetes (yes or no), prevalent atrial fibrillation (yes or no), leisure-time physical activity, body mass index, waist circumference, and alcohol use (6 categories).	Qr1	% FA	0.11	0.31 (mean)
41	Mozaffarian 2011 21810709	Adjusted for age, sex, race (white or nonwhite), education (less than high school, high school, some college, or college graduate), enrollment site, smoking status (never, former, or current), prevalent diabetes (yes or no), prevalent atrial fibrillation (yes or no), leisure-time physical activity, body mass index, waist circumference, and alcohol use (6 categories).	Qr2	% FA	0.39	0.45 (mean)
42	Mozaffarian 2011 21810709	Adjusted for age, sex, race (white or nonwhite), education (less than high school, high school, some college, or college graduate), enrollment site, smoking status (never, former, or current), prevalent diabetes (yes or no), prevalent atrial fibrillation (yes or no), leisure-time physical activity, body mass index, waist circumference, and alcohol use (6 categories).	Qr3	% FA	0.51	0.59 (mean)
43	Mozaffarian 2011 21810709	Adjusted for age, sex, race (white or nonwhite), education (less than high school, high school, some college, or college graduate), enrollment site, smoking status (never, former, or current), prevalent diabetes (yes or no), prevalent atrial fibrillation (yes or no), leisure-time physical activity, body mass index, waist circumference, and alcohol use (6 categories).	Qr4	% FA	0.69	1.04 (mean)
44	Mozaffarian 2011 21810709	Adjusted for age, sex, race (white or nonwhite), education (less than high school, high school, some college, or college graduate), enrollment site, smoking status (never, former, or current), prevalent diabetes (yes or no), prevalent atrial fibrillation (yes or no), leisure-time physical activity, body mass index, waist circumference, and alcohol use (6 categories).	Qr1	% FA	0.11	0.62 (mean)
45	Mozaffarian 2011 21810709	Adjusted for age, sex, race (white or nonwhite), education (less than high school, high school, some college, or college graduate), enrollment site, smoking status (never, former, or current), prevalent diabetes (yes or no), prevalent atrial fibrillation (yes or no), leisure-time physical activity, body mass index, waist circumference, and alcohol use (6 categories).	Qr2	% FA	0.72	0.77 (mean)
46	Lemaitre 2012 22743310	age (y) and sex, enrollment site (4 sites), race (white, nonwhite), education (,high school, high school, college), smoking (never, former, current), leisure-time physical activity (kcal/wk), BMI (kg/m2), waist circumference (cm), and alcohol consumption (g/d).	Qr1	% fat intake	nd	nd
47	Lemaitre 2012 22743310	age (y) and sex, enrollment site (4 sites), race (white, nonwhite), education (,high school, high school, college), smoking (never, former, current), leisure-time physical activity (kcal/wk), BMI (kg/m2), waist circumference (cm), and alcohol consumption (g/d).	Qr2	% fat intake	nd	nd
48	Lemaitre 2012 22743310	age (y) and sex, enrollment site (4 sites), race (white, nonwhite), education (,high school, high school, college), smoking (never, former, current), leisure-time physical activity (kcal/wk), BMI (kg/m2), waist circumference (cm), and alcohol consumption (g/d).	Qr3	% fat intake	nd	nd
49	Lemaitre 2012 22743310	age (y) and sex, enrollment site (4 sites), race (white, nonwhite), education (,high school, high school, college), smoking (never, former, current), leisure-time physical activity (kcal/wk), BMI (kg/m2), waist circumference (cm), and alcohol consumption (g/d).	Qr4	% fat intake	nd	nd
50	Mozaffarian 2011 21810709	Adjusted for age, sex, race (white or nonwhite), education (less than high school, high school, some college, or college graduate), enrollment site, smoking status (never, former, or current), prevalent diabetes (yes or no), prevalent atrial fibrillation (yes or no), leisure-time physical activity, body mass index, waist circumference, and alcohol use (6 categories).	Qr4	% FA	3.55	4.39 (mean)
51	Mozaffarian 2011 21810709	Adjusted for age, sex, race (white or nonwhite), education (less than high school, high school, some college, or college graduate), enrollment site, smoking status (never, former, or current), prevalent diabetes (yes or no), prevalent atrial fibrillation (yes or no), leisure-time physical activity, body mass index, waist circumference, and alcohol use (6 categories).	Qr1	% FA	nd	nd
52	Mozaffarian 2011 21810709	Adjusted for age, sex, race (white or nonwhite), education (less than high school, high school, some college, or college graduate), enrollment site, smoking status (never, former, or current), prevalent diabetes (yes or no), prevalent atrial fibrillation (yes or no), leisure-time physical activity, body mass index, waist circumference, and alcohol use (6 categories).	Qr2	% FA	nd	nd
53	Mozaffarian 2011 21810709	Adjusted for age, sex, race (white or nonwhite), education (less than high school, high school, some college, or college graduate), enrollment site, smoking status (never, former, or current), prevalent diabetes (yes or no), prevalent atrial fibrillation (yes or no), leisure-time physical activity, body mass index, waist circumference, and alcohol use (6 categories).	Qr3	% FA	nd	nd
54	Mozaffarian 2011 21810709	Adjusted for age, sex, race (white or nonwhite), education (less than high school, high school, some college, or college graduate), enrollment site, smoking status (never, former, or current), prevalent diabetes (yes or no), prevalent atrial fibrillation (yes or no), leisure-time physical activity, body mass index, waist circumference, and alcohol use (6 categories).	Qr4	% FA	nd	nd
55	Levitan 2009 19383731	nd	Qt1	g/d	nd	nd
56	Levitan 2009 19383731	nd	Qt2	g/d	nd	nd
57	Levitan 2009 19383731	nd	Qt3	g/d	nd	nd
58	Levitan 2009 19383731	nd	Qt4	g/d	nd	nd

Appendix F
Observational results: congestive heart failure

Row	Study PMID	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
39	Mozaffarian 2011 21810709	3.54	HR	143	nd	6794	0.91	0.67	1.25		
40	Mozaffarian 2011 21810709	0.38	HR	174	nd	6198	Reference group			P trend	0.001
41	Mozaffarian 2011 21810709	0.5	HR	131	nd	6503	0.61	0.45	0.83		
42	Mozaffarian 2011 21810709	0.68	HR	126	nd	6993	0.65	0.47	0.9		
43	Mozaffarian 2011 21810709	8.52	HR	124	nd	6797	0.52	0.38	0.72		
44	Mozaffarian 2011 21810709	0.71	HR	147	nd	6540	Reference group			P trend	0.057
45	Mozaffarian 2011 21810709	0.81	HR	145	nd	6583	0.89	0.66	1.22		
46	Lemaitre 2012 22743310	nd	HR	319	nd	12753	Reference group			P trend	0.97
47	Lemaitre 2012 22743310	nd	HR	280	nd	13472	0.83	0.71	0.98		
48	Lemaitre 2012 22743310	nd	HR	258	nd	13387	0.92	0.77	1.09		
49	Lemaitre 2012 22743310	nd	HR	215	nd	12997	0.99	0.82	1.2		
50	Mozaffarian 2011 21810709	8.17	HR	127	nd	6750	0.84	0.58	1.21		
51	Mozaffarian 2011 21810709	nd	HR	143	nd	6379	Reference group			P trend	0.062
52	Mozaffarian 2011 21810709	nd	HR	153	nd	6605	0.82	0.61	1.11		
53	Mozaffarian 2011 21810709	nd	HR	135	nd	6595	0.8	0.58	1.1		
54	Mozaffarian 2011 21810709	nd	HR	124	nd	6912	0.7	0.49	0.99		
55	Levitan 2009 19383731	nd	HR	nd	nd	nd	Reference group				NS (implied)
56	Levitan 2009 19383731	nd		nd	nd	nd	0.98	0.6	1.58		
57	Levitan 2009 19383731	nd		nd	nd	nd	0.84	0.49	1.43		
58	Levitan 2009 19383731	nd		nd	nd	nd	1.27	0.77	2.09		

Appendix F
Observational results: congestive heart failure

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure	Supplement
59	Levitan 2009 19383731	Cohort of Swedish Men	CHF	nd	Healthy	Healthy Swedish Men	All	nd/44601	7 y	EPA+DHA	Intake	No
60	Wilk 2012 22952185	Physician's Health Study	CHF	nd	Healthy	US male physicians	All	703/19097 (3.68)	4 y	EPA+DHA+DPA	Intake	explicitly excluded fish oil supplements
61	Wilk 2012 22952185	Physician's Health Study	CHF	nd	Healthy	US male physicians	All	703/19097 (3.68)	4 y	EPA+DHA+DPA	Intake	explicitly excluded fish oil supplements
62	Wilk 2012 22952185	Physician's Health Study	CHF	nd	Healthy	US male physicians	All	703/19097 (3.68)	4 y	EPA+DHA+DPA	Intake	explicitly excluded fish oil supplements
63	Wilk 2012 22952185	Physician's Health Study	CHF	nd	Healthy	US male physicians	All	703/19097 (3.68)	4 y	EPA+DHA+DPA	Intake	explicitly excluded fish oil supplements
64	Wilk 2012 22952185	Physician's Health Study	CHF	nd	Healthy	US male physicians	All	703/19097 (3.68)	4 y	EPA+DHA+DPA	Intake	explicitly excluded fish oil supplements
65	Wilk 2012 22952185	Physician's Health Study	CHF	nd	Healthy	US male physicians	All	703/19097 (3.68)	4 y	ALA	Intake	explicitly excluded fish oil supplements
66	Wilk 2012 22952185	Physician's Health Study	CHF	nd	Healthy	US male physicians	All	703/19097 (3.68)	4 y	ALA	Intake	explicitly excluded fish oil supplements
67	Wilk 2012 22952185	Physician's Health Study	CHF	nd	Healthy	US male physicians	All	703/19097 (3.68)	4 y	ALA	Intake	explicitly excluded fish oil supplements
68	Wilk 2012 22952185	Physician's Health Study	CHF	nd	Healthy	US male physicians	All	703/19097 (3.68)	4 y	ALA	Intake	explicitly excluded fish oil supplements
69	Wilk 2012 22952185	Physician's Health Study	CHF	nd	Healthy	US male physicians	All	703/19097 (3.68)	4 y	ALA	Intake	explicitly excluded fish oil supplements
70	Wilk 2012 22952185	Physician's Health Study	CHF	nd	Healthy	US male physicians	All	786/19097 (4.12)	4 y	EPA+DHA+DPA	Plasma	explicitly excluded fish oil supplements
71	Wilk 2012 22952185	Physician's Health Study	CHF	nd	Healthy	US male physicians	All	786/19097 (4.12)	4 y	EPA+DHA+DPA	Plasma	explicitly excluded fish oil supplements
72	Wilk 2012 22952185	Physician's Health Study	CHF	nd	Healthy	US male physicians	All	786/19097 (4.12)	4 y	EPA+DHA+DPA	Plasma	explicitly excluded fish oil supplements
73	Wilk 2012 22952185	Physician's Health Study	CHF	nd	Healthy	US male physicians	All	786/19097 (4.12)	4 y	EPA+DHA+DPA	Plasma	explicitly excluded fish oil supplements
74	Wilk 2012 22952185	Physician's Health Study	CHF	nd	Healthy	US male physicians	All	786/19097 (4.12)	4 y	EPA+DHA+DPA	Plasma	explicitly excluded fish oil supplements
75	Wilk 2012 22952185	Physician's Health Study	CHF	nd	Healthy	US male physicians	All	786/19097 (4.12)	4 y	ALA	Plasma	explicitly excluded fish oil supplements

Appendix F
Observational results: congestive heart failure

Row	Study PMID	Adjustments	Quantile	n3 units	Quantile low	Quantile median
59	Levitan 2009 19383731	nd	Qt5	g/d	nd	nd
60	Wilk 2012 22952185	age, atrial fibrillation, hypertension, BMI, alcohol, current smoking, former smoking, exercise, and valvular heart disease	T1	g/d	nd	0.079
61	Wilk 2012 22952185	age, atrial fibrillation, hypertension, BMI, alcohol, current smoking, former smoking, exercise, and valvular heart disease	T2	g/d	nd	nd
62	Wilk 2012 22952185	age, atrial fibrillation, hypertension, BMI, alcohol, current smoking, former smoking, exercise, and valvular heart disease	T3	g/d	nd	0.152
63	Wilk 2012 22952185	age, atrial fibrillation, hypertension, BMI, alcohol, current smoking, former smoking, exercise, and valvular heart disease	T4	g/d	nd	nd
64	Wilk 2012 22952185	age, atrial fibrillation, hypertension, BMI, alcohol, current smoking, former smoking, exercise, and valvular heart disease	T5	g/d	nd	0.397
65	Wilk 2012 22952185	age, atrial fibrillation, hypertension, BMI, alcohol, current smoking, former smoking, exercise, and valvular heart disease	T1	g/d	nd	0.576
66	Wilk 2012 22952185	age, atrial fibrillation, hypertension, BMI, alcohol, current smoking, former smoking, exercise, and valvular heart disease	T2	g/d	nd	nd
67	Wilk 2012 22952185	age, atrial fibrillation, hypertension, BMI, alcohol, current smoking, former smoking, exercise, and valvular heart disease	T3	g/d	nd	0.765
68	Wilk 2012 22952185	age, atrial fibrillation, hypertension, BMI, alcohol, current smoking, former smoking, exercise, and valvular heart disease	T4	g/d	nd	nd
69	Wilk 2012 22952185	age, atrial fibrillation, hypertension, BMI, alcohol, current smoking, former smoking, exercise, and valvular heart disease	T5	g/d	nd	1
70	Wilk 2012 22952185	age, atrial fibrillation, hypertension, BMI, alcohol, current smoking, former smoking, exercise, and valvular heart disease	T1	% FA	nd	3.204
71	Wilk 2012 22952185	age, atrial fibrillation, hypertension, BMI, alcohol, current smoking, former smoking, exercise, and valvular heart disease	T2	% FA	nd	nd
72	Wilk 2012 22952185	age, atrial fibrillation, hypertension, BMI, alcohol, current smoking, former smoking, exercise, and valvular heart disease	T3	% FA	nd	4.412
73	Wilk 2012 22952185	age, atrial fibrillation, hypertension, BMI, alcohol, current smoking, former smoking, exercise, and valvular heart disease	T4	% FA	nd	nd
74	Wilk 2012 22952185	age, atrial fibrillation, hypertension, BMI, alcohol, current smoking, former smoking, exercise, and valvular heart disease	T5	% FA	nd	6.458
75	Wilk 2012 22952185	age, atrial fibrillation, hypertension, BMI, alcohol, current smoking, former smoking, exercise, and valvular heart disease	T1	% FA	nd	0.097

Appendix F
Observational results: congestive heart failure

Row	Study PMID	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
59	Levitan 2009 19383731	nd		nd	nd	nd	1.19	0.75	1.91		
60	Wilk 2012 22952185	nd	HR	172		31310	1			P trend	0.12
61	Wilk 2012 22952185	nd	HR	151		32151	0.92	0.74	1.14		
62	Wilk 2012 22952185	nd	HR	124		32171	0.84	0.66	1.06		
63	Wilk 2012 22952185	nd	HR	123		32550	0.81	0.64	1.02		
64	Wilk 2012 22952185	nd	HR	133		32113	0.94	0.75	1.18		
65	Wilk 2012 22952185	nd	HR	157		31772	1			P trend	0.32
66	Wilk 2012 22952185	nd	HR	137		32074	0.82	0.65	1.03		
67	Wilk 2012 22952185	nd	HR	131		32302	0.79	0.63	1		
68	Wilk 2012 22952185	nd	HR	138		32186	0.82	0.65	1.03		
69	Wilk 2012 22952185	nd	HR	140		31961	0.83	0.66	1.05		
70	Wilk 2012 22952185	nd	OR	151			1			P trend	0.17
71	Wilk 2012 22952185	nd	OR	182			1.26	0.9	1.75		
72	Wilk 2012 22952185	nd	OR	174			1.18	0.85	1.64		
73	Wilk 2012 22952185	nd	OR	145			0.97	0.69	1.38		
74	Wilk 2012 22952185	nd	OR	134			0.92	0.64	1.33		
75	Wilk 2012 22952185	nd	OR	205			1			P trend	0.03

Appendix F
Observational results: congestive heart failure

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure	Supplement
76	Wilk 2012 22952185	Physician's Health Study	CHF	nd	Healthy	US male physicians	All	786/19097 (4.12)	4 y	ALA	Plasma	explicitly excluded fish oil supplements
77	Wilk 2012 22952185	Physician's Health Study	CHF	nd	Healthy	US male physicians	All	786/19097 (4.12)	4 y	ALA	Plasma	explicitly excluded fish oil supplements
78	Wilk 2012 22952185	Physician's Health Study	CHF	nd	Healthy	US male physicians	All	786/19097 (4.12)	4 y	ALA	Plasma	explicitly excluded fish oil supplements
79	Wilk 2012 22952185	Physician's Health Study	CHF	nd	Healthy	US male physicians	All	786/19097 (4.12)	4 y	ALA	Plasma	explicitly excluded fish oil supplements
80	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	All	87/1684 (5.17)	14.3	ALA	Cholesterol ester	Yes
81	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	All	87/1684 (5.17)	14.3	ALA	Cholesterol ester	Yes
82	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	All	87/1684 (5.17)	14.3	ALA	Cholesterol ester	Yes
83	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	All	87/1684 (5.17)	14.3	ALA	Cholesterol ester	Yes
84	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	All	87/1684 (5.17)	14.3	ALA	Cholesterol ester	Yes
85	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	All	87/1684 (5.17)	14.3	ALA	Phospholipid	Yes
86	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	All	87/1684 (5.17)	14.3	ALA	Phospholipid	Yes
87	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	All	87/1684 (5.17)	14.3	ALA	Phospholipid	Yes
88	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	All	87/1684 (5.17)	14.3	ALA	Phospholipid	Yes
89	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	All	87/1684 (5.17)	14.3	ALA	Phospholipid	Yes
90	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	All	87/1684 (5.17)	14.3	EPA	Cholesterol ester	Yes
91	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	All	87/1684 (5.17)	14.3	EPA	Cholesterol ester	Yes
92	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	All	87/1684 (5.17)	14.3	EPA	Cholesterol ester	Yes

Appendix F
Observational results: congestive heart failure

Row	Study PMID	Adjustments	Quantile	n3 units	Quantile low	Quantile median
76	Wilk 2012 22952185	age, atrial fibrillation, hypertension, BMI, alcohol, current smoking, former smoking, exercise, and valvular heart disease	T2	% FA	nd	nd
77	Wilk 2012 22952185	age, atrial fibrillation, hypertension, BMI, alcohol, current smoking, former smoking, exercise, and valvular heart disease	T3	% FA	nd	0.143
78	Wilk 2012 22952185	age, atrial fibrillation, hypertension, BMI, alcohol, current smoking, former smoking, exercise, and valvular heart disease	T4	% FA	nd	nd
79	Wilk 2012 22952185	age, atrial fibrillation, hypertension, BMI, alcohol, current smoking, former smoking, exercise, and valvular heart disease	T5	% FA	nd	0.306
80	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt1	% of total FA	Est 10% normal	0.269029328
81	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt2	% of total FA	Est 30% normal	0.352315944
82	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt3	% of total FA	Reported mean	0.41
83	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt4	% of total FA	Est 70% normal	0.467684056
84	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt5	% of total FA	Est 90% normal	0.550970672
85	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt1	% of total FA	Est 10% normal	0.075922422
86	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt2	% of total FA	Est 30% normal	0.113779974
87	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt3	% of total FA	Reported mean	0.14
88	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt4	% of total FA	Est 70% normal	0.166220026
89	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt5	% of total FA	Est 90% normal	0.204077578
90	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt1	% of total FA	Est 10% normal	0.191165562
91	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt2	% of total FA	Est 30% normal	0.403167856
92	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt3	% of total FA	Reported mean	0.55

Appendix F
Observational results: congestive heart failure

Row	Study PMID	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
76	Wilk 2012 22952185	nd	OR	158			0.76	0.55	1.05		
77	Wilk 2012 22952185	nd	OR	145			0.71	0.5	1		
78	Wilk 2012 22952185	nd	OR	125			0.66	0.47	0.94		
79	Wilk 2012 22952185	nd	OR	153			0.84	0.56	1.26		
80	Yamagishi 2008 19061714	nd	HR	nd	nd	nd	Reference group			P trend	0.22
81	Yamagishi 2008 19061714	nd	HR	nd	nd	nd	1.2	0.77	1.88		
82	Yamagishi 2008 19061714	SD 0.11	HR	nd	nd	nd	0.84	0.53	1.34		
83	Yamagishi 2008 19061714	nd	HR	nd	nd	nd	1.41	0.91	2.19		
84	Yamagishi 2008 19061714	nd	HR	nd	nd	nd	1.27	0.8	2.02		
85	Yamagishi 2008 19061714	nd	HR	nd	nd	nd	Reference group			P trend	0.17
86	Yamagishi 2008 19061714	nd	HR	nd	nd	nd	1.07	0.68	1.71		
87	Yamagishi 2008 19061714	SD 0.05	HR	nd	nd	nd	1.3	0.86	1.97		
88	Yamagishi 2008 19061714	nd	HR	nd	nd	nd	1.13	0.71	1.8		
89	Yamagishi 2008 19061714	nd	HR	nd	nd	nd	1.44	0.88	2.35		
90	Yamagishi 2008 19061714	nd	HR	nd	nd	nd	Reference group			P trend	0.51
91	Yamagishi 2008 19061714	nd	HR	nd	nd	nd	1.46	0.9	2.39		
92	Yamagishi 2008 19061714	SD 0.28	HR	nd	nd	nd	1.34	0.82	2.19		

Appendix F
Observational results: congestive heart failure

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure	Supplement
93	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	All	87/1684 (5.17)	14.3	EPA	Cholesterol ester	Yes
94	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	All	87/1684 (5.17)	14.3	EPA	Cholesterol ester	Yes
95	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	All	87/1684 (5.17)	14.3	EPA	Phospholipid	Yes
96	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	All	87/1684 (5.17)	14.3	EPA	Phospholipid	Yes
97	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	All	87/1684 (5.17)	14.3	EPA	Phospholipid	Yes
98	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	All	87/1684 (5.17)	14.3	EPA	Phospholipid	Yes
99	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	All	87/1684 (5.17)	14.3	EPA	Phospholipid	Yes
101	**Subgroup analyses**											
102	Hara 2013 23047296	Osaka Acute Coronary Insufficiency Study	CHF	Heart Failure Hospitalization	CVD	AMI patients	Age < 65	nd/337	4 y	DHA	Blood	No
103	Hara 2013 23047296	Osaka Acute Coronary Insufficiency Study	CHF	Heart Failure Hospitalization	CVD	AMI patients	Age>=65	nd/375	4 y	DHA	Blood	No
104	Hara 2013 23047296	Osaka Acute Coronary Insufficiency Study	CHF	Heart Failure Hospitalization	CVD	AMI patients	LDL<100	nd/164	4 y	DHA	Blood	No
105	Hara 2013 23047296	Osaka Acute Coronary Insufficiency Study	CHF	Heart Failure Hospitalization	CVD	AMI patients	LDL>=100	nd/510	4 y	DHA	Blood	No
106	Hara 2013 23047296	Osaka Acute Coronary Insufficiency Study	CHF	Heart Failure Hospitalization	CVD	AMI patients	HDL<40	nd/216	4 y	DHA	Blood	No
107	Hara 2013 23047296	Osaka Acute Coronary Insufficiency Study	CHF	Heart Failure Hospitalization	CVD	AMI patients	HDL>=40	nd/449	4 y	DHA	Blood	No
108	Hara 2013 23047296	Osaka Acute Coronary Insufficiency Study	CHF	Heart Failure Hospitalization	CVD	AMI patients	Statin	nd/431	4 y	DHA	Blood	No
109	Hara 2013 23047296	Osaka Acute Coronary Insufficiency Study	CHF	Heart Failure Hospitalization	CVD	AMI patients	No Statin	nd/281	4 y	DHA	Blood	No
110	Hara 2012 23047296	Osaka Acute Coronary Insufficiency Study	CHF	Heart Failure Hospitalization	CVD	AMI Patients	Male	nd/554	4 y	EPA	Blood	No
111	Hara 2012 23047296	Osaka Acute Coronary Insufficiency Study	CHF	Heart Failure Hospitalization	CVD	AMI Patients	Female	nd/158	4 y	EPA	Blood	No
112	Hara 2012 23047296	Osaka Acute Coronary Insufficiency Study	CHF	Heart Failure Hospitalization	CVD	AMI Patients	HDL<40	nd/216	4 y	EPA	Blood	No
113	Hara 2012 23047296	Osaka Acute Coronary Insufficiency Study	CHF	Heart Failure Hospitalization	CVD	AMI Patients	HDL>=40	nd/449	4 y	EPA	Blood	No
114	Hara 2012 23047296	Osaka Acute Coronary Insufficiency Study	CHF	Heart Failure Hospitalization	CVD	AMI Patients	Statin	nd/431	4 y	EPA	Blood	No
115	Hara 2012 23047296	Osaka Acute Coronary Insufficiency Study	CHF	Heart Failure Hospitalization	CVD	AMI Patients	No statin	nd/281	4 y	EPA	Blood	No

Appendix F
Observational results: congestive heart failure

Row	Study PMID	Adjustments	Quantile	n3 units	Quantile low	Quantile median
93	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt4	% of total FA	Est 70% normal	0.696832144
94	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt5	% of total FA	Est 90% normal	0.908834438
95	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt1	% of total FA	Est 10% normal	0.17553453
96	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt2	% of total FA	Est 30% normal	0.402679846
97	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt3	% of total FA	Reported mean	0.56
98	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt4	% of total FA	Est 70% normal	0.717320154
99	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt5	% of total FA	Est 90% normal	0.94446547
101	**Subgroup analyses**					
102	Hara 2013 23047296	No	T1 vs. T2-3	nd	nd	nd
103	Hara 2013 23047296	No	T1 vs. T2-3	nd	nd	nd
104	Hara 2013 23047296	No	T1 vs. T2-3	nd	nd	nd
105	Hara 2013 23047296	No	T1 vs. T2-3	nd	nd	nd
106	Hara 2013 23047296	No	T1 vs. T2-3	nd	nd	nd
107	Hara 2013 23047296	No	T1 vs. T2-3	nd	nd	nd
108	Hara 2013 23047296	No	T1 vs. T2-3	nd	nd	nd
109	Hara 2013 23047296	No	T1 vs. T2-3	nd	nd	nd
110	Hara 2012 23047296	No	T1 vs. T2-3	nd	nd	nd
111	Hara 2012 23047296	No	T1 vs. T2-3	nd	nd	nd
112	Hara 2012 23047296	No	T1 vs. T2-3	nd	nd	nd
113	Hara 2012 23047296	No	T1 vs. T2-3	nd	nd	nd
114	Hara 2012 23047296	No	T1 vs. T2-3	nd	nd	nd
115	Hara 2012 23047296	No	T1 vs. T2-3	nd	nd	nd

Appendix F
Observational results: congestive heart failure

Row	Study PMID	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
93	Yamagishi 2008 19061714	nd	HR	nd	nd	nd	1.29	0.79	2.09		
94	Yamagishi 2008 19061714	nd	HR	nd	nd	nd	1.29	0.78	2.12		
95	Yamagishi 2008 19061714	nd	HR	nd	nd	nd	Reference group			P trend	0.15
96	Yamagishi 2008 19061714	nd	HR	nd	nd	nd	1.42	0.86	2.35		
97	Yamagishi 2008 19061714	SD 0.30	HR	nd	nd	nd	1.43	0.85	2.4		
98	Yamagishi 2008 19061714	nd	HR	nd	nd	nd	1.51	0.92	2.48		
99	Yamagishi 2008 19061714	nd	HR	nd	nd	nd	1.47	0.87	2.47		
101	**Subgroup analyses**										
102	Hara 2013 23047296	nd	nd	nd	nd	nd	0.52	0.11	2.41	Age interaction	0.051
103	Hara 2013 23047296	nd	nd	nd	nd	nd	3	1.31	6.85		
104	Hara 2013 23047296	nd	nd	nd	nd	nd	3.48	1.21	10.02	LDL interaction	0.0678
105	Hara 2013 23047296	nd	nd	nd	nd	nd	0.88	0.31	2.46		
106	Hara 2013 23047296	nd	nd	nd	nd	nd	4.5	1.16	17.4	HDL interaction	0.0962
107	Hara 2013 23047296	nd	nd	nd	nd	nd	1.17	0.5	2.77		
108	Hara 2013 23047296	nd	nd	nd	nd	nd	0.74	0.28	1.95	Statin interaction	0.003
109	Hara 2013 23047296	nd	nd	nd	nd	nd	6.65	2.31	19.15		
110	Hara 2012 23047296	nd	nd	nd	nd	nd	5.82	2.29	14.75	Sex interaction	0.0081
111	Hara 2012 23047296	nd	nd	nd	nd	nd	0.69	0.19	2.57		
112	Hara 2012 23047296	nd	nd	nd	nd	nd	15.68	1.99	123.8	HDL interaction	0.0344
113	Hara 2012 23047296	nd	nd	nd	nd	nd	1.44	0.62	3.33		
114	Hara 2012 23047296	nd	nd	nd	nd	nd	1.45	0.58	3.6	Statin interaction	0.0482
115	Hara 2012 23047296	nd	nd	nd	nd	nd	6.4	2.06	19.86		

Appendix F
Observational results: congestive heart failure

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure	Supplement
116	Levitan 2009 19383731	Cohort of Swedish Men	CHF	nd	CVD	Healthy Swedish Men	Men with history of MI or DM at baseline	nd/5234	7 y	EPA+DHA	Intake	No
117	Levitan 2009 19383731	Cohort of Swedish Men	CHF	nd	CVD	Healthy Swedish Men	Men with history of MI or DM at baseline	nd/5234	7 y	EPA+DHA	Intake	No
118	Levitan 2009 19383731	Cohort of Swedish Men	CHF	nd	CVD	Healthy Swedish Men	Men with history of MI or DM at baseline	nd/5234	7 y	EPA+DHA	Intake	No
119	Levitan 2009 19383731	Cohort of Swedish Men	CHF	nd	CVD	Healthy Swedish Men	Men with history of MI or DM at baseline	nd/5234	7 y	EPA+DHA	Intake	No
120	Levitan 2009 19383731	Cohort of Swedish Men	CHF	nd	CVD	Healthy Swedish Men	Men with history of MI or DM at baseline	nd/5234	7 y	EPA+DHA	Intake	No
121	Levitan 2009 19383731	Cohort of Swedish Men	CHF	nd	Healthy	Healthy Swedish Men	Men with no history of MI or DM at baseline	563/39367 (1.43)	7 y	EPA+DHA	Intake	No
122	Levitan 2009 19383731	Cohort of Swedish Men	CHF	nd	Healthy	Healthy Swedish Men	Men with no history of MI or DM at baseline	563/39367 (1.43)	7 y	EPA+DHA	Intake	No
123	Levitan 2009 19383731	Cohort of Swedish Men	CHF	nd	Healthy	Healthy Swedish Men	Men with no history of MI or DM at baseline	563/39367 (1.43)	7 y	EPA+DHA	Intake	No
124	Levitan 2009 19383731	Cohort of Swedish Men	CHF	nd	Healthy	Healthy Swedish Men	Men with no history of MI or DM at baseline	563/39367 (1.43)	7 y	EPA+DHA	Intake	No
125	Levitan 2009 19383731	Cohort of Swedish Men	CHF	nd	Healthy	Healthy Swedish Men	Men with no history of MI or DM at baseline	563/39367 (1.43)	7 y	EPA+DHA	Intake	No

Appendix F
Observational results: congestive heart failure

Row	Study PMID	Adjustments	Quantile	n3 units	Quantile low	Quantile median
116	Levitan 2009 19383731	nd	Qt1	nd	nd	nd
117	Levitan 2009 19383731	nd	Qt2	nd	nd	nd
118	Levitan 2009 19383731	nd	Qt3	nd	nd	nd
119	Levitan 2009 19383731	nd	Qt4	nd	nd	nd
120	Levitan 2009 19383731	nd	Qt5	nd	nd	nd
121	Levitan 2009 19383731	body mass index, physical activity, energy, alcohol, fibre, sodium, and red or processed meat consumption, education, family history of myocardial infarction at ,60 years, cigarette smoking, marital status, self-reported history of hypertension, and high cholesterol.	Qt1	nd	0.01	0.15
122	Levitan 2009 19383731	body mass index, physical activity, energy, alcohol, fibre, sodium, and red or processed meat consumption, education, family history of myocardial infarction at ,60 years, cigarette smoking, marital status, self-reported history of hypertension, and high cholesterol.	Qt2	nd	0.24	0.27
123	Levitan 2009 19383731	body mass index, physical activity, energy, alcohol, fibre, sodium, and red or processed meat consumption, education, family history of myocardial infarction at ,60 years, cigarette smoking, marital status, self-reported history of hypertension, and high cholesterol.	Qt3	nd	0.32	0.36
124	Levitan 2009 19383731	body mass index, physical activity, energy, alcohol, fibre, sodium, and red or processed meat consumption, education, family history of myocardial infarction at ,60 years, cigarette smoking, marital status, self-reported history of hypertension, and high cholesterol.	Qt4	nd	0.41	0.46
125	Levitan 2009 19383731	body mass index, physical activity, energy, alcohol, fibre, sodium, and red or processed meat consumption, education, family history of myocardial infarction at ,60 years, cigarette smoking, marital status, self-reported history of hypertension, and high cholesterol.	Qt5	nd	0.55	0.71

Appendix F
Observational results: congestive heart failure

Row	Study PMID	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
116	Levitan 2009 19383731	nd	HR	nd	nd	nd	Reference group				NS (implied)
117	Levitan 2009 19383731	nd	HR	nd	nd	nd	1.04	0.72	1.48		
118	Levitan 2009 19383731	nd	HR	nd	nd	nd	0.87	0.58	1.28		
119	Levitan 2009 19383731	nd	HR	nd	nd	nd	1.12	0.77	1.62		
120	Levitan 2009 19383731	nd	HR	nd	nd	nd	1.3	0.92	1.83		
121	Levitan 2009 19383731	0.22	HR	144	nd	52920	Reference group				NS (implied)
122	Levitan 2009 19383731	0.31	HR	122	nd	53340	0.94	0.74	1.2		
123	Levitan 2009 19383731	0.4	HR	74	nd	53666	0.67	0.5	0.9		
124	Levitan 2009 19383731	0.54	HR	102	nd	53553	0.89	0.68	1.16		
125	Levitan 2009 19383731	8.54	HR	155	nd	52623	1	0.77	1.29		

Appendix F
Observational results: congestive heart failure

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure	Supplement
126	Levitan 2009 19383731	Cohort of Swedish Men	CHF	nd	Healthy	Healthy Swedish Men	Men with no history of MI or DM at baseline, with supplemen	563/39367 (1.43)	7y	EPA+DHA	Intake	Yes
127	Levitan 2009 19383731	Cohort of Swedish Men	CHF	nd	Healthy	Healthy Swedish Men	Men with no history of MI or DM at baseline, with supplemen	563/39367 (1.43)	7y	EPA+DHA	Intake	Yes
128	Levitan 2009 19383731	Cohort of Swedish Men	CHF	nd	Healthy	Healthy Swedish Men	Men with no history of MI or DM at baseline, with supplemen	563/39367 (1.43)	7y	EPA+DHA	Intake	Yes
129	Levitan 2009 19383731	Cohort of Swedish Men	CHF	nd	Healthy	Healthy Swedish Men	Men with no history of MI or DM at baseline, with supplemen	563/39367 (1.43)	7y	EPA+DHA	Intake	Yes
130	Levitan 2009 19383731	Cohort of Swedish Men	CHF	nd	Healthy	Healthy Swedish Men	Men with no history of MI or DM at baseline, with supplemen	563/39367 (1.43)	7y	EPA+DHA	Intake	Yes
131	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	women	110/1908 (5.77)	14.3	DHA	Cholesterol ester	Yes
132	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	women	110/1908 (5.77)	14.3	DHA	Cholesterol ester	Yes
133	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	women	110/1908 (5.77)	14.3	DHA	Cholesterol ester	Yes

Appendix F
Observational results: congestive heart failure

Row	Study PMID	Adjustments	Quantile	n3 units	Quantile low	Quantile median
126	Levitan 2009 19383731	body mass index, physical activity, energy, alcohol, fibre, sodium, and red or processed meat consumption, education, family history of myocardial infarction at ,60 years, cigarette smoking, marital status, self-reported history of hypertension, and high cholesterol.	Qt1	nd	nd	nd
127	Levitan 2009 19383731	body mass index, physical activity, energy, alcohol, fibre, sodium, and red or processed meat consumption, education, family history of myocardial infarction at ,60 years, cigarette smoking, marital status, self-reported history of hypertension, and high cholesterol.	Qt2	nd	nd	nd
128	Levitan 2009 19383731	body mass index, physical activity, energy, alcohol, fibre, sodium, and red or processed meat consumption, education, family history of myocardial infarction at ,60 years, cigarette smoking, marital status, self-reported history of hypertension, and high cholesterol.	Qt3	nd	nd	nd
129	Levitan 2009 19383731	body mass index, physical activity, energy, alcohol, fibre, sodium, and red or processed meat consumption, education, family history of myocardial infarction at ,60 years, cigarette smoking, marital status, self-reported history of hypertension, and high cholesterol.	Qt4	nd	nd	nd
130	Levitan 2009 19383731	body mass index, physical activity, energy, alcohol, fibre, sodium, and red or processed meat consumption, education, family history of myocardial infarction at ,60 years, cigarette smoking, marital status, self-reported history of hypertension, and high cholesterol.	Qt5	nd	nd	nd
131	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt1	% FA	0.12	nd
132	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt2	% FA	0.32	nd
133	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt3	% FA	0.38	nd

Appendix F
Observational results: congestive heart failure

Row	Study PMID	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
126	Levitan 2009 19383731	nd	HR	nd	nd	nd	Reference group				NS (implied)
127	Levitan 2009 19383731	nd	HR	nd	nd	nd	0.99	0.77	1.27		
128	Levitan 2009 19383731	nd	HR	nd	nd	nd	0.73	0.54	0.97		
129	Levitan 2009 19383731	nd	HR	nd	nd	nd	0.97	0.75	1.27		
130	Levitan 2009 19383731	nd	HR	nd	nd	nd	1.05	0.82	1.36		
131	Yamagishi 2008 19061714	0.31	HR	nd	nd	nd	Reference group			P trend	0.001
132	Yamagishi 2008 19061714	0.37	HR	nd	nd	nd	0.58	0.31	1.08		
133	Yamagishi 2008 19061714	0.44	HR	nd	nd	nd	0.48	0.25	0.94		

Appendix F
Observational results: congestive heart failure

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure	Supplement
134	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	women	110/1908 (5.77)	14.3	DHA	Cholesterol ester	Yes
135	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	women	110/1908 (5.77)	14.3	DHA	Cholesterol ester	Yes
136	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	women	110/1908 (5.77)	14.3	DHA	Phospholipid	Yes
137	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	women	110/1908 (5.77)	14.3	DHA	Phospholipid	Yes
138	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	women	110/1908 (5.77)	14.3	DHA	Phospholipid	Yes
139	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	women	110/1908 (5.77)	14.3	DHA	Phospholipid	Yes
140	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	women	110/1908 (5.77)	14.3	DHA	Phospholipid	Yes
141	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	men	87/1684 (5.17)	14.3	DHA	Cholesterol ester	Yes
142	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	men	87/1684 (5.17)	14.3	DHA	Cholesterol ester	Yes
143	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	men	87/1684 (5.17)	14.3	DHA	Cholesterol ester	Yes
144	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	men	87/1684 (5.17)	14.3	DHA	Cholesterol ester	Yes
145	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	men	87/1684 (5.17)	14.3	DHA	Cholesterol ester	Yes
146	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	men	87/1684 (5.17)	14.3	DHA	Phospholipid	Yes

Appendix F
Observational results: congestive heart failure

Row	Study PMID	Adjustments	Quantile	n3 units	Quantile low	Quantile median
134	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt4	% FA	0.45	nd
135	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt5	% FA	0.55	nd
136	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt1	% FA	0	nd
137	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt2	% FA	2.12	nd
138	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt3	% FA	2.48	nd
139	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt4	% FA	2.88	nd
140	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt5	% FA	3.44	nd
141	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt1	% of total FA	Est 10% normal	0.23495175
142	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt2	% of total FA	Est 30% normal	0.356095918
143	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt3	% of total FA	Reported mean (all)	0.44
144	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt4	% of total FA	Est 70% normal	0.523904082
145	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt5	% of total FA	Est 90% normal	0.64504825
146	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt1	% of total FA	Est 10% normal	1.669419107

Appendix F
Observational results: congestive heart failure

Row	Study PMID	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
134	Yamagishi 2008 19061714	0.54	HR	nd	nd	nd	0.47	0.24	0.91		
135	Yamagishi 2008 19061714	1.6	HR	nd	nd	nd	0.25	0.11	0.56		
136	Yamagishi 2008 19061714	2.11	HR	nd	nd	nd	Reference group			P trend	<0.001
137	Yamagishi 2008 19061714	2.47	HR	nd	nd	nd	0.83	0.45	1.55		
138	Yamagishi 2008 19061714	2.87	HR	nd	nd	nd	0.57	0.29	1.09		
139	Yamagishi 2008 19061714	3.43	HR	nd	nd	nd	0.51	0.26	0.99		
140	Yamagishi 2008 19061714	8.88	HR	nd	nd	nd	0.21	0.08	0.57		
141	Yamagishi 2008 19061714	nd	HR	nd	nd	nd	Reference group			P trend	0.26
142	Yamagishi 2008 19061714	nd	HR	nd	nd	nd	1.03	0.57	1.88		
143	Yamagishi 2008 19061714	SD 0.16	HR	nd	nd	nd	0.93	0.49	1.77		
144	Yamagishi 2008 19061714	nd	HR	nd	nd	nd	0.94	0.51	1.76		
145	Yamagishi 2008 19061714	nd	HR	nd	nd	nd	1.54	0.85	2.79		
146	Yamagishi 2008 19061714	nd	HR	nd	nd	nd	Reference group			P trend	0.37

Appendix F
Observational results: congestive heart failure

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure	Supplement
147	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	men	87/1684 (5.17)	14.3	DHA	Phospholipid	Yes
148	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	men	87/1684 (5.17)	14.3	DHA	Phospholipid	Yes
149	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	men	87/1684 (5.17)	14.3	DHA	Phospholipid	Yes
150	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	men	87/1684 (5.17)	14.3	DHA	Phospholipid	Yes
151	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	men	87/1684 (5.17)	14.3	EPA+DHA+DPA	Cholesterol ester	Yes
152	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	men	87/1684 (5.17)	14.3	EPA+DHA+DPA	Cholesterol ester	Yes
153	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	men	87/1684 (5.17)	14.3	EPA+DHA+DPA	Cholesterol ester	Yes
154	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	men	87/1684 (5.17)	14.3	EPA+DHA+DPA	Cholesterol ester	Yes
155	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	men	87/1684 (5.17)	14.3	EPA+DHA+DPA	Cholesterol ester	Yes
156	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	men	87/1684 (5.17)	14.3	EPA+DHA+DPA	Phospholipid	Yes
157	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	men	87/1684 (5.17)	14.3	EPA+DHA+DPA	Phospholipid	Yes
158	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	men	87/1684 (5.17)	14.3	EPA+DHA+DPA	Phospholipid	Yes
159	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	men	87/1684 (5.17)	14.3	EPA+DHA+DPA	Phospholipid	Yes

Appendix F
Observational results: congestive heart failure

Row	Study PMID	Adjustments	Quantile	n3 units	Quantile low	Quantile median
147	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt2	% of total FA	Est 30% normal	2.343283544
148	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt3	% of total FA	Reported mean (all)	2.81
149	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt4	% of total FA	Est 70% normal	3.276716456
150	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt5	% of total FA	Est 90% normal	3.950580893
151	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt1	% of total FA	Est 10% normal	0.500194889
152	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt2	% of total FA	Est 30% normal	0.7954838
153	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt3	% of total FA	Reported mean (all)	1
154	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt4	% of total FA	Est 70% normal	1.2045162
155	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt5	% of total FA	Est 90% normal	1.499805111
156	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt1	% of total FA	Est 10% normal	2.857477762
157	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt2	% of total FA	Est 30% normal	3.697915431
158	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt3	% of total FA	Reported mean (all)	4.28
159	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt4	% of total FA	Est 70% normal	4.862084569

Appendix F
Observational results: congestive heart failure

Row	Study PMID	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
147	Yamagishi 2008 19061714	nd	HR	nd	nd	nd	0.77	0.42	1.4		
148	Yamagishi 2008 19061714	SD 0.89	HR	nd	nd	nd	1.03	0.54	1.96		
149	Yamagishi 2008 19061714	nd	HR	nd	nd	nd	0.92	0.5	1.68		
150	Yamagishi 2008 19061714	nd	HR	nd	nd	nd	1.24	0.68	2.26		
151	Yamagishi 2008 19061714	nd	HR	nd	nd	nd	Reference group			P trend	0.32
152	Yamagishi 2008 19061714	nd	HR	nd	nd	nd	0.97	0.51	1.82		
153	Yamagishi 2008 19061714	SD 0.39	HR	nd	nd	nd	1.49	0.82	2.69		
154	Yamagishi 2008 19061714	nd	HR	nd	nd	nd	0.71	0.35	1.42		
155	Yamagishi 2008 19061714	nd	HR	nd	nd	nd	1.65	0.92	2.98		
156	Yamagishi 2008 19061714	nd	HR	nd	nd	nd	Reference group			P trend	0.2
157	Yamagishi 2008 19061714	nd	HR	nd	nd	nd	0.73	0.39	1.38		
158	Yamagishi 2008 19061714	SD 1.11	HR	nd	nd	nd	1.05	0.56	1.96		
159	Yamagishi 2008 19061714	nd	HR	nd	nd	nd	1.33	0.75	2.36		

Appendix F
Observational results: congestive heart failure

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure	Supplement
160	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	men	87/1684 (5.17)	14.3	EPA+DHA+DPA	Phospholipid	Yes
161	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	women	110/1908 (5.77)	14.3	EPA+DHA+DPA	Cholesterol ester	Yes
162	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	women	110/1908 (5.77)	14.3	EPA+DHA+DPA	Cholesterol ester	Yes
163	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	women	110/1908 (5.77)	14.3	EPA+DHA+DPA	Cholesterol ester	Yes
164	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	women	110/1908 (5.77)	14.3	EPA+DHA+DPA	Cholesterol ester	Yes
165	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	women	110/1908 (5.77)	14.3	EPA+DHA+DPA	Cholesterol ester	Yes
166	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	women	110/1908 (5.77)	14.3	EPA+DHA+DPA	Phospholipid	Yes
167	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	women	110/1908 (5.77)	14.3	EPA+DHA+DPA	Phospholipid	Yes
168	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	women	110/1908 (5.77)	14.3	EPA+DHA+DPA	Phospholipid	Yes
169	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	women	110/1908 (5.77)	14.3	EPA+DHA+DPA	Phospholipid	Yes
170	Yamagishi 2008 19061714	Atherosclerosis Risk in Communities Study	CHF	heart failure	Healthy	white aged 45-64, free of CHD, stroke and HF	women	110/1908 (5.77)	14.3	EPA+DHA+DPA	Phospholipid	Yes

Appendix F
Observational results: congestive heart failure

Row	Study PMID	Adjustments	Quantile	n3 units	Quantile low	Quantile median
160	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt5	% of total FA	Est 90% normal	5.702522238
161	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt1	% of total FA	Est 10% normal	0.500194889
162	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt2	% of total FA	Est 30% normal	0.7954838
163	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt3	% of total FA	Reported mean (all)	1
164	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt4	% of total FA	Est 70% normal	1.2045162
165	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt5	% of total FA	Est 90% normal	1.499805111
166	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt1	% of total FA	Est 10% normal	2.857477762
167	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt2	% of total FA	Est 30% normal	3.697915431
168	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt3	% of total FA	Reported mean (all)	4.28
169	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt4	% of total FA	Est 70% normal	4.862084569
170	Yamagishi 2008 19061714	age, sex, body mass index, systolic blood pressure, antyhypertensive medication use, plasma total and HDL cholesterol, diabetes, smoking status, cigarette-years, ethanol and energy intake, education level and sports index	Qt5	% of total FA	Est 90% normal	5.702522238

Appendix F
Observational results: congestive heart failure

Row	Study PMID	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
160	Yamagishi 2008 19061714	nd	HR	nd	nd	nd	1.16	0.63	2.13		
161	Yamagishi 2008 19061714	nd	HR	nd	nd	nd	Reference group			P trend	0.14
162	Yamagishi 2008 19061714	nd	HR	nd	nd	nd	0.79	0.37	1.68		
163	Yamagishi 2008 19061714	SD 0.39	HR	nd	nd	nd	1.07	0.55	2.1		
164	Yamagishi 2008 19061714	nd	HR	nd	nd	nd	1.05	0.54	2.05		
165	Yamagishi 2008 19061714	nd	HR	nd	nd	nd	0.44	0.19	1.02		
166	Yamagishi 2008 19061714	nd	HR	nd	nd	nd	Reference group			P trend	0.002
167	Yamagishi 2008 19061714	nd	HR	nd	nd	nd	1.1	0.6	2.02		
168	Yamagishi 2008 19061714	SD 1.11	HR	nd	nd	nd	0.58	0.29	1.18		
169	Yamagishi 2008 19061714	nd	HR	nd	nd	nd	0.49	0.24	0.98		
170	Yamagishi 2008 19061714	nd	HR	nd	nd	nd	0.37	0.16	0.84		

Appendix F
Observational results: myocardial Infarction

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA
2	Ascherio 1995 7885425	Health Professional Follow-up Study	MI	Any myocardial infarction	Healthy	Healthy 40-75 yo men without diagnosis of myocardial infarction, angina, stroke, transient ischemic attack, or peripheral arterial disease, or had undergone coronary artery surgery.	All	811/44895 (1.81)	6 y	EPA+DHA
3	Ascherio 1995 7885425	Health Professional Follow-up Study	MI	Any myocardial infarction	Healthy	Healthy 40-75 yo men without diagnosis of myocardial infarction, angina, stroke, transient ischemic attack, or peripheral arterial disease, or had undergone coronary artery surgery.	All	811/44895 (1.81)	6 y	EPA+DHA
4	Ascherio 1995 7885425	Health Professional Follow-up Study	MI	Any myocardial infarction	Healthy	Healthy 40-75 yo men without diagnosis of myocardial infarction, angina, stroke, transient ischemic attack, or peripheral arterial disease, or had undergone coronary artery surgery.	All	811/44895 (1.81)	6 y	EPA+DHA
5	Ascherio 1995 7885425	Health Professional Follow-up Study	MI	Any myocardial infarction	Healthy	Healthy 40-75 yo men without diagnosis of myocardial infarction, angina, stroke, transient ischemic attack, or peripheral arterial disease, or had undergone coronary artery surgery.	All	811/44895 (1.81)	6 y	EPA+DHA
6	Ascherio 1995 7885425	Health Professional Follow-up Study	MI	Any myocardial infarction	Healthy	Healthy 40-75 yo men without diagnosis of myocardial infarction, angina, stroke, transient ischemic attack, or peripheral arterial disease, or had undergone coronary artery surgery.	All	811/44895 (1.81)	6 y	EPA+DHA
7	Iso 2006 16401768	Japan Public Health Center-Based Study - Cohort I	MI	nd	Healthy	Healthy 40-59	All	221/41578 (0.53)	11.5 y	EPA+DHA
8	Iso 2006 16401768	Japan Public Health Center-Based Study - Cohort I	MI	nd	Healthy	Healthy 40-59	All	221/41578 (0.53)	11.5 y	EPA+DHA
9	Iso 2006 16401768	Japan Public Health Center-Based Study - Cohort I	MI	nd	Healthy	Healthy 40-59	All	221/41578 (0.53)	11.5 y	EPA+DHA
10	Iso 2006 16401768	Japan Public Health Center-Based Study - Cohort I	MI	nd	Healthy	Healthy 40-59	All	221/41578 (0.53)	11.5 y	EPA+DHA
11	Iso 2006 16401768	Japan Public Health Center-Based Study - Cohort I	MI	nd	Healthy	Healthy 40-59	All	221/41578 (0.53)	11.5 y	EPA+DHA
12	Morris 1995 7598116	Physician's Health Study	MI	fatal and nonfatal MI	Healthy	US male physicians	All	281/21185 (1.33)	4 y	All n-3
13	Morris 1995 7598116	Physician's Health Study	MI	fatal and nonfatal MI	Healthy	US male physicians	All	281/21185 (1.33)	4 y	All n-3
14	Morris 1995 7598116	Physician's Health Study	MI	fatal and nonfatal MI	Healthy	US male physicians	All	281/21185 (1.33)	4 y	All n-3
15	Morris 1995 7598116	Physician's Health Study	MI	fatal and nonfatal MI	Healthy	US male physicians	All	281/21185 (1.33)	4 y	All n-3
16	Morris 1995 7598116	Physician's Health Study	MI	fatal and nonfatal MI	Healthy	US male physicians	All	281/21185 (1.33)	4 y	All n-3
17	Guallar 1995 7829792	Physician's Health Study	MI	fatal and nonfatal MI	Healthy	US male physicians	All	222 case-control pairs	5 y	EPA
18	Guallar 1995 7829792	Physician's Health Study	MI	fatal and nonfatal MI	Healthy	US male physicians	All	222 case-control pairs	5 y	DHA
19	Guallar 1995 7829792	Physician's Health Study	MI	fatal and nonfatal MI	Healthy	US male physicians	All	222 case-control pairs	5 y	EPA+DHA

Appendix F
Observational results: myocardial Infarction

Row	Study PMID	n3 measure	Supplement	Adjustments	Quantile	n3 units	Quantile low
2	Ascherio 1995 7885425	Intake	No	age, BMI, smoking habits, alcohol consumption, history of hypertension, history of diabetes, history of hypercholesterolemia, family history of myocardial infarction before 60 years of age, profession	Qt1	g/d	0.01
3	Ascherio 1995 7885425	Intake	No	age, BMI, smoking habits, alcohol consumption, history of hypertension, history of diabetes, history of hypercholesterolemia, family history of myocardial infarction before 60 years of age, profession	Qt2	g/d	0.12
4	Ascherio 1995 7885425	Intake	No	age, BMI, smoking habits, alcohol consumption, history of hypertension, history of diabetes, history of hypercholesterolemia, family history of myocardial infarction before 60 years of age, profession	Qt3	g/d	0.2
5	Ascherio 1995 7885425	Intake	No	age, BMI, smoking habits, alcohol consumption, history of hypertension, history of diabetes, history of hypercholesterolemia, family history of myocardial infarction before 60 years of age, profession	Qt4	g/d	0.29
6	Ascherio 1995 7885425	Intake	No	age, BMI, smoking habits, alcohol consumption, history of hypertension, history of diabetes, history of hypercholesterolemia, family history of myocardial infarction before 60 years of age, profession	Qt5	g/d	0.42
7	Iso 2006 16401768	Intake	No	age; sex; cigarette smoking; alcohol intake; body mass index; histories of hypertension and diabetes; medication use for hypercholesterolemia; education level; sports at leisure time; quintiles of dietary intake of fruits, vegetables, saturated fat, monounsaturated fat, n6 polyunsaturated fat, cholesterol, and total energy; and PHC.	Qt1	g/d	nd
8	Iso 2006 16401768	Intake	No	age; sex; cigarette smoking; alcohol intake; body mass index; histories of hypertension and diabetes; medication use for hypercholesterolemia; education level; sports at leisure time; quintiles of dietary intake of fruits, vegetables, saturated fat, monounsaturated fat, n6 polyunsaturated fat, cholesterol, and total energy; and PHC.	Qt2	g/d	nd
9	Iso 2006 16401768	Intake	No	age; sex; cigarette smoking; alcohol intake; body mass index; histories of hypertension and diabetes; medication use for hypercholesterolemia; education level; sports at leisure time; quintiles of dietary intake of fruits, vegetables, saturated fat, monounsaturated fat, n6 polyunsaturated fat, cholesterol, and total energy; and PHC.	Qt3	g/d	nd
10	Iso 2006 16401768	Intake	No	age; sex; cigarette smoking; alcohol intake; body mass index; histories of hypertension and diabetes; medication use for hypercholesterolemia; education level; sports at leisure time; quintiles of dietary intake of fruits, vegetables, saturated fat, monounsaturated fat, n6 polyunsaturated fat, cholesterol, and total energy; and PHC.	Qt4	g/d	nd
11	Iso 2006 16401768	Intake	No	age; sex; cigarette smoking; alcohol intake; body mass index; histories of hypertension and diabetes; medication use for hypercholesterolemia; education level; sports at leisure time; quintiles of dietary intake of fruits, vegetables, saturated fat, monounsaturated fat, n6 polyunsaturated fat, cholesterol, and total energy; and PHC.	Qt5	g/d	nd
12	Morris 1995 7598116	Intake	explicitly excluded fish oil supplements	age, aspirin and beta-carotene assignment, smoking, alcohol consumption, obesity, diabetes, vigorous exercise, parental history of MI before age 60 years, history of hypertension, history of hypercholesterolemia, vitamin supplement use, and saturated fat intake	T1	g/wk	<0.5
13	Morris 1995 7598116	Intake	explicitly excluded fish oil supplements	age, aspirin and beta-carotene assignment, smoking, alcohol consumption, obesity, diabetes, vigorous exercise, parental history of MI before age 60 years, history of hypertension, history of hypercholesterolemia, vitamin supplement use, and saturated fat intake	T2	g/wk	0.5
14	Morris 1995 7598116	Intake	explicitly excluded fish oil supplements	age, aspirin and beta-carotene assignment, smoking, alcohol consumption, obesity, diabetes, vigorous exercise, parental history of MI before age 60 years, history of hypertension, history of hypercholesterolemia, vitamin supplement use, and saturated fat intake	T3	g/wk	1
15	Morris 1995 7598116	Intake	explicitly excluded fish oil supplements	age, aspirin and beta-carotene assignment, smoking, alcohol consumption, obesity, diabetes, vigorous exercise, parental history of MI before age 60 years, history of hypertension, history of hypercholesterolemia, vitamin supplement use, and saturated fat intake	T4	g/wk	1.7
16	Morris 1995 7598116	Intake	explicitly excluded fish oil supplements	age, aspirin and beta-carotene assignment, smoking, alcohol consumption, obesity, diabetes, vigorous exercise, parental history of MI before age 60 years, history of hypertension, history of hypercholesterolemia, vitamin supplement use, and saturated fat intake	T5	g/wk	nd
17	Guallar 1995 7829792	Cholesterol ester	NA	matching: age, smoking status	All	% FA	nd
18	Guallar 1995 7829792	Cholesterol ester	NA	matching: age, smoking status	All	% FA	nd
19	Guallar 1995 7829792	Cholesterol ester	NA	matching: age, smoking status	All	% FA	nd

Appendix F
Observational results: myocardial Infarction

Row	Study PMID	Quantile median	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
2	Ascherio 1995 7885425	nd	0.11	RR	163	9329	50499	Reference group			Q5 vs. Q1	0.48
3	Ascherio 1995 7885425	nd	0.19	RR	166	9220	49902	1	0.81	1.25		
4	Ascherio 1995 7885425	nd	0.28	RR	153	9005	48613	0.92	0.74	1.15		
5	Ascherio 1995 7885425	nd	0.41	RR	144	8860	47722	0.86	0.69	1.08		
6	Ascherio 1995 7885425	nd	6.52	RR	185	8481	45343	1.09	0.88	1.35		
7	Iso 2006 16401768	0.3 (mean)	nd	HR	76		102711	Reference group			P trend	0.02
8	Iso 2006 16401768	0.6 (mean)	nd	HR	44		95861	0.77	0.52	1.15		
9	Iso 2006 16401768	0.9 (mean)	nd	HR	39		95258	0.68	0.43	1.05		
10	Iso 2006 16401768	1.3 (mean)	nd	HR	36		91435	0.66	0.4	1.09		
11	Iso 2006 16401768	2.1 (mean)	nd	HR	26		92062	0.43	0.24	0.78		
12	Morris 1995 7598116	nd	nd	RR	43	4335	nd	1				0.98
13	Morris 1995 7598116	nd	1	RR	66	4134	nd	1.6	1.1	2.4		
14	Morris 1995 7598116	nd	1.7	RR	72	4691	nd	1.4	1	2.2		
15	Morris 1995 7598116	nd	2.3	RR	50	4075	nd	1.2	0.8	1.8		
16	Morris 1995 7598116	nd	>=2.3	RR	50	3950	nd	1.2	0.8	1.8		
17	Guallar 1995 7829792	0.2	nd	RR	222	nd	nd	1.05	0.91	1.21	per % U increase	0.54
18	Guallar 1995 7829792	0.18	nd	RR	222	nd	nd	1.02	0.94	1.11	per % U increase	0.59
19	Guallar 1995 7829792	0.39	nd	RR	222	nd	nd	1.05	0.92	1.19	per % U increase	0.5

Appendix F
Observational results: myocardial Infarction

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA
20	Guallar 1995 7829792	Physician's Health Study	MI	fatal and nonfatal MI	Healthy	US male physicians	All	213 case-control pairs	5 y	EPA
21	Guallar 1995 7829792	Physician's Health Study	MI	fatal and nonfatal MI	Healthy	US male physicians	All	213 case-control pairs	5 y	DHA
22	Guallar 1995 7829792	Physician's Health Study	MI	fatal and nonfatal MI	Healthy	US male physicians	All	213 case-control pairs	5 y	EPA+DHA
23	Bergkvist_2015_25679993	Swedish Mammography Study	MI	fatal and nonfatal MI	Healthy		All	1386/33446 (0.04)	12 y	EPA+DHA
24	Bergkvist_2015_25679993	Swedish Mammography Study	MI	fatal and nonfatal MI	Healthy		All	1386/33446 (0.04)	12 y	EPA+DHA
25	Bergkvist_2015_25679993	Swedish Mammography Study	MI	fatal and nonfatal MI	Healthy		All	1386/33446 (0.04)	12 y	EPA+DHA
26	Bergkvist_2015_25679993	Swedish Mammography Study	MI	fatal and nonfatal MI	Healthy		All	1386/33446 (0.04)	12 y	EPA+DHA

Appendix F
Observational results: myocardial Infarction

Row	Study PMID	n3 measure	Supplement	Adjustments	Quantile	n3 units	Quantile low
20	Guallar 1995 7829792	Phospholipid	NA	matching: age, smoking status	All	% FA	nd
21	Guallar 1995 7829792	Phospholipid	NA	matching: age, smoking status	All	% FA	nd
22	Guallar 1995 7829792	Phospholipid	NA	matching: age, smoking status	All	% FA	nd
23	Bergkvist_2015_2 5679993	intake	yes	Adjusted for attained age (years), postsecondary education (yes/no), family history of myocardial infarction before the age of 60 years (yes/no), ever use of postmenopausal hormones (yes/no), use of aspirin (yes/no), smoking status (never, past or current),waist circumference (b80, 80–87, ≥88 cm),weight loss of ≥5 kg within a year (yes/no), parity (0, ≥1 children), total physical activity (quartiles, MET-h), use of fish oil supplements (yes/no), alcohol consumption (0, N0–4.9, 5.0–14.9, N15.0 g/day), energy intake (continuous, kcal/day), consumption of fruit and vegetables (quartiles, servings/week), dairy products (quartiles, servings/day) and red and processed meat (quartiles, servings/week), dietary intake of saturated fatty acids (quartiles, g/day) and dietary MeHg exposure (quartiles, µg/day).	Qr1	mg/d	nd
24	Bergkvist_2015_2 5679993	intake	yes	Adjusted for attained age (years), postsecondary education (yes/no), family history of myocardial infarction before the age of 60 years (yes/no), ever use of postmenopausal hormones (yes/no), use of aspirin (yes/no), smoking status (never, past or current),waist circumference (b80, 80–87, ≥88 cm),weight loss of ≥5 kg within a year (yes/no), parity (0, ≥1 children), total physical activity (quartiles, MET-h), use of fish oil supplements (yes/no), alcohol consumption (0, N0–4.9, 5.0–14.9, N15.0 g/day), energy intake (continuous, kcal/day), consumption of fruit and vegetables (quartiles, servings/week), dairy products (quartiles, servings/day) and red and processed meat (quartiles, servings/week), dietary intake of saturated fatty acids (quartiles, g/day) and dietary MeHg exposure (quartiles, µg/day).	Qr2	mg/d	nd
25	Bergkvist_2015_2 5679993	intake	yes	Adjusted for attained age (years), postsecondary education (yes/no), family history of myocardial infarction before the age of 60 years (yes/no), ever use of postmenopausal hormones (yes/no), use of aspirin (yes/no), smoking status (never, past or current),waist circumference (b80, 80–87, ≥88 cm),weight loss of ≥5 kg within a year (yes/no), parity (0, ≥1 children), total physical activity (quartiles, MET-h), use of fish oil supplements (yes/no), alcohol consumption (0, N0–4.9, 5.0–14.9, N15.0 g/day), energy intake (continuous, kcal/day), consumption of fruit and vegetables (quartiles, servings/week), dairy products (quartiles, servings/day) and red and processed meat (quartiles, servings/week), dietary intake of saturated fatty acids (quartiles, g/day) and dietary MeHg exposure (quartiles, µg/day).	Qr3	mg/d	nd
26	Bergkvist_2015_2 5679993	intake	yes	Adjusted for attained age (years), postsecondary education (yes/no), family history of myocardial infarction before the age of 60 years (yes/no), ever use of postmenopausal hormones (yes/no), use of aspirin (yes/no), smoking status (never, past or current),waist circumference (b80, 80–87, ≥88 cm),weight loss of ≥5 kg within a year (yes/no), parity (0, ≥1 children), total physical activity (quartiles, MET-h), use of fish oil supplements (yes/no), alcohol consumption (0, N0–4.9, 5.0–14.9, N15.0 g/day), energy intake (continuous, kcal/day), consumption of fruit and vegetables (quartiles, servings/week), dairy products (quartiles, servings/day) and red and processed meat (quartiles, servings/week), dietary intake of saturated fatty acids (quartiles, g/day) and dietary MeHg exposure (quartiles, µg/day).	Qr4	mg/d	nd

Appendix F
Observational results: myocardial Infarction

Row	Study PMID	Quantile median	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
20	Guallar 1995 7829792	0.49	nd	RR	213	nd	nd	1.01	0.84	1.21	per % U increase	0.92
21	Guallar 1995 7829792	2.11	nd	RR	213	nd	nd	1.06	0.81	1.39	per % U increase	0.66
22	Guallar 1995 7829792	2.58	nd	RR	213	nd	nd	1.06	0.8	1.4	per % U increase	0.7
23	Bergkvist_2015_25679993	148	nd	RR	355	nd	96037	Ref			P trend	0.16
24	Bergkvist_2015_25679993	247	nd	RR	312	nd	97727	0.98	0.84	1.16		
25	Bergkvist_2015_25679993	334	nd	RR	289	nd	97907	0.9	0.76	1.07		
26	Bergkvist_2015_25679993	518	nd	RR	430	nd	95867	1.11	0.93	1.33		

Appendix F
Observational results: stroke

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure	Supplement
2	He 2002 12495393	Health Professional Follow-up Study	Stroke, total	stroke defined as sudden or rapid onset of a typical neurological defect of more than 24-hour duration or leading to death that was attributable to cerebrovascular event	Healthy	Healthy 40-75 yo men without diagnosis of myocardial infarction, angina, stroke, transient ischemic attack, or peripheral arterial disease, or had undergone coronary artery surgery.	Men	608/43671 (1.39)	12 y	EPA+DHA	Intake	No
3	He 2002 12495393	Health Professional Follow-up Study	Stroke, total	stroke defined as sudden or rapid onset of a typical neurological defect of more than 24-hour duration or leading to death that was attributable to cerebrovascular event	Healthy	Healthy 40-75 yo men without diagnosis of myocardial infarction, angina, stroke, transient ischemic attack, or peripheral arterial disease, or had undergone coronary artery surgery.	Men	608/43671 (1.39)	12 y	EPA+DHA	Intake	No
4	He 2002 12495393	Health Professional Follow-up Study	Stroke, total	stroke defined as sudden or rapid onset of a typical neurological defect of more than 24-hour duration or leading to death that was attributable to cerebrovascular event	Healthy	Healthy 40-75 yo men without diagnosis of myocardial infarction, angina, stroke, transient ischemic attack, or peripheral arterial disease, or had undergone coronary artery surgery.	Men	608/43671 (1.39)	12 y	EPA+DHA	Intake	No
5	He 2002 12495393	Health Professional Follow-up Study	Stroke, total	stroke defined as sudden or rapid onset of a typical neurological defect of more than 24-hour duration or leading to death that was attributable to cerebrovascular event	Healthy	Healthy 40-75 yo men without diagnosis of myocardial infarction, angina, stroke, transient ischemic attack, or peripheral arterial disease, or had undergone coronary artery surgery.	Men	608/43671 (1.39)	12 y	EPA+DHA	Intake	No
6	He 2002 12495393	Health Professional Follow-up Study	Stroke, total	stroke defined as sudden or rapid onset of a typical neurological defect of more than 24-hour duration or leading to death that was attributable to cerebrovascular event	Healthy	Healthy 40-75 yo men without diagnosis of myocardial infarction, angina, stroke, transient ischemic attack, or peripheral arterial disease, or had undergone coronary artery surgery.	Men	608/43671 (1.39)	12 y	EPA+DHA	Intake	No
7	Iso 2001 11176840	Nurses' Health Study	Stroke, total	nd	Healthy	Healthy 34-59 yo female nurses	Women	608/43671 (1.39)	14 y	EPA+DHA	Intake	no
8	Iso 2001 11176840	Nurses' Health Study	Stroke, total	nd	Healthy	Healthy 34-59 yo female nurses	Women	608/43671 (1.39)	14 y	EPA+DHA	Intake	no
9	Iso 2001 11176840	Nurses' Health Study	Stroke, total	nd	Healthy	Healthy 34-59 yo female nurses	Women	608/43671 (1.39)	14 y	EPA+DHA	Intake	no
10	Iso 2001 11176840	Nurses' Health Study	Stroke, total	nd	Healthy	Healthy 34-59 yo female nurses	Women	608/43671 (1.39)	14 y	EPA+DHA	Intake	no
11	Iso 2001 11176840	Nurses' Health Study	Stroke, total	nd	Healthy	Healthy 34-59 yo female nurses	Women	608/43671 (1.39)	14 y	EPA+DHA	Intake	no

Row	Study PMID	Adjustments	Quantile	n3 units	Quantile low	Quantile median
2	He 2002 12495393	BMI, physcial activity, hx hypertension, smoking status, aspirin use, fish oil, multivitamins, total calorie intake, total fat. Saturated fat, trans-unstaurated fat, alcohol, potassium, magnesium, total servings of fruits and vegatbles, and hypercholsterolemia at baseline.	Qt1	g/d	0	nd
3	He 2002 12495393	BMI, physcial activity, hx hypertension, smoking status, aspirin use, fish oil, multivitamins, total calorie intake, total fat. Saturated fat, trans-unstaurated fat, alcohol, potassium, magnesium, total servings of fruits and vegatbles, and hypercholsterolemia at baseline.	Qt2	g/d	0.05	nd
4	He 2002 12495393	BMI, physcial activity, hx hypertension, smoking status, aspirin use, fish oil, multivitamins, total calorie intake, total fat. Saturated fat, trans-unstaurated fat, alcohol, potassium, magnesium, total servings of fruits and vegatbles, and hypercholsterolemia at baseline.	Qt3	g/d	0.2	nd
5	He 2002 12495393	BMI, physcial activity, hx hypertension, smoking status, aspirin use, fish oil, multivitamins, total calorie intake, total fat. Saturated fat, trans-unstaurated fat, alcohol, potassium, magnesium, total servings of fruits and vegatbles, and hypercholsterolemia at baseline.	Qt4	g/d	0.4	nd
6	He 2002 12495393	BMI, physcial activity, hx hypertension, smoking status, aspirin use, fish oil, multivitamins, total calorie intake, total fat. Saturated fat, trans-unstaurated fat, alcohol, potassium, magnesium, total servings of fruits and vegatbles, and hypercholsterolemia at baseline.	Qt5	g/d	0.6	nd
7	Iso 2001 11176840	joules (continuous), BMI, alcohol intake, menopausal status and postmenopausal hormone use, vigorous exercise, usual aspirin use, multivitamin use, history of HTN, frequency of total fruit and vegetable servings and for nutrient intake of saturated fat, trans-unsaturated fat, linoleic acid, animal protein, calcium	Qt1	g/d	nd	0.077
8	Iso 2001 11176840	joules (continuous), BMI, alcohol intake, menopausal status and postmenopausal hormone use, vigorous exercise, usual aspirin use, multivitamin use, history of HTN, frequency of total fruit and vegetable servings and for nutrient intake of saturated fat, trans-unsaturated fat, linoleic acid, animal protein, calcium	Qt2	g/d	nd	0.118
9	Iso 2001 11176840	joules (continuous), BMI, alcohol intake, menopausal status and postmenopausal hormone use, vigorous exercise, usual aspirin use, multivitamin use, history of HTN, frequency of total fruit and vegetable servings and for nutrient intake of saturated fat, trans-unsaturated fat, linoleic acid, animal protein, calcium	Qt3	g/d	nd	0.171
10	Iso 2001 11176840	joules (continuous), BMI, alcohol intake, menopausal status and postmenopausal hormone use, vigorous exercise, usual aspirin use, multivitamin use, history of HTN, frequency of total fruit and vegetable servings and for nutrient intake of saturated fat, trans-unsaturated fat, linoleic acid, animal protein, calcium	Qt4	g/d	nd	0.221
11	Iso 2001 11176840	joules (continuous), BMI, alcohol intake, menopausal status and postmenopausal hormone use, vigorous exercise, usual aspirin use, multivitamin use, history of HTN, frequency of total fruit and vegetable servings and for nutrient intake of saturated fat, trans-unsaturated fat, linoleic acid, animal protein, calcium	Qt5	g/d	nd	0.481

Appendix F
Observational results: stroke

Row	Study PMID	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
2	He 2002 12495393	<0.05	RR	31	nd	19741	Reference group			p trend	0.71
3	He 2002 12495393	<0.2	RR	197	nd	155579	0.77	0.52	1.14		
4	He 2002 12495393	<0.4	RR	228	nd	175161	0.77	0.52	1.14		
5	He 2002 12495393	<0.6	RR	84	nd	68003	0.71	0.46	1.1		
6	He 2002 12495393	>=0.6	RR	68	nd	43539	0.87	0.56	1.37		
7	Iso 2001 11176840	nd	RR	143	nd	nd	Reference group			P trend	0.12
8	Iso 2001 11176840	nd	RR	121	nd	nd	0.87	0.68	1.11		
9	Iso 2001 11176840	nd	RR	99	nd	nd	0.69	0.53	0.89		
10	Iso 2001 11176840	nd	RR	113	nd	nd	0.83	0.63	1.08		
11	Iso 2001 11176840	nd	RR	198	nd	nd	0.72	0.53	0.99		

Appendix F
Observational results: stroke

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure	Supplement
12	Levitan 2012 22172525	Swedish Mammography Study	Stroke, total	Total stroke	Healthy	Healthy, ages 49-83	Women	1680/34670 (4.85)	10.4 y	ALA	Intake	yes
13	Levitan 2010 20332801	Swedish Mammography Study	Stroke, total	Total stroke	Healthy	Healthy, ages 49-83	Women	1680/34670 (4.85)	10.4 y	ALA	Intake	yes
14	Levitan 2010 20332801	Swedish Mammography Study	Stroke, total	Total stroke	Healthy	Healthy, ages 49-83	Women	1680/34670 (4.85)	10.4 y	ALA	Intake	yes
15	Levitan 2010 20332801	Swedish Mammography Study	Stroke, total	Total stroke	Healthy	Healthy, ages 49-83	Women	1680/34670 (4.85)	10.4 y	ALA	Intake	yes
16	Levitan 2010 20332801	Swedish Mammography Study	Stroke, total	Total stroke	Healthy	Healthy, ages 49-83	Women	1680/34670 (4.85)	10.4 y	ALA	Intake	yes
17	Levitan 2010 20332801	Swedish Mammography Study	Stroke, total	Total stroke	Healthy	Healthy, ages 49-83	Women	1680/34670 (4.85)	10.4 y	EPA+DHA	Intake	yes
18	Levitan 2010 20332801	Swedish Mammography Study	Stroke, total	Total stroke	Healthy	Healthy, ages 49-83	Women	1680/34670 (4.85)	10.4 y	EPA+DHA	Intake	yes
19	Levitan 2010 20332801	Swedish Mammography Study	Stroke, total	Total stroke	Healthy	Healthy, ages 49-83	Women	1680/34670 (4.85)	10.4 y	EPA+DHA	Intake	yes
20	Levitan 2010 20332801	Swedish Mammography Study	Stroke, total	Total stroke	Healthy	Healthy, ages 49-83	Women	1680/34670 (4.85)	10.4 y	EPA+DHA	Intake	yes
21	Levitan 2010 20332801	Swedish Mammography Study	Stroke, total	Total stroke	Healthy	Healthy, ages 49-83	Women	1680/34670 (4.85)	10.4 y	EPA+DHA	Intake	yes
22	Fretts 2014 25159901	Cardiovascular Health Study	Stroke, total	nd	Healthy	Healthy age >= 65y	All	358/2583 (13.85)	12y	ALA	Intake	no
23	Fretts 2014 25159901	Cardiovascular Health Study	Stroke, total	nd	Healthy	Healthy age >= 65y	All	358/2583 (13.85)	12y	ALA	Intake	no
24	Fretts 2014 25159901	Cardiovascular Health Study	Stroke, total	nd	Healthy	Healthy age >= 65y	All	358/2583 (13.85)	12y	ALA	Intake	no
25	Fretts 2014 25159901	Cardiovascular Health Study	Stroke, total	nd	Healthy	Healthy age >= 65y	All	358/2583 (13.85)	12y	ALA	Intake	no
26	Fretts 2014 25159901	Cardiovascular Health Study	Stroke, total	nd	Healthy	Healthy age >= 65y	All	358/2583 (13.85)	12y	ALA	Intake	no
27	Fretts 2014 25159901	Cardiovascular Health Study	Stroke, total	nd	Healthy	Healthy age >= 65y	All	430/2709 (15.87)	16y	ALA	Plasma	no
28	Fretts 2014 25159901	Cardiovascular Health Study	Stroke, total	nd	Healthy	Healthy age >= 65y	All	430/2709 (15.87)	16y	ALA	Plasma	no
29	Fretts 2014 25159901	Cardiovascular Health Study	Stroke, total	nd	Healthy	Healthy age >= 65y	All	430/2709 (15.87)	16y	ALA	Plasma	no
30	Fretts 2014 25159901	Cardiovascular Health Study	Stroke, total	nd	Healthy	Healthy age >= 65y	All	430/2709 (15.87)	16y	ALA	Plasma	no
31	Fretts 2014 25159901	Cardiovascular Health Study	Stroke, total	nd	Healthy	Healthy age >= 65y	All	430/2709 (15.87)	16y	ALA	Plasma	no

Appendix F
Observational results: stroke

Row	Study PMID	Adjustments	Quantile	n3 units	Quantile low	Quantile median
12	Levitan 2012 22172525	We adjusted for BMI (linear), physical activity (linear), energy intake (linear), alcohol consumption (linear), fiber consumption (linear), sodium consumption (linear), daily servings of red or processed meat (linear), education (less than high school, high school, university), family history of myocardial infarction at <60 years (yes, no), cigarette smoking (current, past, never), living alone (yes, no), postmenopausal hormone use (yes, no), self-reported history of hypertension (yes, no) and self-reported history of high cholesterol (yes, no).	Qt1	g/d	nd	0.9
13	Levitan 2010 20332801	We adjusted for BMI (linear), physical activity (linear), energy intake (linear), alcohol consumption (linear), fiber consumption (linear), sodium consumption (linear), daily servings of red or processed meat (linear), education (less than high school, high school, university), family history of myocardial infarction at <60 years (yes, no), cigarette smoking (current, past, never), living alone (yes, no), postmenopausal hormone use (yes, no), self-reported history of hypertension (yes, no) and self-reported history of high cholesterol (yes, no).	Qt2	g/d	nd	1
14	Levitan 2010 20332801	We adjusted for BMI (linear), physical activity (linear), energy intake (linear), alcohol consumption (linear), fiber consumption (linear), sodium consumption (linear), daily servings of red or processed meat (linear), education (less than high school, high school, university), family history of myocardial infarction at <60 years (yes, no), cigarette smoking (current, past, never), living alone (yes, no), postmenopausal hormone use (yes, no), self-reported history of hypertension (yes, no) and self-reported history of high cholesterol (yes, no).	Qt3	g/d	nd	1.1
15	Levitan 2010 20332801	We adjusted for BMI (linear), physical activity (linear), energy intake (linear), alcohol consumption (linear), fiber consumption (linear), sodium consumption (linear), daily servings of red or processed meat (linear), education (less than high school, high school, university), family history of myocardial infarction at <60 years (yes, no), cigarette smoking (current, past, never), living alone (yes, no), postmenopausal hormone use (yes, no), self-reported history of hypertension (yes, no) and self-reported history of high cholesterol (yes, no).	Qt4	g/d	nd	1.3
16	Levitan 2010 20332801	We adjusted for BMI (linear), physical activity (linear), energy intake (linear), alcohol consumption (linear), fiber consumption (linear), sodium consumption (linear), daily servings of red or processed meat (linear), education (less than high school, high school, university), family history of myocardial infarction at <60 years (yes, no), cigarette smoking (current, past, never), living alone (yes, no), postmenopausal hormone use (yes, no), self-reported history of hypertension (yes, no) and self-reported history of high cholesterol (yes, no).	Qt5	g/d	nd	1.5
17	Levitan 2010 20332801	We adjusted for BMI (linear), physical activity (linear), energy intake (linear), alcohol consumption (linear), fiber consumption (linear), sodium consumption (linear), daily servings of red or processed meat (linear), education (less than high school, high school, university), family history of myocardial infarction at <60 years (yes, no), cigarette smoking (current, past, never), living alone (yes, no), postmenopausal hormone use (yes, no), self-reported history of hypertension (yes, no) and self-reported history of high cholesterol (yes, no).	Qt1	mg/d	nd	131
18	Levitan 2010 20332801	We adjusted for BMI (linear), physical activity (linear), energy intake (linear), alcohol consumption (linear), fiber consumption (linear), sodium consumption (linear), daily servings of red or processed meat (linear), education (less than high school, high school, university), family history of myocardial infarction at <60 years (yes, no), cigarette smoking (current, past, never), living alone (yes, no), postmenopausal hormone use (yes, no), self-reported history of hypertension (yes, no) and self-reported history of high cholesterol (yes, no).	Qt2	mg/d	nd	222
19	Levitan 2010 20332801	We adjusted for BMI (linear), physical activity (linear), energy intake (linear), alcohol consumption (linear), fiber consumption (linear), sodium consumption (linear), daily servings of red or processed meat (linear), education (less than high school, high school, university), family history of myocardial infarction at <60 years (yes, no), cigarette smoking (current, past, never), living alone (yes, no), postmenopausal hormone use (yes, no), self-reported history of hypertension (yes, no) and self-reported history of high cholesterol (yes, no).	Qt3	mg/d	nd	289
20	Levitan 2010 20332801	We adjusted for BMI (linear), physical activity (linear), energy intake (linear), alcohol consumption (linear), fiber consumption (linear), sodium consumption (linear), daily servings of red or processed meat (linear), education (less than high school, high school, university), family history of myocardial infarction at <60 years (yes, no), cigarette smoking (current, past, never), living alone (yes, no), postmenopausal hormone use (yes, no), self-reported history of hypertension (yes, no) and self-reported history of high cholesterol (yes, no).	Qt4	mg/d	nd	370
21	Levitan 2010 20332801	We adjusted for BMI (linear), physical activity (linear), energy intake (linear), alcohol consumption (linear), fiber consumption (linear), sodium consumption (linear), daily servings of red or processed meat (linear), education (less than high school, high school, university), family history of myocardial infarction at <60 years (yes, no), cigarette smoking (current, past, never), living alone (yes, no), postmenopausal hormone use (yes, no), self-reported history of hypertension (yes, no) and self-reported history of high cholesterol (yes, no).	Qt5	mg/d	nd	559
22	Fretts 2014 25159901	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt1	% fat intake	0.39	1.33
23	Fretts 2014 25159901	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt2	% fat intake	1.45	1.56
24	Fretts 2014 25159901	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt3	% fat intake	1.65	1.76
25	Fretts 2014 25159901	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt4	% fat intake	1.87	2
26	Fretts 2014 25159901	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt5	% fat intake	2.17	2.44
27	Fretts 2014 25159901	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt1	% FA	0.05	0.09
28	Fretts 2014 25159901	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt2	% FA	0.11	0.12
29	Fretts 2014 25159901	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt3	% FA	0.13	0.14
30	Fretts 2014 25159901	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt4	% FA	0.15	0.17
31	Fretts 2014 25159901	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt5	% FA	0.19	0.22

Appendix F
Observational results: stroke

Row	Study PMID	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
12	Levitan 2012 22172525	nd	RR	350	nd	71329	Reference group			P trend	0.16
13	Levitan 2010 20332801	nd	RR	314	nd	72366	0.93	0.8	1.08		
14	Levitan 2010 20332801	nd	RR	335	nd	71644	1.04	0.9	1.21		
15	Levitan 2010 20332801	nd	RR	326	nd	72237	1.01	0.87	1.17		
16	Levitan 2010 20332801	nd	RR	355	nd	71437	1.09	0.93	1.27		
17	Levitan 2010 20332801	nd	RR	379	nd	70855	Reference group			P trend	0.04
18	Levitan 2010 20332801	nd	RR	319	nd	72278	0.93	0.8	1.08		
19	Levitan 2010 20332801	nd	RR	285	nd	72639	0.87	0.74	1.02		
20	Levitan 2010 20332801	nd	RR	317	nd	72317	0.89	0.76	1.05		
21	Levitan 2010 20332801	nd	RR	380	nd	70924	0.84	0.72	0.99		
22	Fretts 2014 25159901	1.45	HR	70	nd	4691	Reference group			P trend	0.8
23	Fretts 2014 25159901	1.65	HR	64	nd	4785	0.89	0.64	1.26		
24	Fretts 2014 25159901	1.87	HR	75	nd	4891	0.97	0.7	1.35		
25	Fretts 2014 25159901	2.17	HR	81	nd	4997	1.09	0.78	1.51		
26	Fretts 2014 25159901	4.88	HR	68	nd	5380	0.86	0.6	1.21		
27	Fretts 2014 25159901	0.11	HR	85	nd	6208	Reference group			P trend	0.66
28	Fretts 2014 25159901	0.13	HR	80	nd	5792	0.96	0.7	1.31		
29	Fretts 2014 25159901	0.15	HR	94	nd	6026	1.1	0.81	1.49		
30	Fretts 2014 25159901	0.19	HR	80	nd	6132	0.88	0.64	1.2		
31	Fretts 2014 25159901	0.47	HR	91	nd	6589	0.97	0.71	1.31		

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure	Supplement
32	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, total	nd	Healthy	Healthy age >= 65y	All	406/3941 (10.3)	16y	DHA	Plasma	no
33	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, total	nd	Healthy	Healthy age >= 65y	All	406/3941 (10.3)	16y	DHA	Plasma	no
34	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, total	nd	Healthy	Healthy age >= 65y	All	406/3941 (10.3)	16y	DHA	Plasma	no
35	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, total	nd	Healthy	Healthy age >= 65y	All	406/3941 (10.3)	16y	DHA	Plasma	no
36	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, total	nd	Healthy	Healthy age >= 65y	All	406/3941 (10.3)	16y	DHA	Plasma	no
37	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, total	nd	Healthy	Healthy age >= 65y	All	406/3941 (10.3)	16y	EPA	Plasma	no
38	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, total	nd	Healthy	Healthy age >= 65y	All	406/3941 (10.3)	16y	EPA	Plasma	no
39	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, total	nd	Healthy	Healthy age >= 65y	All	406/3941 (10.3)	16y	EPA	Plasma	no
40	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, total	nd	Healthy	Healthy age >= 65y	All	406/3941 (10.3)	16y	EPA	Plasma	no
41	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, total	nd	Healthy	Healthy age >= 65y	All	406/3941 (10.3)	16y	EPA	Plasma	no
42	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, total	nd	Healthy	Healthy age >= 65y	All	406/3941 (10.3)	16y	All n-3	Plasma	no
43	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, total	nd	Healthy	Healthy age >= 65y	All	406/3941 (10.3)	16y	All n-3	Plasma	no
44	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, total	nd	Healthy	Healthy age >= 65y	All	406/3941 (10.3)	16y	All n-3	Plasma	no
45	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, total	nd	Healthy	Healthy age >= 65y	All	406/3941 (10.3)	16y	All n-3	Plasma	no
46	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, total	nd	Healthy	Healthy age >= 65y	All	406/3941 (10.3)	16y	All n-3	Plasma	no
47	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, total	nd	Healthy	Healthy age >= 65y	All	406/3941 (10.3)	16y	DPA	Plasma	no
48	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, total	nd	Healthy	Healthy age >= 65y	All	406/3941 (10.3)	16y	DPA	Plasma	no

Appendix F
Observational results: stroke

Row	Study PMID	Adjustments	Quantile	n3 units	Quantile low	Quantile median
32	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt1	% FA	nd	1.95
33	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt2	% FA	nd	2.44
34	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt3	% FA	nd	2.87
35	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt4	% FA	nd	3.36
36	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt5	% FA	nd	4.34
37	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt1	% FA	nd	0.3
38	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt2	% FA	nd	0.41
39	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt3	% FA	nd	0.51
40	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt4	% FA	nd	0.64
41	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt5	% FA	nd	0.92
42	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt1	% FA	nd	3.17
43	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt2	% FA	nd	3.72
44	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt3	% FA	nd	4.21
45	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt4	% FA	nd	4.8
46	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt5	% FA	nd	6.04
47	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt1	% FA	nd	0.63
48	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt2	% FA	nd	0.75

Appendix F
Observational results: stroke

Row	Study PMID	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
32	Mozaffarian 2013 23546563	nd	HR	nd	nd	nd	Reference group			P trend	0.092
33	Mozaffarian 2013 23546563	nd	HR	nd	nd	nd	1.08	0.8	1.46		
34	Mozaffarian 2013 23546563	nd	HR	nd	nd	nd	1.08	0.8	1.45		
35	Mozaffarian 2013 23546563	nd	HR	nd	nd	nd	0.74	0.53	1.03		
36	Mozaffarian 2013 23546563	nd	HR	nd	nd	nd	0.84	0.59	1.18		
37	Mozaffarian 2013 23546563	nd	HR	nd	nd	nd	Reference group			P trend	0.85
38	Mozaffarian 2013 23546563	nd	HR	nd	nd	nd	1.01	0.74	1.37		
39	Mozaffarian 2013 23546563	nd	HR	nd	nd	nd	0.95	0.69	1.29		
40	Mozaffarian 2013 23546563	nd	HR	nd	nd	nd	0.91	0.66	1.25		
41	Mozaffarian 2013 23546563	nd	HR	nd	nd	nd	1.05	0.76	1.45		
42	Mozaffarian 2013 23546563	nd	HR	nd	nd	nd	Reference group			P trend	0.098
43	Mozaffarian 2013 23546563	nd	HR	nd	nd	nd	0.97	0.72	1.32		
44	Mozaffarian 2013 23546563	nd	HR	nd	nd	nd	0.91	0.67	1.23		
45	Mozaffarian 2013 23546563	nd	HR	nd	nd	nd	0.93	0.68	1.28		
46	Mozaffarian 2013 23546563	nd	HR	nd	nd	nd	0.75	0.53	1.06		
47	Mozaffarian 2013 23546563	nd	HR	nd	nd	nd	Reference group			P trend	0.18
48	Mozaffarian 2013 23546563	nd	HR	nd	nd	nd	0.71	0.53	0.97		

Appendix F
Observational results: stroke

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure	Supplement
49	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, total	nd	Healthy	Healthy age >= 65y	All	406/3941 (10.3)	16y	DPA	Plasma	no
50	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, total	nd	Healthy	Healthy age >= 65y	All	406/3941 (10.3)	16y	DPA	Plasma	no
51	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, total	nd	Healthy	Healthy age >= 65y	All	406/3941 (10.3)	16y	DPA	Plasma	no
52	Morris 1995 7598116	Physician's Health Study	Stroke, total	nd	Healthy	US male physicians	Men	173/21185 (0.82)	4 y	All n-3	Intake	explicitly excluded fish oil supplements
53	Morris 1995 7598116	Physician's Health Study	Stroke, total	nd	Healthy	US male physicians	Men	173/21185 (0.82)	4 y	All n-3	Intake	explicitly excluded fish oil supplements
54	Morris 1995 7598116	Physician's Health Study	Stroke, total	nd	Healthy	US male physicians	Men	173/21185 (0.82)	4 y	All n-3	Intake	explicitly excluded fish oil supplements
55	Morris 1995 7598116	Physician's Health Study	Stroke, total	nd	Healthy	US male physicians	Men	173/21185 (0.82)	4 y	All n-3	Intake	explicitly excluded fish oil supplements
56	Morris 1995 7598116	Physician's Health Study	Stroke, total	nd	Healthy	US male physicians	Men	173/21185 (0.82)	4 y	All n-3	Intake	explicitly excluded fish oil supplements
57	de Goede 2013 22633188	MORGEN	Stroke, total	total stroke	Healthy	adults 20-65 yr	All	179/358 (50)	10.5 yr	ALA	Plasma	No
58	de Goede 2013 22633188	MORGEN	Stroke, total	total stroke	Healthy	adults 20-65 yr	All	179/358 (50)	10.5 yr	EPA+DHA	Plasma	No
59	de Goede 2011 21464993	MORGEN	Stroke, total	Total Stroke	Healthy	Healthy 20-65 yo	All	221/19896 (1.11)	10.5 y	ALA	Intake	No
60	de Goede 2011 21464993	MORGEN	Stroke, total	Total Stroke	Healthy	Healthy 20-65 yo	All	221/19896 (1.11)	10.5 y	ALA	Intake	No
61	de Goede 2011 21464993	MORGEN	Stroke, total	Total Stroke	Healthy	Healthy 20-65 yo	All	221/19896 (1.11)	10.5 y	ALA	Intake	No
62	de Goede 2011 21464993	MORGEN	Stroke, total	Total Stroke	Healthy	Healthy 20-65 yo	All	221/19896 (1.11)	10.5 y	ALA	Intake	No
63	de Goede 2011 21464993	MORGEN	Stroke, total	Total Stroke	Healthy	Healthy 20-65 yo	All	221/19896 (1.11)	10.5 y	ALA	Intake	No
65	**Subgroup analyses**											
66	de Goede 2012 22496770	MORGEN	Stroke, total	Total Stroke	Healthy	Healthy 20-65 yo	Women	nd/11081 (9.2 per 10,000 pt yrs)	10.5 y	EPA+DHA	Intake	No
67	de Goede 2012 22496770	MORGEN	Stroke, total	Total Stroke	Healthy	Healthy 20-65 yo	Women	nd/11081 (9.2 per 10,000 pt yrs)	10.5 y	EPA+DHA	Intake	No
68	de Goede 2012 22496770	MORGEN	Stroke, total	Total Stroke	Healthy	Healthy 20-65 yo	Women	nd/11081 (9.2 per 10,000 pt yrs)	10.5 y	EPA+DHA	Intake	No
69	de Goede 2012 22496770	MORGEN	Stroke, total	Total Stroke	Healthy	Healthy 20-65 yo	Women	nd/11081 (9.2 per 10,000 pt yrs)	10.5 y	EPA+DHA	Intake	No

Appendix F
Observational results: stroke

Row	Study PMID	Adjustments	Quantile	n3 units	Quantile low	Quantile median
49	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt3	% FA	nd	0.82
50	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt4	% FA	nd	0.91
51	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt5	% FA	nd	1.04
52	Morris 1995 7598116	age, aspirin and beta-carotene assignment, smoking, alcohol consumption, obesity, diabetes, vigorous exercise, parental history of MI before age 60 years, history of hypertension, history of hypercholesterolemia, vitamin supplement use, and saturated fat intake	T1	g/wk	<0.5	nd
53	Morris 1995 7598116	age, aspirin and beta-carotene assignment, smoking, alcohol consumption, obesity, diabetes, vigorous exercise, parental history of MI before age 60 years, history of hypertension, history of hypercholesterolemia, vitamin supplement use, and saturated fat intake	T2	g/wk	0.5	nd
54	Morris 1995 7598116	age, aspirin and beta-carotene assignment, smoking, alcohol consumption, obesity, diabetes, vigorous exercise, parental history of MI before age 60 years, history of hypertension, history of hypercholesterolemia, vitamin supplement use, and saturated fat intake	T3	g/wk	1	nd
55	Morris 1995 7598116	age, aspirin and beta-carotene assignment, smoking, alcohol consumption, obesity, diabetes, vigorous exercise, parental history of MI before age 60 years, history of hypertension, history of hypercholesterolemia, vitamin supplement use, and saturated fat intake	T4	g/wk	1.7	nd
56	Morris 1995 7598116	age, aspirin and beta-carotene assignment, smoking, alcohol consumption, obesity, diabetes, vigorous exercise, parental history of MI before age 60 years, history of hypertension, history of hypercholesterolemia, vitamin supplement use, and saturated fat intake	T5	g/wk	nd	nd
57	de Goede 2013 22633188	matched for age, gender, and enrollment data + smoking + BMI + education level + alcohol intake + diabetes + hypertension + hypercholesteroemia		% FA	nd	Cases: 0.53 (SD = 0.14), Controls: 0.52 (SD = 0.15)
58	de Goede 2013 22633188	matched for age, gender, and enrollment data + smoking + BMI + education level + alcohol intake + diabetes + hypertension + hypercholesteroemia		% FA	nd	Cases: 1.43 (SD = 1.04), Controls: 1.23 (SD = 0.56)
59	de Goede 2011 21464993	age, gender, BMI, total energy intake, cigarette smoking, education level, parental history of MI, alcohol intake, intake of vit C, beta-carotene, fiber, SFA, TFA, PUFA other than ALA	Qt1	g/d	nd	1
60	de Goede 2011 21464993	age, gender, BMI, total energy intake, cigarette smoking, education level, parental history of MI, alcohol intake, intake of vit C, beta-carotene, fiber, SFA, TFA, PUFA other than ALA	Qt2	g/d	nd	1.2
61	de Goede 2011 21464993	age, gender, BMI, total energy intake, cigarette smoking, education level, parental history of MI, alcohol intake, intake of vit C, beta-carotene, fiber, SFA, TFA, PUFA other than ALA	Qt3	g/d	nd	1.3
62	de Goede 2011 21464993	age, gender, BMI, total energy intake, cigarette smoking, education level, parental history of MI, alcohol intake, intake of vit C, beta-carotene, fiber, SFA, TFA, PUFA other than ALA	Qt4	g/d	nd	1.5
63	de Goede 2011 21464993	age, gender, BMI, total energy intake, cigarette smoking, education level, parental history of MI, alcohol intake, intake of vit C, beta-carotene, fiber, SFA, TFA, PUFA other than ALA	Qt5	g/d	nd	1.9
65	**Subgroup analyses**					
66	de Goede 2012 22496770	age, smoking, BMI, educational level, parental history of myocardial infarction, alcohol intake, total energy intake, dietary fiber, vit C, beta-careotene, SFA, TFA, MFA, LA, ALA	Qt1	mg/d	nd	36
67	de Goede 2012 22496770	age, smoking, BMI, educational level, parental history of myocardial infarction, alcohol intake, total energy intake, dietary fiber, vit C, beta-careotene, SFA, TFA, MFA, LA, ALA	Qt2	mg/d	57	77
68	de Goede 2012 22496770	age, smoking, BMI, educational level, parental history of myocardial infarction, alcohol intake, total energy intake, dietary fiber, vit C, beta-careotene, SFA, TFA, MFA, LA, ALA	Qt3	mg/d	107	142
69	de Goede 2012 22496770	age, smoking, BMI, educational level, parental history of myocardial infarction, alcohol intake, total energy intake, dietary fiber, vit C, beta-careotene, SFA, TFA, MFA, LA, ALA	Qt4	mg/d	nd	225

Appendix F
Observational results: stroke

Row	Study PMID	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
49	Mozaffarian 2013 23546563	nd	HR	nd	nd	nd	0.7	0.52	0.95		
50	Mozaffarian 2013 23546563	nd	HR	nd	nd	nd	0.85	0.64	1.15		
51	Mozaffarian 2013 23546563	nd	HR	nd	nd	nd	0.74	0.55	1.01		
52	Morris 1995 7598116	nd	RR	39	4335	nd	1				0.49
53	Morris 1995 7598116	1	RR	28	4134	nd	0.9	0.6	1.6		
54	Morris 1995 7598116	1.7	RR	48	4691	nd	1.1	0.7	1.8		
55	Morris 1995 7598116	2.3	RR	27	4075	nd	0.7	0.4	1.2		
56	Morris 1995 7598116	>=2.3	RR	31	3950	nd	1	0.6	1.6		
57	de Goede 2013 22633188	nd	OR	nd	nd	nd	0.94	0.72	1.21		0.8
58	de Goede 2013 22633188	nd	OR	nd	nd	nd	1.16	0.94	1.45		0.07
59	de Goede 2011 21464993	nd	HR	41	4013	nd	Reference group				nd
60	de Goede 2011 21464993	nd	HR	38	4014	nd	0.65	0.43	0.97		
61	de Goede 2011 21464993	nd	HR	38	4014	nd	0.49	0.31	0.76		
62	de Goede 2011 21464993	nd	HR	45	4014	nd	0.53	0.34	0.83		
63	de Goede 2011 21464993	nd	HR	59	4014	nd	0.65	0.41	1.04		
65	**Subgroup analyses**										
66	de Goede 2012 22496770	<57	HR	33	2770	nd	Reference group			P trend	0.02
67	de Goede 2012 22496770	106	HR	28	2770	nd	0.89	0.53	1.49		
68	de Goede 2012 22496770	188	HR	28	2771	nd	0.86	0.51	1.46		
69	de Goede 2012 22496770	>188	HR	17	2770	nd	0.49	0.27	0.91		

Appendix F
Observational results: stroke

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure	Supplement
70	de Goede 2012 22496770	MORGEN	Stroke, total	Total Stroke	Healthy	Healthy 20-65 yo	Men	nd/8988 (12.4 per 10,000 pt yrs)	10.5 y	EPA+DHA	Intake	No
71	de Goede 2012 22496770	MORGEN	Stroke, total	Total Stroke	Healthy	Healthy 20-65 yo	Men	nd/8988 (12.4 per 10,000 pt yrs)	10.5 y	EPA+DHA	Intake	No
72	de Goede 2012 22496770	MORGEN	Stroke, total	Total Stroke	Healthy	Healthy 20-65 yo	Men	nd/8988 (12.4 per 10,000 pt yrs)	10.5 y	EPA+DHA	Intake	No
73	de Goede 2012 22496770	MORGEN	Stroke, total	Total Stroke	Healthy	Healthy 20-65 yo	Men	nd/8988 (12.4 per 10,000 pt yrs)	10.5 y	EPA+DHA	Intake	No
74	Ninomiya_2013_24267237	Hisayama	Stroke, total	incident stroke or CHD defined as acute myocardial infarction, silent myocardial infarction, sudden cardiac death within 1 h after the onset of acute illness, or coronary intervention (coronary artery bypass surgery or angioplasty)	Healthy	Healthy >40 yo		127/3103 (4.09)	5y	EPA	serum	nd
75	Ninomiya_2013_24267237	Hisayama	Stroke, total	incident stroke or CHD defined as acute myocardial infarction, silent myocardial infarction, sudden cardiac death within 1 h after the onset of acute illness, or coronary intervention (coronary artery bypass surgery or angioplasty)	Healthy	Healthy >40 yo		127/3103 (4.09)	5y	EPA	serum	nd
76	Ninomiya_2013_24267237	Hisayama	Stroke, total	incident stroke or CHD defined as acute myocardial infarction, silent myocardial infarction, sudden cardiac death within 1 h after the onset of acute illness, or coronary intervention (coronary artery bypass surgery or angioplasty)	Healthy	Healthy >40 yo		127/3103 (4.09)	5y	EPA	serum	nd

Appendix F
Observational results: stroke

Row	Study PMID	Adjustments	Quantile	n3 units	Quantile low	Quantile median
70	de Goede 2012 22496770	age, smoking, BMI, educational level, parental history of myocardial infarction, alcohol intake, total energy intake, dietary fiber, vit C, beta-careotene, SFA, TFA, MFA, LA, ALA	Qt1	mg/d	nd	44
71	de Goede 2012 22496770	age, smoking, BMI, educational level, parental history of myocardial infarction, alcohol intake, total energy intake, dietary fiber, vit C, beta-careotene, SFA, TFA, MFA, LA, ALA	Qt2	mg/d	66	89
72	de Goede 2012 22496770	age, smoking, BMI, educational level, parental history of myocardial infarction, alcohol intake, total energy intake, dietary fiber, vit C, beta-careotene, SFA, TFA, MFA, LA, ALA	Qt3	mg/d	119	157
73	de Goede 2012 22496770	age, smoking, BMI, educational level, parental history of myocardial infarction, alcohol intake, total energy intake, dietary fiber, vit C, beta-careotene, SFA, TFA, MFA, LA, ALA	Qt4	mg/d	nd	241
74	Ninomiya_2013_24267237	Adjusted for age, sex, hypertension, diabetes, serum total cholesterol, serum high-density lipoprotein cholesterol, serum triglycerides, lipid-modifying agents, body mass index, HS-CRP, current smoking, current drinking, and regular exercise. HS-CRP was removed from the relevant model in the subgroup analysis of HS-CRP.	Qr1	EPA/AA ratio	0	0.22
75	Ninomiya_2013_24267237	Adjusted for age, sex, hypertension, diabetes, serum total cholesterol, serum high-density lipoprotein cholesterol, serum triglycerides, lipid-modifying agents, body mass index, HS-CRP, current smoking, current drinking, and regular exercise. HS-CRP was removed from the relevant model in the subgroup analysis of HS-CRP.	Qr2	EPA/AA ratio	0.29	0.36
76	Ninomiya_2013_24267237	Adjusted for age, sex, hypertension, diabetes, serum total cholesterol, serum high-density lipoprotein cholesterol, serum triglycerides, lipid-modifying agents, body mass index, HS-CRP, current smoking, current drinking, and regular exercise. HS-CRP was removed from the relevant model in the subgroup analysis of HS-CRP.	Qr3	EPA/AA ratio	0.41	0.5

Appendix F
Observational results: stroke

Row	Study PMID	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
70	de Goede 2012 22496770	<66	HR	30	2247	nd	Reference group			P trend	0.36
71	de Goede 2012 22496770	118	HR	33	2247	nd	1.16	0.7	1.92		
72	de Goede 2012 22496770	198	HR	24	2247	nd	0.84	0.48	1.45		
73	de Goede 2012 22496770	>199	HR	28	2247	nd	0.87	0.51	1.48		
74	Ninomiya_2013_24267237	0.29	HR	36	775	1.38	0.87	2.18			0.15
75	Ninomiya_2013_24267237	0.41	HR	25	776	0.83	0.49	1.39			0.48
76	Ninomiya_2013_24267237	0.59	HR	29	776	0.97	0.6	1.59			0.91

Appendix F
Observational results: stroke

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure	Supplement
77	Ninomiya_2013_24267237	Hisayama	Stroke, total	incident stroke or CHD defined as acute myocardial infarction, silent myocardial infarction, sudden cardiac death within 1 h after the onset of acute illness, or coronary intervention (coronary artery bypass surgery or angioplasty)	Healthy	Healthy >40 yo		127/3103 (4.09)	5y	EPA	serum	nd
78	Ninomiya_2013_24267237	Hisayama	Stroke, total	incident stroke or CHD defined as acute myocardial infarction, silent myocardial infarction, sudden cardiac death within 1 h after the onset of acute illness, or coronary intervention (coronary artery bypass surgery or angioplasty)	Healthy	Healthy >40 yo		127/3103 (4.09)	5y	DHA	serum	nd
79	Ninomiya_2013_24267237	Hisayama	Stroke, total	incident stroke or CHD defined as acute myocardial infarction, silent myocardial infarction, sudden cardiac death within 1 h after the onset of acute illness, or coronary intervention (coronary artery bypass surgery or angioplasty)	Healthy	Healthy >40 yo		127/3103 (4.09)	5y	DHA	serum	nd
80	Ninomiya_2013_24267237	Hisayama	Stroke, total	incident stroke or CHD defined as acute myocardial infarction, silent myocardial infarction, sudden cardiac death within 1 h after the onset of acute illness, or coronary intervention (coronary artery bypass surgery or angioplasty)	Healthy	Healthy >40 yo		127/3103 (4.09)	5y	DHA	serum	nd

Appendix F
Observational results: stroke

Row	Study PMID	Adjustments	Quantile	n3 units	Quantile low	Quantile median
77	Ninomiya_2013_24267237	Adjusted for age, sex, hypertension, diabetes, serum total cholesterol, serum high-density lipoprotein cholesterol, serum triglycerides, lipid-modifying agents, body mass index, HS-CRP, current smoking, current drinking, and regular exercise. HS-CRP was removed from the relevant model in the subgroup analysis of HS-CRP.	Qr4	EPA/AA ratio	0.59	0.74
78	Ninomiya_2013_24267237	Adjusted for age, sex, hypertension, diabetes, serum total cholesterol, serum high-density lipoprotein cholesterol, serum triglycerides, lipid-modifying agents, body mass index, HS-CRP, current smoking, current drinking, and regular exercise. HS-CRP was removed from the relevant model in the subgroup analysis of HS-CRP.	Qr1	DHA/AA ratio	0	0.65
79	Ninomiya_2013_24267237	Adjusted for age, sex, hypertension, diabetes, serum total cholesterol, serum high-density lipoprotein cholesterol, serum triglycerides, lipid-modifying agents, body mass index, HS-CRP, current smoking, current drinking, and regular exercise. HS-CRP was removed from the relevant model in the subgroup analysis of HS-CRP.	Qr2	DHA/AA ratio	0.75	0.84
80	Ninomiya_2013_24267237	Adjusted for age, sex, hypertension, diabetes, serum total cholesterol, serum high-density lipoprotein cholesterol, serum triglycerides, lipid-modifying agents, body mass index, HS-CRP, current smoking, current drinking, and regular exercise. HS-CRP was removed from the relevant model in the subgroup analysis of HS-CRP.	Qr3	DHA/AA ratio	0.93	1.02

Appendix F
Observational results: stroke

Row	Study PMID	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
77	Ninomiya_2013_24267237	nd	HR	37	776	Ref				P trend	0.35
78	Ninomiya_2013_24267237	0.75	HR	27	775	1.26	0.75	2.1			0.38
79	Ninomiya_2013_24267237	0.93	HR	31	776	1.14	0.7	1.86			0.61
80	Ninomiya_2013_24267237	1.15	HR	31	776	1.04	0.64	1.68			0.89

Appendix F
Observational results: stroke

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure	Supplement
81	Ninomiya_2013_24267237	Hisayama	Stroke, total	incident stroke or CHD defined as acute myocardial infarction, silent myocardial infarction, sudden cardiac death within 1 h after the onset of acute illness, or coronary intervention (coronary artery bypass surgery or angioplasty)	Healthy	Healthy >40 yo		127/3103 (4.09)	5y	DHA	serum	nd

Appendix F
Observational results: stroke

Row	Study PMID	Adjustments	Quantile	n3 units	Quantile low	Quantile median
81	Ninomiya_2013_24267237	Adjusted for age, sex, hypertension, diabetes, serum total cholesterol, serum high-density lipoprotein cholesterol, serum triglycerides, lipid-modifying agents, body mass index, HS-CRP, current smoking, current drinking, and regular exercise. HS-CRP was removed from the relevant model in the subgroup analysis of HS-CRP.	Qr4	DHA/AA ratio	1.15	1.33

Appendix F
Observational results: stroke

Row	Study PMID	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
81	Ninomiya_2013_24267237	nd	HR	38	776	Ref				P trend	0.38

Appendix F
Observational results: hemorrhagic stroke

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure
2	He 2002 12495393	Health Professional Follow-up Study	Stroke, hemorrhagic	criteria of the national survey of stroke	Healthy	Healthy 40-75 yo men diagnosis of myocardial infarction, angina, stroke, transient ischemic attack, or peripheral arterial disease, or had undergone coronary artery surgery.	Men	106/43671 (0.24)	12 y	EPA+DHA	Intake
3	He 2002 12495393	Health Professional Follow-up Study	Stroke, hemorrhagic	criteria of the national survey of stroke	Healthy	Healthy 40-75 yo men diagnosis of myocardial infarction, angina, stroke, transient ischemic attack, or peripheral arterial disease, or had undergone coronary artery surgery.	Men	106/43671 (0.24)	12 y	EPA+DHA	Intake
4	He 2002 12495393	Health Professional Follow-up Study	Stroke, hemorrhagic	criteria of the national survey of stroke	Healthy	Healthy 40-75 yo men diagnosis of myocardial infarction, angina, stroke, transient ischemic attack, or peripheral arterial disease, or had undergone coronary artery surgery.	Men	106/43671 (0.24)	12 y	EPA+DHA	Intake
5	He 2002 12495393	Health Professional Follow-up Study	Stroke, hemorrhagic	criteria of the national survey of stroke	Healthy	Healthy 40-75 yo men diagnosis of myocardial infarction, angina, stroke, transient ischemic attack, or peripheral arterial disease, or had undergone coronary artery surgery.	Men	106/43671 (0.24)	12 y	EPA+DHA	Intake
6	He 2002 12495393	Health Professional Follow-up Study	Stroke, hemorrhagic	criteria of the national survey of stroke	Healthy	Healthy 40-75 yo men diagnosis of myocardial infarction, angina, stroke, transient ischemic attack, or peripheral arterial disease, or had undergone coronary artery surgery.	Men	106/43671 (0.24)	12 y	EPA+DHA	Intake
7	Iso 2001 11176840	Nurses' Health Study	Stroke, hemorrhagic	nd	Healthy	Healthy 34-59 yo female nurses	Women	181/79839 (0.23)	14 y	EPA+DHA	Intake
8	Iso 2001 11176840	Nurses' Health Study	Stroke, hemorrhagic	nd	Healthy	Healthy 34-59 yo female nurses	Women	181/79839 (0.23)	14 y	EPA+DHA	Intake
9	Iso 2001 11176840	Nurses' Health Study	Stroke, hemorrhagic	nd	Healthy	Healthy 34-59 yo female nurses	Women	181/79839 (0.23)	14 y	EPA+DHA	Intake
10	Iso 2001 11176840	Nurses' Health Study	Stroke, hemorrhagic	nd	Healthy	Healthy 34-59 yo female nurses	Women	181/79839 (0.23)	14 y	EPA+DHA	Intake
11	Iso 2001 11176840	Nurses' Health Study	Stroke, hemorrhagic	nd	Healthy	Healthy 34-59 yo female nurses	Women	181/79839 (0.23)	14 y	EPA+DHA	Intake
12	Levitan 2010 20332801	Swedish Mammography Study	Stroke, hemorrhagic	Hemorrhagic stroke	Healthy	Healthy, ages 49-83	All	233/34670 (0.67)	10.4 y	EPA+DHA	Intake
13	Levitan 2010 20332801	Swedish Mammography Study	Stroke, hemorrhagic	Hemorrhagic stroke	Healthy	Healthy, ages 49-83	All	233/34670 (0.67)	10.4 y	EPA+DHA	Intake
14	Levitan 2010 20332801	Swedish Mammography Study	Stroke, hemorrhagic	Hemorrhagic stroke	Healthy	Healthy, ages 49-83	All	233/34670 (0.67)	10.4 y	EPA+DHA	Intake
15	Levitan 2010 20332801	Swedish Mammography Study	Stroke, hemorrhagic	Hemorrhagic stroke	Healthy	Healthy, ages 49-83	All	233/34670 (0.67)	10.4 y	EPA+DHA	Intake
16	Levitan 2010 20332801	Swedish Mammography Study	Stroke, hemorrhagic	Hemorrhagic stroke	Healthy	Healthy, ages 49-83	All	233/34670 (0.67)	10.4 y	EPA+DHA	Intake
17	Fretts 2014 25159901	Cardiovascular Health Study	Stroke, hemorrhagic		Healthy	Healthy age >= 65y	All	59/2709 (2.18)	16y	ALA	Plasma

Appendix F
Observational results: hemorrhagic stroke

Row	Study PMID	Supplement	Adjustments	Quantile	n3 units	Quantile low	Quantile median
2	He 2002 12495393	No	BMI, physcial activity, hx hypertension, smoking status, aspirin use, fish oil, multivitamins, total calorie intake, total fat. Saturated fat, trans-unstaurated fat, alcohol, potassium, magnesium, total servings of fruits and vegatbles, and hypercholsterolemia at baseline.	Qt1	g/d	0	nd
3	He 2002 12495393	No	BMI, physcial activity, hx hypertension, smoking status, aspirin use, fish oil, multivitamins, total calorie intake, total fat. Saturated fat, trans-unstaurated fat, alcohol, potassium, magnesium, total servings of fruits and vegatbles, and hypercholsterolemia at baseline.	Qt2	g/d	0.05	nd
4	He 2002 12495393	No	BMI, physcial activity, hx hypertension, smoking status, aspirin use, fish oil, multivitamins, total calorie intake, total fat. Saturated fat, trans-unstaurated fat, alcohol, potassium, magnesium, total servings of fruits and vegatbles, and hypercholsterolemia at baseline.	Qt3	g/d	0.2	nd
5	He 2002 12495393	No	BMI, physcial activity, hx hypertension, smoking status, aspirin use, fish oil, multivitamins, total calorie intake, total fat. Saturated fat, trans-unstaurated fat, alcohol, potassium, magnesium, total servings of fruits and vegatbles, and hypercholsterolemia at baseline.	Qt4	g/d	0.4	nd
6	He 2002 12495393	No	BMI, physcial activity, hx hypertension, smoking status, aspirin use, fish oil, multivitamins, total calorie intake, total fat. Saturated fat, trans-unstaurated fat, alcohol, potassium, magnesium, total servings of fruits and vegatbles, and hypercholsterolemia at baseline.	Qt5	g/d	0.6	nd
7	Iso 2001 11176840	no	joules (continuous), BMI, alcohol intake, menopausal status and postmenopausal hormone use, vigorous exercise, usual aspirin use, multivitamin use, history of HTN, frequency of total fruit and vegetable servings and for nutrient intake of saturated fat, trans-unsaturated fat, linoleic acid, animal protein, calcium	Qt1	g/d	nd	0.077
8	Iso 2001 11176840	no	joules (continuous), BMI, alcohol intake, menopausal status and postmenopausal hormone use, vigorous exercise, usual aspirin use, multivitamin use, history of HTN, frequency of total fruit and vegetable servings and for nutrient intake of saturated fat, trans-unsaturated fat, linoleic acid, animal protein, calcium	Qt2	g/d	nd	0.118
9	Iso 2001 11176840	no	joules (continuous), BMI, alcohol intake, menopausal status and postmenopausal hormone use, vigorous exercise, usual aspirin use, multivitamin use, history of HTN, frequency of total fruit and vegetable servings and for nutrient intake of saturated fat, trans-unsaturated fat, linoleic acid, animal protein, calcium	Qt3	g/d	nd	0.171
10	Iso 2001 11176840	no	joules (continuous), BMI, alcohol intake, menopausal status and postmenopausal hormone use, vigorous exercise, usual aspirin use, multivitamin use, history of HTN, frequency of total fruit and vegetable servings and for nutrient intake of saturated fat, trans-unsaturated fat, linoleic acid, animal protein, calcium	Qt4	g/d	nd	0.221
11	Iso 2001 11176840	no	joules (continuous), BMI, alcohol intake, menopausal status and postmenopausal hormone use, vigorous exercise, usual aspirin use, multivitamin use, history of HTN, frequency of total fruit and vegetable servings and for nutrient intake of saturated fat, trans-unsaturated fat, linoleic acid, animal protein, calcium	Qt5	g/d	nd	0.481
12	Levitan 2010 20332801	yes	We adjusted for BMI (linear), physical activity (linear), energy intake (linear), alcohol consumption (linear), fiber consumption (linear), sodium consumption (linear), daily servings of red or processed meat (linear), education (less than high school, high school, university), family history of myocardial infarction at <60 years (yes, no), cigarette smoking (current, past, never), living alone (yes, no), postmenopausal hormone use (yes, no), self-reported history of hypertension (yes, no) and self-reported history of high cholesterol (yes, no).	Qt1	mg/d	nd	131
13	Levitan 2010 20332801	yes	We adjusted for BMI (linear), physical activity (linear), energy intake (linear), alcohol consumption (linear), fiber consumption (linear), sodium consumption (linear), daily servings of red or processed meat (linear), education (less than high school, high school, university), family history of myocardial infarction at <60 years (yes, no), cigarette smoking (current, past, never), living alone (yes, no), postmenopausal hormone use (yes, no), self-reported history of hypertension (yes, no) and self-reported history of high cholesterol (yes, no).	Qt2	mg/d	nd	222
14	Levitan 2010 20332801	yes	We adjusted for BMI (linear), physical activity (linear), energy intake (linear), alcohol consumption (linear), fiber consumption (linear), sodium consumption (linear), daily servings of red or processed meat (linear), education (less than high school, high school, university), family history of myocardial infarction at <60 years (yes, no), cigarette smoking (current, past, never), living alone (yes, no), postmenopausal hormone use (yes, no), self-reported history of hypertension (yes, no) and self-reported history of high cholesterol (yes, no).	Qt3	mg/d	nd	289
15	Levitan 2010 20332801	yes	We adjusted for BMI (linear), physical activity (linear), energy intake (linear), alcohol consumption (linear), fiber consumption (linear), sodium consumption (linear), daily servings of red or processed meat (linear), education (less than high school, high school, university), family history of myocardial infarction at <60 years (yes, no), cigarette smoking (current, past, never), living alone (yes, no), postmenopausal hormone use (yes, no), self-reported history of hypertension (yes, no) and self-reported history of high cholesterol (yes, no).	Qt4	mg/d	nd	370
16	Levitan 2010 20332801	yes	We adjusted for BMI (linear), physical activity (linear), energy intake (linear), alcohol consumption (linear), fiber consumption (linear), sodium consumption (linear), daily servings of red or processed meat (linear), education (less than high school, high school, university), family history of myocardial infarction at <60 years (yes, no), cigarette smoking (current, past, never), living alone (yes, no), postmenopausal hormone use (yes, no), self-reported history of hypertension (yes, no) and self-reported history of high cholesterol (yes, no).	Qt5	mg/d	nd	559
17	Fretts 2014 25159901	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt1	% FA	0.05	0.09

Appendix F
Observational results: hemorrhagic stroke

Row	Study PMID	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
2	He 2002 12495393	<0.05	RR	4	nd	19741	Reference group			p trend	0.87
3	He 2002 12495393	<0.2	RR	41	nd	155579	1.29	0.45	3.75		
4	He 2002 12495393	<0.4	RR	37	nd	175161	1.02	0.35	3		
5	He 2002 12495393	<0.6	RR	13	nd	68003	0.89	0.27	2.87		
6	He 2002 12495393	>=0.6	RR	11	nd	43539	1.14	0.34	3.84		
7	Iso 2001 11176840	nd	RR	48	nd	nd	Reference group			P trend	0.44
8	Iso 2001 11176840	nd	RR	41	nd	nd	0.94	0.61	1.43		
9	Iso 2001 11176840	nd	RR	30	nd	nd	0.66	0.41	1.05		
10	Iso 2001 11176840	nd	RR	36	nd	nd	0.93	0.58	1.49		
11	Iso 2001 11176840	nd	RR	26	nd	nd	0.76	0.43	1.37		
12	Levitan 2010 20332801	nd	RR	51	nd	70855	Reference group			P trend	0.16
13	Levitan 2010 20332801	nd	RR	40	nd	72278	0.82	0.66	1.41		
14	Levitan 2010 20332801	nd	RR	50	nd	72639	1.06	0.56	1.27		
15	Levitan 2010 20332801	nd	RR	54	nd	72317	1.09	0.44	1.07		
16	Levitan 2010 20332801	nd	RR	38	nd	70924	0.68	0.58	1.34		
17	Fretts 2014 25159901	0.11	HR	11	nd	6208	Reference group			P trend	0.83

Appendix F
Observational results: hemorrhagic stroke

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure
18	Fretts 2014 25159901	Cardiovascular Health Study	Stroke, hemorrhagic		Healthy	Healthy age >= 65y	All	59/2709 (2.18)	16y	ALA	Plasma
19	Fretts 2014 25159901	Cardiovascular Health Study	Stroke, hemorrhagic		Healthy	Healthy age >= 65y	All	59/2709 (2.18)	16y	ALA	Plasma
20	Fretts 2014 25159901	Cardiovascular Health Study	Stroke, hemorrhagic		Healthy	Healthy age >= 65y	All	59/2709 (2.18)	16y	ALA	Plasma
21	Fretts 2014 25159901	Cardiovascular Health Study	Stroke, hemorrhagic		Healthy	Healthy age >= 65y	All	59/2709 (2.18)	16y	ALA	Plasma
22	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, hemorrhagic		Healthy	Healthy age >= 65y	All	65/3941 (1.65)	16y	EPA	Plasma
23	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, hemorrhagic		Healthy	Healthy age >= 65y	All	65/3941 (1.65)	16y	EPA	Plasma
24	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, hemorrhagic		Healthy	Healthy age >= 65y	All	65/3941 (1.65)	16y	EPA	Plasma
25	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, hemorrhagic		Healthy	Healthy age >= 65y	All	65/3941 (1.65)	16y	EPA	Plasma
26	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, hemorrhagic		Healthy	Healthy age >= 65y	All	65/3941 (1.65)	16y	EPA	Plasma
27	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, hemorrhagic		Healthy	Healthy age >= 65y	All	65/3941 (1.65)	12y	ALA	Intake
28	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, hemorrhagic		Healthy	Healthy age >= 65y	All	65/3941 (1.65)	12y	ALA	Intake
29	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, hemorrhagic		Healthy	Healthy age >= 65y	All	65/3941 (1.65)	12y	ALA	Intake
30	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, hemorrhagic		Healthy	Healthy age >= 65y	All	65/3941 (1.65)	12y	ALA	Intake
31	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, hemorrhagic		Healthy	Healthy age >= 65y	All	65/3941 (1.65)	12y	ALA	Intake
32	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, hemorrhagic		Healthy	Healthy age >= 65y	All	65/3941 (1.65)	16y	DPA	Plasma
33	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, hemorrhagic		Healthy	Healthy age >= 65y	All	65/3941 (1.65)	16y	DPA	Plasma
34	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, hemorrhagic		Healthy	Healthy age >= 65y	All	65/3941 (1.65)	16y	DPA	Plasma
35	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, hemorrhagic		Healthy	Healthy age >= 65y	All	65/3941 (1.65)	16y	DPA	Plasma
36	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, hemorrhagic		Healthy	Healthy age >= 65y	All	65/3941 (1.65)	16y	DPA	Plasma
37	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, hemorrhagic		Healthy	Healthy age >= 65y	All	65/3941 (1.65)	16y	All n-3	Plasma

Appendix F
Observational results: hemorrhagic stroke

Row	Study PMID	Supplement	Adjustments	Quantile	n3 units	Quantile low	Quantile median
18	Fretts 2014 25159901	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt2	% FA	0.11	0.12
19	Fretts 2014 25159901	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt3	% FA	0.13	0.14
20	Fretts 2014 25159901	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt4	% FA	0.15	0.17
21	Fretts 2014 25159901	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt5	% FA	0.19	0.22
22	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt1	% FA	nd	0.3
23	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt2	% FA	nd	0.41
24	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt3	% FA	nd	0.51
25	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt4	% FA	nd	0.64
26	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt5	% FA	nd	0.92
27	Mozaffarian 2013 23546563	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt1	% fat intake	0.39	1.33
28	Mozaffarian 2013 23546563	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt2	% fat intake	1.45	1.56
29	Mozaffarian 2013 23546563	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt3	% fat intake	1.65	1.76
30	Mozaffarian 2013 23546563	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt4	% fat intake	1.87	2
31	Mozaffarian 2013 23546563	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt5	% fat intake	2.17	2.44
32	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt1	% FA	nd	0.63
33	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt2	% FA	nd	0.75
34	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt3	% FA	nd	0.82
35	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt4	% FA	nd	0.91
36	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt5	% FA	nd	1.04
37	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt1	% FA	nd	3.17

Appendix F
Observational results: hemorrhagic stroke

Row	Study PMID	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
18	Fretts 2014 25159901	0.13	HR	10	nd	5792	1.01	0.42	2.43		
19	Fretts 2014 25159901	0.15	HR	15	nd	6026	1.45	0.65	3.27		
20	Fretts 2014 25159901	0.19	HR	11	nd	6132	0.94	0.39	2.26		
21	Fretts 2014 25159901	0.47	HR	12	nd	6589	0.95	0.4	2.25		
22	Mozaffarian 2013 23546563	nd	HR	nd	nd	nd	Reference group			P trend	0.32
23	Mozaffarian 2013 23546563	nd	HR	nd	nd	nd	1.14	0.56	2.32		
24	Mozaffarian 2013 23546563	nd	HR	nd	nd	nd	1	0.47	2.14		
25	Mozaffarian 2013 23546563	nd	HR	nd	nd	nd	0.9	0.41	1.99		
26	Mozaffarian 2013 23546563	nd	HR	nd	nd	nd	0.7	0.3	1.67		
27	Mozaffarian 2013 23546563	1.45	HR	8	nd	4691	Reference group			P trend	0.16
28	Mozaffarian 2013 23546563	1.65	HR	8	nd	4785	1.19	0.41	3.44		
29	Mozaffarian 2013 23546563	1.87	HR	15	nd	4891	2.12	0.81	5.54		
30	Mozaffarian 2013 23546563	2.17	HR	10	nd	4997	1.52	0.54	4.24		
31	Mozaffarian 2013 23546563	4.88	HR	15	nd	5380	1.96	0.73	5.27		
32	Mozaffarian 2013 23546563	nd	HR	nd	nd	nd	Reference group			P trend	0.39
33	Mozaffarian 2013 23546563	nd	HR	nd	nd	nd	0.58	0.28	1.23		
34	Mozaffarian 2013 23546563	nd	HR	nd	nd	nd	0.33	0.14	0.8		
35	Mozaffarian 2013 23546563	nd	HR	nd	nd	nd	0.75	0.37	1.51		
36	Mozaffarian 2013 23546563	nd	HR	nd	nd	nd	0.66	0.32	1.35		
37	Mozaffarian 2013 23546563	nd	HR	nd	nd	nd	Reference group			P trend	0.86

Appendix F
Observational results: hemorrhagic stroke

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure
38	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, hemorrhagic		Healthy	Healthy age >= 65y	All	65/3941 (1.65)	16y	All n-3	Plasma
39	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, hemorrhagic		Healthy	Healthy age >= 65y	All	65/3941 (1.65)	16y	All n-3	Plasma
40	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, hemorrhagic		Healthy	Healthy age >= 65y	All	65/3941 (1.65)	16y	All n-3	Plasma
41	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, hemorrhagic		Healthy	Healthy age >= 65y	All	65/3941 (1.65)	16y	All n-3	Plasma
42	de Goede 2013 22633188	Cardiovascular Health Study	Stroke, hemorrhagic		Healthy	Healthy age >= 65y	All	50/100 (50)	16y	DHA	Plasma
43	de Goede 2013 22633188	Cardiovascular Health Study	Stroke, hemorrhagic		Healthy	Healthy age >= 65y	All	50/100 (50)	16y	DHA	Plasma
44	Lemaitre 2012 22743310	Cardiovascular Health Study	Stroke, hemorrhagic		Healthy	Healthy age >= 65y	All	nd	16y	DHA	Plasma
45	Lemaitre 2012 22743310	Cardiovascular Health Study	Stroke, hemorrhagic		Healthy	Healthy age >= 65y	All	nd	16y	DHA	Plasma
46	Lemaitre 2012 22743310	Cardiovascular Health Study	Stroke, hemorrhagic		Healthy	Healthy age >= 65y	All	nd	16y	DHA	Plasma
47	de Goede 2010 20335635	MORGEN	Stroke, hemorrhagic	hemorrhagic stroke	Healthy	adults 20-65 yr	All	nd	10.5 yr	ALA	Plasma
48	de Goede 2010 20335635	MORGEN	Stroke, hemorrhagic	hemorrhagic stroke	Healthy	adults 20-65 yr	All	nd	10.5 yr	EPA+DHA	Plasma
50	**Subgroup analyses**										
51	Levitan 2010 20332801	Swedish Mammography Study	Stroke, hemorrhagic	Hemorrhagic stroke	Healthy	Healthy, ages 49-83	Women	233/34670 (0.67)	10.4 y	ALA	Intake
52	Levitan 2010 20332801	Swedish Mammography Study	Stroke, hemorrhagic	Hemorrhagic stroke	Healthy	Healthy, ages 49-83	Women	233/34670 (0.67)	10.4 y	ALA	Intake
53	Levitan 2010 20332801	Swedish Mammography Study	Stroke, hemorrhagic	Hemorrhagic stroke	Healthy	Healthy, ages 49-83	Women	233/34670 (0.67)	10.4 y	ALA	Intake
54	Levitan 2010 20332801	Swedish Mammography Study	Stroke, hemorrhagic	Hemorrhagic stroke	Healthy	Healthy, ages 49-83	Women	233/34670 (0.67)	10.4 y	ALA	Intake

Appendix F
Observational results: hemorrhagic stroke

Row	Study PMID	Supplement	Adjustments	Quantile	n3 units	Quantile low	Quantile median
38	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt2	% FA	nd	3.72
39	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt3	% FA	nd	4.21
40	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt4	% FA	nd	4.8
41	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt5	% FA	nd	6.04
42	de Goede 2013 22633188	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt1	% FA	nd	1.95
43	de Goede 2013 22633188	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt2	% FA	nd	2.44
44	Lemaitre 2012 22743310	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt3	% FA	nd	2.87
45	Lemaitre 2012 22743310	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt4	% FA	nd	3.36
46	Lemaitre 2012 22743310	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt5	% FA	nd	4.34
47	de Goede 2010 20335635	No	matched for age, gender, and enrollment data + smoking + BMI + education level + alcohol intake + diabetes + hypertension + hypercholesteroemia		% FA	nd	Cases: 0.54 (SD = 0.14), Controls: 0.54 (SD = 0.16)
48	de Goede 2010 20335635	No	matched for age, gender, and enrollment data + smoking + BMI + education level + alcohol intake + diabetes + hypertension + hypercholesteroemia		% FA	nd	Cases: 1.29 (SD = 0.78), Controls: 1.12 (SD = 0.40)
50	**Subgroup analyses**						
51	Levitan 2010 20332801	yes	We adjusted for BMI (linear), physical activity (linear), energy intake (linear), alcohol consumption (linear), fiber consumption (linear), sodium consumption (linear), daily servings of red or processed meat (linear), education (less than high school, high school, university), family history of myocardial infarction at <60 years (yes, no), cigarette smoking (current, past, never), living alone (yes, no), postmenopausal hormone use (yes, no), self-reported history of hypertension (yes, no) and self-reported history of high cholesterol (yes, no).	Qt1	g/d	nd	0.9
52	Levitan 2010 20332801	yes	We adjusted for BMI (linear), physical activity (linear), energy intake (linear), alcohol consumption (linear), fiber consumption (linear), sodium consumption (linear), daily servings of red or processed meat (linear), education (less than high school, high school, university), family history of myocardial infarction at <60 years (yes, no), cigarette smoking (current, past, never), living alone (yes, no), postmenopausal hormone use (yes, no), self-reported history of hypertension (yes, no) and self-reported history of high cholesterol (yes, no).	Qt2	g/d	nd	1
53	Levitan 2010 20332801	yes	We adjusted for BMI (linear), physical activity (linear), energy intake (linear), alcohol consumption (linear), fiber consumption (linear), sodium consumption (linear), daily servings of red or processed meat (linear), education (less than high school, high school, university), family history of myocardial infarction at <60 years (yes, no), cigarette smoking (current, past, never), living alone (yes, no), postmenopausal hormone use (yes, no), self-reported history of hypertension (yes, no) and self-reported history of high cholesterol (yes, no).	Qt3	g/d	nd	1.1
54	Levitan 2010 20332801	yes	We adjusted for BMI (linear), physical activity (linear), energy intake (linear), alcohol consumption (linear), fiber consumption (linear), sodium consumption (linear), daily servings of red or processed meat (linear), education (less than high school, high school, university), family history of myocardial infarction at <60 years (yes, no), cigarette smoking (current, past, never), living alone (yes, no), postmenopausal hormone use (yes, no), self-reported history of hypertension (yes, no) and self-reported history of high cholesterol (yes, no).	Qt4	g/d	nd	1.3

Appendix F
Observational results: hemorrhagic stroke

Row	Study PMID	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
38	Mozaffarian 2013 23546563	nd	HR	nd	nd	nd	1.03	0.45	2.35		
39	Mozaffarian 2013 23546563	nd	HR	nd	nd	nd	1.81	0.86	3.82		
40	Mozaffarian 2013 23546563	nd	HR	nd	nd	nd	0.74	0.29	1.88		
41	Mozaffarian 2013 23546563	nd	HR	nd	nd	nd	1.23	0.53	2.89		
42	de Goede 2013 22633188	nd	HR	nd	nd	nd	Reference group			P trend	0.9
43	de Goede 2013 22633188	nd	HR	nd	nd	nd	1.41	0.64	3.09		
44	Lemaitre 2012 22743310	nd	HR	nd	nd	nd	1.61	0.75	3.46		
45	Lemaitre 2012 22743310	nd	HR	nd	nd	nd	0.63	0.24	1.66		
46	Lemaitre 2012 22743310	nd	HR	nd	nd	nd	1.24	0.52	2.94		
47	de Goede 2010 20335635	nd	OR	nd	nd	nd	0.73	0.4	1.32		0.86
48	de Goede 2010 20335635	nd	OR	nd	nd	nd	1.08	0.75	1.57		0.45
50	**Subgroup analyses**										
51	Levitan 2010 20332801	nd	RR	58	nd	71329	Reference group			P trend	0.37
52	Levitan 2010 20332801	nd	RR	39	nd	72366	0.68	0.54	1.25		
53	Levitan 2010 20332801	nd	RR	48	nd	71644	0.86	0.71	1.59		
54	Levitan 2010 20332801	nd	RR	46	nd	72237	0.82	0.73	1.63		

Appendix F
Observational results: hemorrhagic stroke

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure
55	Levitan 2010 20332801	Swedish Mammography Study	Stroke, hemorrhagic	Hemorrhagic stroke	Healthy	Healthy, ages 49-83	Women	233/34670 (0.67)	10.4 y	ALA	Intake
56	de Goede 2010 20335635	MORGEN	Stroke, hemorrhagic	Hemorrhagic Stroke	Healthy	Healthy 20-65 yo	Women	nd	10.5 y	EPA+DHA	Intake
57	de Goede 2010 20335635	MORGEN	Stroke, hemorrhagic	Hemorrhagic Stroke	Healthy	Healthy 20-65 yo	Women	nd	10.5 y	EPA+DHA	Intake
58	de Goede 2010 20335635	MORGEN	Stroke, hemorrhagic	Hemorrhagic Stroke	Healthy	Healthy 20-65 yo	Women	nd	10.5 y	EPA+DHA	Intake
59	de Goede 2010 20335635	MORGEN	Stroke, hemorrhagic	Hemorrhagic Stroke	Healthy	Healthy 20-65 yo	Women	nd	10.5 y	EPA+DHA	Intake
60	de Goede 2010 20335635	MORGEN	Stroke, hemorrhagic	Hemorrhagic Stroke	Healthy	Healthy 20-65 yo	Men	nd	10.5 y	EPA+DHA	Intake
61	de Goede 2010 20335635	MORGEN	Stroke, hemorrhagic	Hemorrhagic Stroke	Healthy	Healthy 20-65 yo	Men	nd	10.5 y	EPA+DHA	Intake
62	de Goede 2010 20335635	MORGEN	Stroke, hemorrhagic	Hemorrhagic Stroke	Healthy	Healthy 20-65 yo	Men	nd	10.5 y	EPA+DHA	Intake
63	de Goede 2010 20335635	MORGEN	Stroke, hemorrhagic	Hemorrhagic Stroke	Healthy	Healthy 20-65 yo	Men	nd	10.5 y	EPA+DHA	Intake

Appendix F
Observational results: hemorrhagic stroke

Row	Study PMID	Supplement	Adjustments	Quantile	n3 units	Quantile low	Quantile median
55	Levitan 2010 20332801	yes	We adjusted for BMI (linear), physical activity (linear), energy intake (linear), alcohol consumption (linear), fiber consumption (linear), sodium consumption (linear), daily servings of red or processed meat (linear), education (less than high school, high school, university), family history of myocardial infarction at <60 years (yes, no), cigarette smoking (current, past, never), living alone (yes, no), postmenopausal hormone use (yes, no), self-reported history of hypertension (yes, no) and self-reported history of high cholesterol (yes, no).	Qt5	g/d	nd	1.5
56	de Goede 2010 20335635	No	age, smoking, BMI, educational level, parental history of myocardial infarction, alcohol intake, total energy intake, dietary fiber, vit C, beta-careotene, SFA, TFA, MFA, LA, ALA	Qt1	mg/d	nd	36
57	de Goede 2010 20335635	No	age, smoking, BMI, educational level, parental history of myocardial infarction, alcohol intake, total energy intake, dietary fiber, vit C, beta-careotene, SFA, TFA, MFA, LA, ALA	Qt2	mg/d	57	77
58	de Goede 2010 20335635	No	age, smoking, BMI, educational level, parental history of myocardial infarction, alcohol intake, total energy intake, dietary fiber, vit C, beta-careotene, SFA, TFA, MFA, LA, ALA	Qt3	mg/d	107	142
59	de Goede 2010 20335635	No	age, smoking, BMI, educational level, parental history of myocardial infarction, alcohol intake, total energy intake, dietary fiber, vit C, beta-careotene, SFA, TFA, MFA, LA, ALA	Qt4	mg/d	nd	225
60	de Goede 2010 20335635	No	age, smoking, BMI, educational level, parental history of myocardial infarction, alcohol intake, total energy intake, dietary fiber, vit C, beta-careotene, SFA, TFA, MFA, LA, ALA	Qt1	mg/d	nd	44
61	de Goede 2010 20335635	No	age, smoking, BMI, educational level, parental history of myocardial infarction, alcohol intake, total energy intake, dietary fiber, vit C, beta-careotene, SFA, TFA, MFA, LA, ALA	Qt2	mg/d	66	89
62	de Goede 2010 20335635	No	age, smoking, BMI, educational level, parental history of myocardial infarction, alcohol intake, total energy intake, dietary fiber, vit C, beta-careotene, SFA, TFA, MFA, LA, ALA	Qt3	mg/d	119	157
63	de Goede 2010 20335635	No	age, smoking, BMI, educational level, parental history of myocardial infarction, alcohol intake, total energy intake, dietary fiber, vit C, beta-careotene, SFA, TFA, MFA, LA, ALA	Qt4	mg/d	nd	241

Appendix F
Observational results: hemorrhagic stroke

Row	Study PMID	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
55	Levitan 2010 20332801	nd	RR	42	nd	71437	0.77	0.43	1.07		
56	de Goede 2010 20335635	<57	HR	9	2770	nd	Reference group			P trend	.18
57	de Goede 2010 20335635	106	HR	7	2770	nd	.73	.27	2		
58	de Goede 2010 20335635	188	HR	10	2771	nd	1	.39	2.57		
59	de Goede 2010 20335635	>188	HR	5	2770	nd	.45	.14	1.42		
60	de Goede 2010 20335635	<66	HR	6	2247	nd	Reference group			P trend	.03
61	de Goede 2010 20335635	118	HR	7	2247	nd	1.22	.4	3.7		
62	de Goede 2010 20335635	198	HR	1	2247	nd	.16	.02	1.32		
63	de Goede 2010 20335635	>199	HR	2	2247	nd	.28	.05	1.46		

Appendix F:
Observational results: ischemic stroke

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure	Supplement
2	He 2002 12495393	Health Professional Follow-up Study	Stroke, ischemic	criteria of the national survey of stroke	Healthy	Healthy 40-75 yo men without diagnosis of myocardial infarction, angina, stroke, transient ischemic attack, or peripheral arterial disease, or had undergone coronary artery surgery.	Men	377/43671 (0.86)	12 y	EPA+DHA	Intake	No
3	He 2002 12495393	Health Professional Follow-up Study	Stroke, ischemic	criteria of the national survey of stroke	Healthy	Healthy 40-75 yo men without diagnosis of myocardial infarction, angina, stroke, transient ischemic attack, or peripheral arterial disease, or had undergone coronary artery surgery.	Men	377/43671 (0.86)	12 y	EPA+DHA	Intake	No
4	He 2002 12495393	Health Professional Follow-up Study	Stroke, ischemic	criteria of the national survey of stroke	Healthy	Healthy 40-75 yo men without diagnosis of myocardial infarction, angina, stroke, transient ischemic attack, or peripheral arterial disease, or had undergone coronary artery surgery.	Men	377/43671 (0.86)	12 y	EPA+DHA	Intake	No
5	He 2002 12495393	Health Professional Follow-up Study	Stroke, ischemic	criteria of the national survey of stroke	Healthy	Healthy 40-75 yo men without diagnosis of myocardial infarction, angina, stroke, transient ischemic attack, or peripheral arterial disease, or had undergone coronary artery surgery.	Men	377/43671 (0.86)	12 y	EPA+DHA	Intake	No
6	He 2002 12495393	Health Professional Follow-up Study	Stroke, ischemic	criteria of the national survey of stroke	Healthy	Healthy 40-75 yo men without diagnosis of myocardial infarction, angina, stroke, transient ischemic attack, or peripheral arterial disease, or had undergone coronary artery surgery.	Men	377/43671 (0.86)	12 y	EPA+DHA	Intake	No
7	Iso 2001 11176840	Nurses' Health Study	Stroke, ischemic		Healthy	Healthy 34-59 yo female nurses	Women	303/79839 (0.38)	14 y	EPA+DHA	Intake	no
8	Iso 2001 11176840	Nurses' Health Study	Stroke, ischemic		Healthy	Healthy 34-59 yo female nurses	Women	303/79839 (0.38)	14 y	EPA+DHA	Intake	no
9	Iso 2001 11176840	Nurses' Health Study	Stroke, ischemic		Healthy	Healthy 34-59 yo female nurses	Women	303/79839 (0.38)	14 y	EPA+DHA	Intake	no
10	Iso 2001 11176840	Nurses' Health Study	Stroke, ischemic		Healthy	Healthy 34-59 yo female nurses	Women	303/79839 (0.38)	14 y	EPA+DHA	Intake	no
11	Iso 2001 11176840	Nurses' Health Study	Stroke, ischemic		Healthy	Healthy 34-59 yo female nurses	Women	303/79839 (0.38)	14 y	EPA+DHA	Intake	no
12	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, ischemic		Healthy	Healthy age >= 65y	All	319/3941 (8.09)	16y	All n-3	Plasma	no
13	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, ischemic		Healthy	Healthy age >= 65y	All	319/3941 (8.09)	16y	All n-3	Plasma	no
14	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, ischemic		Healthy	Healthy age >= 65y	All	319/3941 (8.09)	16y	All n-3	Plasma	no
15	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, ischemic		Healthy	Healthy age >= 65y	All	319/3941 (8.09)	16y	All n-3	Plasma	no
16	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, ischemic		Healthy	Healthy age >= 65y	All	319/3941 (8.09)	16y	All n-3	Plasma	no

Appendix F:
Observational results: ischemic stroke

Row	Study PMID	Adjustments	Quantile	n3 units	Quantile low
2	He 2002 12495393	BMI, physcial activity, hx hypertension, smoking status, aspirin use, fish oil, multivitamins, total calorie intake, total fat. Saturated fat, trans-unstaurated fat, alcohol, potassium, magnesium, total servings of fruits and vegatbles, and hypercholsterolemia at baseline.	Qt1	g/d	0
3	He 2002 12495393	BMI, physcial activity, hx hypertension, smoking status, aspirin use, fish oil, multivitamins, total calorie intake, total fat. Saturated fat, trans-unstaurated fat, alcohol, potassium, magnesium, total servings of fruits and vegatbles, and hypercholsterolemia at baseline.	Qt2	g/d	0.05
4	He 2002 12495393	BMI, physcial activity, hx hypertension, smoking status, aspirin use, fish oil, multivitamins, total calorie intake, total fat. Saturated fat, trans-unstaurated fat, alcohol, potassium, magnesium, total servings of fruits and vegatbles, and hypercholsterolemia at baseline.	Qt3	g/d	0.2
5	He 2002 12495393	BMI, physcial activity, hx hypertension, smoking status, aspirin use, fish oil, multivitamins, total calorie intake, total fat. Saturated fat, trans-unstaurated fat, alcohol, potassium, magnesium, total servings of fruits and vegatbles, and hypercholsterolemia at baseline.	Qt4	g/d	0.4
6	He 2002 12495393	BMI, physcial activity, hx hypertension, smoking status, aspirin use, fish oil, multivitamins, total calorie intake, total fat. Saturated fat, trans-unstaurated fat, alcohol, potassium, magnesium, total servings of fruits and vegatbles, and hypercholsterolemia at baseline.	Qt5	g/d	0.6
7	Iso 2001 11176840	joules (continuous), BMI, alcohol intake, menopausal status and postmenopausal hormone use, vigorous exercise, usual aspirin use, multivitamin use, history of HTN, frequency of total fruit and vegetable servings and for nutrient intake of saturated fat, trans-unsaturated fat, linoleic acid, animal protein, calcium	Qt1	g/d	nd
8	Iso 2001 11176840	joules (continuous), BMI, alcohol intake, menopausal status and postmenopausal hormone use, vigorous exercise, usual aspirin use, multivitamin use, history of HTN, frequency of total fruit and vegetable servings and for nutrient intake of saturated fat, trans-unsaturated fat, linoleic acid, animal protein, calcium	Qt2	g/d	nd
9	Iso 2001 11176840	joules (continuous), BMI, alcohol intake, menopausal status and postmenopausal hormone use, vigorous exercise, usual aspirin use, multivitamin use, history of HTN, frequency of total fruit and vegetable servings and for nutrient intake of saturated fat, trans-unsaturated fat, linoleic acid, animal protein, calcium	Qt3	g/d	nd
10	Iso 2001 11176840	joules (continuous), BMI, alcohol intake, menopausal status and postmenopausal hormone use, vigorous exercise, usual aspirin use, multivitamin use, history of HTN, frequency of total fruit and vegetable servings and for nutrient intake of saturated fat, trans-unsaturated fat, linoleic acid, animal protein, calcium	Qt4	g/d	nd
11	Iso 2001 11176840	joules (continuous), BMI, alcohol intake, menopausal status and postmenopausal hormone use, vigorous exercise, usual aspirin use, multivitamin use, history of HTN, frequency of total fruit and vegetable servings and for nutrient intake of saturated fat, trans-unsaturated fat, linoleic acid, animal protein, calcium	Qt5	g/d	nd
12	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt1	% FA	nd
13	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt2	% FA	nd
14	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt3	% FA	nd
15	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt4	% FA	nd
16	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt5	% FA	nd

Appendix F:
Observational results: ischemic stroke

Row	Study PMID	Quantile median	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
2	He 2002 12495393	nd	<0.05	RR	24	nd	19741	Reference group			p trend	0.73
3	He 2002 12495393	nd	<0.2	RR	112	nd	155579	0.56	0.35	0.88		
4	He 2002 12495393	nd	<0.4	RR	147	nd	175161	0.63	0.4	0.98		
5	He 2002 12495393	nd	<0.6	RR	51	nd	68003	0.54	0.32	0.91		
6	He 2002 12495393	nd	>=0.6	RR	43	nd	43539	0.73	0.43	1.25		
7	Iso 2001 11176840	0.077	nd	RR	72	nd	nd	Reference group			P trend	0.28
8	Iso 2001 11176840	0.118	nd	RR	61	nd	nd	0.83	0.59	1.18		
9	Iso 2001 11176840	0.171	nd	RR	51	nd	nd	0.67	0.47	0.98		
10	Iso 2001 11176840	0.221	nd	RR	63	nd	nd	0.82	0.57	1.18		
11	Iso 2001 11176840	0.481	nd	RR	56	nd	nd	0.71	0.46	1.1		
12	Mozaffarian 2013 23546563	3.17	nd	HR	nd	nd	nd	Reference group			P trend	0.043
13	Mozaffarian 2013 23546563	3.72	nd	HR	nd	nd	nd	0.88	0.63	1.23		
14	Mozaffarian 2013 23546563	4.21	nd	HR	nd	nd	nd	0.77	0.54	1.08		
15	Mozaffarian 2013 23546563	4.8	nd	HR	nd	nd	nd	0.93	0.66	1.31		
16	Mozaffarian 2013 23546563	6.04	nd	HR	nd	nd	nd	0.63	0.43	0.94		

Appendix F:
Observational results: ischemic stroke

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure	Supplement
17	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, ischemic		Healthy	Healthy age >= 65y	All	319/3941 (8.09)	16y	DHA	Plasma	no
18	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, ischemic		Healthy	Healthy age >= 65y	All	319/3941 (8.09)	16y	DHA	Plasma	no
19	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, ischemic		Healthy	Healthy age >= 65y	All	319/3941 (8.09)	16y	DHA	Plasma	no
20	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, ischemic		Healthy	Healthy age >= 65y	All	319/3941 (8.09)	16y	DHA	Plasma	no
21	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, ischemic		Healthy	Healthy age >= 65y	All	319/3941 (8.09)	16y	DHA	Plasma	no
22	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, ischemic		Healthy	Healthy age >= 65y	All	319/3941 (8.09)	16y	EPA	Plasma	no
23	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, ischemic		Healthy	Healthy age >= 65y	All	319/3941 (8.09)	16y	EPA	Plasma	no
24	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, ischemic		Healthy	Healthy age >= 65y	All	319/3941 (8.09)	16y	EPA	Plasma	no
25	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, ischemic		Healthy	Healthy age >= 65y	All	319/3941 (8.09)	16y	EPA	Plasma	no
26	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, ischemic		Healthy	Healthy age >= 65y	All	319/3941 (8.09)	16y	EPA	Plasma	no
27	Fretts 2014 25159901	Cardiovascular Health Study	Stroke, ischemic		Healthy	Healthy age >= 65y	All	278/2583 (10.76)	12y	ALA	Intake	no
28	Fretts 2014 25159901	Cardiovascular Health Study	Stroke, ischemic		Healthy	Healthy age >= 65y	All	278/2583 (10.76)	12y	ALA	Intake	no
29	Fretts 2014 25159901	Cardiovascular Health Study	Stroke, ischemic		Healthy	Healthy age >= 65y	All	278/2583 (10.76)	12y	ALA	Intake	no
30	Fretts 2014 25159901	Cardiovascular Health Study	Stroke, ischemic		Healthy	Healthy age >= 65y	All	278/2583 (10.76)	12y	ALA	Intake	no
31	Fretts 2014 25159901	Cardiovascular Health Study	Stroke, ischemic		Healthy	Healthy age >= 65y	All	278/2583 (10.76)	12y	ALA	Intake	no
32	Fretts 2014 25159901	Cardiovascular Health Study	Stroke, ischemic		Healthy	Healthy age >= 65y	All	337/2709 (12.44)	16y	ALA	Plasma	no
33	Fretts 2014 25159901	Cardiovascular Health Study	Stroke, ischemic		Healthy	Healthy age >= 65y	All	337/2709 (12.44)	16y	ALA	Plasma	no
34	Fretts 2014 25159901	Cardiovascular Health Study	Stroke, ischemic		Healthy	Healthy age >= 65y	All	337/2709 (12.44)	16y	ALA	Plasma	no
35	Fretts 2014 25159901	Cardiovascular Health Study	Stroke, ischemic		Healthy	Healthy age >= 65y	All	337/2709 (12.44)	16y	ALA	Plasma	no
36	Fretts 2014 25159901	Cardiovascular Health Study	Stroke, ischemic		Healthy	Healthy age >= 65y	All	337/2709 (12.44)	16y	ALA	Plasma	no

Appendix F:
Observational results: ischemic stroke

Row	Study PMID	Adjustments	Quantile	n3 units	Quantile low
17	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt1	% FA	nd
18	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt2	% FA	nd
19	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt3	% FA	nd
20	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt4	% FA	nd
21	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt5	% FA	nd
22	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt1	% FA	nd
23	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt2	% FA	nd
24	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt3	% FA	nd
25	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt4	% FA	nd
26	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt5	% FA	nd
27	Fretts 2014 25159901	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt1	% fat intake	0.39
28	Fretts 2014 25159901	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt2	% fat intake	1.45
29	Fretts 2014 25159901	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt3	% fat intake	1.65
30	Fretts 2014 25159901	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt4	% fat intake	1.87
31	Fretts 2014 25159901	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt5	% fat intake	2.17
32	Fretts 2014 25159901	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt1	% FA	0.05
33	Fretts 2014 25159901	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt2	% FA	0.11
34	Fretts 2014 25159901	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt3	% FA	0.13
35	Fretts 2014 25159901	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt4	% FA	0.15
36	Fretts 2014 25159901	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt5	% FA	0.19

Appendix F:
Observational results: ischemic stroke

Row	Study PMID	Quantile median	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
17	Mozaffarian 2013 23546563	1.95	nd	HR	nd	nd	nd	Reference group			P trend	0.052
18	Mozaffarian 2013 23546563	2.44	nd	HR	nd	nd	nd	1.01	0.72	1.41		
19	Mozaffarian 2013 23546563	2.87	nd	HR	nd	nd	nd	1	0.72	1.4		
20	Mozaffarian 2013 23546563	3.36	nd	HR	nd	nd	nd	0.73	0.51	1.06		
21	Mozaffarian 2013 23546563	4.34	nd	HR	nd	nd	nd	0.74	0.5	1.1		
22	Mozaffarian 2013 23546563	0.3	nd	HR	nd	nd	nd	Reference group			P trend	0.74
23	Mozaffarian 2013 23546563	0.41	nd	HR	nd	nd	nd	0.99	0.7	1.41		
24	Mozaffarian 2013 23546563	0.51	nd	HR	nd	nd	nd	0.94	0.66	1.34		
25	Mozaffarian 2013 23546563	0.64	nd	HR	nd	nd	nd	0.83	0.58	1.2		
26	Mozaffarian 2013 23546563	0.92	nd	HR	nd	nd	nd	1.09	0.76	1.57		
27	Fretts 2014 25159901	1.33	1.45	HR	59	nd	4691	Reference group			P trend	0.29
28	Fretts 2014 25159901	1.56	1.65	HR	52	nd	4785	0.89	0.61	1.3		
29	Fretts 2014 25159901	1.76	1.87	HR	54	nd	4891	0.84	0.58	1.22		
30	Fretts 2014 25159901	2	2.17	HR	67	nd	4997	1.08	0.75	1.54		
31	Fretts 2014 25159901	2.44	4.88	HR	46	nd	5380	0.7	0.47	1.04		
32	Fretts 2014 25159901	0.09	0.11	HR	69	nd	6208	Reference group			P trend	0.72
33	Fretts 2014 25159901	0.12	0.13	HR	63	nd	5792	0.92	0.65	1.3		
34	Fretts 2014 25159901	0.14	0.15	HR	70	nd	6026	1.01	0.72	1.43		
35	Fretts 2014 25159901	0.17	0.19	HR	62	nd	6132	0.84	0.59	1.2		
36	Fretts 2014 25159901	0.22	0.47	HR	73	nd	6589	0.97	0.69	1.36		

Appendix F:
Observational results: ischemic stroke

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure	Supplement
37	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, ischemic		Healthy	Healthy age >= 65y	All	319/3941 (8.09)	16y	DPA	Plasma	no
38	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, ischemic		Healthy	Healthy age >= 65y	All	319/3941 (8.09)	16y	DPA	Plasma	no
39	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, ischemic		Healthy	Healthy age >= 65y	All	319/3941 (8.09)	16y	DPA	Plasma	no
40	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, ischemic		Healthy	Healthy age >= 65y	All	319/3941 (8.09)	16y	DPA	Plasma	no
41	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke, ischemic		Healthy	Healthy age >= 65y	All	319/3941 (8.09)	16y	DPA	Plasma	no
42	Yamagishi 2013 23920478	Atherosclerosis Risk in Communities Study	Stroke, ischemic	ischemic stroke	Healthy	white aged 45-64 free of histrory of stroke and or transient ischemic attack	All	168/3870 (4.34)	22	EPA+DHA+DPA	Cholesterol ester	Yes
43	Yamagishi 2013 23920478	Atherosclerosis Risk in Communities Study	Stroke, ischemic	ischemic stroke	Healthy	white aged 45-64 free of histrory of stroke and or transient ischemic attack	All	168/3870 (4.34)	22	EPA+DHA+DPA	Cholesterol ester	Yes
44	Yamagishi 2013 23920478	Atherosclerosis Risk in Communities Study	Stroke, ischemic	ischemic stroke	Healthy	white aged 45-64 free of histrory of stroke and or transient ischemic attack	All	168/3870 (4.34)	22	EPA+DHA+DPA	Cholesterol ester	Yes
45	Yamagishi 2013 23920478	Atherosclerosis Risk in Communities Study	Stroke, ischemic	ischemic stroke	Healthy	white aged 45-64 free of histrory of stroke and or transient ischemic attack	All	168/3870 (4.34)	22	EPA+DHA+DPA	Cholesterol ester	Yes
46	Yamagishi 2013 23920478	Atherosclerosis Risk in Communities Study	Stroke, ischemic	ischemic stroke	Healthy	white aged 45-64 free of histrory of stroke and or transient ischemic attack	All	168/3870 (4.34)	22	EPA+DHA+DPA	Phospholipid	Yes
47	Yamagishi 2013 23920478	Atherosclerosis Risk in Communities Study	Stroke, ischemic	ischemic stroke	Healthy	white aged 45-64 free of histrory of stroke and or transient ischemic attack	All	168/3870 (4.34)	22	EPA+DHA+DPA	Phospholipid	Yes
48	Yamagishi 2013 23920478	Atherosclerosis Risk in Communities Study	Stroke, ischemic	ischemic stroke	Healthy	white aged 45-64 free of histrory of stroke and or transient ischemic attack	All	168/3870 (4.34)	22	EPA+DHA+DPA	Phospholipid	Yes
49	Yamagishi 2013 23920478	Atherosclerosis Risk in Communities Study	Stroke, ischemic	ischemic stroke	Healthy	white aged 45-64 free of histrory of stroke and or transient ischemic attack	All	168/3870 (4.34)	22	EPA+DHA+DPA	Phospholipid	Yes
50	Yamagishi 2013 23920478	Atherosclerosis Risk in Communities Study	Stroke, ischemic	ischemic stroke	Healthy	white aged 45-64 free of histrory of stroke and or transient ischemic attack	All	168/3870 (4.34)	22	ALA	Cholesterol ester	Yes
51	Yamagishi 2013 23920478	Atherosclerosis Risk in Communities Study	Stroke, ischemic	ischemic stroke	Healthy	white aged 45-64 free of histrory of stroke and or transient ischemic attack	All	168/3870 (4.34)	22	ALA	Cholesterol ester	Yes
52	Yamagishi 2013 23920478	Atherosclerosis Risk in Communities Study	Stroke, ischemic	ischemic stroke	Healthy	white aged 45-64 free of histrory of stroke and or transient ischemic attack	All	168/3870 (4.34)	22	ALA	Phospholipid	Yes
53	Yamagishi 2013 23920478	Atherosclerosis Risk in Communities Study	Stroke, ischemic	ischemic stroke	Healthy	white aged 45-64 free of histrory of stroke and or transient ischemic attack	All	168/3870 (4.34)	22	ALA	Phospholipid	Yes
54	Yamagishi 2013 23920478	Atherosclerosis Risk in Communities Study	Stroke, ischemic	ischemic stroke	Healthy	white aged 45-64 free of histrory of stroke and or transient ischemic attack	All	168/3870 (4.34)	22	EPA	Cholesterol ester	Yes
55	Yamagishi 2013 23920478	Atherosclerosis Risk in Communities Study	Stroke, ischemic	ischemic stroke	Healthy	white aged 45-64 free of histrory of stroke and or transient ischemic attack	All	168/3870 (4.34)	22	EPA	Cholesterol ester	Yes
56	Yamagishi 2013 23920478	Atherosclerosis Risk in Communities Study	Stroke, ischemic	ischemic stroke	Healthy	white aged 45-64 free of histrory of stroke and or transient ischemic attack	All	168/3870 (4.34)	22	EPA	Phospholipid	Yes
57	Yamagishi 2013 23920478	Atherosclerosis Risk in Communities Study	Stroke, ischemic	ischemic stroke	Healthy	white aged 45-64 free of histrory of stroke and or transient ischemic attack	All	168/3870 (4.34)	22	EPA	Phospholipid	Yes
58	Yamagishi 2013 23920478	Atherosclerosis Risk in Communities Study	Stroke, ischemic	ischemic stroke	Healthy	white aged 45-64 free of histrory of stroke and or transient ischemic attack	All	168/3870 (4.34)	22	DHA	Cholesterol ester	Yes
59	Yamagishi 2013 23920478	Atherosclerosis Risk in Communities Study	Stroke, ischemic	ischemic stroke	Healthy	white aged 45-64 free of histrory of stroke and or transient ischemic attack	All	168/3870 (4.34)	22	DHA	Cholesterol ester	Yes

Appendix F:
Observational results: ischemic stroke

Row	Study PMID	Adjustments	Quantile	n3 units	Quantile low
37	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt1	% FA	nd
38	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt2	% FA	nd
39	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt3	% FA	nd
40	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt4	% FA	nd
41	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt5	% FA	nd
42	Yamagishi 2013 23920478	adjusted for age, sex, smoking, cigerette-years and alcohol consumption	Qr1	% FA	0.22
43	Yamagishi 2013 23920478	adjusted for age, sex, smoking, cigerette-years and alcohol consumption	Qr2	% FA	0.78
44	Yamagishi 2013 23920478	adjusted for age, sex, smoking, cigerette-years and alcohol consumption	Qr3	% FA	0.94
45	Yamagishi 2013 23920478	adjusted for age, sex, smoking, cigerette-years and alcohol consumption	Qr4	% FA	1.15
46	Yamagishi 2013 23920478	adjusted for age, sex, smoking, cigerette-years and alcohol consumption	Qr1	% FA	1.51
47	Yamagishi 2013 23920478	adjusted for age, sex, smoking, cigerette-years and alcohol consumption	Qr2	% FA	3.58
48	Yamagishi 2013 23920478	adjusted for age, sex, smoking, cigerette-years and alcohol consumption	Qr3	% FA	4.12
49	Yamagishi 2013 23920478	adjusted for age, sex, smoking, cigerette-years and alcohol consumption	Qr4	% FA	4.75
50	Yamagishi 2013 23920478	adjusted for age and sex	Qt1	% FA	nd
51	Yamagishi 2013 23920478	adjusted for age and sex	Qt5	% FA	nd
52	Yamagishi 2013 23920478	adjusted for age and sex	Qt1	% FA	nd
53	Yamagishi 2013 23920478	adjusted for age and sex	Qt5	% FA	nd
54	Yamagishi 2013 23920478	adjusted for age and sex	Qt1	% FA	nd
55	Yamagishi 2013 23920478	adjusted for age and sex	Qt5	% FA	nd
56	Yamagishi 2013 23920478	adjusted for age and sex	Qt1	% FA	nd
57	Yamagishi 2013 23920478	adjusted for age and sex	Qt5	% FA	nd
58	Yamagishi 2013 23920478	adjusted for age and sex	Qt1	% FA	nd
59	Yamagishi 2013 23920478	adjusted for age and sex	Qt5	% FA	nd

Appendix F:
Observational results: ischemic stroke

Row	Study PMID	Quantile median	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
37	Mozaffarian 2013 23546563	0.63	nd	HR	nd	nd	nd	Reference group			P trend	0.22
38	Mozaffarian 2013 23546563	0.75	nd	HR	nd	nd	nd	0.77	0.55	1.08		
39	Mozaffarian 2013 23546563	0.82	nd	HR	nd	nd	nd	0.73	0.52	1.04		
40	Mozaffarian 2013 23546563	0.91	nd	HR	nd	nd	nd	0.78	0.56	1.1		
41	Mozaffarian 2013 23546563	1.04	nd	HR	nd	nd	nd	0.78	0.55	1.1		
42	Yamagishi 2013 23920478	nd	0.77	HR	nd	nd	nd	Reference group			P trend	0.52
43	Yamagishi 2013 23920478	nd	0.93	HR	nd	nd	nd	1.22	0.27	2		
44	Yamagishi 2013 23920478	nd	1.14	HR	nd	nd	nd	1.07	0.07	1.97		
45	Yamagishi 2013 23920478	nd	6.02	HR	nd	nd	nd	1.21	0.21	2.01		
46	Yamagishi 2013 23920478	nd	3.57	HR	nd	nd	nd	Reference group			P trend	0.51
47	Yamagishi 2013 23920478	nd	4.11	HR	nd	nd	nd	1.06	0.1]	1.96		
48	Yamagishi 2013 23920478	nd	4.74	HR	nd	nd	nd	0.8	-0.2	1.8		
49	Yamagishi 2013 23920478	nd	13.5	HR	nd	nd	nd	0.94	0.24	1.94		
50	Yamagishi 2013 23920478	nd	nd	HR	nd	nd	nd	Reference group			P trend	0.61
51	Yamagishi 2013 23920478	nd	nd	HR	nd	nd	nd	1.14	0.76	1.72		
52	Yamagishi 2013 23920478	nd	nd	HR	nd	nd	nd	Reference group			P trend	0.16
53	Yamagishi 2013 23920478	nd	nd	HR	nd	nd	nd	1.29	0.82	2.02		
54	Yamagishi 2013 23920478	nd	nd	HR	nd	nd	nd	Reference group			P trend	0.39
55	Yamagishi 2013 23920478	nd	nd	HR	nd	nd	nd	1.16	0.76	1.76		
56	Yamagishi 2013 23920478	nd	nd	HR	nd	nd	nd	Reference group			P trend	0.37
57	Yamagishi 2013 23920478	nd	nd	HR	nd	nd	nd	1.18	0.78	1.78		
58	Yamagishi 2013 23920478	nd	nd	HR	nd	nd	nd	Reference group			P trend	0.07
59	Yamagishi 2013 23920478	nd	nd	HR	nd	nd	nd	0.7	0.45	1.08		

Appendix F:
Observational results: ischemic stroke

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure	Supplement
60	Yamagishi 2013 23920478	Atherosclerosis Risk in Communities Study	Stroke, ischemic	ischemic stroke	Healthy	white aged 45-64 free of histrory of stroke and or transient ischemic attack	All	168/3870 (4.34)	22	DHA	Phospholipid	Yes
61	Yamagishi 2013 23920478	Atherosclerosis Risk in Communities Study	Stroke, ischemic	ischemic stroke	Healthy	white aged 45-64 free of histrory of stroke and or transient ischemic attack	All	168/3870 (4.34)	22	DHA	Phospholipid	Yes
62	Gronroos 2012 22570739	Atherosclerosis Risk in Communities Study	Stroke, ischemic	ischemic stroke	Healthy	white aged 45-64 free of atrial fibrillation	All	400/3713 (10.77)	17.9	EPA+DHA	Intake	Yes
63	Gronroos 2012 22570739	Atherosclerosis Risk in Communities Study	Stroke, ischemic	ischemic stroke	Healthy	white aged 45-64 free of atrial fibrillation	All	400/3713 (10.77)	17.9	EPA+DHA	Intake	Yes
64	Gronroos 2012 22570739	Atherosclerosis Risk in Communities Study	Stroke, ischemic	ischemic stroke	Healthy	white aged 45-64 free of atrial fibrillation	All	400/3713 (10.77)	17.9	EPA+DHA	Intake	Yes
65	Gronroos 2012 22570739	Atherosclerosis Risk in Communities Study	Stroke, ischemic	ischemic stroke	Healthy	white aged 45-64 free of atrial fibrillation	All	400/3713 (10.77)	17.9	EPA+DHA	Intake	Yes
66	Gronroos 2012 22570739	Atherosclerosis Risk in Communities Study	Stroke, ischemic	ischemic stroke	Healthy	white aged 45-64 free of atrial fibrillation	All	400/3713 (10.77)	17.9	DHA	Intake	Yes
67	Gronroos 2012 22570739	Atherosclerosis Risk in Communities Study	Stroke, ischemic	ischemic stroke	Healthy	white aged 45-64 free of atrial fibrillation	All	400/3713 (10.77)	17.9	DHA	Intake	Yes
68	Gronroos 2012 22570739	Atherosclerosis Risk in Communities Study	Stroke, ischemic	ischemic stroke	Healthy	white aged 45-64 free of atrial fibrillation	All	400/3713 (10.77)	17.9	DHA	Intake	Yes
69	Gronroos 2012 22570739	Atherosclerosis Risk in Communities Study	Stroke, ischemic	ischemic stroke	Healthy	white aged 45-64 free of atrial fibrillation	All	400/3713 (10.77)	17.9	DHA	Intake	Yes
70	Gronroos 2012 22570739	Atherosclerosis Risk in Communities Study	Stroke, ischemic	ischemic stroke	Healthy	white aged 45-64 free of atrial fibrillation	All	400/3713 (10.77)	17.9	EPA	Intake	Yes
71	Gronroos 2012 22570739	Atherosclerosis Risk in Communities Study	Stroke, ischemic	ischemic stroke	Healthy	white aged 45-64 free of atrial fibrillation	All	400/3713 (10.77)	17.9	EPA	Intake	Yes
72	Gronroos 2012 22570739	Atherosclerosis Risk in Communities Study	Stroke, ischemic	ischemic stroke	Healthy	white aged 45-64 free of atrial fibrillation	All	400/3713 (10.77)	17.9	EPA	Intake	Yes
73	Gronroos 2012 22570739	Atherosclerosis Risk in Communities Study	Stroke, ischemic	ischemic stroke	Healthy	white aged 45-64 free of atrial fibrillation	All	400/3713 (10.77)	17.9	EPA	Intake	Yes
74	Gronroos 2012 22570739	Atherosclerosis Risk in Communities Study	Stroke, ischemic	ischemic stroke	Healthy	white aged 45-64 free of atrial fibrillation	All	400/3713 (10.77)	17.9	EPA+DHA	Phospholipid	Yes
75	Gronroos 2012 22570739	Atherosclerosis Risk in Communities Study	Stroke, ischemic	ischemic stroke	Healthy	white aged 45-64 free of atrial fibrillation	All	400/3713 (10.77)	17.9	EPA+DHA	Phospholipid	Yes
76	Gronroos 2012 22570739	Atherosclerosis Risk in Communities Study	Stroke, ischemic	ischemic stroke	Healthy	white aged 45-64 free of atrial fibrillation	All	400/3713 (10.77)	17.9	EPA+DHA	Phospholipid	Yes
77	Gronroos 2012 22570739	Atherosclerosis Risk in Communities Study	Stroke, ischemic	ischemic stroke	Healthy	white aged 45-64 free of atrial fibrillation	All	400/3713 (10.77)	17.9	EPA+DHA	Phospholipid	Yes
78	Gronroos 2012 22570739	Atherosclerosis Risk in Communities Study	Stroke, ischemic	ischemic stroke	Healthy	white aged 45-64 free of atrial fibrillation	All	400/3713 (10.77)	17.9	DHA	Phospholipid	Yes
79	Gronroos 2012 22570739	Atherosclerosis Risk in Communities Study	Stroke, ischemic	ischemic stroke	Healthy	white aged 45-64 free of atrial fibrillation	All	400/3713 (10.77)	17.9	DHA	Phospholipid	Yes
80	Gronroos 2012 22570739	Atherosclerosis Risk in Communities Study	Stroke, ischemic	ischemic stroke	Healthy	white aged 45-64 free of atrial fibrillation	All	400/3713 (10.77)	17.9	DHA	Phospholipid	Yes
81	Gronroos 2012 22570739	Atherosclerosis Risk in Communities Study	Stroke, ischemic	ischemic stroke	Healthy	white aged 45-64 free of atrial fibrillation	All	400/3713 (10.77)	17.9	DHA	Phospholipid	Yes

Appendix F:
Observational results: ischemic stroke

Row	Study PMID	Adjustments	Quantile	n3 units	Quantile low
60	Yamagishi 2013 23920478	adjusted for age and sex	Qt1	% FA	nd
61	Yamagishi 2013 23920478	adjusted for age and sex	Qt5	% FA	nd
62	Gronroos 2012 22570739	adjusted for center, age, race, sex, energy intake, BMI, education, exercise levels, smoking status and amount, alcohol intake, HDL-C, LDL-C, use of cholesterol lowering medications, systolic blood pressure, use of antihypertensive medications, diabetes, coronary heart disease, and ECG-defined left ventricular hypertrophy.	Qr1	% FA	nd
63	Gronroos 2012 22570739	adjusted for center, age, race, sex, energy intake, BMI, education, exercise levels, smoking status and amount, alcohol intake, HDL-C, LDL-C, use of cholesterol lowering medications, systolic blood pressure, use of antihypertensive medications, diabetes, coronary heart disease, and ECG-defined left ventricular hypertrophy.	Qr2	% FA	nd
64	Gronroos 2012 22570739	adjusted for center, age, race, sex, energy intake, BMI, education, exercise levels, smoking status and amount, alcohol intake, HDL-C, LDL-C, use of cholesterol lowering medications, systolic blood pressure, use of antihypertensive medications, diabetes, coronary heart disease, and ECG-defined left ventricular hypertrophy.	Qr3	% FA	nd
65	Gronroos 2012 22570739	adjusted for center, age, race, sex, energy intake, BMI, education, exercise levels, smoking status and amount, alcohol intake, HDL-C, LDL-C, use of cholesterol lowering medications, systolic blood pressure, use of antihypertensive medications, diabetes, coronary heart disease, and ECG-defined left ventricular hypertrophy.	Qr4	% FA	nd
66	Gronroos 2012 22570739	adjusted for center, age, race, sex, energy intake, BMI, education, exercise levels, smoking status and amount, alcohol intake, HDL-C, LDL-C, use of cholesterol lowering medications, systolic blood pressure, use of antihypertensive medications, diabetes, coronary heart disease, and ECG-defined left ventricular hypertrophy.	Qr1	% FA	nd
67	Gronroos 2012 22570739	adjusted for center, age, race, sex, energy intake, BMI, education, exercise levels, smoking status and amount, alcohol intake, HDL-C, LDL-C, use of cholesterol lowering medications, systolic blood pressure, use of antihypertensive medications, diabetes, coronary heart disease, and ECG-defined left ventricular hypertrophy.	Qr2	% FA	nd
68	Gronroos 2012 22570739	adjusted for center, age, race, sex, energy intake, BMI, education, exercise levels, smoking status and amount, alcohol intake, HDL-C, LDL-C, use of cholesterol lowering medications, systolic blood pressure, use of antihypertensive medications, diabetes, coronary heart disease, and ECG-defined left ventricular hypertrophy.	Qr3	% FA	nd
69	Gronroos 2012 22570739	adjusted for center, age, race, sex, energy intake, BMI, education, exercise levels, smoking status and amount, alcohol intake, HDL-C, LDL-C, use of cholesterol lowering medications, systolic blood pressure, use of antihypertensive medications, diabetes, coronary heart disease, and ECG-defined left ventricular hypertrophy.	Qr4	% FA	nd
70	Gronroos 2012 22570739	adjusted for center, age, race, sex, energy intake, BMI, education, exercise levels, smoking status and amount, alcohol intake, HDL-C, LDL-C, use of cholesterol lowering medications, systolic blood pressure, use of antihypertensive medications, diabetes, coronary heart disease, and ECG-defined left ventricular hypertrophy.	Qr1	% FA	nd
71	Gronroos 2012 22570739	adjusted for center, age, race, sex, energy intake, BMI, education, exercise levels, smoking status and amount, alcohol intake, HDL-C, LDL-C, use of cholesterol lowering medications, systolic blood pressure, use of antihypertensive medications, diabetes, coronary heart disease, and ECG-defined left ventricular hypertrophy.	Qr2	% FA	nd
72	Gronroos 2012 22570739	adjusted for center, age, race, sex, energy intake, BMI, education, exercise levels, smoking status and amount, alcohol intake, HDL-C, LDL-C, use of cholesterol lowering medications, systolic blood pressure, use of antihypertensive medications, diabetes, coronary heart disease, and ECG-defined left ventricular hypertrophy.	Qr3	% FA	nd
73	Gronroos 2012 22570739	adjusted for center, age, race, sex, energy intake, BMI, education, exercise levels, smoking status and amount, alcohol intake, HDL-C, LDL-C, use of cholesterol lowering medications, systolic blood pressure, use of antihypertensive medications, diabetes, coronary heart disease, and ECG-defined left ventricular hypertrophy.	Qr4	% FA	nd
74	Gronroos 2012 22570739	adjusted for age, sex, BMI, education, exercise levels, smoking status and amount, alcohol intake, HDL-C, LDL-C, use of cholesterol lowering medications, systolic blood pressure, use of antihypertensive medications, diabetes, coronary heart disease, and ECG-defined left ventricular hypertrophy.	Qr1	% FA	nd
75	Gronroos 2012 22570739	adjusted for age, sex, BMI, education, exercise levels, smoking status and amount, alcohol intake, HDL-C, LDL-C, use of cholesterol lowering medications, systolic blood pressure, use of antihypertensive medications, diabetes, coronary heart disease, and ECG-defined left ventricular hypertrophy.	Qr2	% FA	nd
76	Gronroos 2012 22570739	adjusted for age, sex, BMI, education, exercise levels, smoking status and amount, alcohol intake, HDL-C, LDL-C, use of cholesterol lowering medications, systolic blood pressure, use of antihypertensive medications, diabetes, coronary heart disease, and ECG-defined left ventricular hypertrophy.	Qr3	% FA	nd
77	Gronroos 2012 22570739	adjusted for age, sex, BMI, education, exercise levels, smoking status and amount, alcohol intake, HDL-C, LDL-C, use of cholesterol lowering medications, systolic blood pressure, use of antihypertensive medications, diabetes, coronary heart disease, and ECG-defined left ventricular hypertrophy.	Qr4	% FA	nd
78	Gronroos 2012 22570739	adjusted for age, sex, BMI, education, exercise levels, smoking status and amount, alcohol intake, HDL-C, LDL-C, use of cholesterol lowering medications, systolic blood pressure, use of antihypertensive medications, diabetes, coronary heart disease, and ECG-defined left ventricular hypertrophy.	Qr1	% FA	nd
79	Gronroos 2012 22570739	adjusted for age, sex, BMI, education, exercise levels, smoking status and amount, alcohol intake, HDL-C, LDL-C, use of cholesterol lowering medications, systolic blood pressure, use of antihypertensive medications, diabetes, coronary heart disease, and ECG-defined left ventricular hypertrophy.	Qr2	% FA	nd
80	Gronroos 2012 22570739	adjusted for age, sex, BMI, education, exercise levels, smoking status and amount, alcohol intake, HDL-C, LDL-C, use of cholesterol lowering medications, systolic blood pressure, use of antihypertensive medications, diabetes, coronary heart disease, and ECG-defined left ventricular hypertrophy.	Qr3	% FA	nd
81	Gronroos 2012 22570739	adjusted for age, sex, BMI, education, exercise levels, smoking status and amount, alcohol intake, HDL-C, LDL-C, use of cholesterol lowering medications, systolic blood pressure, use of antihypertensive medications, diabetes, coronary heart disease, and ECG-defined left ventricular hypertrophy.	Qr4	% FA	nd

Appendix F:
Observational results: ischemic stroke

Row	Study PMID	Quantile median	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
60	Yamagishi 2013 23920478	nd	nd	HR	nd	nd	nd	Reference group			P trend	0.08
61	Yamagishi 2013 23920478	nd	nd	HR	nd	nd	nd	0.69	0.46	1.06		
62	Gronroos 2012 22570739	nd	nd	HR	402	nd	61943	Reference group			P trend	0.21
63	Gronroos 2012 22570739	nd	nd	HR	427	nd	62339	1.04	0.9	1.2		
64	Gronroos 2012 22570739	nd	nd	HR	409	nd	62270	1.06	0.91	1.23		
65	Gronroos 2012 22570739	nd	nd	HR	366	nd	63223	0.92	0.79	1.07		
66	Gronroos 2012 22570739	nd	nd	HR	404	nd	61750	Reference group			P trend	0.21
67	Gronroos 2012 22570739	nd	nd	HR	428	nd	62584	1.06	0.92	1.23		
68	Gronroos 2012 22570739	nd	nd	HR	410	nd	62134	1.05	0.9	1.22		
69	Gronroos 2012 22570739	nd	nd	HR	362	nd	63307	0.93	0.8	1.09		
70	Gronroos 2012 22570739	nd	nd	HR	412	nd	61962	Reference group			P trend	0.22
71	Gronroos 2012 22570739	nd	nd	HR	418	nd	62298	1.05	0.91	1.22		
72	Gronroos 2012 22570739	nd	nd	HR	392	nd	62701	1	0.86	1.16		
73	Gronroos 2012 22570739	nd	nd	HR	382	nd	62815	0.93	0.8	1.08		
74	Gronroos 2012 22570739	nd	nd	HR	112	nd	16114	Reference group			P trend	0.54
75	Gronroos 2012 22570739	nd	nd	HR	95	nd	16994	0.8	0.6	1.06		
76	Gronroos 2012 22570739	nd	nd	HR	93	nd	16829	0.81	0.61	1.08		
77	Gronroos 2012 22570739	nd	nd	HR	101	nd	17144	0.87	0.66	1.15		
78	Gronroos 2012 22570739	nd	nd	HR	117	nd	16118	Reference group			P trend	0.47
79	Gronroos 2012 22570739	nd	nd	HR	86	nd	16961	0.71	0.54	0.95		
80	Gronroos 2012 22570739	nd	nd	HR	99	nd	16849	0.82	0.62	1.08		
81	Gronroos 2012 22570739	nd	nd	HR	99	nd	17153	0.84	0.63	1.11		

Appendix F:
Observational results: ischemic stroke

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure	Supplement
82	Gronroos 2012 22570739	Atherosclerosis Risk in Communities Study	Stroke, ischemic	ischemic stroke	Healthy	white aged 45-64 free of atrial fibrillation	All	400/3713 (10.77)	17.9	EPA	Phospholipid	Yes
83	Gronroos 2012 22570739	Atherosclerosis Risk in Communities Study	Stroke, ischemic	ischemic stroke	Healthy	white aged 45-64 free of atrial fibrillation	All	400/3713 (10.77)	17.9	EPA	Phospholipid	Yes
84	Gronroos 2012 22570739	Atherosclerosis Risk in Communities Study	Stroke, ischemic	ischemic stroke	Healthy	white aged 45-64 free of atrial fibrillation	All	400/3713 (10.77)	17.9	EPA	Phospholipid	Yes
85	Gronroos 2012 22570739	Atherosclerosis Risk in Communities Study	Stroke, ischemic	ischemic stroke	Healthy	white aged 45-64 free of atrial fibrillation	All	400/3713 (10.77)	17.9	EPA	Phospholipid	Yes
86	de Goede 2013 22633188	MORGEN	Stroke, ischemic	ischemic stroke	Healthy	adults 20-65 yr	All	93/186 (50)	10.5 yr	ALA	Plasma	No
87	de Goede 2013 22633188	MORGEN	Stroke, ischemic	ischemic stroke	Healthy	adults 20-65 yr	All	93/186 (50)	10.5 yr	EPA+DHA	Plasma	No
88	de Goede 2011 21464993	MORGEN	Stroke, ischemic	Ischemic Stroke	Healthy	Healthy 20-65 yo	All	144/19896 (0.72)	10.5 y	ALA	Intake	No
89	de Goede 2011 21464993	MORGEN	Stroke, ischemic	Ischemic Stroke	Healthy	Healthy 20-65 yo	All	144/19896 (0.72)	10.5 y	ALA	Intake	No
90	de Goede 2011 21464993	MORGEN	Stroke, ischemic	Ischemic Stroke	Healthy	Healthy 20-65 yo	All	144/19896 (0.72)	10.5 y	ALA	Intake	No
91	de Goede 2011 21464993	MORGEN	Stroke, ischemic	Ischemic Stroke	Healthy	Healthy 20-65 yo	All	144/19896 (0.72)	10.5 y	ALA	Intake	No
92	de Goede 2011 21464993	MORGEN	Stroke, ischemic	Ischemic Stroke	Healthy	Healthy 20-65 yo	All	144/19896 (0.72)	10.5 y	ALA	Intake	No
94	**Subgroup analyses**											
95	de Goede 2012 22496770	MORGEN	Stroke, ischemic	Ischemic Stroke	Healthy	Healthy 20-65 yo	Women	nd/11081 (2.6 per 10,000 pt yrs)	10.5 y	EPA+DHA	Intake	No
96	de Goede 2012 22496770	MORGEN	Stroke, ischemic	Ischemic Stroke	Healthy	Healthy 20-65 yo	Women	nd/11081 (2.6 per 10,000 pt yrs)	10.5 y	EPA+DHA	Intake	No
97	de Goede 2012 22496770	MORGEN	Stroke, ischemic	Ischemic Stroke	Healthy	Healthy 20-65 yo	Women	nd/11081 (2.6 per 10,000 pt yrs)	10.5 y	EPA+DHA	Intake	No
98	de Goede 2012 22496770	MORGEN	Stroke, ischemic	Ischemic Stroke	Healthy	Healthy 20-65 yo	Women	nd/11081 (2.6 per 10,000 pt yrs)	10.5 y	EPA+DHA	Intake	No
99	de Goede 2012 22496770	MORGEN	Stroke, ischemic	Ischemic Stroke	Healthy	Healthy 20-65 yo	Men	nd/8988 (5.6 per 10,000 pt yrs)	10.5 y	EPA+DHA	Intake	No
100	de Goede 2012 22496770	MORGEN	Stroke, ischemic	Ischemic Stroke	Healthy	Healthy 20-65 yo	Men	nd/8988 (5.6 per 10,000 pt yrs)	10.5 y	EPA+DHA	Intake	No
101	de Goede 2012 22496770	MORGEN	Stroke, ischemic	Ischemic Stroke	Healthy	Healthy 20-65 yo	Men	nd/8988 (5.6 per 10,000 pt yrs)	10.5 y	EPA+DHA	Intake	No
102	de Goede 2012 22496770	MORGEN	Stroke, ischemic	Ischemic Stroke	Healthy	Healthy 20-65 yo	Men	nd/8988 (5.6 per 10,000 pt yrs)	10.5 y	EPA+DHA	Intake	No

Appendix F:
Observational results: ischemic stroke

Row	Study PMID	Adjustments	Quantile	n3 units	Quantile low
82	Gronroos 2012 22570739	adjusted for age, sex, BMI, education, exercise levels, smoking status and amount, alcohol intake, HDL-C, LDL-C, use of cholesterol lowering medications, systolic blood pressure, use of antihypertensive medications, diabetes, coronary heart disease, and ECG-defined left ventricular hypertrophy.	Qr1	% FA	nd
83	Gronroos 2012 22570739	adjusted for age, sex, BMI, education, exercise levels, smoking status and amount, alcohol intake, HDL-C, LDL-C, use of cholesterol lowering medications, systolic blood pressure, use of antihypertensive medications, diabetes, coronary heart disease, and ECG-defined left ventricular hypertrophy.	Qr2	% FA	nd
84	Gronroos 2012 22570739	adjusted for age, sex, BMI, education, exercise levels, smoking status and amount, alcohol intake, HDL-C, LDL-C, use of cholesterol lowering medications, systolic blood pressure, use of antihypertensive medications, diabetes, coronary heart disease, and ECG-defined left ventricular hypertrophy.	Qr3	% FA	nd
85	Gronroos 2012 22570739	adjusted for age, sex, BMI, education, exercise levels, smoking status and amount, alcohol intake, HDL-C, LDL-C, use of cholesterol lowering medications, systolic blood pressure, use of antihypertensive medications, diabetes, coronary heart disease, and ECG-defined left ventricular hypertrophy.	Qr4	% FA	nd
86	de Goede 2013 22633188	matched for age, gender, and enrollment data + smoking + BMI + education level + alcohol intake + diabetes + hypertension + hypercholesteroemia	all	% FA	nd
87	de Goede 2013 22633188	matched for age, gender, and enrollment data + smoking + BMI + education level + alcohol intake + diabetes + hypertension + hypercholesteroemia	all	% FA	nd
88	de Goede 2011 21464993	age, gender, BMI, total energy intake, cigarette smoking, education level, parental history of MI, alcohol intake, intake of vit C, beta-carotene, fiber, SFA, TFA, PUFA other than ALA	Qt1	g/d	nd
89	de Goede 2011 21464993	age, gender, BMI, total energy intake, cigarette smoking, education level, parental history of MI, alcohol intake, intake of vit C, beta-carotene, fiber, SFA, TFA, PUFA other than ALA	Qt2	g/d	nd
90	de Goede 2011 21464993	age, gender, BMI, total energy intake, cigarette smoking, education level, parental history of MI, alcohol intake, intake of vit C, beta-carotene, fiber, SFA, TFA, PUFA other than ALA	Qt3	g/d	nd
91	de Goede 2011 21464993	age, gender, BMI, total energy intake, cigarette smoking, education level, parental history of MI, alcohol intake, intake of vit C, beta-carotene, fiber, SFA, TFA, PUFA other than ALA	Qt4	g/d	nd
92	de Goede 2011 21464993	age, gender, BMI, total energy intake, cigarette smoking, education level, parental history of MI, alcohol intake, intake of vit C, beta-carotene, fiber, SFA, TFA, PUFA other than ALA	Qt5	g/d	nd
94	**Subgroup analyses**				
95	de Goede 2012 22496770	age, smoking, BMI, educational level, parental history of myocardial infarction, alcohol intake, total energy intake, dietary fiber, vit C, beta-careotene, SFA, TFA, MFA, LA, ALA	Qt1	mg/d	nd
96	de Goede 2012 22496770	age, smoking, BMI, educational level, parental history of myocardial infarction, alcohol intake, total energy intake, dietary fiber, vit C, beta-careotene, SFA, TFA, MFA, LA, ALA	Qt2	mg/d	57
97	de Goede 2012 22496770	age, smoking, BMI, educational level, parental history of myocardial infarction, alcohol intake, total energy intake, dietary fiber, vit C, beta-careotene, SFA, TFA, MFA, LA, ALA	Qt3	mg/d	107
98	de Goede 2012 22496770	age, smoking, BMI, educational level, parental history of myocardial infarction, alcohol intake, total energy intake, dietary fiber, vit C, beta-careotene, SFA, TFA, MFA, LA, ALA	Qt4	mg/d	nd
99	de Goede 2012 22496770	age, smoking, BMI, educational level, parental history of myocardial infarction, alcohol intake, total energy intake, dietary fiber, vit C, beta-careotene, SFA, TFA, MFA, LA, ALA	Qt1	mg/d	nd
100	de Goede 2012 22496770	age, smoking, BMI, educational level, parental history of myocardial infarction, alcohol intake, total energy intake, dietary fiber, vit C, beta-careotene, SFA, TFA, MFA, LA, ALA	Qt2	mg/d	66
101	de Goede 2012 22496770	age, smoking, BMI, educational level, parental history of myocardial infarction, alcohol intake, total energy intake, dietary fiber, vit C, beta-careotene, SFA, TFA, MFA, LA, ALA	Qt3	mg/d	119
102	de Goede 2012 22496770	age, smoking, BMI, educational level, parental history of myocardial infarction, alcohol intake, total energy intake, dietary fiber, vit C, beta-careotene, SFA, TFA, MFA, LA, ALA	Qt4	mg/d	nd

Appendix F:
Observational results: ischemic stroke

Row	Study PMID	Quantile median	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
82	Gronroos 2012 22570739	nd	nd	HR	99	nd	17325	Reference group			P trend	0.33
83	Gronroos 2012 22570739	nd	nd	HR	86	nd	15505	0.98	0.73	1.31		
84	Gronroos 2012 22570739	nd	nd	HR	106	nd	17217	1.04	0.78	1.37		
85	Gronroos 2012 22570739	nd	nd	HR	110	nd	17034	1.12	0.85	1.49		
86	de Goede 2013 22633188	Cases: 0.53 (SD = 0.13), Controls: 0.52 (SD = 0.14)	nd	OR	nd	nd	nd	1.02	0.71	1.46		0.41
87	de Goede 2013 22633188	Cases: 1.57 (SD = 1.25), Controls: 1.25 (SD = 0.60)	nd	OR	nd	nd	nd	1.33	0.96	1.84		0.02
88	de Goede 2011 21464993	1	nd	HR	29	4013	nd	Reference group				nd
89	de Goede 2011 21464993	1.2	nd	HR	26	4014	nd	0.63	0.38	1.04		
90	de Goede 2011 21464993	1.3	nd	HR	22	4014	nd	0.45	0.26	0.79		
91	de Goede 2011 21464993	1.5	nd	HR	26	4014	nd	0.56	0.32	0.97		
92	de Goede 2011 21464993	1.9	nd	HR	41	4014	nd	0.7	0.39	1.26		
94	**Subgroup analyses**											
95	de Goede 2012 22496770	36	<57	HR	19	2770	nd	Reference group				
96	de Goede 2012 22496770	77	106	HR	17	2770	nd	0.98	0.5	1.91	P trend	0.21
97	de Goede 2012 22496770	142	188	HR	17	2771	nd	0.98	0.5	1.93		
98	de Goede 2012 22496770	225	>188	HR	11	2770	nd	0.62	0.29	1.35		
99	de Goede 2012 22496770	44	<66	HR	22	2247	nd	Reference group			P trend	0.61
100	de Goede 2012 22496770	89	118	HR	20	2247	nd	0.93	0.5	1.74		
101	de Goede 2012 22496770	157	198	HR	18	2247	nd	0.87	0.46	1.65		
102	de Goede 2012 22496770	241	>199	HR	20	2247	nd	0.85	0.45	1.6		

Appendix F
Observational results: major adverse cardiac events

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup
2	Virtanen 2008 19064523	Health Professional Follow-up Study	MACE	Total CVD included fatal or nonfatal myocardial infarction and fatal or nonfatal stroke	Healthy	Healthy 40-75 yo men without diagnosis of myocardial infarction, angina, stroke, transient ischemic attack, or peripheral arterial disease, or had undergone coronary artery surgery.	Men
3	Virtanen 2008 19064523	Health Professional Follow-up Study	MACE	Total CVD included fatal or nonfatal myocardial infarction and fatal or nonfatal stroke	Healthy	Healthy 40-75 yo men without diagnosis of myocardial infarction, angina, stroke, transient ischemic attack, or peripheral arterial disease, or had undergone coronary artery surgery.	Men
4	Virtanen 2008 19064523	Health Professional Follow-up Study	MACE	Total CVD included fatal or nonfatal myocardial infarction and fatal or nonfatal stroke	Healthy	Healthy 40-75 yo men without diagnosis of myocardial infarction, angina, stroke, transient ischemic attack, or peripheral arterial disease, or had undergone coronary artery surgery.	Men
5	Virtanen 2008 19064523	Health Professional Follow-up Study	MACE	Total CVD included fatal or nonfatal myocardial infarction and fatal or nonfatal stroke	Healthy	Healthy 40-75 yo men without diagnosis of myocardial infarction, angina, stroke, transient ischemic attack, or peripheral arterial disease, or had undergone coronary artery surgery.	Men
6	Virtanen 2008 19064523	Health Professional Follow-up Study	MACE	Total CVD included fatal or nonfatal myocardial infarction and fatal or nonfatal stroke	Healthy	Healthy 40-75 yo men without diagnosis of myocardial infarction, angina, stroke, transient ischemic attack, or peripheral arterial disease, or had undergone coronary artery surgery.	Men
7	Hellstrand 2014 25008580	Malmo Diet and Cancer	MACE	Incident coronary event or ischemic stroke	Healthy	Healthy, Swedish, 44-74 y.	All
8	Hellstrand 2014 25008580	Malmo Diet and Cancer	MACE	Incident coronary event or ischemic stroke	Healthy	Healthy, Swedish, 44-74 y.	All
9	Hellstrand 2014 25008580	Malmo Diet and Cancer	MACE	Incident coronary event or ischemic stroke	Healthy	Healthy, Swedish, 44-74 y.	All
10	Hellstrand 2014 25008580	Malmo Diet and Cancer	MACE	Incident coronary event or ischemic stroke	Healthy	Healthy, Swedish, 44-74 y.	All
11	Hellstrand 2014 25008580	Malmo Diet and Cancer	MACE	Incident coronary event or ischemic stroke	Healthy	Healthy, Swedish, 44-74 y.	All
12	Hellstrand 2014 25008580	Malmo Diet and Cancer	MACE	Incident coronary event or ischemic stroke	Healthy	Healthy, Swedish, 44-74 y.	All
13	Hellstrand 2014 25008580	Malmo Diet and Cancer	MACE	Incident coronary event or ischemic stroke	Healthy	Healthy, Swedish, 44-74 y.	All
14	Hellstrand 2014 25008580	Malmo Diet and Cancer	MACE	Incident coronary event or ischemic stroke	Healthy	Healthy, Swedish, 44-74 y.	All
15	Hellstrand 2014 25008580	Malmo Diet and Cancer	MACE	Incident coronary event or ischemic stroke	Healthy	Healthy, Swedish, 44-74 y.	All
16	Hellstrand 2014 25008580	Malmo Diet and Cancer	MACE	Incident coronary event or ischemic stroke	Healthy	Healthy, Swedish, 44-74 y.	All
17	Hellstrand 2014 25008580	Malmo Diet and Cancer	MACE	Incident coronary event or ischemic stroke	Healthy	Healthy, Swedish, 44-74 y.	All
18	Hellstrand 2014 25008580	Malmo Diet and Cancer	MACE	Incident coronary event or ischemic stroke	Healthy	Healthy, Swedish, 44-74 y.	All
19	Hellstrand 2014 25008580	Malmo Diet and Cancer	MACE	Incident coronary event or ischemic stroke	Healthy	Healthy, Swedish, 44-74 y.	All
20	Hellstrand 2014 25008580	Malmo Diet and Cancer	MACE	Incident coronary event or ischemic stroke	Healthy	Healthy, Swedish, 44-74 y.	All
21	Hellstrand 2014 25008580	Malmo Diet and Cancer	MACE	Incident coronary event or ischemic stroke	Healthy	Healthy, Swedish, 44-74 y.	All
22	Hellstrand 2014 25008580	Malmo Diet and Cancer	MACE	Incident coronary event or ischemic stroke	Healthy	Healthy, Swedish, 44-74 y.	All

Appendix F
Observational results: major adverse cardiac events

Row	Study PMID	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure	Supplement
2	Virtanen 2008 19064523	3639/40230 (9.05)	18 y	EPA+DHA	Intake	No
3	Virtanen 2008 19064523	3639/40230 (9.05)	18 y	EPA+DHA	Intake	No
4	Virtanen 2008 19064523	3639/40230 (9.05)	18 y	EPA+DHA	Intake	No
5	Virtanen 2008 19064523	3639/40230 (9.05)	18 y	EPA+DHA	Intake	No
6	Virtanen 2008 19064523	3639/40230 (9.05)	18 y	EPA+DHA	Intake	No
7	Hellstrand 2014 25008580	2648/24032 (11.02)	14 y	ALA	Intake	Yes
8	Hellstrand 2014 25008580	2648/24032 (11.02)	14 y	ALA	Intake	Yes
9	Hellstrand 2014 25008580	2648/24032 (11.02)	14 y	ALA	Intake	Yes
10	Hellstrand 2014 25008580	2648/24032 (11.02)	14 y	ALA	Intake	Yes
11	Hellstrand 2014 25008580	2648/24032 (11.02)	14 y	ALA	Intake	Yes
12	Hellstrand 2014 25008580	2648/24032 (11.02)	14 y	EPA+DHA+DPA	Intake	Yes
13	Hellstrand 2014 25008580	2648/24032 (11.02)	14 y	EPA+DHA+DPA	Intake	Yes
14	Hellstrand 2014 25008580	2648/24032 (11.02)	14 y	EPA+DHA+DPA	Intake	Yes
15	Hellstrand 2014 25008580	2648/24032 (11.02)	14 y	EPA+DHA+DPA	Intake	Yes
16	Hellstrand 2014 25008580	2648/24032 (11.02)	14 y	EPA+DHA+DPA	Intake	Yes
17	Hellstrand 2014 25008580	2648/24032 (11.02)	14 y	All n-3	Intake	Yes
18	Hellstrand 2014 25008580	2648/24032 (11.02)	14 y	All n-3	Intake	Yes
19	Hellstrand 2014 25008580	2648/24032 (11.02)	14 y	All n-3	Intake	Yes
20	Hellstrand 2014 25008580	2648/24032 (11.02)	14 y	All n-3	Intake	Yes
21	Hellstrand 2014 25008580	2648/24032 (11.02)	14 y	All n-3	Intake	Yes
22	Hellstrand 2014 25008580	2648/24032 (11.02)	14 y	ALA	Intake	Yes

Appendix F
Observational results: major adverse cardiac events

Row	Study PMID	Adjustments	Quantile	n3 units	Quantile low	Quantile median	Quantile high
2	Virtanen 2008 19064523	Age, BMI, physcial activity, smoking status, hx hypertension, hx diabetes, hx hypercholsterolemia, first-degree family history of myocardial infarction before age 60y, first-degree family history of colon cancer, and aspirin use	Qt1	g/d	0	nd	<0.05
3	Virtanen 2008 19064523	Age, BMI, physcial activity, smoking status, hx hypertension, hx diabetes, hx hypercholsterolemia, first-degree family history of myocardial infarction before age 60y, first-degree family history of colon cancer, and aspirin use	Qt2	g/d	0.05	nd	<0.2
4	Virtanen 2008 19064523	Age, BMI, physcial activity, smoking status, hx hypertension, hx diabetes, hx hypercholsterolemia, first-degree family history of myocardial infarction before age 60y, first-degree family history of colon cancer, and aspirin use	Qt3	g/d	0.2	nd	<0.4
5	Virtanen 2008 19064523	Age, BMI, physcial activity, smoking status, hx hypertension, hx diabetes, hx hypercholsterolemia, first-degree family history of myocardial infarction before age 60y, first-degree family history of colon cancer, and aspirin use	Qt4	g/d	0.4	nd	<0.6
6	Virtanen 2008 19064523	Age, BMI, physcial activity, smoking status, hx hypertension, hx diabetes, hx hypercholsterolemia, first-degree family history of myocardial infarction before age 60y, first-degree family history of colon cancer, and aspirin use	Qt5	g/d	0.6	nd	>=0.6
7	Hellstrand 2014 25008580	age, sex, BMI, diet assessment method version, season, total energy intake, alcohol intake, leisure time physical activity, education, and smoking	Qt1	% kcal	nd	0.52	nd
8	Hellstrand 2014 25008580	age, sex, BMI, diet assessment method version, season, total energy intake, alcohol intake, leisure time physical activity, education, and smoking	Qt2	% kcal	nd	0.63	nd
9	Hellstrand 2014 25008580	age, sex, BMI, diet assessment method version, season, total energy intake, alcohol intake, leisure time physical activity, education, and smoking	Qt3	% kcal	nd	0.72	nd
10	Hellstrand 2014 25008580	age, sex, BMI, diet assessment method version, season, total energy intake, alcohol intake, leisure time physical activity, education, and smoking	Qt4	% kcal	nd	0.82	nd
11	Hellstrand 2014 25008580	age, sex, BMI, diet assessment method version, season, total energy intake, alcohol intake, leisure time physical activity, education, and smoking	Qt5	% kcal	nd	0.99	nd
12	Hellstrand 2014 25008580	age, sex, BMI, diet assessment method version, season, total energy intake, alcohol intake, leisure time physical activity, education, and smoking	Qt1	% kcal	nd	0.07	nd
13	Hellstrand 2014 25008580	age, sex, BMI, diet assessment method version, season, total energy intake, alcohol intake, leisure time physical activity, education, and smoking	Qt2	% kcal	nd	0.13	nd
14	Hellstrand 2014 25008580	age, sex, BMI, diet assessment method version, season, total energy intake, alcohol intake, leisure time physical activity, education, and smoking	Qt3	% kcal	nd	0.19	nd
15	Hellstrand 2014 25008580	age, sex, BMI, diet assessment method version, season, total energy intake, alcohol intake, leisure time physical activity, education, and smoking	Qt4	% kcal	nd	0.3	nd
16	Hellstrand 2014 25008580	age, sex, BMI, diet assessment method version, season, total energy intake, alcohol intake, leisure time physical activity, education, and smoking	Qt5	% kcal	nd	0.53	nd
17	Hellstrand 2014 25008580	age, sex, BMI, diet assessment method version, season, total energy intake, alcohol intake, leisure time physical activity, education, and smoking	Qt1	% kcal	nd	0.68	nd
18	Hellstrand 2014 25008580	age, sex, BMI, diet assessment method version, season, total energy intake, alcohol intake, leisure time physical activity, education, and smoking	Qt2	% kcal	nd	0.83	nd
19	Hellstrand 2014 25008580	age, sex, BMI, diet assessment method version, season, total energy intake, alcohol intake, leisure time physical activity, education, and smoking	Qt3	% kcal	nd	0.96	nd
20	Hellstrand 2014 25008580	age, sex, BMI, diet assessment method version, season, total energy intake, alcohol intake, leisure time physical activity, education, and smoking	Qt4	% kcal	nd	1.1	nd
21	Hellstrand 2014 25008580	age, sex, BMI, diet assessment method version, season, total energy intake, alcohol intake, leisure time physical activity, education, and smoking	Qt5	% kcal	nd	1.37	nd
22	Hellstrand 2014 25008580	age, sex, BMI, diet assessment method version, season, total energy intake, alcohol intake, leisure time physical activity, education, and smoking	All	Per 1 E% increase PUFA intake	nd	nd	nd

Appendix F
Observational results: major adverse cardiac events

Row	Study PMID	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
2	Virtanen 2008 19064523	RR	163	nd	27310	Reference group			p trend	0.63
3	Virtanen 2008 19064523	RR	1245	nd	220099	0.95	0.8	1.12		
4	Virtanen 2008 19064523	RR	1340	nd	248273	0.87	0.74	1.03		
5	Virtanen 2008 19064523	RR	514	nd	94878	0.82	0.69	0.98		
6	Virtanen 2008 19064523	RR	377	nd	54437	0.99	0.82	1.19		
7	Hellstrand 2014 25008580	HR	nd	4806	nd	Reference group				nd
8	Hellstrand 2014 25008580	HR	nd	4807	nd	0.93	0.82	1.06		
9	Hellstrand 2014 25008580	HR	nd	4806	nd	1.04	0.92	1.17		
10	Hellstrand 2014 25008580	HR	nd	4807	nd	0.97	0.85	1.09		
11	Hellstrand 2014 25008580	HR	nd	4806	nd	0.98	0.87	1.11		
12	Hellstrand 2014 25008580	HR	nd	4806	nd	Reference group				nd
13	Hellstrand 2014 25008580	HR	nd	4807	nd	0.96	0.85	1.1		
14	Hellstrand 2014 25008580	HR	nd	4806	nd	1.01	0.89	1.15		
15	Hellstrand 2014 25008580	HR	nd	4807	nd	1	0.88	1.13		
16	Hellstrand 2014 25008580	HR	nd	4806	nd	1	0.86	1.14		
17	Hellstrand 2014 25008580	HR	nd	4806	nd	Reference group				nd
18	Hellstrand 2014 25008580	HR	nd	4807	nd	0.97	0.85	1.1		
19	Hellstrand 2014 25008580	HR	nd	4806	nd	1.02	0.9	1.15		
20	Hellstrand 2014 25008580	HR	nd	4807	nd	1.05	0.93	1.19		
21	Hellstrand 2014 25008580	HR	nd	4806	nd	1	0.88	1.13		
22	Hellstrand 2014 25008580	HR	nd	NA	NA	1.07	0.89	1.29		

Appendix F
Observational results: major adverse cardiac events

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup
23	Hellstrand 2014 25008580	Malmo Diet and Cancer	MACE	Incident coronary event or ischemic stroke	Healthy	Healthy, Swedish, 44-74 y.	All
24	Hellstrand 2014 25008580	Malmo Diet and Cancer	MACE	Incident coronary event or ischemic stroke	Healthy	Healthy, Swedish, 44-74 y.	All
25	Itakura 2011 21099130	JELIS	MACE	sudden cardiac death, fatal or nonfatal MI, unstable angina pectoris, and angioplasty/stenting or CABG	At risk	Patients with hypercholesterolemia on a low-dose statin	All
26	Itakura 2011 21099130	JELIS	MACE	sudden cardiac death, fatal or nonfatal MI, unstable angina pectoris, and angioplasty/stenting or CABG	At risk	Patients with hypercholesterolemia on a low-dose statin	All
27	Itakura 2011 21099130	JELIS	MACE	sudden cardiac death, fatal or nonfatal MI, unstable angina pectoris, and angioplasty/stenting or CABG	At risk	Patients with hypercholesterolemia on a low-dose statin	All
28	Itakura 2011 21099130	JELIS	MACE	sudden cardiac death, fatal or nonfatal MI, unstable angina pectoris, and angioplasty/stenting or CABG	At risk	Patients with hypercholesterolemia on a low-dose statin	All
29	Itakura 2011 21099130	JELIS	MACE	sudden cardiac death, fatal or nonfatal MI, unstable angina pectoris, and angioplasty/stenting or CABG	At risk	Patients with hypercholesterolemia on a low-dose statin	All
30	Itakura 2011 21099130	JELIS	MACE	sudden cardiac death, fatal or nonfatal MI, unstable angina pectoris, and angioplasty/stenting or CABG	At risk	Patients with hypercholesterolemia on a low-dose statin	All
31	Itakura 2011 21099130	JELIS	MACE	sudden cardiac death, fatal or nonfatal MI, unstable angina pectoris, and angioplasty/stenting or CABG	At risk	Patients with hypercholesterolemia on a low-dose statin	All
32	Itakura 2011 21099130	JELIS	MACE	sudden cardiac death, fatal or nonfatal MI, unstable angina pectoris, and angioplasty/stenting or CABG	At risk	Patients with hypercholesterolemia on a low-dose statin	All
33	Itakura 2011 21099130	JELIS	MACE	sudden cardiac death, fatal or nonfatal MI, unstable angina pectoris, and angioplasty/stenting or CABG	At risk	Patients with hypercholesterolemia on a low-dose statin	All
34	Itakura 2011 21099130	JELIS	MACE	sudden cardiac death, fatal or nonfatal MI, unstable angina pectoris, and angioplasty/stenting or CABG	At risk	Patients with hypercholesterolemia on a low-dose statin	All
35	Matsumoto 2013 23098619	Physician's Health Study	MACE	nonfatal MI, fatal MI, percutaneous transluminal coronary angioplasty, coronary artery bypass graft, coronary death, and sudden death	Healthy	US male physicians	Men
36	Matsumoto 2013 23098619	Physician's Health Study	MACE	nonfatal MI, fatal MI, percutaneous transluminal coronary angioplasty, coronary artery bypass graft, coronary death, and sudden death	Healthy	US male physicians	Men
37	Matsumoto 2013 23098619	Physician's Health Study	MACE	nonfatal MI, fatal MI, percutaneous transluminal coronary angioplasty, coronary artery bypass graft, coronary death, and sudden death	Healthy	US male physicians	Men
38	Itakura 2011 21099130	JELIS	MACE	sudden cardiac death, fatal or nonfatal MI, unstable angina pectoris, and angioplasty/stenting or CABG	At risk	Patients with hypercholesterolemia on a low-dose statin	

Appendix F
Observational results: major adverse cardiac events

Row	Study PMID	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure	Supplement
23	Hellstrand 2014 25008580	2648/24032 (11.02)	14 y	EPA+DHA+DPA	Intake	Yes
24	Hellstrand 2014 25008580	2648/24032 (11.02)	14 y	All n-3	Intake	Yes
25	Itakura 2011 21099130	nd/15534 (nd)	4.6 y	EPA	Plasma	0.5
26	Itakura 2011 21099130	nd/15534 (nd)	4.6 y	EPA	Plasma	0.5
27	Itakura 2011 21099130	nd/15534 (nd)	4.6 y	EPA	Plasma	0.5
28	Itakura 2011 21099130	nd/15534 (nd)	4.6 y	EPA	Plasma	0.5
29	Itakura 2011 21099130	nd/15534 (nd)	4.6 y	EPA	Plasma	0.5
30	Itakura 2011 21099130	nd/15534 (nd)	4.6 y	EPA	Plasma	0.5
31	Itakura 2011 21099130	nd/15534 (nd)	4.6 y	EPA	Plasma	0.5
32	Itakura 2011 21099130	nd/15534 (nd)	4.6 y	EPA	Plasma	0.5
33	Itakura 2011 21099130	nd/15534 (nd)	4.6 y	DHA	Plasma	0.5
34	Itakura 2011 21099130	nd/15534 (nd)	4.6 y	DHA	Plasma	0.5
35	Matsumoto 2013 23098619	1000/2000 (50)	nd	SDA	Erythrocyte (log measure)	NA
36	Matsumoto 2013 23098619	1000/2000 (50)	nd	ALA	Erythrocyte (log measure)	NA
37	Matsumoto 2013 23098619	1000/2000 (50)	nd	EPA+DHA+DPA	Erythrocyte (log measure)	NA
38	Itakura 2011 21099130	nd/15534 (d)	4.6 y	EPA	Plasma	0.5

Appendix F

Observational results: major adverse cardiac events

Row	Study PMID	Adjustments	Quantile	n3 units	Quantile low	Quantile median	Quantile high
23	Hellstrand 2014 25008580	age, sex, BMI, diet assessment method version, season, total energy intake, alcohol intake, leisure time physical activity, education, and smoking	All	Per 1 E% increase PUFA intake	nd	nd	nd
24	Hellstrand 2014 25008580	age, sex, BMI, diet assessment method version, season, total energy intake, alcohol intake, leisure time physical activity, education, and smoking	All	Per 1 E% increase PUFA intake	nd	nd	nd
25	Itakura 2011 21099130	age; sex; smoking; history of CAD, DM, HTN; use of drugs for CAD; on-treatment plasma fatty acid concentrations	<Median	mcg/mL	nd	nd	133
26	Itakura 2011 21099130	age; sex; smoking; history of CAD, DM, HTN; use of drugs for CAD; on-treatment plasma fatty acid concentrations	>Median		133	nd	nd
27	Itakura 2011 21099130	age; sex; smoking; history of CAD, DM, HTN; use of drugs for CAD; on-treatment plasma fatty acid concentrations	Lower, by threshold	mcg/mL	nd	nd	100
28	Itakura 2011 21099130	age; sex; smoking; history of CAD, DM, HTN; use of drugs for CAD; on-treatment plasma fatty acid concentrations	≥100 mcg/mL		100	nd	nd
29	Itakura 2011 21099130	age; sex; smoking; history of CAD, DM, HTN; use of drugs for CAD; on-treatment plasma fatty acid concentrations	Lower, by threshold	mcg/mL	nd	nd	150
30	Itakura 2011 21099130	age; sex; smoking; history of CAD, DM, HTN; use of drugs for CAD; on-treatment plasma fatty acid concentrations	≥150 mcg/mL		150	nd	nd
31	Itakura 2011 21099130	age; sex; smoking; history of CAD, DM, HTN; use of drugs for CAD; on-treatment plasma fatty acid concentrations	Lower, by threshold	mcg/mL	nd	nd	200
32	Itakura 2011 21099130	age; sex; smoking; history of CAD, DM, HTN; use of drugs for CAD; on-treatment plasma fatty acid concentrations	≥200 mcg/mL		200	nd	nd
33	Itakura 2011 21099130	age; sex; smoking; history of CAD, DM, HTN; use of drugs for CAD; on-treatment plasma fatty acid concentrations	Lower, by threshold	mcg/mL	nd	nd	160
34	Itakura 2011 21099130	age; sex; smoking; history of CAD, DM, HTN; use of drugs for CAD; on-treatment plasma fatty acid concentrations	Upper, by threshold		160	nd	nd
35	Matsumoto 2013 23098619	matching factors and BMI, smoking status, exercise level, alcohol consumption, history of hypertension, history of diabetes, and history of hypercholesterolemia	All	Per SD increase	nd	nd	nd
36	Matsumoto 2013 23098619	matching factors and BMI, smoking status, exercise level, alcohol consumption, history of hypertension, history of diabetes, and history of hypercholesterolemia	All	Per SD increase	nd	nd	nd
37	Matsumoto 2013 23098619	matching factors and BMI, smoking status, exercise level, alcohol consumption, history of hypertension, history of diabetes, and history of hypercholesterolemia	All	Per SD increase	nd	nd	nd
38	Itakura 2011 21099130	age; sex; smoking; history of CAD, DM, HTN; use of drugs for CAD; on-treatment plasma fatty acid concentrations	Qr1	mcg/mL	nd	nd	86

Appendix F
Observational results: major adverse cardiac events

Row	Study PMID	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
23	Hellstrand 2014 25008580	HR	nd	NA	NA	0.97	0.82	1.16		
24	Hellstrand 2014 25008580	HR	nd	NA	NA	1.02	0.9	1.15		
25	Itakura 2011 21099130	HR	nd	nd	nd	Reference group				
26	Itakura 2011 21099130	HR	nd	nd	nd	0.83	0.68	0.99		0.049
27	Itakura 2011 21099130	HR	nd	nd	nd	Reference group				
28	Itakura 2011 21099130	HR	nd	nd	nd	0.87	0.72	1.03		0.11
29	Itakura 2011 21099130	HR	nd	nd	nd	Reference group				
30	Itakura 2011 21099130	HR	nd	nd	nd	0.82	0.68	0.98		0.032
31	Itakura 2011 21099130	HR	nd	nd	nd	Reference group				
32	Itakura 2011 21099130	HR	nd	nd	nd	0.78	0.69	0.99		0.043
33	Itakura 2011 21099130	HR	nd	nd	nd	Reference group				
34	Itakura 2011 21099130	HR	nd	nd	nd	0.92	0.76	1.13		0.429
35	Matsumoto 2013 23098619	OR	1000	nd	nd	1.03	0.9	1.18		
36	Matsumoto 2013 23098619	OR	1000	nd	nd	1.04	0.94	1.16		
37	Matsumoto 2013 23098619	OR	1000	nd	nd	0.97	0.88	1.07		
38	Itakura 2011 21099130	OR	nd	nd	nd	Reference group				nd

Appendix F
Observational results: major adverse cardiac events

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup
39	Matsumoto 2013 23098619	Physician's Health Study	MACE	nonfatal MI, fatal MI, percutaneous transluminal coronary angioplasty, coronary artery bypass graft, coronary death, and sudden death	Healthy	US male physicians	Men
40	Matsumoto 2013 23098619	Physician's Health Study	MACE	nonfatal MI, fatal MI, percutaneous transluminal coronary angioplasty, coronary artery bypass graft, coronary death, and sudden death	Healthy	US male physicians	Men
41	Morris 1995 7598116	Physician's Health Study	MACE	nonfatal MI, nonfatal stroke, and CV death	Healthy	US male physicians	Men
42	Morris 1995 7598116	Physician's Health Study	MACE	nonfatal MI, nonfatal stroke, and CV death	Healthy	US male physicians	Men
43	Morris 1995 7598116	Physician's Health Study	MACE	nonfatal MI, nonfatal stroke, and CV death	Healthy	US male physicians	Men
44	Morris 1995 7598116	Physician's Health Study	MACE	nonfatal MI, nonfatal stroke, and CV death	Healthy	US male physicians	Men
45	Morris 1995 7598116	Physician's Health Study	MACE	nonfatal MI, nonfatal stroke, and CV death	Healthy	US male physicians	Men
46	Strom 2012 22146511	Danish National Birth Cohort	MACE	cerebrovascular, ischemic heart disease, hypertensive disease hospitalization	Healthy	Pregnant women with mean age of 29.9	Women
47	Strom 2012 22146511	Danish National Birth Cohort	MACE	cerebrovascular, ischemic heart disease, hypertensive disease hospitalization	Healthy	Pregnant women with mean age of 29.9	Women
48	Strom 2012 22146511	Danish National Birth Cohort	MACE	cerebrovascular, ischemic heart disease, hypertensive disease hospitalization	Healthy	Pregnant women with mean age of 29.9	Women
49	Strom 2012 22146511	Danish National Birth Cohort	MACE	cerebrovascular, ischemic heart disease, hypertensive disease hospitalization	Healthy	Pregnant women with mean age of 29.9	Women
50	Strom 2012 22146511	Danish National Birth Cohort	MACE	cerebrovascular, ischemic heart disease, hypertensive disease hospitalization	Healthy	Pregnant women with mean age of 29.9	Women
51	Strom 2012 22146511	Danish National Birth Cohort	MACE	cerebrovascular, ischemic heart disease, hypertensive disease hospitalization	Healthy	Pregnant women with mean age of 29.9	Women
52	Woodward 2011 21345851	Scottish Heart Health Extended Cohort Study	MACE	Cardiovascular death, CHD, cerebrovascular disease, coronary artery bypass graft, or percutaneous coronary angioplasty	Healthy	People in Scotland aged 40-59 years free of CVD at baseline	All
53	Woodward 2011 21345851	Scottish Heart Health Extended Cohort Study	MACE	Cardiovascular death, CHD, cerebrovascular disease, coronary artery bypass graft, or percutaneous coronary angioplasty	Healthy	People in Scotland aged 40-59 years free of CVD at baseline	All
54	Woodward 2011 21345851	Scottish Heart Health Extended Cohort Study	MACE	Cardiovascular death, CHD, cerebrovascular disease, coronary artery bypass graft, or percutaneous coronary angioplasty	Healthy	People in Scotland aged 40-59 years free of CVD at baseline	All
55	Woodward 2011 21345851	Scottish Heart Health Extended Cohort Study	MACE	Cardiovascular death, CHD, cerebrovascular disease, coronary artery bypass graft, or percutaneous coronary angioplasty	Healthy	People in Scotland aged 40-59 years free of CVD at baseline	All
56	Woodward 2011 21345851	Scottish Heart Health Extended Cohort Study	MACE	Cardiovascular death, CHD, cerebrovascular disease, coronary artery bypass graft, or percutaneous coronary angioplasty	Healthy	People in Scotland aged 40-59 years free of CVD at baseline	All
57	Woodward 2011 21345851	Scottish Heart Health Extended Cohort Study	MACE	Cardiovascular death, CHD, cerebrovascular disease, coronary artery bypass graft, or percutaneous coronary angioplasty	Healthy	People in Scotland aged 40-59 years free of CVD at baseline	All

Appendix F
Observational results: major adverse cardiac events

Row	Study PMID	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure	Supplement
39	Matsumoto 2013 23098619	1000/2000 ()	nd	DPA	Erythrocyte (log measure)	NA
40	Matsumoto 2013 23098619	1000/2000 ()	nd	DHA	Erythrocyte (log measure)	NA
41	Morris 1995 7598116	525/21185 (2.48)	4 y	All n-3	Intake	Explicitly excluded fish oil supplements
42	Morris 1995 7598116	525/21185 (2.48)	4 y	All n-3	Intake	Explicitly excluded fish oil supplements
43	Morris 1995 7598116	525/21185 (2.48)	4 y	All n-3	Intake	Explicitly excluded fish oil supplements
44	Morris 1995 7598116	525/21185 (2.48)	4 y	All n-3	Intake	Explicitly excluded fish oil supplements
45	Morris 1995 7598116	525/21185 (2.48)	4 y	All n-3	Intake	Explicitly excluded fish oil supplements
46	Strom 2012 22146511	577/48627 (1.19)	12 y	All n-3	Intake	No
47	Strom 2012 22146511	577/48627 (1.19)	12 y	All n-3	Intake	No
48	Strom 2012 22146511	577/48627 (1.19)	12 y	All n-3	Intake	No
49	Strom 2012 22146511	577/48627 (1.19)	12 y	All n-3	Intake	No
50	Strom 2012 22146511	577/48627 (1.19)	12 y	All n-3	Intake	No
51	Strom 2012 22146511	577/48627 (1.19)	12 y	All n-3	Intake	No
52	Woodward 2011 21345851	870/3944 (22.06)	19.5 (median)	DPA	Adipose tissue	Yes
53	Woodward 2011 21345851	870/3944 (22.06)	19.5 (median)	DPA	Adipose tissue	Yes
54	Woodward 2011 21345851	870/3944 (22.06)	19.5 (median)	DPA	Adipose tissue	Yes
55	Woodward 2011 21345851	870/3944 (22.06)	19.5 (median)	DPA	Adipose tissue	Yes
56	Woodward 2011 21345851	870/3944 (22.06)	19.5 (median)	DHA	Adipose tissue	Yes
57	Woodward 2011 21345851	870/3944 (22.06)	19.5 (median)	DHA	Adipose tissue	Yes

Appendix F

Observational results: major adverse cardiac events

Row	Study PMID	Adjustments	Quantile	n3 units	Quantile low	Quantile median	Quantile high
39	Matsumoto 2013 23098619	matching factors and BMI, smoking status, exercise level, alcohol consumption, history of hypertension, history of diabetes, and history of hypercholesterolemia	All	Per SD increase	nd	nd	nd
40	Matsumoto 2013 23098619	matching factors and BMI, smoking status, exercise level, alcohol consumption, history of hypertension, history of diabetes, and history of hypercholesterolemia	All	Per SD increase	nd	nd	nd
41	Morris 1995 7598116	age, aspirin and beta-carotene assignment, smoking, alcohol consumption, obesity, diabetes, vigorous exercise, parental history of MI before age 60 years, history of hypertension, history of hypercholesterolemia, vitamin supplement use, and saturated fat intake	T1	g/wk	<0.5	nd	nd
42	Morris 1995 7598116	age, aspirin and beta-carotene assignment, smoking, alcohol consumption, obesity, diabetes, vigorous exercise, parental history of MI before age 60 years, history of hypertension, history of hypercholesterolemia, vitamin supplement use, and saturated fat intake	T2	g/wk	0.5	nd	1
43	Morris 1995 7598116	age, aspirin and beta-carotene assignment, smoking, alcohol consumption, obesity, diabetes, vigorous exercise, parental history of MI before age 60 years, history of hypertension, history of hypercholesterolemia, vitamin supplement use, and saturated fat intake	T3	g/wk	1	nd	1.7
44	Morris 1995 7598116	age, aspirin and beta-carotene assignment, smoking, alcohol consumption, obesity, diabetes, vigorous exercise, parental history of MI before age 60 years, history of hypertension, history of hypercholesterolemia, vitamin supplement use, and saturated fat intake	T4	g/wk	1.7	nd	2.3
45	Morris 1995 7598116	age, aspirin and beta-carotene assignment, smoking, alcohol consumption, obesity, diabetes, vigorous exercise, parental history of MI before age 60 years, history of hypertension, history of hypercholesterolemia, vitamin supplement use, and saturated fat intake	T5	g/wk	nd	nd	>=2.3
46	Strom 2012 22146511	nd	Lowest 3%	g/d	nd	nd	nd
47	Strom 2012 22146511	nd	Qt1	g/d	nd	0.13	nd
48	Strom 2012 22146511	nd	Qt2	g/d	nd	0.21	nd
49	Strom 2012 22146511	nd	Qt3	g/d	nd	0.31	nd
50	Strom 2012 22146511	nd	Qt4	g/d	nd	0.45	nd
51	Strom 2012 22146511	nd	Qt5	g/d	nd	0.73	nd
52	Woodward 2011 21345851	sex, age, total serum cholesterol, HDL-cholesterol, systolic blood pressure, history of taking blood pressure medication, cigarettes smoked per day, diabetes, sex, family history of coronary disease and socio-economic status	Qr1	mmol/L	nd	nd	nd
53	Woodward 2011 21345851	sex, age, total serum cholesterol, HDL-cholesterol, systolic blood pressure, history of taking blood pressure medication, cigarettes smoked per day, diabetes, sex, family history of coronary disease and socio-economic status	Qr2	mmol/L	nd	nd	nd
54	Woodward 2011 21345851	sex, age, total serum cholesterol, HDL-cholesterol, systolic blood pressure, history of taking blood pressure medication, cigarettes smoked per day, diabetes, sex, family history of coronary disease and socio-economic status	Qr3	mmol/L	nd	nd	nd
55	Woodward 2011 21345851	sex, age, total serum cholesterol, HDL-cholesterol, systolic blood pressure, history of taking blood pressure medication, cigarettes smoked per day, diabetes, sex, family history of coronary disease and socio-economic status	Qr4	mmol/L	nd	nd	nd
56	Woodward 2011 21345851	sex, age, total serum cholesterol, HDL-cholesterol, systolic blood pressure, history of taking blood pressure medication, cigarettes smoked per day, diabetes, sex, family history of coronary disease and socio-economic status	Qr1	mmol/L	nd	nd	nd
57	Woodward 2011 21345851	sex, age, total serum cholesterol, HDL-cholesterol, systolic blood pressure, history of taking blood pressure medication, cigarettes smoked per day, diabetes, sex, family history of coronary disease and socio-economic status	Qr2	mmol/L	nd	nd	nd

Appendix F
Observational results: major adverse cardiac events

Row	Study PMID	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
39	Matsumoto 2013 23098619	OR	1000	nd	nd	0.96	0.87	1.06		
40	Matsumoto 2013 23098619	OR	1000	nd	nd	0.96	0.9	1.1		
41	Morris 1995 7598116	RR	97	4335	nd	1				0.63
42	Morris 1995 7598116	RR	112	4134	nd	1.3	1	1.8		
43	Morris 1995 7598116	RR	133	4691	nd	1.3	1	1.7		
44	Morris 1995 7598116	RR	85	4075	nd	0.9	0.7	1.3		
45	Morris 1995 7598116	RR	98	3950	nd	1.1	0.8	1.5		
46	Strom 2012 22146511	HR	3	1446	nd	1.91	1.26	2.89		
47	Strom 2012 22146511	HR	99	9407	nd	Reference group				
48	Strom 2012 22146511	HR	115	9509	nd	1.17	0.89	1.52		
49	Strom 2012 22146511	HR	99	9517	nd	1.16	0.76	1.33		
50	Strom 2012 22146511	HR	113	9521	nd	1.12	0.85	1.47	Overall Test for trend	0.023
51	Strom 2012 22146511	HR	122	9227	nd	1.26	0.96	1.65	Overall Chi square test of result	0.035
52	Woodward 2011 21345851	HR	nd	nd	nd	Reference group			Linear	0.02
53	Woodward 2011 21345851	HR	nd	nd	nd	0.91	0.75	1.11	Quadratic	0.03
54	Woodward 2011 21345851	HR	nd	nd	nd	0.85	0.7	1.04		
55	Woodward 2011 21345851	HR	nd	nd	nd	0.77	0.63	0.95		
56	Woodward 2011 21345851	HR	nd	nd	nd	Reference group			Linear	0.03
57	Woodward 2011 21345851	HR	nd	nd	nd	0.86	0.71	1.04	Quadratic	0.0006

Appendix F
Observational results: major adverse cardiac events

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup
58	Woodward 2011 21345851	Scottish Heart Health Extended Cohort Study	MACE	Cardiovascular death, CHD, cerebrovascular disease, coronary artery bypass graft, or percutaneous coronary angioplasty	Healthy	People in Scotland aged 40-59 years free of CVD at baseline	All
59	Woodward 2011 21345851	Scottish Heart Health Extended Cohort Study	MACE	Cardiovascular death, CHD, cerebrovascular disease, coronary artery bypass graft, or percutaneous coronary angioplasty	Healthy	People in Scotland aged 40-59 years free of CVD at baseline	All
60	Itakura 2011 21099130	JELIS	MACE	sudden cardiac death, fatal or nonfatal MI, unstable angina pectoris, and angioplasty/stenting or CABG	At risk	Patients with hypercholesterolemia on a low-dose statin	All
61	Itakura 2011 21099130	JELIS	MACE	sudden cardiac death, fatal or nonfatal MI, unstable angina pectoris, and angioplasty/stenting or CABG	At risk	Patients with hypercholesterolemia on a low-dose statin	All
62	Itakura 2011 21099130	JELIS	MACE	sudden cardiac death, fatal or nonfatal MI, unstable angina pectoris, and angioplasty/stenting or CABG	At risk	Patients with hypercholesterolemia on a low-dose statin	All
63	Matsumoto 2013 23098619	Physician's Health Study	MACE	nonfatal MI, fatal MI, percutaneous transluminal coronary angioplasty, coronary artery bypass graft, coronary death, and sudden death	Healthy	US male physicians	Men
64	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke, death, or other CVD death	Healthy	Healthy, multiethnic Adults	All
65	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke, death, or other CVD death	Healthy	Healthy, multiethnic Adults	All
66	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke, death, or other CVD death	Healthy	Healthy, multiethnic Adults	All
67	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke, death, or other CVD death	Healthy	Healthy, multiethnic Adults	All
68	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke, death, or other CVD death	Healthy	Healthy, multiethnic Adults	All
69	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke, death, or other CVD death	Healthy	Healthy, multiethnic Adults	All
70	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke, death, or other CVD death	Healthy	Healthy, multiethnic Adults	All
71	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke, death, or other CVD death	Healthy	Healthy, multiethnic Adults	All
72	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke, death, or other CVD death	Healthy	Healthy, multiethnic Adults	All
73	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke, death, or other CVD death	Healthy	Healthy, multiethnic Adults	All
74	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke, death, or other CVD death	Healthy	Healthy, multiethnic Adults	All

Appendix F
Observational results: major adverse cardiac events

Row	Study PMID	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure	Supplement
58	Woodward 2011 21345851	870/3944 (22.06)	19.5 (median)	DHA	Adipose tissue	Yes
59	Woodward 2011 21345851	870/3944 (22.06)	19.5 (median)	DHA	Adipose tissue	Yes
60	Itakura 2011 21099130	nd/15534 (nd)	4.6 y	EPA	Plasma	0.5
61	Itakura 2011 21099130	nd/15534 (nd)	4.6 y	EPA	Plasma	0.5
62	Itakura 2011 21099130	nd/15534 (nd)	4.6 y	EPA	Plasma	0.5
63	Matsumoto 2013 23098619	1000/2000 (50)	nd	EPA	Erythrocyte (log measure)	NA
64	de Oliveira 2013 24351702	nd/2837 (nd)	10 y	DPA	Phospholipid	No
65	de Oliveira 2013 24351702	nd/2837 (nd)	10 y	DPA	Phospholipid	No
66	de Oliveira 2013 24351702	nd/2837 (nd)	10 y	DPA	Phospholipid	No
67	de Oliveira 2013 24351702	nd/2837 (nd)	10 y	DPA	Phospholipid	No
68	de Oliveira 2013 24351702	nd/2837 (nd)	10 y	DHA	Phospholipid	No
69	de Oliveira 2013 24351702	nd/2837 (nd)	10 y	DHA	Phospholipid	No
70	de Oliveira 2013 24351702	nd/2837 (nd)	10 y	DHA	Phospholipid	No
71	de Oliveira 2013 24351702	nd/2837 (nd)	10 y	DHA	Phospholipid	No
72	de Oliveira 2013 24351702	nd/2837 (nd)	10 y	EPA+DHA+DPA	Phospholipid	No
73	de Oliveira 2013 24351702	nd/2837 (nd)	10 y	EPA+DHA+DPA	Phospholipid	No
74	de Oliveira 2013 24351702	nd/2837 (nd)	10 y	EPA+DHA+DPA	Phospholipid	No

Appendix F
Observational results: major adverse cardiac events

Row	Study PMID	Adjustments	Quantile	n3 units	Quantile low	Quantile median	Quantile high
58	Woodward 2011 21345851	sex, age, total serum cholesterol, HDL-cholesterol, systolic blood pressure, history of taking blood pressure medication, cigarettes smoked per day, diabetes, sex, family history of coronary disease and socio-economic status	Qr3	mmol/L	nd	nd	nd
59	Woodward 2011 21345851	sex, age, total serum cholesterol, HDL-cholesterol, systolic blood pressure, history of taking blood pressure medication, cigarettes smoked per day, diabetes, sex, family history of coronary disease and socio-economic status	Qr4	mmol/L	nd	nd	nd
60	Itakura 2011 21099130	age; sex; smoking; history of CAD, DM, HTN; use of drugs for CAD; on-treatment plasma fatty acid concentrations	Qr2	mcg/mL	87	nd	99
61	Itakura 2011 21099130	age; sex; smoking; history of CAD, DM, HTN; use of drugs for CAD; on-treatment plasma fatty acid concentrations	Qr3	mcg/mL	100	nd	149
62	Itakura 2011 21099130	age; sex; smoking; history of CAD, DM, HTN; use of drugs for CAD; on-treatment plasma fatty acid concentrations	Qr4	mcg/mL	150	nd	nd
63	Matsumoto 2013 23098619	matching factors and BMI, smoking status, exercise level, alcohol consumption, history of hypertension, history of diabetes, and history of hypercholesterolemia	All	Per SD increase	nd	nd	nd
64	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr1	% FA	nd	0.72	nd
65	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr2	% FA	nd	0.88	nd
66	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr3	% FA	nd	1.01	nd
67	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr4	% FA	nd	1.21	nd
68	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr1	% FA	nd	2.5	nd
69	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr2	% FA	nd	3.5	nd
70	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr3	% FA	nd	4.5	nd
71	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr4	% FA	nd	6	nd
72	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr1	% FA	nd	3.9	nd
73	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr2	% FA	nd	5	nd
74	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr3	% FA	nd	6.3	nd

Appendix F
Observational results: major adverse cardiac events

Row	Study PMID	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
58	Woodward 2011 21345851	HR	nd	nd	nd	0.75	0.62	0.92		
59	Woodward 2011 21345851	HR	nd	nd	nd	0.76	0.62	0.93		
60	Itakura 2011 21099130	HR	nd	nd	nd	0.98	0.7	1.36		
61	Itakura 2011 21099130	HR	nd	nd	nd	0.95	0.76	1.2		
62	Itakura 2011 21099130	HR	nd	nd	nd	0.8	0.64	0.99		
63	Matsumoto 2013 23098619	OR	1000	nd	nd	0.94	0.85	1.03		
64	de Oliveira 2013 24351702	HR	56	752	19778	Reference group			P trend	0.11
65	de Oliveira 2013 24351702	HR	58	701	nd	1.05	0.72	1.53		
66	de Oliveira 2013 24351702	HR	43	747	nd	0.77	0.51	1.16		
67	de Oliveira 2013 24351702	HR	32	637	nd	0.75	0.48	1.18		
68	de Oliveira 2013 24351702	HR	59	694	19778	Reference group			P trend	<0.001
69	de Oliveira 2013 24351702	HR	61	738	nd	0.95	0.65	1.39		
70	de Oliveira 2013 24351702	HR	46	693	nd	0.7	0.45	1.08		
71	de Oliveira 2013 24351702	HR	23	712	nd	0.39	0.22	0.67		
72	de Oliveira 2013 24351702	HR	63	736	19778	Reference group			P trend	0.002
73	de Oliveira 2013 24351702	HR	59	688	nd	0.97	0.67	1.4		
74	de Oliveira 2013 24351702	HR	40	713	nd	0.64	0.41	1		

Appendix F
Observational results: major adverse cardiac events

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup
75	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke, death, or other CVD death	Healthy	Healthy, multiethnic Adults	All
76	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke death, or other CVD death	Healthy	Healthy, multiethnic Adults	All
77	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke death, or other CVD death	Healthy	Healthy, multiethnic Adults	All
78	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke death, or other CVD death	Healthy	Healthy, multiethnic Adults	All
79	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke death, or other CVD death	Healthy	Healthy, multiethnic Adults	All
80	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke death, or other CVD death	Healthy	Healthy, multiethnic Adults	All
81	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke death, or other CVD death	Healthy	Healthy, multiethnic Adults	All
82	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke death, or other CVD death	Healthy	Healthy, multiethnic Adults	All
83	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke death, or other CVD death	Healthy	Healthy, multiethnic Adults	All
84	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke death, or other CVD death	Healthy	Healthy, multiethnic Adults	All
85	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke death, or other CVD death	Healthy	Healthy, multiethnic Adults	All
86	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke death, or other CVD death	Healthy	Healthy, multiethnic Adults	All
87	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke death, or other CVD death	Healthy	Healthy, multiethnic Adults	All
88	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke death, or other CVD death	Healthy	Healthy, multiethnic Adults	All
89	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke death, or other CVD death	Healthy	Healthy, multiethnic Adults	All
90	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke death, or other CVD death	Healthy	Healthy, multiethnic Adults	All
91	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke death, or other CVD death	Healthy	Healthy, multiethnic Adults	All

Appendix F
Observational results: major adverse cardiac events

Row	Study PMID	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure	Supplement
75	de Oliveira 2013 24351702	nd/2837 (nd)	10 y	EPA+DHA+DPA	Phospholipid	No
76	de Oliveira 2013 24351702	nd/2372 (nd)	10 y	EPA	Intake	No
77	de Oliveira 2013 24351702	nd/2372 (nd)	10 y	EPA	Intake	No
78	de Oliveira 2013 24351702	nd/2372 (nd)	10 y	EPA	Intake	No
79	de Oliveira 2013 24351702	nd/2372 (nd)	10 y	EPA	Intake	No
80	de Oliveira 2013 24351702	nd/2372 (nd)	10 y	DPA	Intake	No
81	de Oliveira 2013 24351702	nd/2372 (nd)	10 y	DPA	Intake	No
82	de Oliveira 2013 24351702	nd/2372 (nd)	10 y	DPA	Intake	No
83	de Oliveira 2013 24351702	nd/2372 (nd)	10 y	DPA	Intake	No
84	de Oliveira 2013 24351702	nd/2372 (nd)	10 y	DHA	Intake	No
85	de Oliveira 2013 24351702	nd/2372 (nd)	10 y	DHA	Intake	No
86	de Oliveira 2013 24351702	nd/2372 (nd)	10 y	DHA	Intake	No
87	de Oliveira 2013 24351702	nd/2372 (nd)	10 y	DHA	Intake	No
88	de Oliveira 2013 24351702	nd/2837 (nd)	10 y	EPA+DHA+DPA	Intake	No
89	de Oliveira 2013 24351702	nd/2837 (nd)	10 y	EPA+DHA+DPA	Intake	No
90	de Oliveira 2013 24351702	nd/2837 (nd)	10 y	EPA+DHA+DPA	Intake	No
91	de Oliveira 2013 24351702	nd/2837 (nd)	10 y	EPA+DHA+DPA	Intake	No

Appendix F
Observational results: major adverse cardiac events

Row	Study PMID	Adjustments	Quantile	n3 units	Quantile low	Quantile median	Quantile high
75	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr4	% FA	nd	8.7	nd
76	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr1	mg/d	nd	10	nd
77	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr2	mg/d	nd	20	nd
78	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr3	mg/d	nd	40	nd
79	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr4	mg/d	nd	90	nd
80	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr1	mg/d	nd	4	nd
81	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr2	mg/d	nd	10	nd
82	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr3	mg/d	nd	19	nd
83	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr4	mg/d	nd	39	nd
84	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr1	mg/d	nd	20	nd
85	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr2	mg/d	nd	50	nd
86	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr3	mg/d	nd	80	nd
87	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr4	mg/d	nd	150	nd
88	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr1	mg/d	nd	40	nd
89	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr2	mg/d	nd	80	nd
90	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr3	mg/d	nd	140	nd
91	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr4	mg/d	nd	280	nd

Appendix F
Observational results: major adverse cardiac events

Row	Study PMID	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
75	de Oliveira 2013 24351702	HR	27	700	nd	0.47	0.28	0.79		
76	de Oliveira 2013 24351702	HR	56	599	19778	Reference group			P trend	0.03
77	de Oliveira 2013 24351702	HR	40	547	nd	0.94	0.62	1.42		
78	de Oliveira 2013 24351702	HR	33	585	nd	0.65	0.42	1.03		
79	de Oliveira 2013 24351702	HR	32	641	nd	0.6	0.37	0.98		
80	de Oliveira 2013 24351702	HR	53	622	19778	Reference group			P trend	0.02
81	de Oliveira 2013 24351702	HR	50	618	nd	1.1	0.74	1.63		
82	de Oliveira 2013 24351702	HR	30	559	nd	0.67	0.42	1.07		
83	de Oliveira 2013 24351702	HR	28	573	nd	0.59	0.35	0.97		
84	de Oliveira 2013 24351702	HR	46	606	19778	Reference group			P trend	0.048
85	de Oliveira 2013 24351702	HR	45	572	nd	0.98	0.64	1.49		
86	de Oliveira 2013 24351702	HR	42	600	nd	0.92	0.59	1.44		
87	de Oliveira 2013 24351702	HR	28	594	nd	0.6	0.35	1.02		
88	de Oliveira 2013 24351702	HR	47	600	19778	Reference group			P trend	0.05
89	de Oliveira 2013 24351702	HR	47	546	nd	1.16	0.77	1.75		
90	de Oliveira 2013 24351702	HR	39	651	nd	0.81	0.52	1.28		
91	de Oliveira 2013 24351702	HR	28	575	nd	0.64	0.38	1.09		

Appendix F
Observational results: major adverse cardiac events

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup
92	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke, death, or other CVD death	Healthy	Healthy, multiethnic Adults	All
93	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke, death, or other CVD death	Healthy	Healthy, multiethnic Adults	All
94	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke, death, or other CVD death	Healthy	Healthy, multiethnic Adults	All
95	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke, death, or other CVD death	Healthy	Healthy, multiethnic Adults	All
96	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke death, or other CVD death	Healthy	Healthy, multiethnic Adults	All
97	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke death, or other CVD death	Healthy	Healthy, multiethnic Adults	All
98	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke death, or other CVD death	Healthy	Healthy, multiethnic Adults	All
99	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke death, or other CVD death	Healthy	Healthy, multiethnic Adults	All
100	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke, death, or other CVD death	Healthy	Healthy, multiethnic Adults	All
101	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke, death, or other CVD death	Healthy	Healthy, multiethnic Adults	All
102	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke, death, or other CVD death	Healthy	Healthy, multiethnic Adults	All
103	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke, death, or other CVD death	Healthy	Healthy, multiethnic Adults	All
104	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke, death, or other CVD death	Healthy	Healthy, multiethnic Adults	All
105	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke, death, or other CVD death	Healthy	Healthy, multiethnic Adults	All
106	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke, death, or other CVD death	Healthy	Healthy, multiethnic Adults	All
107	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke, death, or other CVD death	Healthy	Healthy, multiethnic Adults	All
109	**Subgroup analyses**						

Appendix F
Observational results: major adverse cardiac events

Row	Study PMID	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure	Supplement
92	de Oliveira 2013 24351702	nd/2837 (nd)	10 y	ALA	Phospholipid	No
93	de Oliveira 2013 24351702	nd/2837 (nd)	10 y	ALA	Phospholipid	No
94	de Oliveira 2013 24351702	nd/2837 (nd)	10 y	ALA	Phospholipid	No
95	de Oliveira 2013 24351702	nd/2837 (nd)	10 y	ALA	Phospholipid	No
96	de Oliveira 2013 24351702	nd/2372 (nd)	10 y	ALA	Intake	No
97	de Oliveira 2013 24351702	nd/2372 (nd)	10 y	ALA	Intake	No
98	de Oliveira 2013 24351702	nd/2372 (nd)	10 y	ALA	Intake	No
99	de Oliveira 2013 24351702	nd/2372 (nd)	10 y	ALA	Intake	No
100	de Oliveira 2013 24351702	189/2837 (6.66)	10 y	EPA	Phospholipid	No
101	de Oliveira 2013 24351702	189/2837 (6.66)	10 y	EPA	Phospholipid	No
102	de Oliveira 2013 24351702	189/2837 (6.66)	10 y	EPA	Phospholipid	No
103	de Oliveira 2013 24351702	189/2837 (6.66)	10 y	EPA	Phospholipid	No
104	de Oliveira 2013 24351702	189/2837 (6.66)	10 y	EPA	Phospholipid	No
105	de Oliveira 2013 24351702	189/2837 (6.66)	10 y	DPA	Phospholipid	No
106	de Oliveira 2013 24351702	189/2837 (6.66)	10 y	DHA	Phospholipid	No
107	de Oliveira 2013 24351702	189/2837 (6.66)	10 y	EPA+DHA+DPA	Phospholipid	No
109	**Subgroup analyses**					

Appendix F

Observational results: major adverse cardiac events

Row	Study PMID	Adjustments	Quantile	n3 units	Quantile low	Quantile median	Quantile high
92	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr1	% FA	nd	0.11	nd
93	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr2	% FA	nd	0.15	nd
94	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr3	% FA	nd	0.19	nd
95	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr4	% FA	nd	0.25	nd
96	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr1	mg/d	nd	390	nd
97	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr2	mg/d	nd	690	nd
98	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr3	mg/d	nd	1020	nd
99	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr4	mg/d	nd	1610	nd
100	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr1	% FA	nd	0.4	nd
101	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr2	% FA	nd	0.6	nd
102	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr3	% FA	nd	0.86	nd
103	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	Qr4	% FA	nd	1.62	nd
104	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	All	% FA	nd	nd	nd
105	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	All	% FA	nd	nd	nd
106	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	All	% FA	nd	nd	nd
107	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	All	% FA	nd	nd	nd
109	**Subgroup analyses**						

Appendix F
Observational results: major adverse cardiac events

Row	Study PMID	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
92	de Oliveira 2013 24351702	HR	63	883	19778	Reference group			P trend	0.51
93	de Oliveira 2013 24351702	HR	37	569	nd	0.96	0.63	1.43		
94	de Oliveira 2013 24351702	HR	46	757	nd	0.92	0.62	1.35		
95	de Oliveira 2013 24351702	HR	43	628	nd	1.19	0.79	1.78		
96	de Oliveira 2013 24351702	HR	44	700	19778	Reference group			P trend	0.2
97	de Oliveira 2013 24351702	HR	42	592	nd	0.88	0.56	1.34		
98	de Oliveira 2013 24351702	HR	43	555	nd	0.94	0.55	1.59		
99	de Oliveira 2013 24351702	HR	32	525	nd	0.61	0.29	1.28		
100	de Oliveira 2013 24351702	HR	66	732	19778	Reference group			P trend	0.01
101	de Oliveira 2013 24351702	HR	48	711	nd	0.75	0.51	1.09		
102	de Oliveira 2013 24351702	HR	47	695	nd	0.84	0.56	1.25		
103	de Oliveira 2013 24351702	HR	28	699	nd	0.49	0.3	0.79		
104	de Oliveira 2013 24351702	HR	189	NA	19778	0.59	0.4	0.86	P Interaction	0.9
105	de Oliveira 2013 24351702	HR	189	NA	19778	0.71	0.49	1.02	P Interaction	0.01
106	de Oliveira 2013 24351702	HR	189	NA	19778	0.48	0.3	0.75	P Interaction	0.85
107	de Oliveira 2013 24351702	HR	189	NA	19778	0.46	0.29	0.72	P Interaction	0.88
109	**Subgroup analyses**									

Appendix F

Observational results: major adverse cardiac events

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup
110	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke, death, or other CVD death	Healthy	Healthy, multiethnic Adults	White
111	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke, death, or other CVD death	Healthy	Healthy, multiethnic Adults	Chinese
112	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke, death, or other CVD death	Healthy	Healthy, multiethnic Adults	African American
113	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke, death, or other CVD death	Healthy	Healthy, multiethnic Adults	Hispanic
114	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke, death, or other CVD death	Healthy	Healthy, multiethnic Adults	White
115	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke, death, or other CVD death	Healthy	Healthy, multiethnic Adults	Chinese
116	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke, death, or other CVD death	Healthy	Healthy, multiethnic Adults	African American
117	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke, death, or other CVD death	Healthy	Healthy, multiethnic Adults	Hispanic
118	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke, death, or other CVD death	Healthy	Healthy, multiethnic Adults	White
119	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke, death, or other CVD death	Healthy	Healthy, multiethnic Adults	Chinese
120	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke, death, or other CVD death	Healthy	Healthy, multiethnic Adults	African American
121	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke, death, or other CVD death	Healthy	Healthy, multiethnic Adults	Hispanic
122	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke, death, or other CVD death	Healthy	Healthy, multiethnic Adults	White
123	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke, death, or other CVD death	Healthy	Healthy, multiethnic Adults	Chinese
124	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke, death, or other CVD death	Healthy	Healthy, multiethnic Adults	African American
125	de Oliveira 2013 24351702	MESA	MACE	MI, resuscitated cardiac arrest, CHD death, other atherosclerotic death, angina, stroke, stroke, death, or other CVD death	Healthy	Healthy, multiethnic Adults	Hispanic

Appendix F
Observational results: major adverse cardiac events

Row	Study PMID	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure	Supplement
110	de Oliveira 2013 24351702	62/724 (8.56)	10 y	DPA	Phospholipid	No
111	de Oliveira 2013 24351702	28/712 (3.93)	10 y	DPA	Phospholipid	No
112	de Oliveira 2013 24351702	48/696 (6.9)	10 y	DPA	Phospholipid	No
113	de Oliveira 2013 24351702	51/705 (7.23)	10 y	DPA	Phospholipid	No
114	de Oliveira 2013 24351702	62/724 (8.56)	10 y	DHA	Phospholipid	No
115	de Oliveira 2013 24351702	28/712 (3.93)	10 y	DHA	Phospholipid	No
116	de Oliveira 2013 24351702	48/696 (6.9)	10 y	DHA	Phospholipid	No
117	de Oliveira 2013 24351702	51/705 (7.23)	10 y	DHA	Phospholipid	No
118	de Oliveira 2013 24351702	62/724 (8.56)	10 y	EPA+DHA+DPA	Phospholipid	No
119	de Oliveira 2013 24351702	28/712 (3.93)	10 y	EPA+DHA+DPA	Phospholipid	No
120	de Oliveira 2013 24351702	48/696 (6.9)	10 y	EPA+DHA+DPA	Phospholipid	No
121	de Oliveira 2013 24351702	51/705 (7.23)	10 y	EPA+DHA+DPA	Phospholipid	No
122	de Oliveira 2013 24351702	62/724 (8.56)	10 y	EPA	Phospholipid	No
123	de Oliveira 2013 24351702	28/712 (3.93)	10 y	EPA	Phospholipid	No
124	de Oliveira 2013 24351702	48/696 (6.9)	10 y	EPA	Phospholipid	No
125	de Oliveira 2013 24351702	51/705 (7.23)	10 y	EPA	Phospholipid	No

Appendix F
Observational results: major adverse cardiac events

Row	Study PMID	Adjustments	Quantile	n3 units	Quantile low	Quantile median	Quantile high
110	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	nd	nd	nd	nd	nd
111	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	nd	nd	nd	nd	nd
112	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	nd	nd	nd	nd	nd
113	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	nd	nd	nd	nd	nd
114	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	nd	nd	nd	nd	nd
115	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	nd	nd	nd	nd	nd
116	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	nd	nd	nd	nd	nd
117	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	nd	nd	nd	nd	nd
118	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	nd	nd	nd	nd	nd
119	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	nd	nd	nd	nd	nd
120	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	nd	nd	nd	nd	nd
121	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	nd	nd	nd	nd	nd
122	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	nd	nd	nd	nd	nd
123	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	nd	nd	nd	nd	nd
124	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	nd	nd	nd	nd	nd
125	de Oliveira 2013 24351702	field center, age, sex, race/ethnicity, education(<highschool, high school, >high school), cigarete smoking(never, current, former, and pack-years), alcohol, physical activity, BMI, prevalent diabetes, total energy intake, weekly dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, transfat intake	nd	nd	nd	nd	nd

Appendix F
Observational results: major adverse cardiac events

Row	Study PMID	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
110	de Oliveira 2013 24351702	HR	62	NA	nd	0.41	0.21	0.82		
111	de Oliveira 2013 24351702	HR	28	NA	nd	0.3	0.11	0.81		
112	de Oliveira 2013 24351702	HR	48	NA	nd	1.51	0.74	3.09		
113	de Oliveira 2013 24351702	HR	51	NA	nd	1.33	0.61	2.9		
114	de Oliveira 2013 24351702	HR	62	NA	nd	0.34	0.15	0.81		
115	de Oliveira 2013 24351702	HR	28	NA	nd	0.37	0.12	1.08		
116	de Oliveira 2013 24351702	HR	48	NA	nd	0.42	0.17	1.05		
117	de Oliveira 2013 24351702	HR	51	NA	nd	0.73	0.25	2.13		
118	de Oliveira 2013 24351702	HR	62	NA	nd	0.28	0.12	0.68		
119	de Oliveira 2013 24351702	HR	28	NA	nd	0.37	0.13	1.03		
120	de Oliveira 2013 24351702	HR	48	NA	nd	0.51	0.2	1.27		
121	de Oliveira 2013 24351702	HR	51	NA	nd	0.79	0.26	2.38		
122	de Oliveira 2013 24351702	HR	62	NA	nd	0.38	0.18	0.79		
123	de Oliveira 2013 24351702	HR	28	NA	nd	0.57	0.25	1.28		
124	de Oliveira 2013 24351702	HR	48	NA	nd	0.77	0.4	1.5		
125	de Oliveira 2013 24351702	HR	51	NA	nd	0.87	0.34	2.22		

Appendix F Observational results: coronary artery bypass graft surgery

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA
2	Ascherio 1995 7885425	Health Professional Follow-up Study	Revascularization	CABG	Healthy	Healthy 40-75 yo men without diagnosis of myocardial infarction, angina, stroke, transient ischemic attack, or peripheral arterial disease, or had undergone coronary artery surgery.	All	735/44895 (1.64)	6 y	EPA+DHA
3	Ascherio 1995 7885425	Health Professional Follow-up Study	Revascularization	CABG	Healthy	Healthy 40-75 yo men without diagnosis of myocardial infarction, angina, stroke, transient ischemic attack, or peripheral arterial disease, or had undergone coronary artery surgery.	All	735/44895 (1.64)	6 y	EPA+DHA
4	Ascherio 1995 7885425	Health Professional Follow-up Study	Revascularization	CABG	Healthy	Healthy 40-75 yo men without diagnosis of myocardial infarction, angina, stroke, transient ischemic attack, or peripheral arterial disease, or had undergone coronary artery surgery.	All	735/44895 (1.64)	6 y	EPA+DHA
5	Ascherio 1995 7885425	Health Professional Follow-up Study	Revascularization	CABG	Healthy	Healthy 40-75 yo men without diagnosis of myocardial infarction, angina, stroke, transient ischemic attack, or peripheral arterial disease, or had undergone coronary artery surgery.	All	735/44895 (1.64)	6 y	EPA+DHA
6	Ascherio 1995 7885425	Health Professional Follow-up Study	Revascularization	CABG	Healthy	Healthy 40-75 yo men without diagnosis of myocardial infarction, angina, stroke, transient ischemic attack, or peripheral arterial disease, or had undergone coronary artery surgery.	All	735/44895 (1.64)	6 y	EPA+DHA

Appendix F Observational results: coronary artery bypass graft surgery

Row	Study PMID	n3 measure	Supplement	Adjustments	Quantile	n3 units	Quantile low	Quantile median	Quantile high	Metric	n Cases
2	Ascherio 1995 7885425	Intake	No	age, BMI, smoking habits, alcohol consumption, history of hypertension, history of diabetes, history of hypercholesterolemia, family history of myocardial infarction before 60 years of age, profession	Qt1	g/d	0.01	nd	0.11	RR	131
3	Ascherio 1995 7885425	Intake	No	age, BMI, smoking habits, alcohol consumption, history of hypertension, history of diabetes, history of hypercholesterolemia, family history of myocardial infarction before 60 years of age, profession	Qt2	g/d	0.12	nd	0.19	RR	132
4	Ascherio 1995 7885425	Intake	No	age, BMI, smoking habits, alcohol consumption, history of hypertension, history of diabetes, history of hypercholesterolemia, family history of myocardial infarction before 60 years of age, profession	Qt3	g/d	0.2	nd	0.28	RR	142
5	Ascherio 1995 7885425	Intake	No	age, BMI, smoking habits, alcohol consumption, history of hypertension, history of diabetes, history of hypercholesterolemia, family history of myocardial infarction before 60 years of age, profession	Qt4	g/d	0.29	nd	0.41	RR	161
6	Ascherio 1995 7885425	Intake	No	age, BMI, smoking habits, alcohol consumption, history of hypertension, history of diabetes, history of hypercholesterolemia, family history of myocardial infarction before 60 years of age, profession	Qt5	g/d	0.42	nd	6.52	RR	169

Appendix F Observational results: coronary artery bypass graft surgery

Row	Study PMID	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
2	Ascherio 1995 7885425	9329	50499	Reference group			Q5 vs. Q1	0.09
3	Ascherio 1995 7885425	9220	49902	0.97	0.76	1.24		
4	Ascherio 1995 7885425	9005	48613	1.05	0.82	1.33		
5	Ascherio 1995 7885425	8860	47722	1.15	0.91	1.45		
6	Ascherio 1995 7885425	8481	45343	1.16	0.92	1.47		

Appendix F
Observational results: all-cause death

Outcome	Study PMID	Study Name	Outcome2	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure
2	Dolecek 1992 1579579	MRFIT	Death, all-cause	CVD, Cancer and other	Healthy	Men aged 35-57 assigned to the usual care group	Men	522/6258 (8.34)	10.5 y	EPA+DHA+DPA	Intake
3	Dolecek 1992 1579579	MRFIT	Death, all-cause	CVD, Cancer and other	Healthy	Men aged 35-57 assigned to the usual care group	Men	522/6258 (8.34)	10.5 y	EPA+DHA+DPA	Intake
4	Dolecek 1992 1579579	MRFIT	Death, all-cause	CVD, Cancer and other	Healthy	Men aged 35-57 assigned to the usual care group	Men	522/6258 (8.34)	10.5 y	EPA+DHA+DPA	Intake
5	Dolecek 1992 1579579	MRFIT	Death, all-cause	CVD, Cancer and other	Healthy	Men aged 35-57 assigned to the usual care group	Men	522/6258 (8.34)	10.5 y	EPA+DHA+DPA	Intake
6	Dolecek 1992 1579579	MRFIT	Death, all-cause	CVD, Cancer and other	Healthy	Men aged 35-57 assigned to the usual care group	Men	522/6258 (8.34)	10.5 y	EPA+DHA+DPA	Intake
7	Dolecek 1992 1579579	MRFIT	Death, all-cause	CVD, Cancer and other	Healthy	Men aged 35-57 assigned to the usual care group	Men	522/6258 (8.34)	10.5 y	EPA+DHA+DPA	Intake
8	Dolecek 1992 1579579	MRFIT	Death, all-cause	CVD, Cancer and other	Healthy	Men aged 35-57 assigned to the usual care group	Men	522/6258 (8.34)	10.5 y	EPA+DHA+DPA	Intake
9	Dolecek 1992 1579579	MRFIT	Death, all-cause	CVD, Cancer and other	Healthy	Men aged 35-57 assigned to the usual care group	Men	522/6258 (8.34)	10.5 y	EPA+DHA+DPA	Intake
10	Dolecek 1992 1579579	MRFIT	Death, all-cause	CVD, Cancer and other	Healthy	Men aged 35-57 assigned to the usual care group	Men	522/6258 (8.34)	10.5 y	EPA+DHA+DPA	Intake
11	Dolecek 1992 1579579	MRFIT	Death, all-cause	CVD, Cancer and other	Healthy	Men aged 35-57 assigned to the usual care group	Men	522/6258 (8.34)	10.5 y	EPA+DHA+DPA	Intake
12	Dolecek 1992 1579579	MRFIT	Death, all-cause	CVD, Cancer and other	Healthy	Men aged 35-57 assigned to the usual care group	Men	522/6258 (8.34)	10.5 y	ALA	Intake
13	Dolecek 1992 1579579	MRFIT	Death, all-cause	CVD, Cancer and other	Healthy	Men aged 35-57 assigned to the usual care group	Men	522/6258 (8.34)	10.5 y	ALA	Intake
14	Dolecek 1992 1579579	MRFIT	Death, all-cause	CVD, Cancer and other	Healthy	Men aged 35-57 assigned to the usual care group	Men	522/6258 (8.34)	10.5 y	ALA	Intake
15	Dolecek 1992 1579579	MRFIT	Death, all-cause	CVD, Cancer and other	Healthy	Men aged 35-57 assigned to the usual care group	Men	522/6258 (8.34)	10.5 y	ALA	Intake
16	Dolecek 1992 1579579	MRFIT	Death, all-cause	CVD, Cancer and other	Healthy	Men aged 35-57 assigned to the usual care group	Men	522/6258 (8.34)	10.5 y	ALA	Intake
17	Dolecek 1992 1579579	MRFIT	Death, all-cause	CVD, Cancer and other	Healthy	Men aged 35-57 assigned to the usual care group	Men	522/6258 (8.34)	10.5 y	ALA	Intake
18	Dolecek 1992 1579579	MRFIT	Death, all-cause	CVD, Cancer and other	Healthy	Men aged 35-57 assigned to the usual care group	Men	522/6258 (8.34)	10.5 y	ALA	Intake
19	Dolecek 1992 1579579	MRFIT	Death, all-cause	CVD, Cancer and other	Healthy	Men aged 35-57 assigned to the usual care group	Men	522/6258 (8.34)	10.5 y	ALA	Intake
20	Dolecek 1992 1579579	MRFIT	Death, all-cause	CVD, Cancer and other	Healthy	Men aged 35-57 assigned to the usual care group	Men	522/6258 (8.34)	10.5 y	ALA	Intake
21	Dolecek 1992 1579579	MRFIT	Death, all-cause	CVD, Cancer and other	Healthy	Men aged 35-57 assigned to the usual care group	Men	522/6258 (8.34)	10.5 y	ALA	Intake
22	Dolecek 1992 1579579	MRFIT	Death, all-cause	CVD, Cancer and other	Healthy	Men aged 35-57 assigned to the usual care group	Men	522/6258 (8.34)	10.5 y	ALA	Intake
23	Dolecek 1992 1579579	MRFIT	Death, all-cause	CVD, Cancer and other	Healthy	Men aged 35-57 assigned to the usual care group	Men	522/6258 (8.34)	10.5 y	ALA	Intake
24	Hara 2013 23047296	Osaka Acute Coronary Insufficiency Study	Death, all-cause	nd	CVD	AMI patients	No statin	nd/671 (nd)	4 y	DHA	Blood
25	Hara 2013 23047296	Osaka Acute Coronary Insufficiency Study	Death, all-cause	nd	CVD	AMI patients	No statin	nd/671 (nd)	4 y	DHA	Blood
26	Hara 2013 23047296	Osaka Acute Coronary Insufficiency Study	Death, all-cause	nd	CVD	AMI patients	No statin	nd/671 (nd)	4 y	DHA	Blood
27	Hara 2013 23047296	Osaka Acute Coronary Insufficiency Study	Death, all-cause	nd	CVD	AMI patients	No statin	nd/671 (nd)	4 y	EPA	Blood

Appendix F
Observational results: all-cause death

Outcome	Study PMID	Supplement	Adjustments	Quantile	n3 units	Quantile low	Quantile median
2	Dolecek 1992 1579579	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt1	g/d	nd	0 (mean)
3	Dolecek 1992 1579579	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt2	g/d	nd	0.009 (mean)
4	Dolecek 1992 1579579	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt3	g/d	nd	0.046 (mean)
5	Dolecek 1992 1579579	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt4	g/d	nd	0.153 (mean)
6	Dolecek 1992 1579579	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt5	g/d	nd	0.664 (mean)
7	Dolecek 1992 1579579	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt1	% kcal	nd	0 (mean)
8	Dolecek 1992 1579579	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt2	% kcal	nd	0.004 (mean)
9	Dolecek 1992 1579579	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt3	% kcal	nd	0.019 (mean)
10	Dolecek 1992 1579579	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt4	% kcal	nd	0.063 (mean)
11	Dolecek 1992 1579579	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt5	% kcal	nd	0.284 (mean)
12	Dolecek 1992 1579579	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt1	g/d	nd	0.873 (mean)
13	Dolecek 1992 1579579	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt2	g/d	nd	1.273 (mean)
14	Dolecek 1992 1579579	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt3	g/d	nd	1.577 (mean)
15	Dolecek 1992 1579579	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt4	g/d	nd	1.926 (mean)
16	Dolecek 1992 1579579	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt5	g/d	nd	2.802 (mean)
17	Dolecek 1992 1579579	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	All	g/d	nd	nd
18	Dolecek 1992 1579579	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt1	% kcal	nd	0.424 (mean)
19	Dolecek 1992 1579579	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt2	% kcal	nd	0.544 (mean)
20	Dolecek 1992 1579579	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt3	% kcal	nd	0.63 (mean)
21	Dolecek 1992 1579579	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt4	% kcal	nd	0.732 (mean)
22	Dolecek 1992 1579579	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt5	% kcal	nd	0.98 (mean)
23	Dolecek 1992 1579579	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	All	% kcal	all	nd
24	Hara 2013 23047296	No	Propensity score	T1	mcg/mL	nd	nd
25	Hara 2013 23047296	No	Propensity score	T2	mcg/mL	61.4	nd
26	Hara 2013 23047296	No	Propensity score	T3	mcg/mL	83.5	nd
27	Hara 2013 23047296	No	Propensity score	T1	mcg/mL	nd	nd

Appendix F
Observational results: all-cause death

Outcome	Study PMID	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
2	Dolecek 1992 1579579	nd	RR	nd	1307	nd	Reference group				<0.10
3	Dolecek 1992 1579579	nd	RR	nd	1197	nd	1.09	nd	nd	nd	
4	Dolecek 1992 1579579	nd	RR	nd	1251	nd	1.02	nd	nd	nd	
5	Dolecek 1992 1579579	nd	RR	nd	1252	nd	0.85	nd	nd	nd	
6	Dolecek 1992 1579579	nd	RR	nd	1251	nd	0.75	nd	nd	nd	
7	Dolecek 1992 1579579	nd	RR	nd	1307	nd	Reference group				<0.10
8	Dolecek 1992 1579579	nd	RR	nd	1196	nd	1.09	nd	nd	nd	
9	Dolecek 1992 1579579	nd	RR	nd	1252	nd	0.97	nd	nd	nd	
10	Dolecek 1992 1579579	nd	RR	nd	1252	nd	0.92	nd	nd	nd	
11	Dolecek 1992 1579579	nd	RR	nd	1251	nd	0.73	nd	nd	nd	
12	Dolecek 1992 1579579	nd	RR	nd	1251	nd	Reference group				<0.05
13	Dolecek 1992 1579579	nd	RR	nd	1253	nd	0.96	nd	nd	nd	
14	Dolecek 1992 1579579	nd	RR	nd	1251	nd	0.69	nd	nd	nd	
15	Dolecek 1992 1579579	nd	RR	nd	1251	nd	0.89	nd	nd	nd	
16	Dolecek 1992 1579579	nd	RR	nd	1252	nd	0.69	nd	nd	nd	
17	Dolecek 1992 1579579	nd	HR	522	6258	nd	0.834435359	nd	nd	nd	<0.05
18	Dolecek 1992 1579579	nd	RR	nd	1251	nd	Reference group				<0.05
19	Dolecek 1992 1579579	nd	RR	nd	1252	nd	0.86	nd	nd	nd	
20	Dolecek 1992 1579579	nd	RR	nd	1252	nd	0.85	nd	nd	nd	
21	Dolecek 1992 1579579	nd	RR	nd	1252	nd	0.75	nd	nd	nd	
22	Dolecek 1992 1579579	nd	RR	nd	1251	nd	0.68	nd	nd	nd	
23	Dolecek 1992 1579579	nd	HR	522	6258	nd	0.51845606	nd	nd	nd	<0.05
24	Hara 2013 23047296	61.4	HR	nd	239	nd	0.523560209	0.281690141	0.970873786	T2-3 vs. T1	0.0386
25	Hara 2013 23047296	83.5	HR	nd	236	nd	nd	nd	nd	nd	
26	Hara 2013 23047296	nd	HR	nd	237	nd	nd	nd	nd	nd	
27	Hara 2013 23047296	24.6	HR	nd	237	nd	0.689655172	0.374531835	1.265822785	T2-3 vs. T1	0.2315

Appendix F
Observational results: all-cause death

Outcome	Study PMID	Study Name	Outcome2	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure
28	Hara 2013 23047296	Osaka Acute Coronary Insufficiency Study	Death, all-cause	nd	CVD	AMI patients	No statin	nd/671 (nd)	4 y	EPA	Blood
29	Hara 2013 23047296	Osaka Acute Coronary Insufficiency Study	Death, all-cause	nd	CVD	AMI patients	No statin	nd/671 (nd)	4 y	EPA	Blood
30	Mozaffarian 2013 23546563	Cardiovascular Health Study	Death, all-cause	Total mortality	Healthy	Healthy age >= 65y	All	1625/3941 (41.2)	16y	All n-3	Plasma
31	Mozaffarian 2013 23546563	Cardiovascular Health Study	Death, all-cause	Total mortality	Healthy	Healthy age >= 65y	All	1625/3941 (41.2)	16y	All n-3	Plasma
32	Mozaffarian 2013 23546563	Cardiovascular Health Study	Death, all-cause	Total mortality	Healthy	Healthy age >= 65y	All	1625/3941 (41.2)	16y	All n-3	Plasma
33	Mozaffarian 2013 23546563	Cardiovascular Health Study	Death, all-cause	Total mortality	Healthy	Healthy age >= 65y	All	1625/3941 (41.2)	16y	All n-3	Plasma
34	Mozaffarian 2013 23546563	Cardiovascular Health Study	Death, all-cause	Total mortality	Healthy	Healthy age >= 65y	All	1625/3941 (41.2)	16y	All n-3	Plasma
35	Mozaffarian 2013 23546563	Cardiovascular Health Study	Death, all-cause	Total mortality	Healthy	Healthy age >= 65y	All	1625/3941 (41.2)	16y	DHA	Plasma
36	Mozaffarian 2013 23546563	Cardiovascular Health Study	Death, all-cause	Total mortality	Healthy	Healthy age >= 65y	All	1625/3941 (41.2)	16y	DHA	Plasma
37	Mozaffarian 2013 23546563	Cardiovascular Health Study	Death, all-cause	Total mortality	Healthy	Healthy age >= 65y	All	1625/3941 (41.2)	16y	DHA	Plasma
38	Mozaffarian 2013 23546563	Cardiovascular Health Study	Death, all-cause	Total mortality	Healthy	Healthy age >= 65y	All	1625/3941 (41.2)	16y	DHA	Plasma
39	Mozaffarian 2013 23546563	Cardiovascular Health Study	Death, all-cause	Total mortality	Healthy	Healthy age >= 65y	All	1625/3941 (41.2)	16y	DHA	Plasma
40	Mozaffarian 2013 23546563	Cardiovascular Health Study	Death, all-cause	Total mortality	Healthy	Healthy age >= 65y	All	1625/3941 (41.2)	16y	EPA	Plasma
41	Mozaffarian 2013 23546563	Cardiovascular Health Study	Death, all-cause	Total mortality	Healthy	Healthy age >= 65y	All	1625/3941 (41.2)	16y	EPA	Plasma
42	Mozaffarian 2013 23546563	Cardiovascular Health Study	Death, all-cause	Total mortality	Healthy	Healthy age >= 65y	All	1625/3941 (41.2)	16y	EPA	Plasma
43	Mozaffarian 2013 23546563	Cardiovascular Health Study	Death, all-cause	Total mortality	Healthy	Healthy age >= 65y	All	1625/3941 (41.2)	16y	EPA	Plasma
44	Mozaffarian 2013 23546563	Cardiovascular Health Study	Death, all-cause	Total mortality	Healthy	Healthy age >= 65y	All	1625/3941 (41.2)	16y	EPA	Plasma
45	Fretts 2014 25159901	Cardiovascular Health Study	Death, all-cause	Total mortality	Healthy	Healthy age >= 65y	All	1517/2583 (58.7)	12y	ALA	Intake

Appendix F
Observational results: all-cause death

Outcome	Study PMID	Supplement	Adjustments	Quantile	n3 units	Quantile low	Quantile median
28	Hara 2013 23047296	No	Propensity score	T2	mcg/mL	24.6	nd
29	Hara 2013 23047296	No	Propensity score	T3	mcg/mL	38.8	nd
30	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt1	% FA	nd	3.17
31	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt2	% FA	nd	3.72
32	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt3	% FA	nd	4.21
33	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt4	% FA	nd	4.8
34	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt5	% FA	nd	6.04
35	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt1	% FA	nd	1.95
36	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt2	% FA	nd	2.44
37	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt3	% FA	nd	2.87
38	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt4	% FA	nd	3.36
39	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt5	% FA	nd	4.34
40	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt1	% FA	nd	0.3
41	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt2	% FA	nd	0.41
42	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt3	% FA	nd	0.51
43	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt4	% FA	nd	0.64
44	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt5	% FA	nd	0.92
45	Fretts 2014 25159901	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt1	% fat intake	0.39	1.33

Appendix F
Observational results: all-cause death

Outcome	Study PMID	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
28	Hara 2013 23047296	38.8	HR	nd	237	nd	nd	nd	nd	nd	
29	Hara 2013 23047296	nd	HR	nd	238	nd	nd	nd	nd	nd	
30	Mozaffarian 2013 23546563	nd	HR	347	nd	5879	Reference group			P trend	<0.001
31	Mozaffarian 2013 23546563	nd	HR	343	nd	6158	0.9	0.78	1.05		
32	Mozaffarian 2013 23546563	nd	HR	340	nd	6077	0.93	0.8	1.08		
33	Mozaffarian 2013 23546563	nd	HR	309	nd	6242	0.85	0.72	0.99		
34	Mozaffarian 2013 23546563	nd	HR	286	nd	6437	0.7	0.59	0.83		
35	Mozaffarian 2013 23546563	nd	HR	349	nd	5999	Reference group			P trend	<0.001
36	Mozaffarian 2013 23546563	nd	HR	326	nd	6095	0.98	0.84	1.14		
37	Mozaffarian 2013 23546563	nd	HR	343	nd	6168	0.95	0.81	1.1		
38	Mozaffarian 2013 23546563	nd	HR	317	nd	6179	0.89	0.76	1.04		
39	Mozaffarian 2013 23546563	nd	HR	290	nd	6389	0.77	0.65	0.91		
40	Mozaffarian 2013 23546563	nd	HR	371	nd	5779	Reference group			P trend	0.001
41	Mozaffarian 2013 23546563	nd	HR	354	nd	5884	0.99	0.86	1.15		
42	Mozaffarian 2013 23546563	nd	HR	314	nd	6307	0.87	0.74	1.01		
43	Mozaffarian 2013 23546563	nd	HR	290	nd	6478	0.78	0.67	0.92		
44	Mozaffarian 2013 23546563	nd	HR	296	nd	6381	0.8	0.68	0.95		
45	Fretts 2014 25159901	1.45	HR	328	nd	4875	Reference group			P trend	<0.0001

Appendix F
Observational results: all-cause death

Outcome	Study PMID	Study Name	Outcome2	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure
46	Fretts 2014 25159901	Cardiovascular Health Study	Death, all-cause	Total mortality	Healthy	Healthy age >= 65y	All	1517/2583 (58.7)	12y	ALA	Intake
47	Fretts 2014 25159901	Cardiovascular Health Study	Death, all-cause	Total mortality	Healthy	Healthy age >= 65y	All	1517/2583 (58.7)	12y	ALA	Intake
48	Fretts 2014 25159901	Cardiovascular Health Study	Death, all-cause	Total mortality	Healthy	Healthy age >= 65y	All	1517/2583 (58.7)	12y	ALA	Intake
49	Fretts 2014 25159901	Cardiovascular Health Study	Death, all-cause	Total mortality	Healthy	Healthy age >= 65y	All	1517/2583 (58.7)	12y	ALA	Intake
50	Fretts 2014 25159901	Cardiovascular Health Study	Death, all-cause	Total mortality	Healthy	Healthy age >= 65y	All	1757/2709 (64.9)	16y	ALA	Plasma
51	Fretts 2014 25159901	Cardiovascular Health Study	Death, all-cause	Total mortality	Healthy	Healthy age >= 65y	All	1757/2709 (64.9)	16y	ALA	Plasma
52	Fretts 2014 25159901	Cardiovascular Health Study	Death, all-cause	Total mortality	Healthy	Healthy age >= 65y	All	1757/2709 (64.9)	16y	ALA	Plasma
53	Fretts 2014 25159901	Cardiovascular Health Study	Death, all-cause	Total mortality	Healthy	Healthy age >= 65y	All	1757/2709 (64.9)	16y	ALA	Plasma
54	Fretts 2014 25159901	Cardiovascular Health Study	Death, all-cause	Total mortality	Healthy	Healthy age >= 65y	All	1757/2709 (64.9)	16y	ALA	Plasma
55	Mozaffarian 2013 23546563	Cardiovascular Health Study	Death, all-cause	Total mortality	Healthy	Healthy age >= 65y	All	1625/3941 (41.2)	16y	DPA	Plasma
56	Mozaffarian 2013 23546563	Cardiovascular Health Study	Death, all-cause	Total mortality	Healthy	Healthy age >= 65y	All	1625/3941 (41.2)	16y	DPA	Plasma
57	Mozaffarian 2013 23546563	Cardiovascular Health Study	Death, all-cause	Total mortality	Healthy	Healthy age >= 65y	All	1625/3941 (41.2)	16y	DPA	Plasma
58	Mozaffarian 2013 23546563	Cardiovascular Health Study	Death, all-cause	Total mortality	Healthy	Healthy age >= 65y	All	1625/3941 (41.2)	16y	DPA	Plasma
59	Mozaffarian 2013 23546563	Cardiovascular Health Study	Death, all-cause	Total mortality	Healthy	Healthy age >= 65y	All	1625/3941 (41.2)	16y	DPA	Plasma
60	Nagata 2002 12397000	Takayama	Death, all-cause	all cause mortality	Healthy	Healthy >35, from Takayama	Men	1163/13355 (8.71)	7 y	EPA+DHA	Intake
61	Nagata 2002 12397000	Takayama	Death, all-cause	all cause mortality	Healthy	Healthy >35, from Takayama	Men	1163/13355 (8.71)	7 y	EPA+DHA	Intake
62	Nagata 2002 12397000	Takayama	Death, all-cause	all cause mortality	Healthy	Healthy >35, from Takayama	Men	1163/13355 (8.71)	7 y	EPA+DHA	Intake
63	Nagata 2002 12397000	Takayama	Death, all-cause	all cause mortality	Healthy	Healthy >35, from Takayama	Men	1163/13355 (8.71)	7 y	EPA+DHA	Intake
64	Nagata 2002 12397000	Takayama	Death, all-cause	all cause mortality	Healthy	Healthy >35, from Takayama	Men	1163/13355 (8.71)	7 y	EPA+DHA	Intake
65	Nagata 2002 12397000	Takayama	Death, all-cause	all cause mortality	Healthy	Healthy >35, from Takayama	Women	899/17125 (5.25)	7 y	EPA+DHA	Intake
66	Nagata 2002 12397000	Takayama	Death, all-cause	all cause mortality	Healthy	Healthy >35, from Takayama	Women	899/17125 (5.25)	7 y	EPA+DHA	Intake
67	Nagata 2002 12397000	Takayama	Death, all-cause	all cause mortality	Healthy	Healthy >35, from Takayama	Women	899/17125 (5.25)	7 y	EPA+DHA	Intake
68	Nagata 2002 12397000	Takayama	Death, all-cause	all cause mortality	Healthy	Healthy >35, from Takayama	Women	899/17125 (5.25)	7 y	EPA+DHA	Intake

Appendix F
Observational results: all-cause death

Outcome	Study PMID	Supplement	Adjustments	Quantile	n3 units	Quantile low	Quantile median
46	Fretts 2014 25159901	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt2	% fat intake	1.45	1.56
47	Fretts 2014 25159901	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt3	% fat intake	1.65	1.76
48	Fretts 2014 25159901	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt4	% fat intake	1.87	2
49	Fretts 2014 25159901	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt5	% fat intake	2.17	2.44
50	Fretts 2014 25159901	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt1	% FA	0.05	0.09
51	Fretts 2014 25159901	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt2	% FA	0.11	0.12
52	Fretts 2014 25159901	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt3	% FA	0.13	0.14
53	Fretts 2014 25159901	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt4	% FA	0.15	0.17
54	Fretts 2014 25159901	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt5	% FA	0.19	0.22
55	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt1	% FA	nd	0.63
56	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt2	% FA	nd	0.75
57	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt3	% FA	nd	0.82
58	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt4	% FA	nd	0.91
59	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt5	% FA	nd	1.04
60	Nagata 2002 12397000	No	age, total energy, marital status, BMI, smoking status, alcohol intake, coffee intake, exercise, and history of hypertension and diabetes	Qt1	mg/d	nd	410
61	Nagata 2002 12397000	No	age, total energy, marital status, BMI, smoking status, alcohol intake, coffee intake, exercise, and history of hypertension and diabetes	Qt2	mg/d	nd	602
62	Nagata 2002 12397000	No	age, total energy, marital status, BMI, smoking status, alcohol intake, coffee intake, exercise, and history of hypertension and diabetes	Qt3	mg/d	nd	788
63	Nagata 2002 12397000	No	age, total energy, marital status, BMI, smoking status, alcohol intake, coffee intake, exercise, and history of hypertension and diabetes	Qt4	mg/d	nd	1051
64	Nagata 2002 12397000	No	age, total energy, marital status, BMI, smoking status, alcohol intake, coffee intake, exercise, and history of hypertension and diabetes	Qt5	mg/d	nd	1582
65	Nagata 2002 12397000	No	age,total energy, marital status, years of education, alcohol intake, smoking status(never, former, current), age at menarche, menopausal status, exercise, and history of diabetes mellitus	Qt1	mg/d	nd	332
66	Nagata 2002 12397000	No	age,total energy, marital status, years of education, alcohol intake, smoking status(never, former, current), age at menarche, menopausal status, exercise, and history of diabetes mellitus	Qt2	mg/d	nd	486
67	Nagata 2002 12397000	No	age,total energy, marital status, years of education, alcohol intake, smoking status(never, former, current), age at menarche, menopausal status, exercise, and history of diabetes mellitus	Qt3	mg/d	nd	635
68	Nagata 2002 12397000	No	age,total energy, marital status, years of education, alcohol intake, smoking status(never, former, current), age at menarche, menopausal status, exercise, and history of diabetes mellitus	Qt4	mg/d	nd	832

Appendix F
Observational results: all-cause death

Outcome	Study PMID	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
46	Fretts 2014 25159901	1.65	HR	328	nd	4987	0.98	0.84	1.15		
47	Fretts 2014 25159901	1.87	HR	301	nd	5096	0.88	0.75	1.03		
48	Fretts 2014 25159901	2.17	HR	298	nd	5291	0.86	0.73	1.02		
49	Fretts 2014 25159901	4.88	HR	262	nd	5600	0.73	0.61	0.88		
50	Fretts 2014 25159901	0.11	HR	360	nd	6483	Reference group			P trend	0.11
51	Fretts 2014 25159901	0.13	HR	354	nd	6025	1.09	0.93	1.26		
52	Fretts 2014 25159901	0.15	HR	359	nd	6315	1.09	0.94	1.27		
53	Fretts 2014 25159901	0.19	HR	331	nd	6352	0.95	0.81	1.11		
54	Fretts 2014 25159901	0.47	HR	353	nd	6936	0.93	0.79	1.08		
55	Mozaffarian 2013 23546563	nd	HR	353	nd	5963	Reference group			P trend	0.004
56	Mozaffarian 2013 23546563	nd	HR	307	nd	6209	0.77	0.66	0.9		
57	Mozaffarian 2013 23546563	nd	HR	330	nd	6262	0.82	0.71	0.96		
58	Mozaffarian 2013 23546563	nd	HR	332	nd	6083	0.82	0.71	0.96		
59	Mozaffarian 2013 23546563	nd	HR	303	nd	6312	0.76	0.65	0.89		
60	Nagata 2002 12397000	nd	HR	205	18281 pt-yrs		Reference group			P trend	0.38
61	Nagata 2002 12397000	nd	HR	198	18315 pt-yrs		0.82	0.67	0.99		
62	Nagata 2002 12397000	nd	HR	225	nd	18186	0.87	0.72	1.05		
63	Nagata 2002 12397000	nd	HR	258	nd	18138	0.88	0.73	1.06		
64	Nagata 2002 12397000	nd	HR	277	nd	18116	0.87	0.73	1.05		
65	Nagata 2002 12397000	nd	HR	216	nd	21838	Reference group			P trend	0.01
66	Nagata 2002 12397000	nd	HR	179	nd	22111	0.92	0.76	1.13		
67	Nagata 2002 12397000	nd	HR	163	nd	22032	0.84	0.69	1.04		
68	Nagata 2002 12397000	nd	HR	178	nd	22025	0.9	0.73	1.09		

Appendix F
Observational results: all-cause death

Outcome	Study PMID	Study Name	Outcome2	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure
69	Nagata 2002 12397000	Takayama	Death, all-cause	all cause mortality	Healthy	Healthy >35, from Takayama	Women	899/17125 (5.25)	7 y	EPA+DHA	Intake
70	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	Death, all-cause	nd	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	EPA	Intake
71	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	Death, all-cause	nd	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	EPA	Intake
72	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	Death, all-cause	nd	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	EPA	Intake
73	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	Death, all-cause	nd	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	EPA	Intake
74	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	Death, all-cause	nd	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	EPA	Intake
75	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	Death, all-cause	nd	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	DHA	Intake
76	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	Death, all-cause	nd	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	DHA	Intake
77	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	Death, all-cause	nd	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	DHA	Intake
78	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	Death, all-cause	nd	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	DHA	Intake
79	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	Death, all-cause	nd	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	DHA	Intake
80	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	Death, all-cause	nd	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	EPA+DHA	Intake
81	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	Death, all-cause	nd	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	EPA+DHA	Intake
82	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	Death, all-cause	nd	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	EPA+DHA	Intake
83	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	Death, all-cause	nd	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	EPA+DHA	Intake
84	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	Death, all-cause	nd	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	EPA+DHA	Intake
85	Warensjo 2008 18614742	ULSAM	Death, all-cause	Total Mortality	Healthy	Healthy	All	1012/2009 (19.0/ 1000 person-yrs)	30.7	ALA	Plasma
86	Warensjo 2008 18614742	ULSAM	Death, all-cause	Total Mortality	Healthy	Healthy	All	1012/2009 (19.0/ 1000 person-yrs)	30.7	EPA	Plasma

Appendix F
Observational results: all-cause death

Outcome	Study PMID	Supplement	Adjustments	Quantile	n3 units	Quantile low	Quantile median
69	Nagata 2002 12397000	No	age,total energy, marital status, years of education, alcohol intake, smoking status(never, former, current), age at menarche, menopausal status, exercise, and history of diabetes mellitus	Qt5	mg/d	nd	1253
70	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt1	g/d	nd	0.006 (men), 0.005 (women)
71	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt2	g/d	nd	0.01 (men), 0.01 (women)
72	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt3	g/d	nd	0.02 (men), 0.02 (women)
73	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt4	g/d	nd	0.03 (men), 0.03 (women)
74	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt5	g/d	nd	0.07 (men), 0.06 (women)
75	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt1	g/d	nd	0.009 (men), 0.008 (women)
76	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt2	g/d	nd	0.02 (men), 0.02 (women)
77	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt3	g/d	nd	0.05 (men), 0.04 (women)
78	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt4	g/d	nd	0.08 (men), 0.08 (women)
79	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt5	g/d	nd	0.15 (men), 0.15 (women)
80	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt1	g/d	nd	nd
81	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt2	g/d	nd	nd
82	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt3	g/d	nd	nd
83	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt4	g/d	nd	nd
84	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt5	g/d	nd	nd
85	Warensjo 2008 18614742	NA	total cholestrol, BMI, smoking, physical activity, hypertension	All	% FA	nd	0.66 (SD = 0.16)
86	Warensjo 2008 18614742	NA	total cholestrol, BMI, smoking, physical activity, hypertension	All	% FA	0.9	1.3

Appendix F
Observational results: all-cause death

Outcome	Study PMID	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
69	Nagata 2002 12397000	nd	HR	163	nd	22118	0.77	0.52	0.94		
70	Takata 2013 23788668	nd	HR	2043	26860	nd	Reference group			P trend	<0.0001
71	Takata 2013 23788668	nd	HR	1220	nd	nd	0.88	0.81	0.94		
72	Takata 2013 23788668	nd	HR	1015	26860	nd	0.89	0.82	0.96		
73	Takata 2013 23788668	nd	HR	855	nd	nd	0.89	0.81	0.97		
74	Takata 2013 23788668	nd	HR	703	26858	nd	0.79	0.72	0.87		
75	Takata 2013 23788668	nd	HR	2057	26860	nd	Reference group			P trend	<0.0001
76	Takata 2013 23788668	nd	HR	1189	nd	nd	0.84	0.78	0.91		
77	Takata 2013 23788668	nd	HR	991	26860	nd	0.86	0.79	0.93		
78	Takata 2013 23788668	nd	HR	885	nd	nd	0.88	0.81	0.96		
79	Takata 2013 23788668	nd	HR	714	26858	nd	0.78	0.71	0.86		
80	Takata 2013 23788668	nd	HR	2053	26860	nd	Reference group			P trend	<0.0001
81	Takata 2013 23788668	nd	HR	1197	nd	nd	0.86	0.8	0.93		
82	Takata 2013 23788668	nd	HR	993	26860	nd	0.87	0.87	0.94		
83	Takata 2013 23788668	nd	HR	881	nd	nd	0.9	0.9	0.98		
84	Takata 2013 23788668	nd	HR	712	26858	nd	0.79	0.79	0.87		
85	Warensjo 2008 18614742	nd	HR	nd	nd	nd	1.03	0.97	1.1	Per % FA unit	
86	Warensjo 2008 18614742	1.6	HR	nd	nd	nd	1	0.94	1.08	Per % FA unit	

Appendix F
Observational results: all-cause death

Outcome	Study PMID	Study Name	Outcome2	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure
87	Warensjo 2008 18614742	ULSAM	Death, all-cause	Total Mortality	Healthy	Healthy	All	1012/2009 (19.0/ 1000 person-yrs)	30.7	DHA	Plasma
88	Yamagishi 2008 18786479	JACC	Death, all-cause	nd	Healthy	Healthy 40-79 yo	All	7008/57972 (12.09)	12.7 y	All n-3	Intake
89	Yamagishi 2008 18786479	JACC	Death, all-cause	nd	Healthy	Healthy 40-79 yo	All	7008/57972 (12.09)	12.7 y	All n-3	Intake
90	Yamagishi 2008 18786479	JACC	Death, all-cause	nd	Healthy	Healthy 40-79 yo	All	7008/57972 (12.09)	12.7 y	All n-3	Intake
91	Yamagishi 2008 18786479	JACC	Death, all-cause	nd	Healthy	Healthy 40-79 yo	All	7008/57972 (12.09)	12.7 y	All n-3	Intake
92	Yamagishi 2008 18786479	JACC	Death, all-cause	nd	Healthy	Healthy 40-79 yo	All	7008/57972 (12.09)	12.7 y	All n-3	Intake
93	Bell 2014 24496442	VITAL	Death, all-cause	Total mortality	Healthy	Men and women aged 50-76	All	3037/70287 (0.04)	6 y	EPA+DHA	Intake
94	Bell 2014 24496442	VITAL	Death, all-cause	Total mortality	Healthy	Men and women aged 50-76	All	3037/70287 (0.04)	6 y	EPA+DHA	Intake
95	Bell 2014 24496442	VITAL	Death, all-cause	Total mortality	Healthy	Men and women aged 50-76	All	3037/70287 (0.04)	6 y	EPA+DHA	Intake

Appendix F
Observational results: all-cause death

Outcome	Study PMID	Supplement	Adjustments	Quantile	n3 units	Quantile low	Quantile median
87	Warensjo 2008 18614742	NA	total cholestrol, BMI, smoking, physical activity, hypertension	All	% FA	0.56	0.68
88	Yamagishi 2008 18786479	No	age, sex, htn and dm history, smoking status, alcohol consumption, BMI, mental stress, walking, sports, education, total energy, dietary intake of cholesterol/saturated and omega-3FA/vegetables/fruit	Qt1	g/d	0.05	nd
89	Yamagishi 2008 18786479	No	age, sex, htn and dm history, smoking status, alcohol consumption, BMI, mental stress, walking, sports, education, total energy, dietary intake of cholesterol/saturated and omega-3FA/vegetables/fruit	Qt2	g/d	1.18	nd
90	Yamagishi 2008 18786479	No	age, sex, htn and dm history, smoking status, alcohol consumption, BMI, mental stress, walking, sports, education, total energy, dietary intake of cholesterol/saturated and omega-3FA/vegetables/fruit	Qt3	g/d	1.47	nd
91	Yamagishi 2008 18786479	No	age, sex, htn and dm history, smoking status, alcohol consumption, BMI, mental stress, walking, sports, education, total energy, dietary intake of cholesterol/saturated and omega-3FA/vegetables/fruit	Qt4	g/d	1.75	nd
92	Yamagishi 2008 18786479	No	age, sex, htn and dm history, smoking status, alcohol consumption, BMI, mental stress, walking, sports, education, total energy, dietary intake of cholesterol/saturated and omega-3FA/vegetables/fruit	Qt5	g/d	2.11	nd
93	Bell 2014 24496442	yes	age (as the time scale), sex, race/ethnicity, marital status (married/living together, never married, separated/divorced, widowed, or missing), education (high school graduate or less, some college, or college/advanced degree), total energy intake (kcal/day; continuous), body mass index (weight (kg)/height (m)2 (none, <1 drink/day, 1–2 drinks/day, >2 drinks/day, or missing), average physical activity in the 10 years before baseline (MET-hours/week; tertiles), self-rated health (excellent, very good, good, fair, or poor), mammogram in the last 2 years (yes/no), prostate-specific antigen test in the last 2 years (yes/no), sigmoidoscopy in the last 10 years (yes/no), current use of cholesterol-lowering medication (yes/no), aspirin use in the past 10 years (none, low, high, or missing), use of nonaspirin nonsteroidal antiinflammatory drugs in the past 10 years (none, low, high, or missing), smoking (never, 1–12.5 pack-years, 12.6–35.0 pack-years, or >35.0 pack-years), morbidity score,c percentage of calories derived from trans fat (quartiles), percentage of calories derived from saturated fat (quartiles), number of servings per day of fruits (quartiles), number of servings per day of vegetables (quartiles), years of estrogen therapy (none, <5, 5–9, ≥10, or missing), years of estrogen + progestin therapy (none, <5, 5–9, ≥10, or missing), age at menopause (≤39 years, 40–44 years, 45–49 years, 50–54 years, ≥55 years, or missing), age at death of father (≤59 years, 60–69 years, 70–79 years, 80–89 years, or ≥90 years), and age at death of mother (≤59 years, 60–69 years, 70–79 years, 80–89 years, or ≥90 years)	Qr1	g/day	0	nd
94	Bell 2014 24496442	yes	age (as the time scale), sex, race/ethnicity, marital status (married/living together, never married, separated/divorced, widowed, or missing), education (high school graduate or less, some college, or college/advanced degree), total energy intake (kcal/day; continuous), body mass index (weight (kg)/height (m)2 (none, <1 drink/day, 1–2 drinks/day, >2 drinks/day, or missing), average physical activity in the 10 years before baseline (MET-hours/week; tertiles), self-rated health (excellent, very good, good, fair, or poor), mammogram in the last 2 years (yes/no), prostate-specific antigen test in the last 2 years (yes/no), sigmoidoscopy in the last 10 years (yes/no), current use of cholesterol-lowering medication (yes/no), aspirin use in the past 10 years (none, low, high, or missing), use of nonaspirin nonsteroidal antiinflammatory drugs in the past 10 years (none, low, high, or missing), smoking (never, 1–12.5 pack-years, 12.6–35.0 pack-years, or >35.0 pack-years), morbidity score,c percentage of calories derived from trans fat (quartiles), percentage of calories derived from saturated fat (quartiles), number of servings per day of fruits (quartiles), number of servings per day of vegetables (quartiles), years of estrogen therapy (none, <5, 5–9, ≥10, or missing), years of estrogen + progestin therapy (none, <5, 5–9, ≥10, or missing), age at menopause (≤39 years, 40–44 years, 45–49 years, 50–54 years, ≥55 years, or missing), age at death of father (≤59 years, 60–69 years, 70–79 years, 80–89 years, or ≥90 years), and age at death of mother (≤59 years, 60–69 years, 70–79 years, 80–89 years, or ≥90 years)	Qr2	g/day	0.082	nd
95	Bell 2014 24496442	yes	age (as the time scale), sex, race/ethnicity, marital status (married/living together, never married, separated/divorced, widowed, or missing), education (high school graduate or less, some college, or college/advanced degree), total energy intake (kcal/day; continuous), body mass index (weight (kg)/height (m)2 (none, <1 drink/day, 1–2 drinks/day, >2 drinks/day, or missing), average physical activity in the 10 years before baseline (MET-hours/week; tertiles), self-rated health (excellent, very good, good, fair, or poor), mammogram in the last 2 years (yes/no), prostate-specific antigen test in the last 2 years (yes/no), sigmoidoscopy in the last 10 years (yes/no), current use of cholesterol-lowering medication (yes/no), aspirin use in the past 10 years (none, low, high, or missing), use of nonaspirin nonsteroidal antiinflammatory drugs in the past 10 years (none, low, high, or missing), smoking (never, 1–12.5 pack-years, 12.6–35.0 pack-years, or >35.0 pack-years), morbidity score,c percentage of calories derived from trans fat (quartiles), percentage of calories derived from saturated fat (quartiles), number of servings per day of fruits (quartiles), number of servings per day of vegetables (quartiles), years of estrogen therapy (none, <5, 5–9, ≥10, or missing), years of estrogen + progestin therapy (none, <5, 5–9, ≥10, or missing), age at menopause (≤39 years, 40–44 years, 45–49 years, 50–54 years, ≥55 years, or missing), age at death of father (≤59 years, 60–69 years, 70–79 years, 80–89 years, or ≥90 years), and age at death of mother (≤59 years, 60–69 years, 70–79 years, 80–89 years, or ≥90 years)	Qr3	g/day	0.174	nd

Appendix F
Observational results: all-cause death

Outcome	Study PMID	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
87	Warensjo 2008 18614742	0.81	HR	nd	nd	nd	0.95	0.89	1.02	Per % FA unit	
88	Yamagishi 2008 18786479	1.18	HR	1252	11594	735904	Reference group				0.1
89	Yamagishi 2008 18786479	1.47	HR	1262	11595	735904	0.97	0.9	1.06		
90	Yamagishi 2008 18786479	1.75	HR	1328	11594	735904	0.94	0.86	1.02		
91	Yamagishi 2008 18786479	2.11	HR	1415	11595	735904	0.94	0.85	1.03		
92	Yamagishi 2008 18786479	5.06	HR	1751	11594	735904	0.92	0.84	1.02		
93	Bell 2014 24496442	0.082	HR	935	17703	nd	1	nd	nd		0.004
94	Bell 2014 24496442	0.174	HR	785	17485	nd	0.83	0.75	0.91		
95	Bell 2014 24496442	0.322	HR	667	17601	nd	0.69	0.62	0.76		

Appendix F
Observational results: all-cause death

Outcome	Study PMID	Study Name	Outcome2	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure
96	Bell 2014 24496442	VITAL	Death, all-cause	Total mortality	Healthy	Men and women aged 50-76	All	3037/70287 (0.04)	6 y	EPA+DHA	Intake
97	Bell 2014 24496442	VITAL	Death, all-cause	Total mortality	Healthy	Men and women aged 50-76	All	3037/70287 (0.04)	6 y	EPA	Intake
98	Bell 2014 24496442	VITAL	Death, all-cause	Total mortality	Healthy	Men and women aged 50-76	All	3037/70287 (0.04)	6 y	EPA	Intake
99	Bell 2014 24496442	VITAL	Death, all-cause	Total mortality	Healthy	Men and women aged 50-76	All	3037/70287 (0.04)	6 y	EPA	Intake

Appendix F
Observational results: all-cause death

Outcome	Study PMID	Supplement	Adjustments	Quantile	n3 units	Quantile low	Quantile median
96	Bell 2014 24496442	yes	age (as the time scale), sex, race/ethnicity, marital status (married/living together, never married, separated/divorced, widowed, or missing), education (high school graduate or less, some college, or college/advanced degree), total energy intake (kcal/day; continuous), body mass index (weight (kg)/height (m)2 (none, <1 drink/day, 1–2 drinks/day, >2 drinks/day, or missing), average physical activity in the 10 years before baseline (MET-hours/week; tertiles), self-rated health (excellent, very good, good, fair, or poor), mammogram in the last 2 years (yes/no), prostate-specific antigen test in the last 2 years (yes/no), sigmoidoscopy in the last 10 years (yes/no), current use of cholesterol-lowering medication (yes/no), aspirin use in the past 10 years (none, low, high, or missing), use of nonaspirin nonsteroidal antiinflammatory drugs in the past 10 years (none, low, high, or missing), smoking (never, 1–12.5 pack-years, 12.6–35.0 pack-years, or >35.0 pack-years), morbidity score,c percentage of calories derived from trans fat (quartiles), percentage of calories derived from saturated fat (quartiles), number of servings per day of fruits (quartiles), number of servings per day of vegetables (quartiles), years of estrogen therapy (none, <5, 5–9, ≥10, or missing), years of estrogen + progestin therapy (none, <5, 5–9, ≥10, or missing), age at menopause (≤39 years, 40–44 years, 45–49 years, 50–54 years, ≥55 years, or missing), age at death of father (≤59 years, 60–69 years, 70–79 years, 80–89 years, or ≥90 years), and age at death of mother (≤59 years, 60–69 years, 70–79 years, 80–89 years, or ≥90 years)	Qr4	g/day	0.322	nd
97	Bell 2014 24496442	yes	age (as the time scale), sex, race/ethnicity, marital status (married/living together, never married, separated/divorced, widowed, or missing), education (high school graduate or less, some college, or college/advanced degree), total energy intake (kcal/day; continuous), body mass index (weight (kg)/height (m)2 (none, <1 drink/day, 1–2 drinks/day, >2 drinks/day, or missing), average physical activity in the 10 years before baseline (MET-hours/week; tertiles), self-rated health (excellent, very good, good, fair, or poor), mammogram in the last 2 years (yes/no), prostate-specific antigen test in the last 2 years (yes/no), sigmoidoscopy in the last 10 years (yes/no), current use of cholesterol-lowering medication (yes/no), aspirin use in the past 10 years (none, low, high, or missing), use of nonaspirin nonsteroidal antiinflammatory drugs in the past 10 years (none, low, high, or missing), smoking (never, 1–12.5 pack-years, 12.6–35.0 pack-years, or >35.0 pack-years), morbidity score,c percentage of calories derived from trans fat (quartiles), percentage of calories derived from saturated fat (quartiles), number of servings per day of fruits (quartiles), number of servings per day of vegetables (quartiles), years of estrogen therapy (none, <5, 5–9, ≥10, or missing), years of estrogen + progestin therapy (none, <5, 5–9, ≥10, or missing), age at menopause (≤39 years, 40–44 years, 45–49 years, 50–54 years, ≥55 years, or missing), age at death of father (≤59 years, 60–69 years, 70–79 years, 80–89 years, or ≥90 years), and age at death of mother (≤59 years, 60–69 years, 70–79 years, 80–89 years, or ≥90 years)	Qr1	g/day	0	nd
98	Bell 2014 24496442	yes	age (as the time scale), sex, race/ethnicity, marital status (married/living together, never married, separated/divorced, widowed, or missing), education (high school graduate or less, some college, or college/advanced degree), total energy intake (kcal/day; continuous), body mass index (weight (kg)/height (m)2 (none, <1 drink/day, 1–2 drinks/day, >2 drinks/day, or missing), average physical activity in the 10 years before baseline (MET-hours/week; tertiles), self-rated health (excellent, very good, good, fair, or poor), mammogram in the last 2 years (yes/no), prostate-specific antigen test in the last 2 years (yes/no), sigmoidoscopy in the last 10 years (yes/no), current use of cholesterol-lowering medication (yes/no), aspirin use in the past 10 years (none, low, high, or missing), use of nonaspirin nonsteroidal antiinflammatory drugs in the past 10 years (none, low, high, or missing), smoking (never, 1–12.5 pack-years, 12.6–35.0 pack-years, or >35.0 pack-years), morbidity score,c percentage of calories derived from trans fat (quartiles), percentage of calories derived from saturated fat (quartiles), number of servings per day of fruits (quartiles), number of servings per day of vegetables (quartiles), years of estrogen therapy (none, <5, 5–9, ≥10, or missing), years of estrogen + progestin therapy (none, <5, 5–9, ≥10, or missing), age at menopause (≤39 years, 40–44 years, 45–49 years, 50–54 years, ≥55 years, or missing), age at death of father (≤59 years, 60–69 years, 70–79 years, 80–89 years, or ≥90 years), and age at death of mother (≤59 years, 60–69 years, 70–79 years, 80–89 years, or ≥90 years)	Qr2	g/day	0.027	nd
99	Bell 2014 24496442	yes	age (as the time scale), sex, race/ethnicity, marital status (married/living together, never married, separated/divorced, widowed, or missing), education (high school graduate or less, some college, or college/advanced degree), total energy intake (kcal/day; continuous), body mass index (weight (kg)/height (m)2 (none, <1 drink/day, 1–2 drinks/day, >2 drinks/day, or missing), average physical activity in the 10 years before baseline (MET-hours/week; tertiles), self-rated health (excellent, very good, good, fair, or poor), mammogram in the last 2 years (yes/no), prostate-specific antigen test in the last 2 years (yes/no), sigmoidoscopy in the last 10 years (yes/no), current use of cholesterol-lowering medication (yes/no), aspirin use in the past 10 years (none, low, high, or missing), use of nonaspirin nonsteroidal antiinflammatory drugs in the past 10 years (none, low, high, or missing), smoking (never, 1–12.5 pack-years, 12.6–35.0 pack-years, or >35.0 pack-years), morbidity score,c percentage of calories derived from trans fat (quartiles), percentage of calories derived from saturated fat (quartiles), number of servings per day of fruits (quartiles), number of servings per day of vegetables (quartiles), years of estrogen therapy (none, <5, 5–9, ≥10, or missing), years of estrogen + progestin therapy (none, <5, 5–9, ≥10, or missing), age at menopause (≤39 years, 40–44 years, 45–49 years, 50–54 years, ≥55 years, or missing), age at death of father (≤59 years, 60–69 years, 70–79 years, 80–89 years, or ≥90 years), and age at death of mother (≤59 years, 60–69 years, 70–79 years, 80–89 years, or ≥90 years)	Qr3	g/day	0.058	nd

Appendix F
Observational results: all-cause death

Outcome	Study PMID	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
96	Bell 2014 24496442	nd	HR	650	17498	nd	0.64	0.58	0.71		
97	Bell 2014 24496442	0.027	HR	922	17573	nd	1	nd	nd		0.014
98	Bell 2014 24496442	0.058	HR	762	17571	nd	0.81	0.73	0.89		
99	Bell 2014 24496442	0.112	HR	664	17572	nd	0.69	0.62	0.76		

Appendix F
Observational results: all-cause death

Outcome	Study PMID	Study Name	Outcome2	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure
100	Bell 2014 24496442	VITAL	Death, all-cause	Total mortality	Healthy	Men and women aged 50-76	All	3037/70287 (0.04)	6 y	EPA	Intake
101	Bell 2014 24496442	VITAL	Death, all-cause	Total mortality	Healthy	Men and women aged 50-76	All	3037/70287 (0.04)	6 y	DHA	Intake
102	Bell 2014 24496442	VITAL	Death, all-cause	Total mortality	Healthy	Men and women aged 50-76	All	3037/70287 (0.04)	6 y	DHA	Intake
103	Bell 2014 24496442	VITAL	Death, all-cause	Total mortality	Healthy	Men and women aged 50-76	All	3037/70287 (0.04)	6 y	DHA	Intake

Appendix F
Observational results: all-cause death

Outcome	Study PMID	Supplement	Adjustments	Quantile	n3 units	Quantile low	Quantile median
100	Bell 2014 24496442	yes	age (as the time scale), sex, race/ethnicity, marital status (married/living together, never married, separated/divorced, widowed, or missing), education (high school graduate or less, some college, or college/advanced degree), total energy intake (kcal/day; continuous), body mass index (weight (kg)/height (m)2 (none, <1 drink/day, 1–2 drinks/day, >2 drinks/day, or missing), average physical activity in the 10 years before baseline (MET-hours/week; tertiles), self-rated health (excellent, very good, good, fair, or poor), mammogram in the last 2 years (yes/no), prostate-specific antigen test in the last 2 years (yes/no), sigmoidoscopy in the last 10 years (yes/no), current use of cholesterol-lowering medication (yes/no), aspirin use in the past 10 years (none, low, high, or missing), use of nonaspirin nonsteroidal antiinflammatory drugs in the past 10 years (none, low, high, or missing), smoking (never, 1–12.5 pack-years, 12.6–35.0 pack-years, or >35.0 pack-years), morbidity score,c percentage of calories derived from trans fat (quartiles), percentage of calories derived from saturated fat (quartiles), number of servings per day of fruits (quartiles), number of servings per day of vegetables (quartiles), years of estrogen therapy (none, <5, 5–9, ≥10, or missing), years of estrogen + progestin therapy (none, <5, 5–9, ≥10, or missing), age at menopause (≤39 years, 40–44 years, 45–49 years, 50–54 years, ≥55 years, or missing), age at death of father (≤59 years, 60–69 years, 70–79 years, 80–89 years, or ≥90 years), and age at death of mother (≤59 years, 60–69 years, 70–79 years, 80–89 years, or ≥90 years)	Qr4	g/day	0.112	nd
101	Bell 2014 24496442	yes	age (as the time scale), sex, race/ethnicity, marital status (married/living together, never married, separated/divorced, widowed, or missing), education (high school graduate or less, some college, or college/advanced degree), total energy intake (kcal/day; continuous), body mass index (weight (kg)/height (m)2 (none, <1 drink/day, 1–2 drinks/day, >2 drinks/day, or missing), average physical activity in the 10 years before baseline (MET-hours/week; tertiles), self-rated health (excellent, very good, good, fair, or poor), mammogram in the last 2 years (yes/no), prostate-specific antigen test in the last 2 years (yes/no), sigmoidoscopy in the last 10 years (yes/no), current use of cholesterol-lowering medication (yes/no), aspirin use in the past 10 years (none, low, high, or missing), use of nonaspirin nonsteroidal antiinflammatory drugs in the past 10 years (none, low, high, or missing), smoking (never, 1–12.5 pack-years, 12.6–35.0 pack-years, or >35.0 pack-years), morbidity score,c percentage of calories derived from trans fat (quartiles), percentage of calories derived from saturated fat (quartiles), number of servings per day of fruits (quartiles), number of servings per day of vegetables (quartiles), years of estrogen therapy (none, <5, 5–9, ≥10, or missing), years of estrogen + progestin therapy (none, <5, 5–9, ≥10, or missing), age at menopause (≤39 years, 40–44 years, 45–49 years, 50–54 years, ≥55 years, or missing), age at death of father (≤59 years, 60–69 years, 70–79 years, 80–89 years, or ≥90 years), and age at death of mother (≤59 years, 60–69 years, 70–79 years, 80–89 years, or ≥90 years)	Qr1	g/day	0	nd
102	Bell 2014 24496442	yes	age (as the time scale), sex, race/ethnicity, marital status (married/living together, never married, separated/divorced, widowed, or missing), education (high school graduate or less, some college, or college/advanced degree), total energy intake (kcal/day; continuous), body mass index (weight (kg)/height (m)2 (none, <1 drink/day, 1–2 drinks/day, >2 drinks/day, or missing), average physical activity in the 10 years before baseline (MET-hours/week; tertiles), self-rated health (excellent, very good, good, fair, or poor), mammogram in the last 2 years (yes/no), prostate-specific antigen test in the last 2 years (yes/no), sigmoidoscopy in the last 10 years (yes/no), current use of cholesterol-lowering medication (yes/no), aspirin use in the past 10 years (none, low, high, or missing), use of nonaspirin nonsteroidal antiinflammatory drugs in the past 10 years (none, low, high, or missing), smoking (never, 1–12.5 pack-years, 12.6–35.0 pack-years, or >35.0 pack-years), morbidity score,c percentage of calories derived from trans fat (quartiles), percentage of calories derived from saturated fat (quartiles), number of servings per day of fruits (quartiles), number of servings per day of vegetables (quartiles), years of estrogen therapy (none, <5, 5–9, ≥10, or missing), years of estrogen + progestin therapy (none, <5, 5–9, ≥10, or missing), age at menopause (≤39 years, 40–44 years, 45–49 years, 50–54 years, ≥55 years, or missing), age at death of father (≤59 years, 60–69 years, 70–79 years, 80–89 years, or ≥90 years), and age at death of mother (≤59 years, 60–69 years, 70–79 years, 80–89 years, or ≥90 years)	Qr2	g/day	0.054	nd
103	Bell 2014 24496442	yes	age (as the time scale), sex, race/ethnicity, marital status (married/living together, never married, separated/divorced, widowed, or missing), education (high school graduate or less, some college, or college/advanced degree), total energy intake (kcal/day; continuous), body mass index (weight (kg)/height (m)2 (none, <1 drink/day, 1–2 drinks/day, >2 drinks/day, or missing), average physical activity in the 10 years before baseline (MET-hours/week; tertiles), self-rated health (excellent, very good, good, fair, or poor), mammogram in the last 2 years (yes/no), prostate-specific antigen test in the last 2 years (yes/no), sigmoidoscopy in the last 10 years (yes/no), current use of cholesterol-lowering medication (yes/no), aspirin use in the past 10 years (none, low, high, or missing), use of nonaspirin nonsteroidal antiinflammatory drugs in the past 10 years (none, low, high, or missing), smoking (never, 1–12.5 pack-years, 12.6–35.0 pack-years, or >35.0 pack-years), morbidity score,c percentage of calories derived from trans fat (quartiles), percentage of calories derived from saturated fat (quartiles), number of servings per day of fruits (quartiles), number of servings per day of vegetables (quartiles), years of estrogen therapy (none, <5, 5–9, ≥10, or missing), years of estrogen + progestin therapy (none, <5, 5–9, ≥10, or missing), age at menopause (≤39 years, 40–44 years, 45–49 years, 50–54 years, ≥55 years, or missing), age at death of father (≤59 years, 60–69 years, 70–79 years, 80–89 years, or ≥90 years), and age at death of mother (≤59 years, 60–69 years, 70–79 years, 80–89 years, or ≥90 years)	Qr3	g/day	0.113	nd

Appendix F
Observational results: all-cause death

Outcome	Study PMID	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
100	Bell 2014 24496442	nd	HR	689	17571	nd	0.68	0.62	0.76		
101	Bell 2014 24496442	0.054	HR	933	17572	nd	1	nd	nd		0.004
102	Bell 2014 24496442	0.113	HR	806	17572	nd	0.84	0.76	0.92		
103	Bell 2014 24496442	0.207	HR	662	17572	nd	0.69	0.62	0.76		

Appendix F
Observational results: all-cause death

Outcome	Study PMID	Study Name	Outcome2	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure
104	Bell 2014 24496442	VITAL	Death, all-cause	Total mortality	Healthy	Men and women aged 50-76	All	3037/70287 (0.04)	6 y	DHA	Intake
106	**Subgroup analyses**										
107	Hara 2013 23047296	Osaka Acute Coronary Insufficiency Study	Death, all-cause	nd	CVD	AMI patients	DM	nd/250 (nd)	4 y	EPA	Blood
108	Hara 2013 23047296	Osaka Acute Coronary Insufficiency Study	Death, all-cause	nd	CVD	AMI patients	No DM	nd/462 (nd)	4 y	EPA	Blood
109	Hara 2013 23047296	Osaka Acute Coronary Insufficiency Study	Death, all-cause	nd	CVD	AMI patients	HTN	nd/470 (nd)	4 y	EPA	Blood
110	Hara 2013 23047296	Osaka Acute Coronary Insufficiency Study	Death, all-cause	nd	CVD	AMI patients	No HTN	nd/232 (nd)	4 y	EPA	Blood
111	Hara 2013 23047296	Osaka Acute Coronary Insufficiency Study	Death, all-cause	nd	CVD	AMI patients	Statin	nd/431 (nd)	4 y	EPA	Blood
112	Hara 2013 23047296	Osaka Acute Coronary Insufficiency Study	Death, all-cause	nd	CVD	AMI patients	No Statin	nd/281 (nd)	4 y	EPA	Blood

Appendix F
Observational results: all-cause death

Outcome	Study PMID	Supplement	Adjustments	Quantile	n3 units	Quantile low	Quantile median
104	Bell 2014 24496442	yes	age (as the time scale), sex, race/ethnicity, marital status (married/living together, never married, separated/divorced, widowed, or missing), education (high school graduate or less, some college, or college/advanced degree), total energy intake (kcal/day; continuous), body mass index (weight (kg)/height (m)2 (none, <1 drink/day, 1–2 drinks/day, >2 drinks/day, or missing), average physical activity in the 10 years before baseline (MET-hours/week; tertiles), self-rated health (excellent, very good, good, fair, or poor), mammogram in the last 2 years (yes/no), prostate-specific antigen test in the last 2 years (yes/no), sigmoidoscopy in the last 10 years (yes/no), current use of cholesterol-lowering medication (yes/no), aspirin use in the past 10 years (none, low, high, or missing), use of nonaspirin nonsteroidal antiinflammatory drugs in the past 10 years (none, low, high, or missing), smoking (never, 1–12.5 pack-years, 12.6–35.0 pack-years, or >35.0 pack-years), morbidity score,c percentage of calories derived from trans fat (quartiles), percentage of calories derived from saturated fat (quartiles), number of servings per day of fruits (quartiles), number of servings per day of vegetables (quartiles), years of estrogen therapy (none, <5, 5–9, ≥10, or missing), years of estrogen + progestin therapy (none, <5, 5–9, ≥10, or missing), age at menopause (≤39 years, 40–44 years, 45–49 years, 50–54 years, ≥55 years, or missing), age at death of father (≤59 years, 60–69 years, 70–79 years, 80–89 years, or ≥90 years), and age at death of mother (≤59 years, 60–69 years, 70–79 years, 80–89 years, or ≥90 years)	Qr4	g/day	0.207	nd
106	**Subgroup analyses**						
107	Hara 2013 23047296	No	No	T1 vs. T2-3	nd	nd	nd
108	Hara 2013 23047296	No	No	T1 vs. T2-3	nd	nd	nd
109	Hara 2013 23047296	No	No	T1 vs. T2-3	nd	nd	nd
110	Hara 2013 23047296	No	No	T1 vs. T2-3	nd	nd	nd
111	Hara 2013 23047296	No	No	T1 vs. T2-3	nd	nd	nd
112	Hara 2013 23047296	No	No	T1 vs. T2-3	nd	nd	nd

Appendix F
Observational results: all-cause death

Outcome	Study PMID	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
104	Bell 2014 24496442	nd	HR	636	17572	nd	0.63	0.57	0.69		
106	**Subgroup analyses**										
107	Hara 2013 23047296	nd	HR	nd	nd	nd	2.73	1.06	7.03	DM interaction	0.0887
108	Hara 2013 23047296	nd	HR	nd	nd	nd	0.92	0.4	2.1		
109	Hara 2013 23047296	nd	HR	nd	nd	nd	0.96	0.47	1.96	HTN interaction	0.0145
110	Hara 2013 23047296	nd	HR	nd	nd	nd	8.23	1.75	38.77		
111	Hara 2013 23047296	nd	HR	nd	nd	nd	2.64	1.11	6.26	Statin interaction	0.0615
112	Hara 2013 23047296	nd	HR	nd	nd	nd	0.83	0.35	2.01		

Appendix F
Observational results: cardiac death

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup
2	Ascherio 1995 7885425	Health Professional Follow-up Study	Cardiac death	Fatal coronary heart disease including sudden death	Healthy	Healthy 40-75 yo men without diagnosis of myocardial infarction, angina, stroke, transient ischemic attack, or peripheral arterial disease, or had undergone coronary artery surgery.	All	264/44895 (0.59)	6 y
3	Ascherio 1995 7885425	Health Professional Follow-up Study	Cardiac death	Fatal coronary heart disease including sudden death	Healthy	Healthy 40-75 yo men without diagnosis of myocardial infarction, angina, stroke, transient ischemic attack, or peripheral arterial disease, or had undergone coronary artery surgery.	All	264/44895 (0.59)	6 y
4	Ascherio 1995 7885425	Health Professional Follow-up Study	Cardiac death	Fatal coronary heart disease including sudden death	Healthy	Healthy 40-75 yo men without diagnosis of myocardial infarction, angina, stroke, transient ischemic attack, or peripheral arterial disease, or had undergone coronary artery surgery.	All	264/44895 (0.59)	6 y
5	Ascherio 1995 7885425	Health Professional Follow-up Study	Cardiac death	Fatal coronary heart disease including sudden death	Healthy	Healthy 40-75 yo men without diagnosis of myocardial infarction, angina, stroke, transient ischemic attack, or peripheral arterial disease, or had undergone coronary artery surgery.	All	264/44895 (0.59)	6 y
6	Ascherio 1995 7885425	Health Professional Follow-up Study	Cardiac death	Fatal coronary heart disease including sudden death	Healthy	Healthy 40-75 yo men without diagnosis of myocardial infarction, angina, stroke, transient ischemic attack, or peripheral arterial disease, or had undergone coronary artery surgery.	All	264/44895 (0.59)	6 y
7	Matsumoto 2013 23098619	Physician's Health Study	Cardiac death	fatally MI, coronary death, and sudden death	Healthy	US male physicians	All	165/2000 (8.25)	nd
8	Matsumoto 2013 23098619	Physician's Health Study	Cardiac death	fatally MI, coronary death, and sudden death	Healthy	US male physicians	All	165/2000 (8.25)	nd
9	Matsumoto 2013 23098619	Physician's Health Study	Cardiac death	fatally MI, coronary death, and sudden death	Healthy	US male physicians	All	165/2000 (8.25)	nd
10	Matsumoto 2013 23098619	Physician's Health Study	Cardiac death	fatally MI, coronary death, and sudden death	Healthy	US male physicians	All	165/2000 (8.25)	nd
11	Matsumoto 2013 23098619	Physician's Health Study	Cardiac death	fatally MI, coronary death, and sudden death	Healthy	US male physicians	All	165/2000 (8.25)	nd
12	Matsumoto 2013 23098619	Physician's Health Study	Cardiac death	fatally MI, coronary death, and sudden death	Healthy	US male physicians	All	165/2000 (8.25)	nd

Appendix F
Observational results: cardiac death

Row	Study PMID	n3 FA	n3 measure	Supplement	Adjustments	Quantile	n3 units	Quantile low	Quantile median	Quantile high
2	Ascherio 1995 7885425	EPA+DHA	Intake	No	age, BMI, smoking habits, alcohol consumption, history of hypertension, history of diabetes, history of hypercholesterolemia, family history of myocardial infarction before 60 years of age, profession	Qt1	g/d	0.01	nd	0.11
3	Ascherio 1995 7885425	EPA+DHA	Intake	No	age, BMI, smoking habits, alcohol consumption, history of hypertension, history of diabetes, history of hypercholesterolemia, family history of myocardial infarction before 60 years of age, profession	Qt2	g/d	0.12	nd	0.19
4	Ascherio 1995 7885425	EPA+DHA	Intake	No	age, BMI, smoking habits, alcohol consumption, history of hypertension, history of diabetes, history of hypercholesterolemia, family history of myocardial infarction before 60 years of age, profession	Qt3	g/d	0.2	nd	0.28
5	Ascherio 1995 7885425	EPA+DHA	Intake	No	age, BMI, smoking habits, alcohol consumption, history of hypertension, history of diabetes, history of hypercholesterolemia, family history of myocardial infarction before 60 years of age, profession	Qt4	g/d	0.29	nd	0.41
6	Ascherio 1995 7885425	EPA+DHA	Intake	No	age, BMI, smoking habits, alcohol consumption, history of hypertension, history of diabetes, history of hypercholesterolemia, family history of myocardial infarction before 60 years of age, profession	Qt5	g/d	0.42	nd	6.52
7	Matsumoto 2013 23098619	SDA	Erythrocyte (log measure)	NA	matching factors and BMI, smoking status, exercise level, alcohol consumption, history of hypertension, history of diabetes, and history of hypercholesterolemia	All	Per SD increase	nd	nd	nd
8	Matsumoto 2013 23098619	ALA	Erythrocyte (log measure)	NA	matching factors and BMI, smoking status, exercise level, alcohol consumption, history of hypertension, history of diabetes, and history of hypercholesterolemia	All	Per SD increase	nd	nd	nd
9	Matsumoto 2013 23098619	EPA+DHA+DPA	Erythrocyte (log measure)	NA	matching factors and BMI, smoking status, exercise level, alcohol consumption, history of hypertension, history of diabetes, and history of hypercholesterolemia	All	Per SD increase	nd	nd	nd
10	Matsumoto 2013 23098619	EPA	Erythrocyte (log measure)	NA	matching factors and BMI, smoking status, exercise level, alcohol consumption, history of hypertension, history of diabetes, and history of hypercholesterolemia	All	Per SD increase	nd	nd	nd
11	Matsumoto 2013 23098619	DPA	Erythrocyte (log measure)	NA	matching factors and BMI, smoking status, exercise level, alcohol consumption, history of hypertension, history of diabetes, and history of hypercholesterolemia	All	Per SD increase	nd	nd	nd
12	Matsumoto 2013 23098619	DHA	Erythrocyte (log measure)	NA	matching factors and BMI, smoking status, exercise level, alcohol consumption, history of hypertension, history of diabetes, and history of hypercholesterolemia	All	Per SD increase	nd	nd	nd

Appendix F
Observational results: cardiac death

Row	Study PMID	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
2	Ascherio 1995 7885425	RR	50	9329	50499	Reference group			Q5 vs. Q1	0.94
3	Ascherio 1995 7885425	RR	58	9220	49902	1.14	0.78	1.66		
4	Ascherio 1995 7885425	RR	49	9005	48613	0.95	0.64	1.41		
5	Ascherio 1995 7885425	RR	53	8860	47722	1.03	0.7	1.52		
6	Ascherio 1995 7885425	RR	54	8481	45343	1.03	0.7	1.52		
7	Matsumoto 2013 23098619	OR	165	nd	nd	1.05	0.75	1.45		
8	Matsumoto 2013 23098619	OR	165	nd	nd	1.19	0.89	1.6		
9	Matsumoto 2013 23098619	OR	165	nd	nd	0.98	0.76	1.25		
10	Matsumoto 2013 23098619	OR	165	nd	nd	0.96	0.74	1.23		
11	Matsumoto 2013 23098619	OR	165	nd	nd	0.99	0.77	1.27		
12	Matsumoto 2013 23098619	OR	165	nd	nd	0.99	0.78	1.26		

Appendix F Observational results: death from coronary heart disease

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA
2	Dolecek 1992 1579579	MRFIT	CHD death	Coronary Heart Disease	Healthy	Men aged 35-57 assigned to the usual care group	Men	175/6258 (2.8)	10.5 y	EPA+DHA+DPA
3	Dolecek 1992 1579579	MRFIT	CHD death	Coronary Heart Disease	Healthy	Men aged 35-57 assigned to the usual care group	Men	175/6258 (2.8)	10.5 y	EPA+DHA+DPA
4	Dolecek 1992 1579579	MRFIT	CHD death	Coronary Heart Disease	Healthy	Men aged 35-57 assigned to the usual care group	Men	175/6258 (2.8)	10.5 y	EPA+DHA+DPA
5	Dolecek 1992 1579579	MRFIT	CHD death	Coronary Heart Disease	Healthy	Men aged 35-57 assigned to the usual care group	Men	175/6258 (2.8)	10.5 y	EPA+DHA+DPA
6	Dolecek 1992 1579579	MRFIT	CHD death	Coronary Heart Disease	Healthy	Men aged 35-57 assigned to the usual care group	Men	175/6258 (2.8)	10.5 y	EPA+DHA+DPA
7	Dolecek 1992 1579579	MRFIT	CHD death	Coronary Heart Disease	Healthy	Men aged 35-57 assigned to the usual care group	Men	175/6258 (2.8)	10.5 y	EPA+DHA+DPA
8	Dolecek 1992 1579579	MRFIT	CHD death	Coronary Heart Disease	Healthy	Men aged 35-57 assigned to the usual care group	Men	175/6258 (2.8)	10.5 y	EPA+DHA+DPA
9	Dolecek 1992 1579579	MRFIT	CHD death	Coronary Heart Disease	Healthy	Men aged 35-57 assigned to the usual care group	Men	175/6258 (2.8)	10.5 y	EPA+DHA+DPA
10	Dolecek 1992 1579579	MRFIT	CHD death	Coronary Heart Disease	Healthy	Men aged 35-57 assigned to the usual care group	Men	175/6258 (2.8)	10.5 y	EPA+DHA+DPA
11	Dolecek 1992 1579579	MRFIT	CHD death	Coronary Heart Disease	Healthy	Men aged 35-57 assigned to the usual care group	Men	175/6258 (2.8)	10.5 y	EPA+DHA+DPA
12	Dolecek 1992 1579579	MRFIT	CHD death	Coronary Heart Disease	Healthy	Men aged 35-57 assigned to the usual care group	Men	175/6258 (2.8)	10.5 y	EPA+DHA+DPA
13	Dolecek 1992 1579579	MRFIT	CHD death	Coronary Heart Disease	Healthy	Men aged 35-57 assigned to the usual care group	Men	175/6258 (2.8)	10.5 y	EPA+DHA+DPA
14	Dolecek 1992 1579579	MRFIT	CHD death	Coronary Heart Disease	Healthy	Men aged 35-57 assigned to the usual care group	Men	175/6258 (2.8)	10.5 y	ALA
15	Dolecek 1992 1579579	MRFIT	CHD death	Coronary Heart Disease	Healthy	Men aged 35-57 assigned to the usual care group	Men	175/6258 (2.8)	10.5 y	ALA
16	Dolecek 1992 1579579	MRFIT	CHD death	Coronary Heart Disease	Healthy	Men aged 35-57 assigned to the usual care group	Men	175/6258 (2.8)	10.5 y	ALA
17	Dolecek 1992 1579579	MRFIT	CHD death	Coronary Heart Disease	Healthy	Men aged 35-57 assigned to the usual care group	Men	175/6258 (2.8)	10.5 y	ALA
18	Dolecek 1992 1579579	MRFIT	CHD death	Coronary Heart Disease	Healthy	Men aged 35-57 assigned to the usual care group	Men	175/6258 (2.8)	10.5 y	ALA
19	Dolecek 1992 1579579	MRFIT	CHD death	Coronary Heart Disease	Healthy	Men aged 35-57 assigned to the usual care group	Men	175/6258 (2.8)	10.5 y	ALA
20	Dolecek 1992 1579579	MRFIT	CHD death	Coronary Heart Disease	Healthy	Men aged 35-57 assigned to the usual care group	Men	175/6258 (2.8)	10.5 y	ALA
21	Dolecek 1992 1579579	MRFIT	CHD death	Coronary Heart Disease	Healthy	Men aged 35-57 assigned to the usual care group	Men	175/6258 (2.8)	10.5 y	ALA
22	Dolecek 1992 1579579	MRFIT	CHD death	Coronary Heart Disease	Healthy	Men aged 35-57 assigned to the usual care group	Men	175/6258 (2.8)	10.5 y	ALA
23	Dolecek 1992 1579579	MRFIT	CHD death	Coronary Heart Disease	Healthy	Men aged 35-57 assigned to the usual care group	Men	175/6258 (2.8)	10.5 y	ALA
24	Dolecek 1992 1579579	MRFIT	CHD death	Coronary Heart Disease	Healthy	Men aged 35-57 assigned to the usual care group	Men	175/6258 (2.8)	10.5 y	ALA
25	Dolecek 1992 1579579	MRFIT	CHD death	Coronary Heart Disease	Healthy	Men aged 35-57 assigned to the usual care group	Men	175/6258 (2.8)	10.5 y	ALA
26	Hu 2002 11939867	Nurses' Health Study	CHD death	fatal CHD	Healthy	Healthy 34-59 yo female nurses	Women	484/84688 (0.57)	16 y	EPA+DHA

Appendix F Observational results: death from coronary heart disease

Row	Study PMID	n3 measure	Supplement	Adjustments	Quantile	n3 units
2	Dolecek 1992 1579579	Intake	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt1	g/d
3	Dolecek 1992 1579579	Intake	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt2	g/d
4	Dolecek 1992 1579579	Intake	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt3	g/d
5	Dolecek 1992 1579579	Intake	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt4	g/d
6	Dolecek 1992 1579579	Intake	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt5	g/d
7	Dolecek 1992 1579579	Intake	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	All	g/d
8	Dolecek 1992 1579579	Intake	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt1	% kcal
9	Dolecek 1992 1579579	Intake	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt2	% kcal
10	Dolecek 1992 1579579	Intake	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt3	% kcal
11	Dolecek 1992 1579579	Intake	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt4	% kcal
12	Dolecek 1992 1579579	Intake	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt5	% kcal
13	Dolecek 1992 1579579	Intake	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	All	% kcal
14	Dolecek 1992 1579579	Intake	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt1	g/d
15	Dolecek 1992 1579579	Intake	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt2	g/d
16	Dolecek 1992 1579579	Intake	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt3	g/d
17	Dolecek 1992 1579579	Intake	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt4	g/d
18	Dolecek 1992 1579579	Intake	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt5	g/d
19	Dolecek 1992 1579579	Intake	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	All	g/d
20	Dolecek 1992 1579579	Intake	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt1	% kcal
21	Dolecek 1992 1579579	Intake	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt2	% kcal
22	Dolecek 1992 1579579	Intake	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt3	% kcal
23	Dolecek 1992 1579579	Intake	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt4	% kcal
24	Dolecek 1992 1579579	Intake	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt5	% kcal
25	Dolecek 1992 1579579	Intake	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	All	% kcal
26	Hu 2002 11939867	Intake	no	age, time periods, smoking status (never, past, curent), BMI (<22, 22-22.9, 23-24.9, 25-28.9, 29+ kg/m2), alcohol intake (0, <5, 5-14, 15+), menopausal status and postmenopausal hormone use, vigorous to moderate activity (<1, 1-1.9, 2-3.9, 4-6.9, 7+ hours/week), number of times aspirin was used per week (<1, 1-2, 3-6, 7-14, 15+), multivitamin use (yes vs. no), vitamin E supplement use (yes vs. no), history of HTN (yes vs. no), hypercholesterolemia (yes vs. no), diabetes (yes vs. no)	Qt1	% kcal

Appendix F Observational results: death from coronary heart disease

Row	Study PMID	Quantile low	Quantile median	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
2	Dolecek 1992 1579579	nd	0 (mean)	nd	RR	nd	1307	nd	Reference group	nd	nd		<0.05
3	Dolecek 1992 1579579	nd	0.009 (mean)	nd	RR	nd	1197	nd	1.08	nd	nd		
4	Dolecek 1992 1579579	nd	0.046 (mean)	nd	RR	nd	1251	nd	0.92	nd	nd		
5	Dolecek 1992 1579579	nd	0.153 (mean)	nd	RR	nd	1252	nd	0.89	nd	nd		
6	Dolecek 1992 1579579	nd	0.664 (mean)	nd	RR	nd	1251	nd	0.61	nd	nd		
7	Dolecek 1992 1579579	nd	nd	nd	HR	175	6258	nd	0.393057251	nd	nd		<0.05
8	Dolecek 1992 1579579	nd	0 (mean)	nd	RR	nd	1307	nd	Reference group	nd	nd		<0.05
9	Dolecek 1992 1579579	nd	0.004 (mean)	nd	RR	nd	1196	nd	1.07	nd	nd		
10	Dolecek 1992 1579579	nd	0.019 (mean)	nd	RR	nd	1252	nd	0.82	nd	nd		
11	Dolecek 1992 1579579	nd	0.063 (mean)	nd	RR	nd	1252	nd	1.12	nd	nd		
12	Dolecek 1992 1579579	nd	0.284 (mean)	nd	RR	nd	1251	nd	0.5	nd	nd		
13	Dolecek 1992 1579579	nd	nd	nd	HR	175	6258	nd	0.624065468	nd	nd		<0.05
14	Dolecek 1992 1579579	nd	0.873 (mean)	nd	RR	nd	1251	nd	Reference group	nd	nd		NS
15	Dolecek 1992 1579579	nd	1.273 (mean)	nd	RR	nd	1253	nd	0.96	nd	nd		
16	Dolecek 1992 1579579	nd	1.577 (mean)	nd	RR	nd	1251	nd	0.56	nd	nd		
17	Dolecek 1992 1579579	nd	1.926 (mean)	nd	RR	nd	1251	nd	0.96	nd	nd		
18	Dolecek 1992 1579579	nd	2.802 (mean)	nd	RR	nd	1252	nd	0.66	nd	nd		
19	Dolecek 1992 1579579	nd	nd	nd	HR	175	6258	nd	0.835687951	nd	nd		NS
20	Dolecek 1992 1579579	nd	0.424 (mean)	nd	RR	nd	1251	nd	Reference group	nd	nd		<0.05
21	Dolecek 1992 1579579	nd	0.544 (mean)	nd	RR	nd	1252	nd	0.72	nd	nd		
22	Dolecek 1992 1579579	nd	0.63 (mean)	nd	RR	nd	1252	nd	0.8	nd	nd		
23	Dolecek 1992 1579579	nd	0.732 (mean)	nd	RR	nd	1252	nd	0.61	nd	nd		
24	Dolecek 1992 1579579	nd	0.98 (mean)	nd	RR	nd	1251	nd	0.58	nd	nd		
25	Dolecek 1992 1579579	nd	nd	nd	HR	175	6258	nd	0.427714227	nd	nd		<0.05
26	Hu 2002 11939867	nd	0.03	nd	RR	81	nd	255434	Reference group	nd	nd	P trend	<0.001

Appendix F Observational results: death from coronary heart disease

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA
27	Hu 2002 11939867	Nurses' Health Study	CHD death	fatal CHD	Healthy	Healthy 34-59 yo female nurses	Women	484/84688 (0.57)	16 y	EPA+DHA
28	Hu 2002 11939867	Nurses' Health Study	CHD death	fatal CHD	Healthy	Healthy 34-59 yo female nurses	Women	484/84688 (0.57)	16 y	EPA+DHA
29	Hu 2002 11939867	Nurses' Health Study	CHD death	fatal CHD	Healthy	Healthy 34-59 yo female nurses	Women	484/84688 (0.57)	16 y	EPA+DHA
30	Hu 2002 11939867	Nurses' Health Study	CHD death	fatal CHD	Healthy	Healthy 34-59 yo female nurses	Women	484/84688 (0.57)	16 y	EPA+DHA
31	Iso 2006 16401768	Japan Public Health Center-Based Study - Cohort I	CHD death	Fatal coronary events	Healthy	Healthy 40-59	All	62/41578 (0.15)	11.5 y	EPA+DHA
32	Iso 2006 16401768	Japan Public Health Center-Based Study - Cohort I	CHD death	Fatal coronary events	Healthy	Healthy 40-59	All	62/41578 (0.15)	11.5 y	EPA+DHA
33	Iso 2006 16401768	Japan Public Health Center-Based Study - Cohort I	CHD death	Fatal coronary events	Healthy	Healthy 40-59	All	62/41578 (0.15)	11.5 y	EPA+DHA
34	Iso 2006 16401768	Japan Public Health Center-Based Study - Cohort I	CHD death	Fatal coronary events	Healthy	Healthy 40-59	All	62/41578 (0.15)	11.5 y	EPA+DHA
35	Iso 2006 16401768	Japan Public Health Center-Based Study - Cohort I	CHD death	Fatal coronary events	Healthy	Healthy 40-59	All	62/41578 (0.15)	11.5 y	EPA+DHA
36	Mozaffarian 2013 23546563	Cardiovascular Health Study	CHD death	Total CHD mortality	Healthy	Healthy age >= 65y	All	359/3941 (9.11)	16y	EPA
37	Mozaffarian 2013 23546563	Cardiovascular Health Study	CHD death	Total CHD mortality	Healthy	Healthy age >= 65y	All	359/3941 (9.11)	16y	EPA
38	Mozaffarian 2013 23546563	Cardiovascular Health Study	CHD death	Total CHD mortality	Healthy	Healthy age >= 65y	All	359/3941 (9.11)	16y	EPA
39	Mozaffarian 2013 23546563	Cardiovascular Health Study	CHD death	Total CHD mortality	Healthy	Healthy age >= 65y	All	359/3941 (9.11)	16y	EPA
40	Mozaffarian 2013 23546563	Cardiovascular Health Study	CHD death	Total CHD mortality	Healthy	Healthy age >= 65y	All	359/3941 (9.11)	16y	EPA
41	Fretts 2014 25159901	Cardiovascular Health Study	CHD death	Total CHD mortality	Healthy	Healthy age >= 65y	All	280/2583 (10.84)	12y	ALA
42	Fretts 2014 25159901	Cardiovascular Health Study	CHD death	Total CHD mortality	Healthy	Healthy age >= 65y	All	280/2583 (10.84)	12y	ALA
43	Fretts 2014 25159901	Cardiovascular Health Study	CHD death	Total CHD mortality	Healthy	Healthy age >= 65y	All	280/2583 (10.84)	12y	ALA
44	Fretts 2014 25159901	Cardiovascular Health Study	CHD death	Total CHD mortality	Healthy	Healthy age >= 65y	All	280/2583 (10.84)	12y	ALA
45	Fretts 2014 25159901	Cardiovascular Health Study	CHD death	Total CHD mortality	Healthy	Healthy age >= 65y	All	280/2583 (10.84)	12y	ALA

Appendix F Observational results: death from coronary heart disease

Row	Study PMID	n3 measure	Supplement	Adjustments	Quantile	n3 units
27	Hu 2002 11939867	Intake	no	age, time periods, smoking status (never, past, curent), BMI (<22, 22-22.9, 23-24.9, 25-28.9, 29+ kg/m2), alcohol intake (0, <5, 5-14, 15+), menopausal status and postmenopausal hormone use, vigorous to moderate activity (<1, 1-1.9, 2-3.9, 4-6.9, 7+ hours/week), number of times aspirin was used per week (<1, 1-2, 3-6, 7-14, 15+), multivitamin use (yes vs. no), vitamin E supplement use (yes vs. no), history of HTN (yes vs. no), hypercholesterolemia (yes vs. no), diabetes (yes vs. no)	Qt2	% kcal
28	Hu 2002 11939867	Intake	no	age, time periods, smoking status (never, past, curent), BMI (<22, 22-22.9, 23-24.9, 25-28.9, 29+ kg/m2), alcohol intake (0, <5, 5-14, 15+), menopausal status and postmenopausal hormone use, vigorous to moderate activity (<1, 1-1.9, 2-3.9, 4-6.9, 7+ hours/week), number of times aspirin was used per week (<1, 1-2, 3-6, 7-14, 15+), multivitamin use (yes vs. no), vitamin E supplement use (yes vs. no), history of HTN (yes vs. no), hypercholesterolemia (yes vs. no), diabetes (yes vs. no)	Qt3	% kcal
29	Hu 2002 11939867	Intake	no	age, time periods, smoking status (never, past, curent), BMI (<22, 22-22.9, 23-24.9, 25-28.9, 29+ kg/m2), alcohol intake (0, <5, 5-14, 15+), menopausal status and postmenopausal hormone use, vigorous to moderate activity (<1, 1-1.9, 2-3.9, 4-6.9, 7+ hours/week), number of times aspirin was used per week (<1, 1-2, 3-6, 7-14, 15+), multivitamin use (yes vs. no), vitamin E supplement use (yes vs. no), history of HTN (yes vs. no), hypercholesterolemia (yes vs. no), diabetes (yes vs. no)	Qt4	% kcal
30	Hu 2002 11939867	Intake	no	age, time periods, smoking status (never, past, curent), BMI (<22, 22-22.9, 23-24.9, 25-28.9, 29+ kg/m2), alcohol intake (0, <5, 5-14, 15+), menopausal status and postmenopausal hormone use, vigorous to moderate activity (<1, 1-1.9, 2-3.9, 4-6.9, 7+ hours/week), number of times aspirin was used per week (<1, 1-2, 3-6, 7-14, 15+), multivitamin use (yes vs. no), vitamin E supplement use (yes vs. no), history of HTN (yes vs. no), hypercholesterolemia (yes vs. no), diabetes (yes vs. no)	Qt5	% kcal
31	Iso 2006 16401768	Intake	No	age; sex; cigarette smoking; alcohol intake; body mass index; histories of hypertension and diabetes; medication use for hypercholesterolemia; education level; sports at leisure time; quintiles of dietary intake of fruits, vegetables, saturated fat, monounsaturated fat, n6 polyunsaturated fat, cholesterol, and total energy; and PHC.	Qt1	g/d
32	Iso 2006 16401768	Intake	No	age; sex; cigarette smoking; alcohol intake; body mass index; histories of hypertension and diabetes; medication use for hypercholesterolemia; education level; sports at leisure time; quintiles of dietary intake of fruits, vegetables, saturated fat, monounsaturated fat, n6 polyunsaturated fat, cholesterol, and total energy; and PHC.	Qt2	g/d
33	Iso 2006 16401768	Intake	No	age; sex; cigarette smoking; alcohol intake; body mass index; histories of hypertension and diabetes; medication use for hypercholesterolemia; education level; sports at leisure time; quintiles of dietary intake of fruits, vegetables, saturated fat, monounsaturated fat, n6 polyunsaturated fat, cholesterol, and total energy; and PHC.	Qt3	g/d
34	Iso 2006 16401768	Intake	No	age; sex; cigarette smoking; alcohol intake; body mass index; histories of hypertension and diabetes; medication use for hypercholesterolemia; education level; sports at leisure time; quintiles of dietary intake of fruits, vegetables, saturated fat, monounsaturated fat, n6 polyunsaturated fat, cholesterol, and total energy; and PHC.	Qt4	g/d
35	Iso 2006 16401768	Intake	No	age; sex; cigarette smoking; alcohol intake; body mass index; histories of hypertension and diabetes; medication use for hypercholesterolemia; education level; sports at leisure time; quintiles of dietary intake of fruits, vegetables, saturated fat, monounsaturated fat, n6 polyunsaturated fat, cholesterol, and total energy; and PHC.	Qt5	g/d
36	Mozaffarian 2013 23546563	Plasma	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt1	% FA
37	Mozaffarian 2013 23546563	Plasma	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt2	% FA
38	Mozaffarian 2013 23546563	Plasma	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt3	% FA
39	Mozaffarian 2013 23546563	Plasma	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt4	% FA
40	Mozaffarian 2013 23546563	Plasma	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt5	% FA
41	Fretts 2014 25159901	Intake	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt1	% fat intake
42	Fretts 2014 25159901	Intake	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt2	% fat intake
43	Fretts 2014 25159901	Intake	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt3	% fat intake
44	Fretts 2014 25159901	Intake	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt4	% fat intake
45	Fretts 2014 25159901	Intake	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt5	% fat intake

Row	Study PMID	Quantile low	Quantile median	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
27	Hu 2002 11939867	nd	0.05	nd	RR	143	nd	270898	0.93	0.7	1.24		
28	Hu 2002 11939867	nd	0.08	nd	RR	103	nd	263131	0.69	0.51	0.95		
29	Hu 2002 11939867	nd	0.14	nd	RR	73	nd	259454	0.54	0.39	0.76		
30	Hu 2002 11939867	nd	0.24	nd	RR	84	nd	258583	0.63	0.45	0.88		
31	Iso 2006 16401768	nd	0.3 (mean)	nd	HR	10	nd	102711	Reference group			P trend	0.1
32	Iso 2006 16401768	nd	0.6 (mean)	nd	HR	6	nd	95861	0.64	0.23	1.76		
33	Iso 2006 16401768	nd	0.9 (mean)	nd	HR	14	nd	95258	1.44	0.64	3.24		
34	Iso 2006 16401768	nd	1.3 (mean)	nd	HR	14	nd	91435	1.46	0.65	3.29		
35	Iso 2006 16401768	nd	2.1 (mean)	nd	HR	18	nd	92062	1.79	0.82	3.87		
36	Mozaffarian 2013 23546563	nd	0.3	nd	HR	nd	nd	nd	Reference group			P trend	0.121
37	Mozaffarian 2013 23546563	nd	0.41	nd	HR	nd	nd	nd	0.98	0.71	1.36		
38	Mozaffarian 2013 23546563	nd	0.51	nd	HR	nd	nd	nd	0.94	0.68	1.31		
39	Mozaffarian 2013 23546563	nd	0.64	nd	HR	nd	nd	nd	0.9	0.64	1.26		
40	Mozaffarian 2013 23546563	nd	0.92	nd	HR	nd	nd	nd	0.77	0.54	1.11		
41	Fretts 2014 25159901	0.39	1.33	1.45	HR	61	nd	4875	Reference group			P trend	0.54
42	Fretts 2014 25159901	1.45	1.56	1.65	HR	55	nd	4987	0.89	0.62	1.29		
43	Fretts 2014 25159901	1.65	1.76	1.87	HR	50	nd	5096	0.83	0.57	1.21		
44	Fretts 2014 25159901	1.87	2	2.17	HR	62	nd	5291	0.94	0.65	1.36		
45	Fretts 2014 25159901	2.17	2.44	4.88	HR	52	nd	5600	0.85	0.58	1.26		

Appendix F Observational results: death from coronary heart disease

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA
46	Fretts 2014 25159901	Cardiovascular Health Study	CHD death	Total CHD mortality	Healthy	Healthy age >= 65y	All	331/2709 (12.22)	16y	ALA
47	Fretts 2014 25159901	Cardiovascular Health Study	CHD death	Total CHD mortality	Healthy	Healthy age >= 65y	All	331/2709 (12.22)	16y	ALA
48	Fretts 2014 25159901	Cardiovascular Health Study	CHD death	Total CHD mortality	Healthy	Healthy age >= 65y	All	331/2709 (12.22)	16y	ALA
49	Fretts 2014 25159901	Cardiovascular Health Study	CHD death	Total CHD mortality	Healthy	Healthy age >= 65y	All	331/2709 (12.22)	16y	ALA
50	Fretts 2014 25159901	Cardiovascular Health Study	CHD death	Total CHD mortality	Healthy	Healthy age >= 65y	All	331/2709 (12.22)	16y	ALA
51	Mozaffarian 2013 23546563	Cardiovascular Health Study	CHD death	Total CHD mortality	Healthy	Healthy age >= 65y	All	359/3941 (9.11)	16y	DPA
52	Mozaffarian 2013 23546563	Cardiovascular Health Study	CHD death	Total CHD mortality	Healthy	Healthy age >= 65y	All	359/3941 (9.11)	16y	DPA
53	Mozaffarian 2013 23546563	Cardiovascular Health Study	CHD death	Total CHD mortality	Healthy	Healthy age >= 65y	All	359/3941 (9.11)	16y	DPA
54	Mozaffarian 2013 23546563	Cardiovascular Health Study	CHD death	Total CHD mortality	Healthy	Healthy age >= 65y	All	359/3941 (9.11)	16y	DPA
55	Mozaffarian 2013 23546563	Cardiovascular Health Study	CHD death	Total CHD mortality	Healthy	Healthy age >= 65y	All	359/3941 (9.11)	16y	DPA
56	Mozaffarian 2013 23546563	Cardiovascular Health Study	CHD death	Total CHD mortality	Healthy	Healthy age >= 65y	All	359/3941 (9.11)	16y	All n-3
57	Mozaffarian 2013 23546563	Cardiovascular Health Study	CHD death	Total CHD mortality	Healthy	Healthy age >= 65y	All	359/3941 (9.11)	16y	All n-3
58	Mozaffarian 2013 23546563	Cardiovascular Health Study	CHD death	Total CHD mortality	Healthy	Healthy age >= 65y	All	359/3941 (9.11)	16y	All n-3
59	Mozaffarian 2013 23546563	Cardiovascular Health Study	CHD death	Total CHD mortality	Healthy	Healthy age >= 65y	All	359/3941 (9.11)	16y	All n-3
60	Mozaffarian 2013 23546563	Cardiovascular Health Study	CHD death	Total CHD mortality	Healthy	Healthy age >= 65y	All	359/3941 (9.11)	16y	All n-3
61	Mozaffarian 2013 23546563	Cardiovascular Health Study	CHD death	Total CHD mortality	Healthy	Healthy age >= 65y	All	359/3941 (9.11)	16y	DHA
62	Mozaffarian 2013 23546563	Cardiovascular Health Study	CHD death	Total CHD mortality	Healthy	Healthy age >= 65y	All	359/3941 (9.11)	16y	DHA
63	Mozaffarian 2013 23546563	Cardiovascular Health Study	CHD death	Total CHD mortality	Healthy	Healthy age >= 65y	All	359/3941 (9.11)	16y	DHA
64	Mozaffarian 2013 23546563	Cardiovascular Health Study	CHD death	Total CHD mortality	Healthy	Healthy age >= 65y	All	359/3941 (9.11)	16y	DHA

Appendix F Observational results: death from coronary heart disease

Row	Study PMID	n3 measure	Supplement	Adjustments	Quantile	n3 units
46	Fretts 2014 25159901	Plasma	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt1	% FA
47	Fretts 2014 25159901	Plasma	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt2	% FA
48	Fretts 2014 25159901	Plasma	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt3	% FA
49	Fretts 2014 25159901	Plasma	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt4	% FA
50	Fretts 2014 25159901	Plasma	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt5	% FA
51	Mozaffarian 2013 23546563	Plasma	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt1	% FA
52	Mozaffarian 2013 23546563	Plasma	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt2	% FA
53	Mozaffarian 2013 23546563	Plasma	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt3	% FA
54	Mozaffarian 2013 23546563	Plasma	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt4	% FA
55	Mozaffarian 2013 23546563	Plasma	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt5	% FA
56	Mozaffarian 2013 23546563	Plasma	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt1	% FA
57	Mozaffarian 2013 23546563	Plasma	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt2	% FA
58	Mozaffarian 2013 23546563	Plasma	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt3	% FA
59	Mozaffarian 2013 23546563	Plasma	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt4	% FA
60	Mozaffarian 2013 23546563	Plasma	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt5	% FA
61	Mozaffarian 2013 23546563	Plasma	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt1	% FA
62	Mozaffarian 2013 23546563	Plasma	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt2	% FA
63	Mozaffarian 2013 23546563	Plasma	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt3	% FA
64	Mozaffarian 2013 23546563	Plasma	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt4	% FA

Appendix F Observational results: death from coronary heart disease

Row	Study PMID	Quantile low	Quantile median	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
46	Fretts 2014 25159901	0.05	0.09	0.11	HR	101	nd	6483	Reference group			P trend	0.98
47	Fretts 2014 25159901	0.11	0.12	0.13	HR	64	nd	6025	1.06	0.75	1.51		
48	Fretts 2014 25159901	0.13	0.14	0.15	HR	69	nd	6315	1.16	0.82	1.65		
49	Fretts 2014 25159901	0.15	0.17	0.19	HR	64	nd	6352	1.02	0.71	1.45		
50	Fretts 2014 25159901	0.19	0.22	0.47	HR	66	nd	6936	1.03	0.72	1.46		
51	Mozaffarian 2013 23546563	nd	0.63	nd	HR	nd	nd	nd	Reference group			P trend	0.36
52	Mozaffarian 2013 23546563	nd	0.75	nd	HR	nd	nd	nd	0.69	0.49	0.97		
53	Mozaffarian 2013 23546563	nd	0.82	nd	HR	nd	nd	nd	0.99	0.72	1.37		
54	Mozaffarian 2013 23546563	nd	0.91	nd	HR	nd	nd	nd	0.82	0.59	1.15		
55	Mozaffarian 2013 23546563	nd	1.04	nd	HR	nd	nd	nd	0.79	0.56	1.11		
56	Mozaffarian 2013 23546563	nd	3.17	nd	HR	nd	nd	nd	Reference group			P trend	0.002
57	Mozaffarian 2013 23546563	nd	3.72	nd	HR	nd	nd	nd	0.88	0.64	1.22		
58	Mozaffarian 2013 23546563	nd	4.21	nd	HR	nd	nd	nd	1.03	0.75	1.41		
59	Mozaffarian 2013 23546563	nd	4.8	nd	HR	nd	nd	nd	0.62	0.43	0.89		
60	Mozaffarian 2013 23546563	nd	6.04	nd	HR	nd	nd	nd	0.6	0.42	0.87		
61	Mozaffarian 2013 23546563	nd	1.95	nd	HR	nd	nd	nd	Reference group			P trend	0.003
62	Mozaffarian 2013 23546563	nd	2.44	nd	HR	nd	nd	nd	0.98	0.71	1.36		
63	Mozaffarian 2013 23546563	nd	2.87	nd	HR	nd	nd	nd	0.96	0.69	1.32		
64	Mozaffarian 2013 23546563	nd	3.36	nd	HR	nd	nd	nd	0.77	0.55	1.08		

Appendix F Observational results: death from coronary heart disease

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA
65	Mozaffarian 2013 23546563	Cardiovascular Health Study	CHD death	Total CHD mortality	Healthy	Healthy age >= 65y	All	359/3941 (9.11)	16y	DHA
66	Miyagawa 2014 24468152	NIPPON DATA80	CHD death	CHD	Healthy	healthy individual with mean age of 50	All	171/9190 (1.86)	24 y	EPA+DHA
67	Miyagawa 2014 24468152	NIPPON DATA80	CHD death	CHD	Healthy	healthy individual with mean age of 50	All	171/9190 (1.86)	24 y	EPA+DHA
68	Miyagawa 2014 24468152	NIPPON DATA80	CHD death	CHD	Healthy	healthy individual with mean age of 50	All	171/9190 (1.86)	24 y	EPA+DHA
69	Miyagawa 2014 24468152	NIPPON DATA80	CHD death	CHD	Healthy	healthy individual with mean age of 50	All	171/9190 (1.86)	24 y	EPA+DHA
70	Miyagawa 2014 24468152	NIPPON DATA80	CHD death	CHD	Healthy	healthy individual with mean age of 50	All	171/9190 (1.86)	24 y	All n-3
71	Miyagawa 2014 24468152	NIPPON DATA80	CHD death	CHD	Healthy	healthy individual with mean age of 50	All	171/9190 (1.86)	24 y	All n-3
72	Miyagawa 2014 24468152	NIPPON DATA80	CHD death	CHD	Healthy	healthy individual with mean age of 50	All	171/9190 (1.86)	24 y	All n-3
73	Miyagawa 2014 24468152	NIPPON DATA80	CHD death	CHD	Healthy	healthy individual with mean age of 50	All	171/9190 (1.86)	24 y	All n-3
74	Miyagawa 2014 24468152	NIPPON DATA80	CHD death	CHD	Healthy	healthy individual with mean age of 50	All	171/9190 (1.86)	24 y	EPA
75	Miyagawa 2014 24468152	NIPPON DATA80	CHD death	CHD	Healthy	healthy individual with mean age of 50	All	171/9190 (1.86)	24 y	EPA
76	Miyagawa 2014 24468152	NIPPON DATA80	CHD death	CHD	Healthy	healthy individual with mean age of 50	All	171/9190 (1.86)	24 y	EPA
77	Miyagawa 2014 24468152	NIPPON DATA80	CHD death	CHD	Healthy	healthy individual with mean age of 50	All	171/9190 (1.86)	24 y	EPA
78	Miyagawa 2014 24468152	NIPPON DATA80	CHD death	CHD	Healthy	healthy individual with mean age of 50	All	171/9190 (1.86)	24 y	DHA
79	Miyagawa 2014 24468152	NIPPON DATA80	CHD death	CHD	Healthy	healthy individual with mean age of 50	All	171/9190 (1.86)	24 y	DHA
80	Miyagawa 2014 24468152	NIPPON DATA80	CHD death	CHD	Healthy	healthy individual with mean age of 50	All	171/9190 (1.86)	24 y	DHA
81	Miyagawa 2014 24468152	NIPPON DATA80	CHD death	CHD	Healthy	healthy individual with mean age of 50	All	171/9190 (1.86)	24 y	DHA
82	Pietinen 1997 9149659	Alpha-Tocopherol Beta-Carotene Cancer Prevention	CHD death	coronary death	Healthy	health smoking men aged 50-69 years	Men	581/21930 (2.65)	6 y	ALA
83	Pietinen 1997 9149659	Alpha-Tocopherol Beta-Carotene Cancer Prevention	CHD death	coronary death	Healthy	health smoking men aged 50-69 years	Men	581/21930 (2.65)	6 y	ALA
84	Pietinen 1997 9149659	Alpha-Tocopherol Beta-Carotene Cancer Prevention	CHD death	coronary death	Healthy	health smoking men aged 50-69 years	Men	581/21930 (2.65)	6 y	ALA
85	Pietinen 1997 9149659	Alpha-Tocopherol Beta-Carotene Cancer Prevention	CHD death	coronary death	Healthy	health smoking men aged 50-69 years	Men	581/21930 (2.65)	6 y	ALA
86	Pietinen 1997 9149659	Alpha-Tocopherol Beta-Carotene Cancer Prevention	CHD death	coronary death	Healthy	health smoking men aged 50-69 years	Men	581/21930 (2.65)	6 y	ALA

Appendix F Observational results: death from coronary heart disease

Row	Study PMID	n3 measure	Supplement	Adjustments	Quantile	n3 units
65	Mozaffarian 2013 23546563	Plasma	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt5	% FA
66	Miyagawa 2014 24468152	Intake	no	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr1	% kcal
67	Miyagawa 2014 24468152	Intake	no	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr2	% kcal
68	Miyagawa 2014 24468152	Intake	no	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr3	% kcal
69	Miyagawa 2014 24468152	Intake	no	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr4	% kcal
70	Miyagawa 2014 24468152	Intake	no	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr1	% kcal
71	Miyagawa 2014 24468152	Intake	no	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr2	% kcal
72	Miyagawa 2014 24468152	Intake	no	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr3	% kcal
73	Miyagawa 2014 24468152	Intake	no	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr4	% kcal
74	Miyagawa 2014 24468152	Intake	no	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr1	% kcal
75	Miyagawa 2014 24468152	Intake	no	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr2	% kcal
76	Miyagawa 2014 24468152	Intake	no	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr3	% kcal
77	Miyagawa 2014 24468152	Intake	no	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr4	% kcal
78	Miyagawa 2014 24468152	Intake	no	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr1	% kcal
79	Miyagawa 2014 24468152	Intake	no	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr2	% kcal
80	Miyagawa 2014 24468152	Intake	no	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr3	% kcal
81	Miyagawa 2014 24468152	Intake	no	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr4	% kcal
82	Pietinen 1997 9149659	Intake	no	age, treatment group, smoking, body mass index, blood pressure, intakes of energy, alcohol, and fiber (quintiles), education (<7, 7-11, >11 years), and physical activity (<1, 1-2, >2 times per week).	Qt1	g/d
83	Pietinen 1997 9149659	Intake	no	age, treatment group, smoking, body mass index, blood pressure, intakes of energy, alcohol, and fiber (quintiles), education (<7, 7-11, >11 years), and physical activity (<1, 1-2, >2 times per week).	Qt2	g/d
84	Pietinen 1997 9149659	Intake	no	age, treatment group, smoking, body mass index, blood pressure, intakes of energy, alcohol, and fiber (quintiles), education (<7, 7-11, >11 years), and physical activity (<1, 1-2, >2 times per week).	Qt3	g/d
85	Pietinen 1997 9149659	Intake	no	age, treatment group, smoking, body mass index, blood pressure, intakes of energy, alcohol, and fiber (quintiles), education (<7, 7-11, >11 years), and physical activity (<1, 1-2, >2 times per week).	Qt4	g/d
86	Pietinen 1997 9149659	Intake	no	age, treatment group, smoking, body mass index, blood pressure, intakes of energy, alcohol, and fiber (quintiles), education (<7, 7-11, >11 years), and physical activity (<1, 1-2, >2 times per week).	Qt5	g/d

Appendix F Observational results: death from coronary heart disease

Row	Study PMID	Quantile low	Quantile median	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
65	Mozaffarian 2013 23546563	nd	4.34	nd	HR	nd	nd	nd	0.6	0.41	0.87		
66	Miyagawa 2014 24468152	men 0.00, women 0.02	men 0.18, women 0.19	men 0.23, women 0.25	HR	39	nd	47402	1	nd	nd	overal effect for trend	0.713
67	Miyagawa 2014 24468152	men 0.24, women 0.26	men 0.29, women 0.32	men 0.35, women 0.38	HR	43	nd	50196	1.01	0.66	1.57		
68	Miyagawa 2014 24468152	men 0.36, women 0.39	men 0.43, women 0.46	men 0.51, women 0.55	HR	43	nd	47359	0.95	0.61	1.46		
69	Miyagawa 2014 24468152	men 0.52, women 0.56	men 0.65, women 0.70	men 2.34 women 2.43	HR	46	nd	47940	0.94	0.61	1.45		
70	Miyagawa 2014 24468152	men 0.20, women 0.21	nd	men 0.85, women 0.93	HR	52	nd	45771	1	nd	nd	overal effect for trend	0.395
71	Miyagawa 2014 24468152	men 0.86, women 0.94	nd	men 1.05, women 1.15	HR	47	nd	49814	1.06	0.71	1.57		
72	Miyagawa 2014 24468152	men 1.06, women 1.16	nd	men 1.28, women 1.39	HR	34	nd	48876	0.81	0.52	1.25		
73	Miyagawa 2014 24468152	men 1.29, women 1.40	nd	men 3.92 women 3.66	HR	38	nd	48438	0.89	0.58	1.36		
74	Miyagawa 2014 24468152	men 0.00, women 0.00	nd	men 0.08, women 0.09	HR	41	nd	49312	1	nd	nd	overal effect for trend	0.518
75	Miyagawa 2014 24468152	men 0.09, women 0.10	nd	men 0.13, women 0.14	HR	44	nd	49840	1.01	0.66	1.54		
76	Miyagawa 2014 24468152	men 0.14, women 0.15	nd	men 0.19, women 0.21	HR	41	nd	45546	0.92	0.59	1.42		
77	Miyagawa 2014 24468152	men 0.20, women 0.22	nd	men 0.95, women 0.98	HR	45	nd	48200	0.89	0.58	1.36		
78	Miyagawa 2014 24468152	men 0.00, women 0.10	nd	men 0.15, women 0.16	HR	40	nd	49413	1	nd	nd	overal effect for trend	0.565
79	Miyagawa 2014 24468152	men 0.16, women 0.17	nd	men 0.22, women 0.23	HR	43	nd	46366	1.11	0.72	1.71		
80	Miyagawa 2014 24468152	men 0.23, women 0.24	nd	men 0.31, women 0.34	HR	44	nd	50022	0.96	0.63	1.48		
81	Miyagawa 2014 24468152	men 0.32, women 0.35	nd	men 1.39, women 1.45	HR	44	nd	47097	0.94	0.61	1.44		
82	Pietinen 1997 9149659	nd	0.9	nd	RR	149	nd	25277	1	nd	nd	Overall Test for trend	0.77
83	Pietinen 1997 9149659	nd	1.2	nd	RR	127	nd	25821	0.8	0.94	1.11		
84	Pietinen 1997 9149659	nd	1.5	nd	RR	124	nd	26226	0.84	0.99	1.17		
85	Pietinen 1997 9149659	nd	1.9	nd	RR	122	nd	25961	0.86	1.01	1.2		
86	Pietinen 1997 9149659	nd	2.5	nd	RR	113	nd	26103	0.8	0.96	1.14		

Appendix F Observational results: death from coronary heart disease

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA
87	Pietinen 1997 9149659	Alpha-Tocopherol Beta-Carotene Cancer Prevention	CHD death	coronary death	Healthy	health smoking men aged 50-69 years	Men	581/21930 (2.65)	6 y	EPA+DHA+DPA
88	Pietinen 1997 9149659	Alpha-Tocopherol Beta-Carotene Cancer Prevention	CHD death	coronary death	Healthy	health smoking men aged 50-69 years	Men	581/21930 (2.65)	6 y	EPA+DHA+DPA
89	Pietinen 1997 9149659	Alpha-Tocopherol Beta-Carotene Cancer Prevention	CHD death	coronary death	Healthy	health smoking men aged 50-69 years	Men	581/21930 (2.65)	6 y	EPA+DHA+DPA
90	Pietinen 1997 9149659	Alpha-Tocopherol Beta-Carotene Cancer Prevention	CHD death	coronary death	Healthy	health smoking men aged 50-69 years	Men	581/21930 (2.65)	6 y	EPA+DHA+DPA
91	Pietinen 1997 9149659	Alpha-Tocopherol Beta-Carotene Cancer Prevention	CHD death	coronary death	Healthy	health smoking men aged 50-69 years	Men	581/21930 (2.65)	6 y	EPA+DHA+DPA
92	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	CHD death	ischemic heart disease death	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	EPA
93	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	CHD death	ischemic heart disease death	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	EPA
94	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	CHD death	ischemic heart disease death	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	EPA
95	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	CHD death	ischemic heart disease death	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	EPA
96	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	CHD death	ischemic heart disease death	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	EPA
97	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	CHD death	ischemic heart disease death	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	DHA
98	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	CHD death	ischemic heart disease death	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	DHA
99	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	CHD death	ischemic heart disease death	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	DHA
100	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	CHD death	ischemic heart disease death	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	DHA
101	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	CHD death	ischemic heart disease death	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	DHA
102	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	CHD death	ischemic heart disease death	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	EPA+DHA
103	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	CHD death	ischemic heart disease death	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	EPA+DHA
104	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	CHD death	ischemic heart disease death	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	EPA+DHA
105	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	CHD death	ischemic heart disease death	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	EPA+DHA
106	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	CHD death	ischemic heart disease death	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	EPA+DHA
107	Vedtofte 2014 24964401	Pooling Project of Cohort Studies on Diet and Coronary Disease	CHD death	fatal CHD	Healthy	healthy 49 to 61 y	All	1751/229043 (0.76)	4-10 y	ALA
108	Yamagishi 2008 18786479	JACC	CHD death	ischemic heart disease death	Healthy	Healthy 40-79 yo	All	419/57972 (0.72)	12.7 y	All n-3
109	Yamagishi 2008 18786479	JACC	CHD death	ischemic heart disease death	Healthy	Healthy 40-79 yo	All	419/57972 (0.72)	12.7 y	All n-3

Appendix F Observational results: death from coronary heart disease

Row	Study PMID	n3 measure	Supplement	Adjustments	Quantile	n3 units
87	Pietinen 1997 9149659	Intake	no	age, treatment group, smoking, body mass index, blood pressure, intakes of energy, alcohol, and fiber (quintiles), education (<7, 7-11, >11 years), and physical activity (<1, 1-2, >2 times per week).	Qt1	g/d
88	Pietinen 1997 9149659	Intake	no	age, treatment group, smoking, body mass index, blood pressure, intakes of energy, alcohol, and fiber (quintiles), education (<7, 7-11, >11 years), and physical activity (<1, 1-2, >2 times per week).	Qt2	g/d
89	Pietinen 1997 9149659	Intake	no	age, treatment group, smoking, body mass index, blood pressure, intakes of energy, alcohol, and fiber (quintiles), education (<7, 7-11, >11 years), and physical activity (<1, 1-2, >2 times per week).	Qt3	g/d
90	Pietinen 1997 9149659	Intake	no	age, treatment group, smoking, body mass index, blood pressure, intakes of energy, alcohol, and fiber (quintiles), education (<7, 7-11, >11 years), and physical activity (<1, 1-2, >2 times per week).	Qt4	g/d
91	Pietinen 1997 9149659	Intake	no	age, treatment group, smoking, body mass index, blood pressure, intakes of energy, alcohol, and fiber (quintiles), education (<7, 7-11, >11 years), and physical activity (<1, 1-2, >2 times per week).	Qt5	g/d
92	Takata 2013 23788668	Intake	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt1	g/d
93	Takata 2013 23788668	Intake	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt2	g/d
94	Takata 2013 23788668	Intake	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt3	g/d
95	Takata 2013 23788668	Intake	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt4	g/d
96	Takata 2013 23788668	Intake	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt5	g/d
97	Takata 2013 23788668	Intake	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt1	g/d
98	Takata 2013 23788668	Intake	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt2	g/d
99	Takata 2013 23788668	Intake	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt3	g/d
100	Takata 2013 23788668	Intake	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt4	g/d
101	Takata 2013 23788668	Intake	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt5	g/d
102	Takata 2013 23788668	Intake	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt1	g/d
103	Takata 2013 23788668	Intake	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt2	g/d
104	Takata 2013 23788668	Intake	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt3	g/d
105	Takata 2013 23788668	Intake	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt4	g/d
106	Takata 2013 23788668	Intake	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt5	g/d
107	Vedtofte 2014 24964401	Intake	NA (no ALA supplememt)	age at baseline, calendar year, smoking habits, BMI, physical activity, educational level, history of hypertension, alcohol intake, total energy intake (where alcohol is excluded), fiber intake, MUFA, SFA, trans-fatty acid, long-chain n-3 FA, and linoleic acid intake	All	g/d
108	Yamagishi 2008 18786479	Intake	No	age, sex, htn and dm history, smoking status, alcohol consumption, BMI, mental stress, walking, sports, education, total energy, dietary intake of cholesterol/saturated and omega-3FA/vegetables/fruit	Qt1	g/d
109	Yamagishi 2008 18786479	Intake	No	age, sex, htn and dm history, smoking status, alcohol consumption, BMI, mental stress, walking, sports, education, total energy, dietary intake of cholesterol/saturated and omega-3FA/vegetables/fruit	Qt2	g/d

Appendix F Observational results: death from coronary heart disease

Row	Study PMID	Quantile low	Quantile median	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
87	Pietinen 1997 9149659	nd	0.2	nd	RR	126	nd	26032	1	nd	nd	Overall Test for trend	0.118
88	Pietinen 1997 9149659	nd	0.3	nd	RR	114	nd	26081	0.8	0.94	1.12		
89	Pietinen 1997 9149659	nd	0.4	nd	RR	120	nd	29590	0.87	1.03	1.21		
90	Pietinen 1997 9149659	nd	0.5	nd	RR	130	nd	25855	0.86	1.02	1.2		
91	Pietinen 1997 9149659	nd	0.8	nd	RR	145	nd	25470	0.97	1.15	1.35		
92	Takata 2013 23788668	nd	0.006 (men), 0.005 (women)	nd	HR	187	26860	nd	Reference group			P trend	0.25
93	Takata 2013 23788668	nd	0.01 (men), 0.01 (women)	nd	HR	102	nd	nd	0.83	0.64	1.06		
94	Takata 2013 23788668	nd	0.02 (men), 0.02 (women)	nd	HR	70	26860	nd	0.71	0.53	0.95		
95	Takata 2013 23788668	nd	0.03 (men), 0.03 (women)	nd	HR	57	nd	nd	0.71	0.52	0.98		
96	Takata 2013 23788668	nd	0.07 (men), 0.06 (women)	nd	HR	60	26858	nd	0.84	0.6	1.16		
97	Takata 2013 23788668	nd	0.009 (men), 0.008 (women)	nd	HR	194	26860	nd	Reference group			P trend	0.31
98	Takata 2013 23788668	nd	0.02 (men), 0.02 (women)	nd	HR	91	nd	nd	0.72	0.51	1		
99	Takata 2013 23788668	nd	0.05 (men), 0.04 (women)	nd	HR	67	26860	nd	0.65	0.47	0.9		
100	Takata 2013 23788668	nd	0.08 (men), 0.08 (women)	nd	HR	65	nd	nd	0.76	0.56	1.02		
101	Takata 2013 23788668	nd	0.15 (men), 0.15 (women)	nd	HR	59	26858	nd	0.79	0.57	1.09		
102	Takata 2013 23788668	nd	nd	nd	HR	195	26860	nd	Reference group			P trend	0.31
103	Takata 2013 23788668	nd	nd	nd	HR	91	nd	nd	0.72	0.55	0.93		
104	Takata 2013 23788668	nd	nd	nd	HR	66	26860	nd	0.64	0.48	0.86		
105	Takata 2013 23788668	nd	nd	nd	HR	65	nd	nd	0.76	0.57	1.03		
106	Takata 2013 23788668	nd	nd	nd	HR	59	26858	nd	0.79	0.57	1.09		
107	Vedtofte 2014 24964401	nd	nd	nd	HR	nd	nd	nd	0.88	0.68	1.14	per g/d increase	
108	Yamagishi 2008 18786479	0.05	nd	1.18	HR	75	11594	735904	Reference group				0.58
109	Yamagishi 2008 18786479	1.18	nd	1.47	HR	86	11595	735904	1.17	0.84	1.62		

Appendix F Observational results: death from coronary heart disease

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA
110	Yamagishi 2008 18786479	JACC	CHD death	ischemic heart disease death	Healthy	Healthy 40-79 yo	All	419/57972 (0.72)	12.7 y	All n-3
111	Yamagishi 2008 18786479	JACC	CHD death	ischemic heart disease death	Healthy	Healthy 40-79 yo	All	419/57972 (0.72)	12.7 y	All n-3
112	Yamagishi 2008 18786479	JACC	CHD death	ischemic heart disease death	Healthy	Healthy 40-79 yo	All	419/57972 (0.72)	12.7 y	All n-3
113	de Goede 2010 20335635	MORGEN	CHD death	fatal CHD	Healthy	Healthy 20-65 yo	All	82/21055 (0.39)	11.3 y	EPA+DHA
114	de Goede 2010 20335635	MORGEN	CHD death	fatal CHD	Healthy	Healthy 20-65 yo	All	82/21055 (0.39)	11.3 y	EPA+DHA
115	de Goede 2010 20335635	MORGEN	CHD death	fatal CHD	Healthy	Healthy 20-65 yo	All	82/21055 (0.39)	11.3 y	EPA+DHA
116	de Goede 2010 20335635	MORGEN	CHD death	fatal CHD	Healthy	Healthy 20-65 yo	All	82/21055 (0.39)	11.3 y	EPA+DHA
117	Koh_2013_24343844	The Singapore Chinese Health Study	CHD death		Healthy		All	2697/60298 (0.05)	5y	All n-3
118	Koh_2013_24343844	The Singapore Chinese Health Study	CHD death		Healthy		All	2697/60298 (0.05)	5y	All n-3
119	Koh_2013_24343844	The Singapore Chinese Health Study	CHD death		Healthy		All	2697/60298 (0.05)	5y	All n-3
120	Koh_2013_24343844	The Singapore Chinese Health Study	CHD death		Healthy		All	2697/60298 (0.05)	5y	All n-3
121	Koh_2013_24343844	The Singapore Chinese Health Study	CHD death		Healthy		All	2697/60298 (0.05)	5y	All n-3
122	Koh_2013_24343844	The Singapore Chinese Health Study	CHD death		Healthy		All	2697/60298 (0.05)	5y	All n-3
123	Koh_2013_24343844	The Singapore Chinese Health Study	CHD death		Healthy		All	2697/60298 (0.05)	5y	All n-3
124	Koh_2013_24343844	The Singapore Chinese Health Study	CHD death		Healthy		All	2697/60298 (0.05)	5y	All n-3
125	Koh_2013_24343844	The Singapore Chinese Health Study	CHD death		Healthy		All	2697/60298 (0.05)	5y	All n-3
126	Koh_2013_24343844	The Singapore Chinese Health Study	CHD death		Healthy		All	2697/60298 (0.05)	5y	All n-3
126	Koh_2013_24343844	The Singapore Chinese Health Study	CHD death		Healthy		All	2697/60298 (0.05)	5y	All n-3
126	Koh_2013_24343844	The Singapore Chinese Health Study	CHD death		Healthy		All	2697/60298 (0.05)	5y	All n-3

Appendix F Observational results:
death from coronary heart disease

Row	Study PMID	n3 measure	Supplement	Adjustments	Quantile	n3 units
110	Yamagishi 2008 18786479	Intake	No	age, sex, htn and dm history, smoking status, alcohol consumption, BMI, mental stress, walking, sports, education, total energy, dietary intake of cholesterol/saturated and omega-3FA/vegetables/fruit	Qt3	g/d
111	Yamagishi 2008 18786479	Intake	No	age, sex, htn and dm history, smoking status, alcohol consumption, BMI, mental stress, walking, sports, education, total energy, dietary intake of cholesterol/saturated and omega-3FA/vegetables/fruit	Qt4	g/d
112	Yamagishi 2008 18786479	Intake	No	age, sex, htn and dm history, smoking status, alcohol consumption, BMI, mental stress, walking, sports, education, total energy, dietary intake of cholesterol/saturated and omega-3FA/vegetables/fruit	Qt5	g/d
113	de Goede 2010 20335635	Intake	No	age, gender, BMI, total energy intake, ethanol intake, cigarette smoking, social economic status, vitamin/mineral supplement use, use of drugs for hypertension/hypercholesterolemia, family history of CVD, SFA, fruit, and vegetables	Qt1	g/d
114	de Goede 2010 20335635	Intake	No	age, gender, BMI, total energy intake, ethanol intake, cigarette smoking, social economic status, vitamin/mineral supplement use, use of drugs for hypertension/hypercholesterolemia, family history of CVD, SFA, fruit, and vegetables	Qt2	g/d
115	de Goede 2010 20335635	Intake	No	age, gender, BMI, total energy intake, ethanol intake, cigarette smoking, social economic status, vitamin/mineral supplement use, use of drugs for hypertension/hypercholesterolemia, family history of CVD, SFA, fruit, and vegetables	Qt3	g/d
116	de Goede 2010 20335635	Intake	No	age, gender, BMI, total energy intake, ethanol intake, cigarette smoking, social economic status, vitamin/mineral supplement use, use of drugs for hypertension/hypercholesterolemia, family history of CVD, SFA, fruit, and vegetables	Qt4	g/d
117	Koh_2013_24343844	Intake	No	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr1	nd
118	Koh_2013_24343844	Intake	No	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr2	nd
119	Koh_2013_24343844	Intake	No	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr3	nd
120	Koh_2013_24343844	Intake	No	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr4	nd
121	Koh_2013_24343844	Intake	No	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr1	nd
122	Koh_2013_24343844	Intake	No	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr2	nd
123	Koh_2013_24343844	Intake	No	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr3	nd
124	Koh_2013_24343844	Intake	No	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr4	nd
125	Koh_2013_24343844	Intake	No	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr1	nd
126	Koh_2013_24343844	Intake	No	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr2	nd
126	Koh_2013_24343844	Intake	No	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr3	nd
126	Koh_2013_24343844	Intake	No	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr4	nd

Appendix F Observational results: death from coronary heart disease

Row	Study PMID	Quantile low	Quantile median	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
110	Yamagishi 2008 18786479	1.47	nd	1.75	HR	78	11594	735904	0.98	0.69	1.4		
111	Yamagishi 2008 18786479	1.75	nd	2.11	HR	81	11595	735904	1	0.68	1.45		
112	Yamagishi 2008 18786479	2.11	nd	5.06	HR	99	11594	735904	0.95	0.62	1.43		
113	de Goede 2010 20335635	nd	40	<62	HR	24	5336	nd	Reference group			P trend	0.05
114	de Goede 2010 20335635	62	84	113	HR	18	5335	nd	0.68	0.36	1.25		
115	de Goede 2010 20335635	114	151	194	HR	20	5335	nd	0.65	0.36	1.19		
116	de Goede 2010 20335635	>194	234	nd	HR	20	5336	nd	0.51	0.27	0.94		
117	Koh_2013_24343844	nd	nd	nd	HR	726	15181		Ref			P trend	0.04
118	Koh_2013_24343844	nd	nd	nd	HR	678	15022		0.92	0.81	1.03		
119	Koh_2013_24343844	nd	nd	nd	HR	675	15023		0.92	0.8	1.03		
120	Koh_2013_24343844	nd	nd	nd	HR	618	15072		0.85	0.73	0.98		
121	Koh_2013_24343844	nd	nd	nd	HR	680	15181		Ref			P trend	0.02
122	Koh_2013_24343844	nd	nd	nd	HR	689	15022		0.99	0.88	1.1		
123	Koh_2013_24343844	nd	nd	nd	HR	700	15023		0.97	0.85	1.09		
124	Koh_2013_24343844	nd	nd	nd	HR	628	15072		0.86	0.74	0.99		
125	Koh_2013_24343844	nd	nd	nd	HR	730	15181		Ref			P trend	0.001
126	Koh_2013_24343844	nd	nd	nd	HR	733	15022		1.01	0.9	1.13		
126	Koh_2013_24343844	nd	nd	nd	HR	651	15023		0.9	0.79	1.01		
126	Koh_2013_24343844	nd	nd	nd	HR	583	15072		0.82	0.71	0.93		

Appendix F Observational results: death from coronary heart disease

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA
128	**Subgroup analyses**									
129	Vedtofte 2014 24964401	Pooling Project of Cohort Studies on Diet and Coronary Disease	CHD death	fatal CHD	Healthy	healthy 49 to 61 y	Women	560/148675 (0.38)	4-10 y	ALA
130	Vedtofte 2014 24964401	Pooling Project of Cohort Studies on Diet and Coronary Disease	CHD death	fatal CHD	Healthy	healthy 49 to 61 y	Men	1191/80368 (1.48)	4-10 y	ALA

Row	Study PMID	n3 measure	Supplement	Adjustments	Quantile	n3 units
128	**Subgroup analyses**					
129	Vedtofte 2014 24964401	Intake	NA (no ALA supplememt)	age at baseline, calendar year, smoking habits, BMI, physical activity, educational level, history of hypertension, alcohol intake, total energy intake (where alcohol is excluded), fiber intake, MUFA, SFA, trans-fatty acid, long-chain n-3 FA, and linoleic acid intake	All	g/d
130	Vedtofte 2014 24964401	Intake	NA (no ALA supplememt)	age at baseline, calendar year, smoking habits, BMI, physical activity, educational level, history of hypertension, alcohol intake, total energy intake (where alcohol is excluded), fiber intake, MUFA, SFA, trans-fatty acid, long-chain n-3 FA, and linoleic acid intake	All	g/d

Appendix F Observational results: death from coronary heart disease

Row	Study PMID	Quantile low	Quantile median	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
128	**Subgroup analyses**												
129	Vedtofte 2014 24964401	nd	nd	nd	HR	nd	nd	nd	1.23	0.8	1.89	per g/d increase	
130	Vedtofte 2014 24964401	nd	nd	nd	HR	nd	nd	nd	0.77	0.58	1.01	per g/d increase	

Appendix F Observational results: death from cardiovascular disease

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure
2	Dolecek 1992 1579579	MRFIT	CVD death	CVD mortality	Healthy	Men aged 35-57 assigned to the usual care group	Men	232/6258 (3.71)	10.5 y	EPA+DHA+DPA	Intake
3	Dolecek 1992 1579579	MRFIT	CVD death	CVD mortality	Healthy	Men aged 35-57 assigned to the usual care group	Men	232/6258 (3.71)	10.5 y	EPA+DHA+DPA	Intake
4	Dolecek 1992 1579579	MRFIT	CVD death	CVD mortality	Healthy	Men aged 35-57 assigned to the usual care group	Men	232/6258 (3.71)	10.5 y	EPA+DHA+DPA	Intake
5	Dolecek 1992 1579579	MRFIT	CVD death	CVD mortality	Healthy	Men aged 35-57 assigned to the usual care group	Men	232/6258 (3.71)	10.5 y	EPA+DHA+DPA	Intake
6	Dolecek 1992 1579579	MRFIT	CVD death	CVD mortality	Healthy	Men aged 35-57 assigned to the usual care group	Men	232/6258 (3.71)	10.5 y	EPA+DHA+DPA	Intake
7	Dolecek 1992 1579579	MRFIT	CVD death	all cardiovascular disease	Healthy	Men aged 35-57 assigned to the usual care group	Men	232/6258 (3.71)	10.5 y	EPA+DHA+DPA	Intake
8	Dolecek 1992 1579579	MRFIT	CVD death	CVD mortality	Healthy	Men aged 35-57 assigned to the usual care group	Men	232/6258 (3.71)	10.5 y	EPA+DHA+DPA	Intake
9	Dolecek 1992 1579579	MRFIT	CVD death	CVD mortality	Healthy	Men aged 35-57 assigned to the usual care group	Men	232/6258 (3.71)	10.5 y	EPA+DHA+DPA	Intake
10	Dolecek 1992 1579579	MRFIT	CVD death	CVD mortality	Healthy	Men aged 35-57 assigned to the usual care group	Men	232/6258 (3.71)	10.5 y	EPA+DHA+DPA	Intake
11	Dolecek 1992 1579579	MRFIT	CVD death	CVD mortality	Healthy	Men aged 35-57 assigned to the usual care group	Men	232/6258 (3.71)	10.5 y	EPA+DHA+DPA	Intake
12	Dolecek 1992 1579579	MRFIT	CVD death	CVD mortality	Healthy	Men aged 35-57 assigned to the usual care group	Men	232/6258 (3.71)	10.5 y	EPA+DHA+DPA	Intake
13	Dolecek 1992 1579579	MRFIT	CVD death	all cardiovascular disease	Healthy	Men aged 35-57 assigned to the usual care group	Men	232/6258 (3.71)	10.5 y	EPA+DHA+DPA	Intake
14	Dolecek 1992 1579579	MRFIT	CVD death	CVD mortality	Healthy	Men aged 35-57 assigned to the usual care group	Men	232/6258 (3.71)	10.5 y	ALA	Intake
15	Dolecek 1992 1579579	MRFIT	CVD death	CVD mortality	Healthy	Men aged 35-57 assigned to the usual care group	Men	232/6258 (3.71)	10.5 y	ALA	Intake
16	Dolecek 1992 1579579	MRFIT	CVD death	CVD mortality	Healthy	Men aged 35-57 assigned to the usual care group	Men	232/6258 (3.71)	10.5 y	ALA	Intake
17	Dolecek 1992 1579579	MRFIT	CVD death	CVD mortality	Healthy	Men aged 35-57 assigned to the usual care group	Men	232/6258 (3.71)	10.5 y	ALA	Intake
18	Dolecek 1992 1579579	MRFIT	CVD death	CVD mortality	Healthy	Men aged 35-57 assigned to the usual care group	Men	232/6258 (3.71)	10.5 y	ALA	Intake
19	Dolecek 1992 1579579	MRFIT	CVD death	all cardiovascular disease	Healthy	Men aged 35-57 assigned to the usual care group	Men	232/6258 (3.71)	10.5 y	ALA	Intake
20	Dolecek 1992 1579579	MRFIT	CVD death	CVD mortality	Healthy	Men aged 35-57 assigned to the usual care group	Men	232/6258 (3.71)	10.5 y	ALA	Intake
21	Dolecek 1992 1579579	MRFIT	CVD death	CVD mortality	Healthy	Men aged 35-57 assigned to the usual care group	Men	232/6258 (3.71)	10.5 y	ALA	Intake
22	Dolecek 1992 1579579	MRFIT	CVD death	CVD mortality	Healthy	Men aged 35-57 assigned to the usual care group	Men	232/6258 (3.71)	10.5 y	ALA	Intake
23	Dolecek 1992 1579579	MRFIT	CVD death	CVD mortality	Healthy	Men aged 35-57 assigned to the usual care group	Men	232/6258 (3.71)	10.5 y	ALA	Intake
24	Dolecek 1992 1579579	MRFIT	CVD death	CVD mortality	Healthy	Men aged 35-57 assigned to the usual care group	Men	232/6258 (3.71)	10.5 y	ALA	Intake
25	Dolecek 1992 1579579	MRFIT	CVD death	all cardiovascular disease	Healthy	Men aged 35-57 assigned to the usual care group	Men	232/6258 (3.71)	10.5 y	ALA	Intake
26	Mozaffarian 2013 23546563	Cardiovascular Health Study	CVD death	Total CVD mortality	Healthy	Healthy age >= 65y	All	570/3941 (14.46)	16y	All n-3	Plasma

Appendix F Observational results: death from cardiovascular disease

Row	Study PMID	Supplement	Adjustments	Quantile	n3 units	Quantile low	Quantile median
2	Dolecek 1992 1579579	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt1	g/d	nd	0 (mean)
3	Dolecek 1992 1579579	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt2	g/d	nd	0.009 (mean)
4	Dolecek 1992 1579579	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt3	g/d	nd	0.046 (mean)
5	Dolecek 1992 1579579	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt4	g/d	nd	0.153 (mean)
6	Dolecek 1992 1579579	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt5	g/d	nd	0.664 (mean)
7	Dolecek 1992 1579579	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	All	g/d	nd	nd
8	Dolecek 1992 1579579	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt1	% kcal	nd	0 (mean)
9	Dolecek 1992 1579579	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt2	% kcal	nd	0.004 (mean)
10	Dolecek 1992 1579579	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt3	% kcal	nd	0.019 (mean)
11	Dolecek 1992 1579579	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt4	% kcal	nd	0.063 (mean)
12	Dolecek 1992 1579579	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt5	% kcal	nd	0.284 (mean)
13	Dolecek 1992 1579579	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	All	% kcal	nd	nd
14	Dolecek 1992 1579579	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt1	g/d	nd	0.873 (mean)
15	Dolecek 1992 1579579	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt2	g/d	nd	1.273 (mean)
16	Dolecek 1992 1579579	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt3	g/d	nd	1.577 (mean)
17	Dolecek 1992 1579579	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt4	g/d	nd	1.926 (mean)
18	Dolecek 1992 1579579	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt5	g/d	nd	2.802 (mean)
19	Dolecek 1992 1579579	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	All	g/d	nd	nd
20	Dolecek 1992 1579579	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt1	% kcal	nd	0.424 (mean)
21	Dolecek 1992 1579579	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt2	% kcal	nd	0.544 (mean)
22	Dolecek 1992 1579579	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt3	% kcal	nd	0.63 (mean)
23	Dolecek 1992 1579579	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt4	% kcal	nd	0.732 (mean)
24	Dolecek 1992 1579579	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	Qt5	% kcal	nd	0.98 (mean)
25	Dolecek 1992 1579579	nd	age ,race, smoking, baseline diastolic blood pressure, high density lipoprotein, low density lipoprotein	All	% kcal	nd	nd
26	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt1	% FA	nd	3.17

Appendix F Observational results: death from cardiovascular disease

Row	Study PMID	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
2	Dolecek 1992 1579579	nd	RR	nd	1307	nd	Reference group				<0.10
3	Dolecek 1992 1579579	nd	RR	nd	1197	nd	1.06	nd	nd		
4	Dolecek 1992 1579579	nd	RR	nd	1251	nd	0.93	nd	nd		
5	Dolecek 1992 1579579	nd	RR	nd	1252	nd	0.93	nd	nd		
6	Dolecek 1992 1579579	nd	RR	nd	1251	nd	0.6	nd	nd		
7	Dolecek 1992 1579579	nd	HR	232	6258	nd	0.38	nd	nd		<0.01
8	Dolecek 1992 1579579	nd	RR	nd	1307	nd	Reference group				<0.10
9	Dolecek 1992 1579579	nd	RR	nd	1196	nd	1.08	nd	nd		
10	Dolecek 1992 1579579	nd	RR	nd	1252	nd	0.81	nd	nd		
11	Dolecek 1992 1579579	nd	RR	nd	1252	nd	1.08	nd	nd		
12	Dolecek 1992 1579579	nd	RR	nd	1251	nd	0.55	nd	nd		
13	Dolecek 1992 1579579	nd	HR	232	6258	nd	0.64	nd	nd		<0.01
14	Dolecek 1992 1579579	nd	RR	nd	1251	nd	Reference group				<0.10
15	Dolecek 1992 1579579	nd	RR	nd	1253	nd	0.93	nd	nd		
16	Dolecek 1992 1579579	nd	RR	nd	1251	nd	0.66	nd	nd		
17	Dolecek 1992 1579579	nd	RR	nd	1251	nd	0.88	nd	nd		
18	Dolecek 1992 1579579	nd	RR	nd	1252	nd	0.61	nd	nd		
19	Dolecek 1992 1579579	nd	HR	232	6258	nd	0.82	nd	nd		<0.10
20	Dolecek 1992 1579579	nd	RR	nd	1251	nd	Reference group				<0.05
21	Dolecek 1992 1579579	nd	RR	nd	1252	nd	0.86	nd	nd		
22	Dolecek 1992 1579579	nd	RR	nd	1252	nd	0.97	nd	nd		
23	Dolecek 1992 1579579	nd	RR	nd	1252	nd	0.66	nd	nd		
24	Dolecek 1992 1579579	nd	RR	nd	1251	nd	0.66	nd	nd		
25	Dolecek 1992 1579579	nd	HR	232	6258	nd	0.46	nd	nd		<0.05
26	Mozaffarian 2013 23546563	nd	HR	nd	nd	nd	Reference group			P trend	<0.001

Appendix F Observational results: death from cardiovascular disease

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure
27	Mozaffarian 2013 23546563	Cardiovascular Health Study	CVD death	Total CVD mortality	Healthy	Healthy age >= 65y	All	570/3941 (14.46)	16y	All n-3	Plasma
28	Mozaffarian 2013 23546563	Cardiovascular Health Study	CVD death	Total CVD mortality	Healthy	Healthy age >= 65y	All	570/3941 (14.46)	16y	All n-3	Plasma
29	Mozaffarian 2013 23546563	Cardiovascular Health Study	CVD death	Total CVD mortality	Healthy	Healthy age >= 65y	All	570/3941 (14.46)	16y	All n-3	Plasma
30	Mozaffarian 2013 23546563	Cardiovascular Health Study	CVD death	Total CVD mortality	Healthy	Healthy age >= 65y	All	570/3941 (14.46)	16y	All n-3	Plasma
31	Mozaffarian 2013 23546563	Cardiovascular Health Study	CVD death	Total CVD mortality	Healthy	Healthy age >= 65y	All	570/3941 (14.46)	16y	DHA	Plasma
32	Mozaffarian 2013 23546563	Cardiovascular Health Study	CVD death	Total CVD mortality	Healthy	Healthy age >= 65y	All	570/3941 (14.46)	16y	DHA	Plasma
33	Mozaffarian 2013 23546563	Cardiovascular Health Study	CVD death	Total CVD mortality	Healthy	Healthy age >= 65y	All	570/3941 (14.46)	16y	DHA	Plasma
34	Mozaffarian 2013 23546563	Cardiovascular Health Study	CVD death	Total CVD mortality	Healthy	Healthy age >= 65y	All	570/3941 (14.46)	16y	DHA	Plasma
35	Mozaffarian 2013 23546563	Cardiovascular Health Study	CVD death	Total CVD mortality	Healthy	Healthy age >= 65y	All	570/3941 (14.46)	16y	DHA	Plasma
36	Mozaffarian 2013 23546563	Cardiovascular Health Study	CVD death	Total CVD mortality	Healthy	Healthy age >= 65y	All	570/3941 (14.46)	16y	EPA	Plasma
37	Mozaffarian 2013 23546563	Cardiovascular Health Study	CVD death	Total CVD mortality	Healthy	Healthy age >= 65y	All	570/3941 (14.46)	16y	EPA	Plasma
38	Mozaffarian 2013 23546563	Cardiovascular Health Study	CVD death	Total CVD mortality	Healthy	Healthy age >= 65y	All	570/3941 (14.46)	16y	EPA	Plasma
39	Mozaffarian 2013 23546563	Cardiovascular Health Study	CVD death	Total CVD mortality	Healthy	Healthy age >= 65y	All	570/3941 (14.46)	16y	EPA	Plasma
40	Mozaffarian 2013 23546563	Cardiovascular Health Study	CVD death	Total CVD mortality	Healthy	Healthy age >= 65y	All	570/3941 (14.46)	16y	EPA	Plasma
41	Fretts 2014 25159901	Cardiovascular Health Study	CVD death	Total CVD mortality	Healthy	Healthy age >= 65y	All	429/2583 (16.61)	12y	ALA	Intake
42	Fretts 2014 25159901	Cardiovascular Health Study	CVD death	Total CVD mortality	Healthy	Healthy age >= 65y	All	429/2583 (16.61)	12y	ALA	Intake
43	Fretts 2014 25159901	Cardiovascular Health Study	CVD death	Total CVD mortality	Healthy	Healthy age >= 65y	All	429/2583 (16.61)	12y	ALA	Intake
44	Fretts 2014 25159901	Cardiovascular Health Study	CVD death	Total CVD mortality	Healthy	Healthy age >= 65y	All	429/2583 (16.61)	12y	ALA	Intake
45	Fretts 2014 25159901	Cardiovascular Health Study	CVD death	Total CVD mortality	Healthy	Healthy age >= 65y	All	429/2583 (16.61)	12y	ALA	Intake

Row	Study PMID	Supplement	Adjustments	Quantile	n3 units	Quantile low	Quantile median
27	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt2	% FA	nd	3.72
28	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt3	% FA	nd	4.21
29	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt4	% FA	nd	4.8
30	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt5	% FA	nd	6.04
31	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt1	% FA	nd	1.95
32	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt2	% FA	nd	2.44
33	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt3	% FA	nd	2.87
34	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt4	% FA	nd	3.36
35	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt5	% FA	nd	4.34
36	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt1	% FA	nd	0.3
37	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt2	% FA	nd	0.41
38	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt3	% FA	nd	0.51
39	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt4	% FA	nd	0.64
40	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt5	% FA	nd	0.92
41	Fretts 2014 25159901	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt1	% fat intake	0.39	1.33
42	Fretts 2014 25159901	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt2	% fat intake	1.45	1.56
43	Fretts 2014 25159901	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt3	% fat intake	1.65	1.76
44	Fretts 2014 25159901	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt4	% fat intake	1.87	2
45	Fretts 2014 25159901	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt5	% fat intake	2.17	2.44

Appendix F Observational results: death from cardiovascular disease

Row	Study PMID	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
27	Mozaffarian 2013 23546563	nd	HR	nd	nd	nd	0.92	0.71	1.19		
28	Mozaffarian 2013 23546563	nd	HR	nd	nd	nd	1.05	0.82	1.35		
29	Mozaffarian 2013 23546563	nd	HR	nd	nd	nd	0.74	0.56	0.98		
30	Mozaffarian 2013 23546563	nd	HR	nd	nd	nd	0.65	0.48	0.87		
31	Mozaffarian 2013 23546563	nd	HR	nd	nd	nd	Reference group			P trend	0.002
32	Mozaffarian 2013 23546563	nd	HR	nd	nd	nd	1.09	0.84	1.41		
33	Mozaffarian 2013 23546563	nd	HR	nd	nd	nd	1.01	0.78	1.3		
34	Mozaffarian 2013 23546563	nd	HR	nd	nd	nd	0.92	0.7	1.2		
35	Mozaffarian 2013 23546563	nd	HR	nd	nd	nd	0.66	0.49	0.89		
36	Mozaffarian 2013 23546563	nd	HR	nd	nd	nd	Reference group			P trend	0.009
37	Mozaffarian 2013 23546563	nd	HR	nd	nd	nd	1.01	0.79	1.3		
38	Mozaffarian 2013 23546563	nd	HR	nd	nd	nd	0.87	0.67	1.14		
39	Mozaffarian 2013 23546563	nd	HR	nd	nd	nd	0.81	0.62	1.06		
40	Mozaffarian 2013 23546563	nd	HR	nd	nd	nd	0.72	0.54	0.96		
41	Fretts 2014 25159901	1.45	HR	89	nd	4875	Reference group			P trend	0.92
42	Fretts 2014 25159901	1.65	HR	83	nd	4987	0.93	0.68	1.25		
43	Fretts 2014 25159901	1.87	HR	76	nd	5096	0.83	0.61	1.14		
44	Fretts 2014 25159901	2.17	HR	92	nd	5291	0.97	0.72	1.31		
45	Fretts 2014 25159901	4.88	HR	89	nd	5600	0.96	0.71	1.32		

Appendix F Observational results: death from cardiovascular disease

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure
46	Fretts 2014 25159901	Cardiovascular Health Study	CVD death	Total CVD mortality	Healthy	Healthy age >= 65y	All	519/2709 (19.16)	16y	ALA	Plasma
47	Fretts 2014 25159901	Cardiovascular Health Study	CVD death	Total CVD mortality	Healthy	Healthy age >= 65y	All	519/2709 (19.16)	16y	ALA	Plasma
48	Fretts 2014 25159901	Cardiovascular Health Study	CVD death	Total CVD mortality	Healthy	Healthy age >= 65y	All	519/2709 (19.16)	16y	ALA	Plasma
49	Fretts 2014 25159901	Cardiovascular Health Study	CVD death	Total CVD mortality	Healthy	Healthy age >= 65y	All	519/2709 (19.16)	16y	ALA	Plasma
50	Fretts 2014 25159901	Cardiovascular Health Study	CVD death	Total CVD mortality	Healthy	Healthy age >= 65y	All	519/2709 (19.16)	16y	ALA	Plasma
51	Mozaffarian 2013 23546563	Cardiovascular Health Study	CVD death	Total CVD mortality	Healthy	Healthy age >= 65y	All	570/3941 (14.46)	16y	DPA	Plasma
52	Mozaffarian 2013 23546563	Cardiovascular Health Study	CVD death	Total CVD mortality	Healthy	Healthy age >= 65y	All	570/3941 (14.46)	16y	DPA	Plasma
53	Mozaffarian 2013 23546563	Cardiovascular Health Study	CVD death	Total CVD mortality	Healthy	Healthy age >= 65y	All	570/3941 (14.46)	16y	DPA	Plasma
54	Mozaffarian 2013 23546563	Cardiovascular Health Study	CVD death	Total CVD mortality	Healthy	Healthy age >= 65y	All	570/3941 (14.46)	16y	DPA	Plasma
55	Mozaffarian 2013 23546563	Cardiovascular Health Study	CVD death	Total CVD mortality	Healthy	Healthy age >= 65y	All	570/3941 (14.46)	16y	DPA	Plasma
56	Miyagawa 2014 24468152	NIPPON DATA80	CVD death	CHD, Stroke and Heart failure	Healthy	healthy individual with mean age of 50	All	879/9190 (9.56)	24 y	EPA+DHA	Intake
57	Miyagawa 2014 24468152	NIPPON DATA80	CVD death	CHD, Stroke and Heart failure	Healthy	healthy individual with mean age of 50	All	879/9190 (9.56)	24 y	EPA+DHA	Intake
58	Miyagawa 2014 24468152	NIPPON DATA80	CVD death	CHD, Stroke and Heart failure	Healthy	healthy individual with mean age of 50	All	879/9190 (9.56)	24 y	EPA+DHA	Intake
59	Miyagawa 2014 24468152	NIPPON DATA80	CVD death	CHD, Stroke and Heart failure	Healthy	healthy individual with mean age of 50	All	879/9190 (9.56)	24 y	EPA+DHA	Intake
60	Miyagawa 2014 24468152	NIPPON DATA80	CVD death	CHD, Stroke and Heart failure	Healthy	healthy individual with mean age of 50	All	879/9190 (9.56)	24 y	All n-3	Intake
61	Miyagawa 2014 24468152	NIPPON DATA80	CVD death	CHD, Stroke and Heart failure	Healthy	healthy individual with mean age of 50	All	879/9190 (9.56)	24 y	All n-3	Intake
62	Miyagawa 2014 24468152	NIPPON DATA80	CVD death	CHD, Stroke and Heart failure	Healthy	healthy individual with mean age of 50	All	879/9190 (9.56)	24 y	All n-3	Intake
63	Miyagawa 2014 24468152	NIPPON DATA80	CVD death	CHD, Stroke and Heart failure	Healthy	healthy individual with mean age of 50	All	879/9190 (9.56)	24 y	All n-3	Intake
64	Miyagawa 2014 24468152	NIPPON DATA80	CVD death	CHD, Stroke and Heart failure	Healthy	healthy individual with mean age of 50	All	879/9190 (9.56)	24 y	EPA	Intake
65	Miyagawa 2014 24468152	NIPPON DATA80	CVD death	CHD, Stroke and Heart failure	Healthy	healthy individual with mean age of 50	All	879/9190 (9.56)	24 y	EPA	Intake
66	Miyagawa 2014 24468152	NIPPON DATA80	CVD death	CHD, Stroke and Heart failure	Healthy	healthy individual with mean age of 50	All	879/9190 (9.56)	24 y	EPA	Intake
67	Miyagawa 2014 24468152	NIPPON DATA80	CVD death	CHD, Stroke and Heart failure	Healthy	healthy individual with mean age of 50	All	879/9190 (9.56)	24 y	EPA	Intake
68	Miyagawa 2014 24468152	NIPPON DATA80	CVD death	CHD, Stroke and Heart failure	Healthy	healthy individual with mean age of 50	All	879/9190 (9.56)	24 y	DHA	Intake

Row	Study PMID	Supplement	Adjustments	Quantile	n3 units	Quantile low	Quantile median
46	Fretts 2014 25159901	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt1	% FA	0.05	0.09
47	Fretts 2014 25159901	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt2	% FA	0.11	0.12
48	Fretts 2014 25159901	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt3	% FA	0.13	0.14
49	Fretts 2014 25159901	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt4	% FA	0.15	0.17
50	Fretts 2014 25159901	no	age, sex, race, enrolment site, education, smoking status, diabetes, BMI, waist circumference, physical activity, alcohol consumption and treated hypertension.	Qt5	% FA	0.19	0.22
51	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt1	% FA	nd	0.63
52	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt2	% FA	nd	0.75
53	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt3	% FA	nd	0.82
54	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt4	% FA	nd	0.91
55	Mozaffarian 2013 23546563	no	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt5	% FA	nd	1.04
56	Miyagawa 2014 24468152	no	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr1	% kcal	men 0.00, women 0.02	men 0.18, women 0.19
57	Miyagawa 2014 24468152	no	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr2	% kcal	men 0.24, women 0.26	men 0.29, women 0.32
58	Miyagawa 2014 24468152	no	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr3	% kcal	men 0.36, women 0.39	men 0.43, women 0.46
59	Miyagawa 2014 24468152	no	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr4	% kcal	men 0.52, women 0.56	men 0.65, women 0.70
60	Miyagawa 2014 24468152	no	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr1	% kcal	men 0.20, women 0.21	nd
61	Miyagawa 2014 24468152	no	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr2	% kcal	men 0.86, women 0.94	nd
62	Miyagawa 2014 24468152	no	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr3	% kcal	men 1.06, women 1.16	nd
63	Miyagawa 2014 24468152	no	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr4	% kcal	men 1.29, women 1.40	nd
64	Miyagawa 2014 24468152	no	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr1	% kcal	men 0.00, women 0.00	nd
65	Miyagawa 2014 24468152	no	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr2	% kcal	men 0.09, women 0.10	nd
66	Miyagawa 2014 24468152	no	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr3	% kcal	men 0.14, women 0.15	nd
67	Miyagawa 2014 24468152	no	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr4	% kcal	men 0.20, women 0.22	nd
68	Miyagawa 2014 24468152	no	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr1	% kcal	men 0.00, women 0.10	nd

Appendix F Observational results: death from cardiovascular disease

Row	Study PMID	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
46	Fretts 2014 25159901	0.11	HR	101	nd	6483	Reference group			P trend	0.87
47	Fretts 2014 25159901	0.13	HR	108	nd	6025	1.15	0.87	1.53		
48	Fretts 2014 25159901	0.15	HR	102	nd	6315	1.08	0.81	1.44		
49	Fretts 2014 25159901	0.19	HR	102	nd	6352	1.05	0.79	1.4		
50	Fretts 2014 25159901	0.47	HR	106	nd	6936	1.02	0.77	1.36		
51	Mozaffarian 2013 23546563	nd	HR	nd	nd	nd	Reference group			P trend	0.021
52	Mozaffarian 2013 23546563	nd	HR	nd	nd	nd	0.73	0.56	0.95		
53	Mozaffarian 2013 23546563	nd	HR	nd	nd	nd	0.82	0.63	1.06		
54	Mozaffarian 2013 23546563	nd	HR	nd	nd	nd	0.8	0.62	1.03		
55	Mozaffarian 2013 23546563	nd	HR	nd	nd	nd	0.68	0.52	0.89		
56	Miyagawa 2014 24468152	men 0.23, women 0.25	HR	222	nd	47402	1	nd	nd	overal effect for trend	0.144
57	Miyagawa 2014 24468152	men 0.35, women 0.38	HR	210	nd	50196	0.87	0.72	1.05		
58	Miyagawa 2014 24468152	men 0.51, women 0.55	HR	216	nd	47359	0.88	0.73	1.06		
59	Miyagawa 2014 24468152	men 2.34 women 2.43	HR	231	nd	47940	0.85	0.7	1.02		
60	Miyagawa 2014 24468152	men 0.85, women 0.93	HR	281	nd	45771	1	nd	nd	overal effect for trend	0.187
61	Miyagawa 2014 24468152	men 1.05, women 1.15	HR	222	nd	49814	0.95	0.8	1.14		
62	Miyagawa 2014 24468152	men 1.28, women 1.39	HR	179	nd	48876	0.85	0.71	1.03		
63	Miyagawa 2014 24468152	men 3.92 women 3.66	HR	197	nd	48438	0.91	0.76	1.09		
64	Miyagawa 2014 24468152	men 0.08, women 0.09	HR	221	nd	49312	1	nd	nd	overal effect for trend	0.209
65	Miyagawa 2014 24468152	men 0.13, women 0.14	HR	220	nd	49840	0.92	0.76	1.11		
66	Miyagawa 2014 24468152	men 0.19, women 0.21	HR	201	nd	45546	0.88	0.72	1.06		
67	Miyagawa 2014 24468152	men 0.95, women 0.98	HR	237	nd	48200	0.89	0.74	1.07		
68	Miyagawa 2014 24468152	men 0.15, women 0.16	HR	234	nd	49413	1	nd	nd	overal effect for trend	0.099

Appendix F Observational results: death from cardiovascular disease

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure
69	Miyagawa 2014 24468152	NIPPON DATA80	CVD death	CHD, Stroke and Heart failure	Healthy	healthy individual with mean age of 50	All	879/9190 (9.56)	24 y	DHA	Intake
70	Miyagawa 2014 24468152	NIPPON DATA80	CVD death	CHD, Stroke and Heart failure	Healthy	healthy individual with mean age of 50	All	879/9190 (9.56)	24 y	DHA	Intake
71	Miyagawa 2014 24468152	NIPPON DATA80	CVD death	CHD, Stroke and Heart failure	Healthy	healthy individual with mean age of 50	All	879/9190 (9.56)	24 y	DHA	Intake
72	Morris 1995 7598116	Physician's Health Study	CVD death	acute MI, other IHD, sudden death, and other CVD	Healthy	Healthy male physicians	Men	121/21185 (0.57)	4 y	All n-3	Intake
73	Morris 1995 7598116	Physician's Health Study	CVD death	acute MI, other IHD, sudden death, and other CVD	Healthy	Healthy male physicians	Men	121/21185 (0.57)	4 y	All n-3	Intake
74	Morris 1995 7598116	Physician's Health Study	CVD death	acute MI, other IHD, sudden death, and other CVD	Healthy	Healthy male physicians	Men	121/21185 (0.57)	4 y	All n-3	Intake
75	Morris 1995 7598116	Physician's Health Study	CVD death	acute MI, other IHD, sudden death, and other CVD	Healthy	Healthy male physicians	Men	121/21185 (0.57)	4 y	All n-3	Intake
76	Morris 1995 7598116	Physician's Health Study	CVD death	acute MI, other IHD, sudden death, and other CVD	Healthy	Healthy male physicians	Men	121/21185 (0.57)	4 y	All n-3	Intake
77	Nagata 2002 12397000	Takayama	CVD death	death CVD	Healthy	Healthy >35, from Takayama	Men	308/13355 (2.31)	7 y	EPA+DHA	Intake
78	Nagata 2002 12397000	Takayama	CVD death	death CVD	Healthy	Healthy >35, from Takayama	Men	308/13355 (2.31)	7 y	EPA+DHA	Intake
79	Nagata 2002 12397000	Takayama	CVD death	death CVD	Healthy	Healthy >35, from Takayama	Men	308/13355 (2.31)	7 y	EPA+DHA	Intake
80	Nagata 2002 12397000	Takayama	CVD death	death CVD	Healthy	Healthy >35, from Takayama	Men	308/13355 (2.31)	7 y	EPA+DHA	Intake
81	Nagata 2002 12397000	Takayama	CVD death	death CVD	Healthy	Healthy >35, from Takayama	Men	308/13355 (2.31)	7 y	EPA+DHA	Intake
82	Nagata 2002 12397000	Takayama	CVD death	death CVD	Healthy	Healthy >35, from Takayama	Women	327/17125 (1.91)	7 y	EPA+DHA	Intake
83	Nagata 2002 12397000	Takayama	CVD death	death CVD	Healthy	Healthy >35, from Takayama	Women	327/17125 (1.91)	7 y	EPA+DHA	Intake
84	Nagata 2002 12397000	Takayama	CVD death	death CVD	Healthy	Healthy >35, from Takayama	Women	327/17125 (1.91)	7 y	EPA+DHA	Intake
85	Nagata 2002 12397000	Takayama	CVD death	death CVD	Healthy	Healthy >35, from Takayama	Women	327/17125 (1.91)	7 y	EPA+DHA	Intake
86	Nagata 2002 12397000	Takayama	CVD death	death CVD	Healthy	Healthy >35, from Takayama	Women	327/17125 (1.91)	7 y	EPA+DHA	Intake
87	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	CVD death	Ischemic heart disease, stroke, acute MI, other CVD deaths	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	EPA	Intake
88	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	CVD death	Ischemic heart disease, stroke, acute MI, other CVD deaths	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	EPA	Intake
89	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	CVD death	Ischemic heart disease, stroke, acute MI, other CVD deaths	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	EPA	Intake

Appendix F Observational results: death from cardiovascular disease

Row	Study PMID	Supplement	Adjustments	Quantile	n3 units	Quantile low	Quantile median
69	Miyagawa 2014 24468152	no	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr2	% kcal	men 0.16, women 0.17	nd
70	Miyagawa 2014 24468152	no	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr3	% kcal	men 0.23, women 0.24	nd
71	Miyagawa 2014 24468152	no	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr4	% kcal	men 0.32, women 0.35	nd
72	Morris 1995 7598116	explicitly excluded fish oil supplements	age, aspirin and beta-carotene assignment, smoking, alcohol consumption, obesity, diabetes, vigorous exercise, parental history of MI before age 60 years, history of hypertension, history of hypercholesterolemia, vitamin supplement use, and saturated fat intake	T1	g/wk	<0.5	nd
73	Morris 1995 7598116	explicitly excluded fish oil supplements	age, aspirin and beta-carotene assignment, smoking, alcohol consumption, obesity, diabetes, vigorous exercise, parental history of MI before age 60 years, history of hypertension, history of hypercholesterolemia, vitamin supplement use, and saturated fat intake	T2	g/wk	0.5	nd
74	Morris 1995 7598116	explicitly excluded fish oil supplements	age, aspirin and beta-carotene assignment, smoking, alcohol consumption, obesity, diabetes, vigorous exercise, parental history of MI before age 60 years, history of hypertension, history of hypercholesterolemia, vitamin supplement use, and saturated fat intake	T3	g/wk	1	nd
75	Morris 1995 7598116	explicitly excluded fish oil supplements	age, aspirin and beta-carotene assignment, smoking, alcohol consumption, obesity, diabetes, vigorous exercise, parental history of MI before age 60 years, history of hypertension, history of hypercholesterolemia, vitamin supplement use, and saturated fat intake	T4	g/wk	1.7	nd
76	Morris 1995 7598116	explicitly excluded fish oil supplements	age, aspirin and beta-carotene assignment, smoking, alcohol consumption, obesity, diabetes, vigorous exercise, parental history of MI before age 60 years, history of hypertension, history of hypercholesterolemia, vitamin supplement use, and saturated fat intake	T5	g/wk	nd	nd
77	Nagata 2002 12397000	No	age, total energy, marital status, BMI, smoking status, alcohol intake, coffee intake, exercise,, and history of hypertension and diabetes	Qt1	mg/d	nd	410
78	Nagata 2002 12397000	No	age, total energy, marital status, BMI, smoking status, alcohol intake, coffee intake, exercise,, and history of hypertension and diabetes	Qt2	mg/d	nd	602
79	Nagata 2002 12397000	No	age, total energy, marital status, BMI, smoking status, alcohol intake, coffee intake, exercise,, and history of hypertension and diabetes	Qt3	mg/d	nd	788
80	Nagata 2002 12397000	No	age, total energy, marital status, BMI, smoking status, alcohol intake, coffee intake, exercise,, and history of hypertension and diabetes	Qt4	mg/d	nd	1051
81	Nagata 2002 12397000	No	age, total energy, marital status, BMI, smoking status, alcohol intake, coffee intake, exercise,, and history of hypertension and diabetes	Qt5	mg/d	nd	1582
82	Nagata 2002 12397000	No	age, total energy, marital status, BMI, smoking status, alcohol intake, coffee intake, exercise, and history of diabetes	Qt1	mg/d	nd	332
83	Nagata 2002 12397000	No	age, total energy, marital status, BMI, smoking status, alcohol intake, coffee intake, exercise, and history of diabetes	Qt2	mg/d	nd	486
84	Nagata 2002 12397000	No	age, total energy, marital status, BMI, smoking status, alcohol intake, coffee intake, exercise, and history of diabetes	Qt3	mg/d	nd	635
85	Nagata 2002 12397000	No	age, total energy, marital status, BMI, smoking status, alcohol intake, coffee intake, exercise, and history of diabetes	Qt4	mg/d	nd	832
86	Nagata 2002 12397000	No	age, total energy, marital status, BMI, smoking status, alcohol intake, coffee intake, exercise, and history of diabetes	Qt5	mg/d	nd	1253
87	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt1	g/d	nd	0.006 (men), 0.005 (women)
88	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt2	g/d	nd	0.01 (men), 0.01 (women)
89	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt3	g/d	nd	0.02 (men), 0.02 (women)

Appendix F Observational results: death from cardiovascular disease

Row	Study PMID	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
69	Miyagawa 2014 24468152	men 0.22, women 0.23	HR	198	nd	46366	0.88	0.73	1.07		
70	Miyagawa 2014 24468152	men 0.31, women 0.34	HR	221	nd	50022	0.86	0.72	1.04		
71	Miyagawa 2014 24468152	men 1.39, women 1.45	HR	226	nd	47097	0.85	0.7	1.02		
72	Morris 1995 7598116	nd	RR	21	4335		1				0.8
73	Morris 1995 7598116	1	RR	27	4134		1.6	0.8	3		
74	Morris 1995 7598116	1.7	RR	31	4691		1.6	0.9	3		
75	Morris 1995 7598116	2.3	RR	17	4075		0.9	0.5	1.9		
76	Morris 1995 7598116	>=2.3	RR	25	3950		1.5	0.8	2.9		
77	Nagata 2002 12397000	nd	HR	60	nd	18281	Reference group			P trend	0.27
78	Nagata 2002 12397000	nd	HR	53	nd	18315	0.74	0.51	1.08		
79	Nagata 2002 12397000	nd	HR	53	nd	18186	0.71	0.49	1.03		
80	Nagata 2002 12397000	nd	HR	71	nd	18138	0.82	0.58	1.15		
81	Nagata 2002 12397000	nd	HR	71	nd	18116	0.76	0.54	1.07		
82	Nagata 2002 12397000	nd	HR	85	nd	21838	Reference group			P trend	0.16
83	Nagata 2002 12397000	nd	HR	60	nd	22111	0.82	0.59	1.15		
84	Nagata 2002 12397000	nd	HR	57	nd	22032	0.79	0.58	1.11		
85	Nagata 2002 12397000	nd	HR	64	nd	22025	0.86	0.62	1.2		
86	Nagata 2002 12397000	nd	HR	61	nd	22118	0.77	0.55	1		
87	Takata 2013 23788668	nd	HR	715	26860	nd	Reference group			P trend	0.03
88	Takata 2013 23788668	nd	HR	362	nd	nd	0.81	0.71	0.92		
89	Takata 2013 23788668	nd	HR	290	26860	nd	0.83	0.72	0.96		

Appendix F Observational results: death from cardiovascular disease

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure
90	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	CVD death	Ischemic heart disease, stroke, acute MI, other CVD deaths	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	EPA	Intake
91	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	CVD death	Ischemic heart disease, stroke, acute MI, other CVD deaths	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	EPA	Intake
92	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	CVD death	Ischemic heart disease, stroke, acute MI, other CVD deaths	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	DHA	Intake
93	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	CVD death	Ischemic heart disease, stroke, acute MI, other CVD deaths	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	DHA	Intake
94	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	CVD death	Ischemic heart disease, stroke, acute MI, other CVD deaths	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	DHA	Intake
95	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	CVD death	Ischemic heart disease, stroke, acute MI, other CVD deaths	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	DHA	Intake
96	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	CVD death	Ischemic heart disease, stroke, acute MI, other CVD deaths	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	DHA	Intake
97	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	CVD death	Ischemic heart disease, stroke, acute MI, other CVD deaths	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	EPA+DHA	Intake
98	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	CVD death	Ischemic heart disease, stroke, acute MI, other CVD deaths	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	EPA+DHA	Intake
99	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	CVD death	Ischemic heart disease, stroke, acute MI, other CVD deaths	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	EPA+DHA	Intake
100	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	CVD death	Ischemic heart disease, stroke, acute MI, other CVD deaths	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	EPA+DHA	Intake
101	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	CVD death	Ischemic heart disease, stroke, acute MI, other CVD deaths	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	EPA+DHA	Intake
102	Warensjo 2008 18614742	ULSAM	CVD death	Cardiovascular disease mortality	Healthy	Healthy	All	461/2009 (22.95)	30.7	ALA	Plasma
103	Warensjo 2008 18614742	ULSAM	CVD death	Cardiovascular disease mortality	Healthy	Healthy	All	461/2009 (19.0/ 1000 person-yrs)	30.7	EPA	Plasma
104	Warensjo 2008 18614742	ULSAM	CVD death	Cardiovascular disease mortality	Healthy	Healthy	All	461/2009 (19.0/ 1000 person-yrs)	30.7	DHA	Plasma
105	Yamagishi 2008 18786479	JACC	CVD death	Total CVD mortality	Healthy	Healthy 40-79 yo	All	2045/57972 (3.53)	12.7 y	All n-3	Intake
106	Yamagishi 2008 18786479	JACC	CVD death	Total CVD mortality	Healthy	Healthy 40-79 yo	All	2045/57972 (3.53)	12.7 y	All n-3	Intake
107	Yamagishi 2008 18786479	JACC	CVD death	Total CVD mortality	Healthy	Healthy 40-79 yo	All	2045/57972 (3.53)	12.7 y	All n-3	Intake
108	Yamagishi 2008 18786479	JACC	CVD death	Total CVD mortality	Healthy	Healthy 40-79 yo	All	2045/57972 (3.53)	12.7 y	All n-3	Intake
109	Yamagishi 2008 18786479	JACC	CVD death	Total CVD mortality	Healthy	Healthy 40-79 yo	All	2045/57972 (3.53)	12.7 y	All n-3	Intake

Appendix F Observational results: death from cardiovascular disease

Row	Study PMID	Supplement	Adjustments	Quantile	n3 units	Quantile low	Quantile median
90	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt4	g/d	nd	0.03 (men), 0.03 (women)
91	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt5	g/d	nd	0.07 (men), 0.06 (women)
92	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt1	g/d	nd	0.009 (men), 0.008 (women)
93	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt2	g/d	nd	0.02 (men), 0.02 (women)
94	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt3	g/d	nd	0.05 (men), 0.04 (women)
95	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt4	g/d	nd	0.08 (men), 0.08 (women)
96	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt5	g/d	nd	0.15 (men), 0.15 (women)
97	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt1	g/d	nd	nd
98	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt2	g/d	nd	nd
99	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt3	g/d	nd	nd
100	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt4	g/d	nd	nd
101	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt5	g/d	nd	nd
102	Warensjo 2008 18614742	NA	total cholestrol, BMI, smoking, physical activity, hypertension	All	% FA	nd	0.66 (SD = 0.16)
103	Warensjo 2008 18614742	NA	total cholestrol, BMI, smoking, physical activity, hypertension	All	% FA	0.9	1.3
104	Warensjo 2008 18614742	NA	total cholestrol, BMI, smoking, physical activity, hypertension	All	% FA	0.56	0.68
105	Yamagishi 2008 18786479	No	age, sex, htn and dm history, smoking status, alcohol consumption, BMI, mental stress, walking, sports, education, total energy, dietary intake of cholesterol/saturated and omega-3FA/vegetables/fruit	Qt1	g/d	0.05	nd
106	Yamagishi 2008 18786479	No	age, sex, htn and dm history, smoking status, alcohol consumption, BMI, mental stress, walking, sports, education, total energy, dietary intake of cholesterol/saturated and omega-3FA/vegetables/fruit	Qt2	g/d	1.18	nd
107	Yamagishi 2008 18786479	No	age, sex, htn and dm history, smoking status, alcohol consumption, BMI, mental stress, walking, sports, education, total energy, dietary intake of cholesterol/saturated and omega-3FA/vegetables/fruit	Qt3	g/d	1.47	nd
108	Yamagishi 2008 18786479	No	age, sex, htn and dm history, smoking status, alcohol consumption, BMI, mental stress, walking, sports, education, total energy, dietary intake of cholesterol/saturated and omega-3FA/vegetables/fruit	Qt4	g/d	1.75	nd
109	Yamagishi 2008 18786479	No	age, sex, htn and dm history, smoking status, alcohol consumption, BMI, mental stress, walking, sports, education, total energy, dietary intake of cholesterol/saturated and omega-3FA/vegetables/fruit	Qt5	g/d	2.11	nd

Appendix F Observational results: death from cardiovascular disease

Row	Study PMID	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
90	Takata 2013 23788668	nd	HR	232	nd	nd	0.83	0.7	0.97		
91	Takata 2013 23788668	nd	HR	190	26858	nd	0.75	0.62	0.89		
92	Takata 2013 23788668	nd	HR	707	26860	nd	Reference group			P trend	0.01
93	Takata 2013 23788668	nd	HR	359	nd	nd	0.81	0.71	0.92		
94	Takata 2013 23788668	nd	HR	272	26860	nd	0.78	0.67	0.9		
95	Takata 2013 23788668	nd	HR	260	nd	nd	0.89	0.76	1.03		
96	Takata 2013 23788668	nd	HR	193	26858	nd	0.76	0.63	0.9		
97	Takata 2013 23788668	nd	HR	714	26860	nd	Reference group			P trend	0.02
98	Takata 2013 23788668	nd	HR	356	nd	nd	0.82	0.63	1.08		
99	Takata 2013 23788668	nd	HR	271	26860	nd	0.78	0.67	0.9		
100	Takata 2013 23788668	nd	HR	258	nd	nd	0.9	0.77	1.05		
101	Takata 2013 23788668	nd	HR	190	26858	nd	0.74	0.62	0.88		
102	Warensjo 2008 18614742	nd	HR	nd	nd	nd	1.1	1	1.21	Per % FA unit	
103	Warensjo 2008 18614742	1.6	HR	nd	nd	nd	0.99	0.9	1.09	Per % FA unit	
104	Warensjo 2008 18614742	0.81	HR	nd	nd	nd	0.92	0.84	1.02	Per % FA unit	
105	Yamagishi 2008 18786479	1.18	HR	360	11594	735904	Reference group				0.01
106	Yamagishi 2008 18786479	1.47	HR	367	11595	735904	0.93	0.8	1.09		
107	Yamagishi 2008 18786479	1.75	HR	412	11594	735904	0.91	0.78	1.07		
108	Yamagishi 2008 18786479	2.11	HR	388	11595	735904	0.81	0.68	0.96		
109	Yamagishi 2008 18786479	5.06	HR	518	11594	735904	0.81	0.67	0.98		

Appendix F Observational results: death from cardiovascular disease

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure
110	Koh_2013_24343844	The Singapore Chinese Health Study	CVD death		Healthy		All	4780/60298 (0.79)	5 y	All n-3	Intake
111	Koh_2013_24343844	The Singapore Chinese Health Study	CVD death		Healthy		All	4780/60298 (0.79)	5 y	All n-3	Intake
112	Koh_2013_24343844	The Singapore Chinese Health Study	CVD death		Healthy		All	4780/60298 (0.79)	5 y	All n-3	Intake
113	Koh_2013_24343844	The Singapore Chinese Health Study	CVD death		Healthy		All	4780/60298 (0.79)	5 y	All n-3	Intake
114	Koh_2013_24343844	The Singapore Chinese Health Study	CVD death		Healthy		All	4780/60298 (0.79)	5 y	EPA + DHA	Intake
115	Koh_2013_24343844	The Singapore Chinese Health Study	CVD death		Healthy		All	4780/60298 (0.79)	5 y	EPA + DHA	Intake
116	Koh_2013_24343844	The Singapore Chinese Health Study	CVD death		Healthy		All	4780/60298 (0.79)	5 y	EPA + DHA	Intake
117	Koh_2013_24343844	The Singapore Chinese Health Study	CVD death		Healthy		All	4780/60298 (0.79)	5 y	EPA + DHA	Intake
118	Koh_2013_24343844	The Singapore Chinese Health Study	CVD death		Healthy		All	4780/60298 (0.79)	5 y	ALA	Intake
119	Koh_2013_24343844	The Singapore Chinese Health Study	CVD death		Healthy		All	4780/60298 (0.79)	5 y	ALA	Intake
120	Koh_2013_24343844	The Singapore Chinese Health Study	CVD death		Healthy		All	4780/60298 (0.79)	5 y	ALA	Intake
121	Koh_2013_24343844	The Singapore Chinese Health Study	CVD death		Healthy		All	4780/60298 (0.79)	5 y	ALA	Intake
123	Subgroup analyses										
124	Koh_2013_24343844	The Singapore Chinese Health Study	CVD death		CVD		prior history of CHD or stroke	nd/860	5 y	All n-3	intake
125	Koh_2013_24343844	The Singapore Chinese Health Study	CVD death		CVD		prior history of CHD or stroke	nd/860	5 y	All n-3	intake
126	Koh_2013_24343844	The Singapore Chinese Health Study	CVD death		CVD		prior history of CHD or stroke	nd/860	5 y	All n-3	intake
127	Koh_2013_24343844	The Singapore Chinese Health Study	CVD death		CVD		prior history of CHD or stroke	nd/860	5 y	All n-3	intake

Row	Study PMID	Supplement	Adjustments	Quantile	n3 units	Quantile low	Quantile median
110	Koh_2013_24343844	No	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr1	nd	nd	nd
111	Koh_2013_24343844	No	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr2	nd	nd	nd
112	Koh_2013_24343844	No	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr3	nd	nd	nd
113	Koh_2013_24343844	No	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr4	nd	nd	nd
114	Koh_2013_24343844	No	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr1	nd	nd	nd
115	Koh_2013_24343844	No	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr2	nd	nd	nd
116	Koh_2013_24343844	No	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr3	nd	nd	nd
117	Koh_2013_24343844	No	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr4	nd	nd	nd
118	Koh_2013_24343844	No	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr1	nd	nd	nd
119	Koh_2013_24343844	No	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr2	nd	nd	nd
120	Koh_2013_24343844	No	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr3	nd	nd	nd
121	Koh_2013_24343844	No	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr4	nd	nd	nd
123	Subgroup analyses						
124	Koh_2013_24343844	no	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr1	nd	nd	nd
125	Koh_2013_24343844	no	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr2	nd	nd	nd
126	Koh_2013_24343844	no	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr3	nd	nd	nd
127	Koh_2013_24343844	no	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr4	nd	nd	nd

Appendix F Observational results: death from cardiovascular disease

Row	Study PMID	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
110	Koh_2013_24343844	nd	HR	1329	15181	nd	Ref			P trend	0.003
111	Koh_2013_24343844	nd	HR	1200	15022	nd	0.88	0.81	0.96		
112	Koh_2013_24343844	nd	HR	1196	15023	nd	0.88	0.8	0.97		
113	Koh_2013_24343844	nd	HR	1055	15072	nd	0.83	0.74	0.92		
114	Koh_2013_24343844	nd	HR	1236	15181	nd	Ref			P trend	0.004
115	Koh_2013_24343844	nd	HR	1233	15022	nd	0.96	0.89	1.05		
116	Koh_2013_24343844	nd	HR	1188	15023	nd	0.9	0.82	0.99		
117	Koh_2013_24343844	nd	HR	1123	15072	nd	0.86	0.77	0.96		
118	Koh_2013_24343844	nd	HR	1342	15181	nd	Ref			P trend	<0.001
119	Koh_2013_24343844	nd	HR	1267	15022	nd	0.94	0.86	1.02		
120	Koh_2013_24343844	nd	HR	1156	15023	nd	0.87	0.79	0.95		
121	Koh_2013_24343844	nd	HR	1015	15072	nd	0.81	0.73	0.9		
123	Subgroup analyses										
124	Koh_2013_24343844	nd	HR	206	nd		Ref			P trend	0.35
125	Koh_2013_24343844	nd	HR	204	nd		0.84	0.68	1.04		
126	Koh_2013_24343844	nd	HR	222	nd		0.9	0.71	1.14		
127	Koh_2013_24343844	nd	HR	228	nd		0.85	0.66	1.1		

Appendix F Observational results: death from cardiovascular disease

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure
128	Koh_2013_24343844	The Singapore Chinese Health Study	CVD death		CVD		prior history of CHD or stroke	nd/860	5 y	EPA + DHA	intake
129	Koh_2013_24343844	The Singapore Chinese Health Study	CVD death		CVD		prior history of CHD or stroke	nd/860	5 y	EPA + DHA	intake
130	Koh_2013_24343844	The Singapore Chinese Health Study	CVD death		CVD		prior history of CHD or stroke	nd/860	5 y	EPA + DHA	intake
131	Koh_2013_24343844	The Singapore Chinese Health Study	CVD death		CVD		prior history of CHD or stroke	nd/860	5 y	EPA + DHA	intake
132	Koh_2013_24343844	The Singapore Chinese Health Study	CVD death		CVD		prior history of CHD or stroke	nd/860	5 y	ALA	intake
133	Koh_2013_24343844	The Singapore Chinese Health Study	CVD death		CVD		prior history of CHD or stroke	nd/860	5 y	ALA	intake
134	Koh_2013_24343844	The Singapore Chinese Health Study	CVD death		CVD		prior history of CHD or stroke	nd/860	5 y	ALA	intake
135	Koh_2013_24343844	The Singapore Chinese Health Study	CVD death		CVD		prior history of CHD or stroke	nd/860	5 y	ALA	intake
136	Koh_2013_24343844	The Singapore Chinese Health Study	CVD death		Healthy		no prior history of CHD or stroke	nd/3920	5 y	All n-3	intake
137	Koh_2013_24343844	The Singapore Chinese Health Study	CVD death		Healthy		no prior history of CHD or stroke	nd/3920	5 y	All n-3	intake
138	Koh_2013_24343844	The Singapore Chinese Health Study	CVD death		Healthy		no prior history of CHD or stroke	nd/3920	5 y	All n-3	intake
139	Koh_2013_24343844	The Singapore Chinese Health Study	CVD death		Healthy		no prior history of CHD or stroke	nd/3920	5 y	All n-3	intake
140	Koh_2013_24343844	The Singapore Chinese Health Study	CVD death		Healthy		no prior history of CHD or stroke	nd/3920	5 y	EPA + DHA	intake
141	Koh_2013_24343844	The Singapore Chinese Health Study	CVD death		Healthy		no prior history of CHD or stroke	nd/3920	5 y	EPA + DHA	intake
142	Koh_2013_24343844	The Singapore Chinese Health Study	CVD death		Healthy		no prior history of CHD or stroke	nd/3920	5 y	EPA + DHA	intake
143	Koh_2013_24343844	The Singapore Chinese Health Study	CVD death		Healthy		no prior history of CHD or stroke	nd/3920	5 y	EPA + DHA	intake
144	Koh_2013_24343844	The Singapore Chinese Health Study	CVD death		Healthy		no prior history of CHD or stroke	nd/3920	5 y	ALA	intake

Row	Study PMID	Supplement	Adjustments	Quantile	n3 units	Quantile low	Quantile median
128	Koh_2013_24343844	no	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr1	nd	nd	nd
129	Koh_2013_24343844	no	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr2	nd	nd	nd
130	Koh_2013_24343844	no	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr3	nd	nd	nd
131	Koh_2013_24343844	no	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr4	nd	nd	nd
132	Koh_2013_24343844	no	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr1	nd	nd	nd
133	Koh_2013_24343844	no	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr2	nd	nd	nd
134	Koh_2013_24343844	no	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr3	nd	nd	nd
135	Koh_2013_24343844	no	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr4	nd	nd	nd
136	Koh_2013_24343844	no	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr1	nd	nd	nd
137	Koh_2013_24343844	no	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr2	nd	nd	nd
138	Koh_2013_24343844	no	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr3	nd	nd	nd
139	Koh_2013_24343844	no	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr4	nd	nd	nd
140	Koh_2013_24343844	no	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr1	nd	nd	nd
141	Koh_2013_24343844	no	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr2	nd	nd	nd
142	Koh_2013_24343844	no	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr3	nd	nd	nd
143	Koh_2013_24343844	no	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr4	nd	nd	nd
144	Koh_2013_24343844	no	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr1	nd	nd	nd

Appendix F Observational results: death from cardiovascular disease

Row	Study PMID	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
128	Koh_2013_24343844	nd	HR	197	nd		Ref			P trend	0.47
129	Koh_2013_24343844	nd	HR	212	nd		1	0.81	1.22		
130	Koh_2013_24343844	nd	HR	241	nd		1.03	0.83	1.29		
131	Koh_2013_24343844	nd	HR	210	nd		0.92	0.71	1.19		
132	Koh_2013_24343844	nd	HR	212	nd		Ref			P trend	0.14
133	Koh_2013_24343844	nd	HR	234	nd		1.08	0.88	1.32		
134	Koh_2013_24343844	nd	HR	190	nd		0.85	0.68	1.06		
135	Koh_2013_24343844	nd	HR	224	nd		0.87	0.69	1.1		
136	Koh_2013_24343844	nd	HR	1123	nd		Ref			P trend	0.006
137	Koh_2013_24343844	nd	HR	996	nd		0.89	0.81	0.98		
138	Koh_2013_24343844	nd	HR	974	nd		0.88	0.79	0.98		
139	Koh_2013_24343844	nd	HR	827	nd		0.83	0.73	0.94		
140	Koh_2013_24343844	nd	HR	1039	nd		Ref			P trend	0.002
141	Koh_2013_24343844	nd	HR	1021	nd		0.94	0.86	1.03		
142	Koh_2013_24343844	nd	HR	947	nd		0.87	0.79	0.96		
143	Koh_2013_24343844	nd	HR	913	nd		0.84	0.74	0.95		
144	Koh_2013_24343844	nd	HR	1130	nd		Ref			P trend	<0.001

Appendix F Observational results: death from cardiovascular disease

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure
145	Koh_2013_24343844	The Singapore Chinese Health Study	CVD death		Healthy		no prior history of CHD or stroke	nd/3920	5 y	ALA	intake
146	Koh_2013_24343844	The Singapore Chinese Health Study	CVD death		Healthy		no prior history of CHD or stroke	nd/3920	5 y	ALA	intake
147	Koh_2013_24343844	The Singapore Chinese Health Study	CVD death		Healthy		no prior history of CHD or stroke	nd/3920	5 y	ALA	intake
148	Bell 2014 24496442	VITAL	CVD death		Healthy	Men and women aged 50-76	History of CVD at baseline	nd/362	6 y	EPA+DHA	Intake
149	Bell 2014 24496442	VITAL	CVD death		Healthy	Men and women aged 50-76	History of CVD at baseline	nd/362	6 y	EPA+DHA	Intake
150	Bell 2014 24496442	VITAL	CVD death		Healthy	Men and women aged 50-76	History of CVD at baseline	nd/362	6 y	EPA+DHA	Intake
151	Bell 2014 24496442	VITAL	CVD death		Healthy	Men and women aged 50-76	History of CVD at baseline	nd/362	6 y	EPA+DHA	Intake

Appendix F Observational results: death from cardiovascular disease

Row	Study PMID	Supplement	Adjustments	Quantile	n3 units	Quantile low	Quantile median
145	Koh_2013_24343844	no	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr2	nd	nd	nd
146	Koh_2013_24343844	no	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr3	nd	nd	nd
147	Koh_2013_24343844	no	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr4	nd	nd	nd
148	Bell 2014 24496442	yes	age (as the time scale), sex, race/ethnicity, marital status (married/living together, never married, separated/divorced, widowed, or missing), education (high school graduate or less, some college, or college/advanced degree), total energy intake (kcal/day; continuous), body mass index (weight (kg)/height (m)2 (none, <1 drink/day, 1–2 drinks/day, >2 drinks/day, or missing), average physical activity in the 10 years before baseline (MET-hours/week; tertiles), self-rated health (excellent, very good, good, fair, or poor), mammogram in the last 2 years (yes/no), prostate-specific antigen test in the last 2 years (yes/no), sigmoidoscopy in the last 10 years (yes/no), current use of cholesterol-lowering medication (yes/no), aspirin use in the past 10 years (none, low, high, or missing), use of nonaspirin nonsteroidal antiinflammatory drugs in the past 10 years (none, low, high, or missing), smoking (never, 1–12.5 pack-years, 12.6–35.0 pack-years, or >35.0 pack-years), morbidity score,c percentage of calories derived from trans fat (quartiles), percentage of calories derived from saturated fat (quartiles), number of servings per day of fruits (quartiles), number of servings per day of vegetables (quartiles), years of estrogen therapy (none, <5, 5–9, ≥10, or missing), years of estrogen + progestin therapy (none, <5, 5–9, ≥10, or missing), age at menopause (≤39 years, 40–44 years, 45–49 years, 50–54 years, ≥55 years, or missing), age at death of father (≤59 years, 60–69 years, 70–79 years, 80–89 years, or ≥90 years), and age at death of mother (≤59 years, 60–69 years, 70–79 years, 80–89 years, or ≥90 years)	Qr1	g/day	0	nd
149	Bell 2014 24496442	yes	age (as the time scale), sex, race/ethnicity, marital status (married/living together, never married, separated/divorced, widowed, or missing), education (high school graduate or less, some college, or college/advanced degree), total energy intake (kcal/day; continuous), body mass index (weight (kg)/height (m)2 (none, <1 drink/day, 1–2 drinks/day, >2 drinks/day, or missing), average physical activity in the 10 years before baseline (MET-hours/week; tertiles), self-rated health (excellent, very good, good, fair, or poor), mammogram in the last 2 years (yes/no), prostate-specific antigen test in the last 2 years (yes/no), sigmoidoscopy in the last 10 years (yes/no), current use of cholesterol-lowering medication (yes/no), aspirin use in the past 10 years (none, low, high, or missing), use of nonaspirin nonsteroidal antiinflammatory drugs in the past 10 years (none, low, high, or missing), smoking (never, 1–12.5 pack-years, 12.6–35.0 pack-years, or >35.0 pack-years), morbidity score,c percentage of calories derived from trans fat (quartiles), percentage of calories derived from saturated fat (quartiles), number of servings per day of fruits (quartiles), number of servings per day of vegetables (quartiles), years of estrogen therapy (none, <5, 5–9, ≥10, or missing), years of estrogen + progestin therapy (none, <5, 5–9, ≥10, or missing), age at menopause (≤39 years, 40–44 years, 45–49 years, 50–54 years, ≥55 years, or missing), age at death of father (≤59 years, 60–69 years, 70–79 years, 80–89 years, or ≥90 years), and age at death of mother (≤59 years, 60–69 years, 70–79 years, 80–89 years, or ≥90 years)	Qr2	g/day	0.082	nd
150	Bell 2014 24496442	yes	age (as the time scale), sex, race/ethnicity, marital status (married/living together, never married, separated/divorced, widowed, or missing), education (high school graduate or less, some college, or college/advanced degree), total energy intake (kcal/day; continuous), body mass index (weight (kg)/height (m)2 (none, <1 drink/day, 1–2 drinks/day, >2 drinks/day, or missing), average physical activity in the 10 years before baseline (MET-hours/week; tertiles), self-rated health (excellent, very good, good, fair, or poor), mammogram in the last 2 years (yes/no), prostate-specific antigen test in the last 2 years (yes/no), sigmoidoscopy in the last 10 years (yes/no), current use of cholesterol-lowering medication (yes/no), aspirin use in the past 10 years (none, low, high, or missing), use of nonaspirin nonsteroidal antiinflammatory drugs in the past 10 years (none, low, high, or missing), smoking (never, 1–12.5 pack-years, 12.6–35.0 pack-years, or >35.0 pack-years), morbidity score,c percentage of calories derived from trans fat (quartiles), percentage of calories derived from saturated fat (quartiles), number of servings per day of fruits (quartiles), number of servings per day of vegetables (quartiles), years of estrogen therapy (none, <5, 5–9, ≥10, or missing), years of estrogen + progestin therapy (none, <5, 5–9, ≥10, or missing), age at menopause (≤39 years, 40–44 years, 45–49 years, 50–54 years, ≥55 years, or missing), age at death of father (≤59 years, 60–69 years, 70–79 years, 80–89 years, or ≥90 years), and age at death of mother (≤59 years, 60–69 years, 70–79 years, 80–89 years, or ≥90 years)	Qr3	g/day	0.174	nd
151	Bell 2014 24496442	yes		Qr4	g/day	0.322	nd

Appendix F Observational results: death from cardiovascular disease

Row	Study PMID	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
145	Koh_2013_24343844	nd	HR	1033	nd		0.91	0.83	1		
146	Koh_2013_24343844	nd	HR	966	nd		0.89	0.8	0.98		
147	Koh_2013_24343844	nd	HR	791	nd		0.81	0.72	0.9		
148	Bell 2014 24496442	0.082	HR	98	nd	nd	1	nd	nd		0.167
149	Bell 2014 24496442	0.174	HR	91	nd	nd	1.01	0.74	1.37		
150	Bell 2014 24496442	0.322	HR	80	nd	nd	0.81	0.58	1.14		
151	Bell 2014 24496442	nd	HR	93	nd	nd	0.82	0.57	1.17		

Appendix F Observational results: death from cardiovascular disease

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure
152	Bell 2014 24496442	VITAL	CVD death		Healthy	Men and women aged 50-76	No history of CVD at baseline	nd/400	6 y	EPA+DHA	Intake
153	Bell 2014 24496442	VITAL	CVD death		Healthy	Men and women aged 50-76	No history of CVD at baseline	nd/400	6 y	EPA+DHA	Intake
154	Bell 2014 24496442	VITAL	CVD death		Healthy	Men and women aged 50-76	No history of CVD at baseline	nd/400	6 y	EPA+DHA	Intake
155	Bell 2014 24496442	VITAL	CVD death		Healthy	Men and women aged 50-76	No history of CVD at baseline	nd/400	6 y	EPA+DHA	Intake

Appendix F Observational results: death from cardiovascular disease

Row	Study PMID	Supplement	Adjustments	Quantile	n3 units	Quantile low	Quantile median
152	Bell 2014 24496442	yes	age (as the time scale), sex, race/ethnicity, marital status (married/living together, never married, separated/divorced, widowed, or missing), education (high school graduate or less, some college, or college/advanced degree), total energy intake (kcal/day; continuous), body mass index (weight (kg)/height (m)2 (none, <1 drink/day, 1–2 drinks/day, >2 drinks/day, or missing), average physical activity in the 10 years before baseline (MET-hours/week; tertiles), self-rated health (excellent, very good, good, fair, or poor), mammogram in the last 2 years (yes/no), prostate-specific antigen test in the last 2 years (yes/no), sigmoidoscopy in the last 10 years (yes/no), current use of cholesterol-lowering medication (yes/no), aspirin use in the past 10 years (none, low, high, or missing), use of nonaspirin nonsteroidal antiinflammatory drugs in the past 10 years (none, low, high, or missing), smoking (never, 1–12.5 pack-years, 12.6–35.0 pack-years, or >35.0 pack-years), morbidity score,c percentage of calories derived from trans fat (quartiles), percentage of calories derived from saturated fat (quartiles), number of servings per day of fruits (quartiles), number of servings per day of vegetables (quartiles), years of estrogen therapy (none, <5, 5–9, ≥10, or missing), years of estrogen + progestin therapy (none, <5, 5–9, ≥10, or missing), age at menopause (≤39 years, 40–44 years, 45–49 years, 50–54 years, ≥55 years, or missing), age at death of father (≤59 years, 60–69 years, 70–79 years, 80–89 years, or ≥90 years), and age at death of mother (≤59 years, 60–69 years, 70–79 years, 80–89 years, or ≥90 years)	Qr1	g/day	0	nd
153	Bell 2014 24496442	yes	age (as the time scale), sex, race/ethnicity, marital status (married/living together, never married, separated/divorced, widowed, or missing), education (high school graduate or less, some college, or college/advanced degree), total energy intake (kcal/day; continuous), body mass index (weight (kg)/height (m)2 (none, <1 drink/day, 1–2 drinks/day, >2 drinks/day, or missing), average physical activity in the 10 years before baseline (MET-hours/week; tertiles), self-rated health (excellent, very good, good, fair, or poor), mammogram in the last 2 years (yes/no), prostate-specific antigen test in the last 2 years (yes/no), sigmoidoscopy in the last 10 years (yes/no), current use of cholesterol-lowering medication (yes/no), aspirin use in the past 10 years (none, low, high, or missing), use of nonaspirin nonsteroidal antiinflammatory drugs in the past 10 years (none, low, high, or missing), smoking (never, 1–12.5 pack-years, 12.6–35.0 pack-years, or >35.0 pack-years), morbidity score,c percentage of calories derived from trans fat (quartiles), percentage of calories derived from saturated fat (quartiles), number of servings per day of fruits (quartiles), number of servings per day of vegetables (quartiles), years of estrogen therapy (none, <5, 5–9, ≥10, or missing), years of estrogen + progestin therapy (none, <5, 5–9, ≥10, or missing), age at menopause (≤39 years, 40–44 years, 45–49 years, 50–54 years, ≥55 years, or missing), age at death of father (≤59 years, 60–69 years, 70–79 years, 80–89 years, or ≥90 years), and age at death of mother (≤59 years, 60–69 years, 70–79 years, 80–89 years, or ≥90 years)	Qr2	g/day	0.082	nd
154	Bell 2014 24496442	yes	age (as the time scale), sex, race/ethnicity, marital status (married/living together, never married, separated/divorced, widowed, or missing), education (high school graduate or less, some college, or college/advanced degree), total energy intake (kcal/day; continuous), body mass index (weight (kg)/height (m)2 (none, <1 drink/day, 1–2 drinks/day, >2 drinks/day, or missing), average physical activity in the 10 years before baseline (MET-hours/week; tertiles), self-rated health (excellent, very good, good, fair, or poor), mammogram in the last 2 years (yes/no), prostate-specific antigen test in the last 2 years (yes/no), sigmoidoscopy in the last 10 years (yes/no), current use of cholesterol-lowering medication (yes/no), aspirin use in the past 10 years (none, low, high, or missing), use of nonaspirin nonsteroidal antiinflammatory drugs in the past 10 years (none, low, high, or missing), smoking (never, 1–12.5 pack-years, 12.6–35.0 pack-years, or >35.0 pack-years), morbidity score,c percentage of calories derived from trans fat (quartiles), percentage of calories derived from saturated fat (quartiles), number of servings per day of fruits (quartiles), number of servings per day of vegetables (quartiles), years of estrogen therapy (none, <5, 5–9, ≥10, or missing), years of estrogen + progestin therapy (none, <5, 5–9, ≥10, or missing), age at menopause (≤39 years, 40–44 years, 45–49 years, 50–54 years, ≥55 years, or missing), age at death of father (≤59 years, 60–69 years, 70–79 years, 80–89 years, or ≥90 years), and age at death of mother (≤59 years, 60–69 years, 70–79 years, 80–89 years, or ≥90 years)	Qr3	g/day	0.174	nd
155	Bell 2014 24496442	yes	age (as the time scale), sex, race/ethnicity, marital status (married/living together, never married, separated/divorced, widowed, or missing), education (high school graduate or less, some college, or college/advanced degree), total energy intake (kcal/day; continuous), body mass index (weight (kg)/height (m)2 (none, <1 drink/day, 1–2 drinks/day, >2 drinks/day, or missing), average physical activity in the 10 years before baseline (MET-hours/week; tertiles), self-rated health (excellent, very good, good, fair, or poor), mammogram in the last 2 years (yes/no), prostate-specific antigen test in the last 2 years (yes/no), sigmoidoscopy in the last 10 years (yes/no), current use of cholesterol-lowering medication (yes/no), aspirin use in the past 10 years (none, low, high, or missing), use of nonaspirin nonsteroidal antiinflammatory drugs in the past 10 years (none, low, high, or missing), smoking (never, 1–12.5 pack-years, 12.6–35.0 pack-years, or >35.0 pack-years), morbidity score,c percentage of calories derived from trans fat (quartiles), percentage of calories derived from saturated fat (quartiles), number of servings per day of fruits (quartiles), number of servings per day of vegetables (quartiles), years of estrogen therapy (none, <5, 5–9, ≥10, or missing), years of estrogen + progestin therapy (none, <5, 5–9, ≥10, or missing), age at menopause (≤39 years, 40–44 years, 45–49 years, 50–54 years, ≥55 years, or missing), age at death of father (≤59 years, 60–69 years, 70–79 years, 80–89 years, or ≥90 years), and age at death of mother (≤59 years, 60–69 years, 70–79 years, 80–89 years, or ≥90 years)	Qr4	g/day	0.322	nd

Appendix F Observational results: death from cardiovascular disease

Row	Study PMID	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
152	Bell 2014 24496442	0.082	HR	129	nd	nd	1	nd	nd		0.799
153	Bell 2014 24496442	0.174	HR	92	nd	nd	0.77	0.58	1.02		
154	Bell 2014 24496442	0.322	HR	84	nd	nd	0.78	0.57	1.05		
155	Bell 2014 24496442	nd	HR	95	nd	nd	0.91	0.66	1.27		

Appendix F
Observational results: death from congestive heart failure

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure	Supplement
2	Yamagishi 2008 18786479	JACC	CHF death	nd	Healthy	Healthy 40-79 yo	All	307/57972 (0.53)	12.7 y	All n-3	Intake	No
3	Yamagishi 2008 18786479	JACC	CHF death	nd	Healthy	Healthy 40-79 yo	All	307/57972 (0.53)	12.7 y	All n-3	Intake	No
4	Yamagishi 2008 18786479	JACC	CHF death	nd	Healthy	Healthy 40-79 yo	All	307/57972 (0.53)	12.7 y	All n-3	Intake	No
5	Yamagishi 2008 18786479	JACC	CHF death	nd	Healthy	Healthy 40-79 yo	All	307/57972 (0.53)	12.7 y	All n-3	Intake	No
6	Yamagishi 2008 18786479	JACC	CHF death	nd	Healthy	Healthy 40-79 yo	All	307/57972 (0.53)	12.7 y	All n-3	Intake	No

Appendix F
Observational results: death from congestive heart failure

Row	Study PMID	Adjustments	Quantile	n3 units	Quantile low	Quantile median	Quantile high	Metric	n Cases	N quantile	Person Years
2	Yamagishi 2008 18786479	age, sex, htn and dm history, smoking status, alcohol consumption, BMI, mental stress, walking, sports, education, total energy, dietary intake of cholesterol/saturated and omega-3FA/vegetables/fruit	Qt1	g/d	0.05	nd	1.18	HR	68	11594	735904
3	Yamagishi 2008 18786479	age, sex, htn and dm history, smoking status, alcohol consumption, BMI, mental stress, walking, sports, education, total energy, dietary intake of cholesterol/saturated and omega-3FA/vegetables/fruit	Qt2	g/d	1.18	nd	1.47	HR	53	11595	735904
4	Yamagishi 2008 18786479	age, sex, htn and dm history, smoking status, alcohol consumption, BMI, mental stress, walking, sports, education, total energy, dietary intake of cholesterol/saturated and omega-3FA/vegetables/fruit	Qt3	g/d	1.47	nd	1.75	HR	50	11594	735904
5	Yamagishi 2008 18786479	age, sex, htn and dm history, smoking status, alcohol consumption, BMI, mental stress, walking, sports, education, total energy, dietary intake of cholesterol/saturated and omega-3FA/vegetables/fruit	Qt4	g/d	1.75	nd	2.11	HR	58	11595	735904
6	Yamagishi 2008 18786479	age, sex, htn and dm history, smoking status, alcohol consumption, BMI, mental stress, walking, sports, education, total energy, dietary intake of cholesterol/saturated and omega-3FA/vegetables/fruit	Qt5	g/d	2.11	nd	5.06	HR	78	11594	735904

Appendix F

Observational results: death from congestive heart failure

Row	Study PMID	Estimate	CI low	CI high	Comparison	P value
2	Yamagishi 2008 18786479	Reference group				0.03
3	Yamagishi 2008 18786479	0.69	0.47	1.01		
4	Yamagishi 2008 18786479	0.56	0.37	0.85		
5	Yamagishi 2008 18786479	0.6	0.39	0.92		
6	Yamagishi 2008 18786479	0.58	0.36	0.93		

Appendix F Observational results: death from myocardial infarction

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure	Supplement
2	Yamagishi 2008 18786479	JACC	MI death	nd	Healthy	Healthy 40-79 yo	All	329/57972 (0.57)	12.7 y	All n-3	Intake	No
3	Yamagishi 2008 18786479	JACC	MI death	nd	Healthy	Healthy 40-79 yo	All	329/57972 (0.57)	12.7 y	All n-3	Intake	No
4	Yamagishi 2008 18786479	JACC	MI death	nd	Healthy	Healthy 40-79 yo	All	329/57972 (0.57)	12.7 y	All n-3	Intake	No
5	Yamagishi 2008 18786479	JACC	MI death	nd	Healthy	Healthy 40-79 yo	All	329/57972 (0.57)	12.7 y	All n-3	Intake	No
6	Yamagishi 2008 18786479	JACC	MI death	nd	Healthy	Healthy 40-79 yo	All	329/57972 (0.57)	12.7 y	All n-3	Intake	No
7	Yuan 2001 11682363	Shanghai	MI death	death from MI	Healthy	Healthy, 45-64 yo	All	113/18244 (0.62)	12 y	All n-3	Intake	no
8	Yuan 2001 11682363	Shanghai	MI death	death from MI	Healthy	Healthy, 45-64 yo	All	113/18244 (0.62)	12 y	All n-3	Intake	no
9	Yuan 2001 11682363	Shanghai	MI death	death from MI	Healthy	Healthy, 45-64 yo	All	113/18244 (0.62)	12 y	All n-3	Intake	no
10	Yuan 2001 11682363	Shanghai	MI death	death from MI	Healthy	Healthy, 45-64 yo	All	113/18244 (0.62)	12 y	All n-3	Intake	no
11	Yuan 2001 11682363	Shanghai	MI death	death from MI	Healthy	Healthy, 45-64 yo	All	113/18244 (0.62)	12 y	All n-3	Intake	no
12	de Goede 2010 20335635	MORGEN	MI death	fatal MI	Healthy	Healthy 20-65 yo	All	64/21055 (0.3)	11.3 y	EPA+DHA	Intake	No
13	de Goede 2010 20335635	MORGEN	MI death	fatal MI	Healthy	Healthy 20-65 yo	All	64/21055 (0.3)	11.3 y	EPA+DHA	Intake	No
14	de Goede 2010 20335635	MORGEN	MI death	fatal MI	Healthy	Healthy 20-65 yo	All	64/21055 (0.3)	11.3 y	EPA+DHA	Intake	No
15	de Goede 2010 20335635	MORGEN	MI death	fatal MI	Healthy	Healthy 20-65 yo	All	64/21055 (0.3)	11.3 y	EPA+DHA	Intake	No

Appendix F Observational results: death from myocardial infarction

Row	Study PMID	Adjustments	Quantile	n3 units	Quantile low	Quantile median	Quantile high
2	Yamagishi 2008 18786479	age, sex, htn and dm history, smoking status, alcohol consumption, BMI, mental stress, walking, sports, education, total energy, dietary intake of cholesterol/saturated and omega-3FA/vegetables/fruit	Qt1	g/d	0.05	nd	1.18
3	Yamagishi 2008 18786479	age, sex, htn and dm history, smoking status, alcohol consumption, BMI, mental stress, walking, sports, education, total energy, dietary intake of cholesterol/saturated and omega-3FA/vegetables/fruit	Qt2	g/d	1.18	nd	1.47
4	Yamagishi 2008 18786479	age, sex, htn and dm history, smoking status, alcohol consumption, BMI, mental stress, walking, sports, education, total energy, dietary intake of cholesterol/saturated and omega-3FA/vegetables/fruit	Qt3	g/d	1.47	nd	1.75
5	Yamagishi 2008 18786479	age, sex, htn and dm history, smoking status, alcohol consumption, BMI, mental stress, walking, sports, education, total energy, dietary intake of cholesterol/saturated and omega-3FA/vegetables/fruit	Qt4	g/d	1.75	nd	2.11
6	Yamagishi 2008 18786479	age, sex, htn and dm history, smoking status, alcohol consumption, BMI, mental stress, walking, sports, education, total energy, dietary intake of cholesterol/saturated and omega-3FA/vegetables/fruit	Qt5	g/d	2.11	nd	5.06
7	Yuan 2001 11682363	In addition to age (years) and total energy intake (calories/day), the multivariate Cox proportional hazards model included level of education (primary school or less, middle school or higher), body mass index (<18.5, 18.5–<21, 21–<23.5, 23.5–<26, =26 kg/m2), current smoker at recruitment (no, yes), average no. of cigarettes smoked per day (continuous), no. of alcoholic drinks consumed per week (none, 1–14, 15–28, =29), history of diabetes (no, yes), and history of hypertension (no, yes).	Qt1	g/wk	nd	mean 0.15	0.26
8	Yuan 2001 11682363	In addition to age (years) and total energy intake (calories/day), the multivariate Cox proportional hazards model included level of education (primary school or less, middle school or higher), body mass index (<18.5, 18.5–<21, 21–<23.5, 23.5–<26, =26 kg/m2), current smoker at recruitment (no, yes), average no. of cigarettes smoked per day (continuous), no. of alcoholic drinks consumed per week (none, 1–14, 15–28, =29), history of diabetes (no, yes), and history of hypertension (no, yes).	Qt2	g/wk	0.27	mean 0.38	0.43
9	Yuan 2001 11682363	In addition to age (years) and total energy intake (calories/day), the multivariate Cox proportional hazards model included level of education (primary school or less, middle school or higher), body mass index (<18.5, 18.5–<21, 21–<23.5, 23.5–<26, =26 kg/m2), current smoker at recruitment (no, yes), average no. of cigarettes smoked per day (continuous), no. of alcoholic drinks consumed per week (none, 1–14, 15–28, =29), history of diabetes (no, yes), and history of hypertension (no, yes).	Qt3	g/wk	0.44	mean 0.65	0.72
10	Yuan 2001 11682363	In addition to age (years) and total energy intake (calories/day), the multivariate Cox proportional hazards model included level of education (primary school or less, middle school or higher), body mass index (<18.5, 18.5–<21, 21–<23.5, 23.5–<26, =26 kg/m2), current smoker at recruitment (no, yes), average no. of cigarettes smoked per day (continuous), no. of alcoholic drinks consumed per week (none, 1–14, 15–28, =29), history of diabetes (no, yes), and history of hypertension (no, yes).	Qt4	g/wk	0.73	mean 0.91	1.09
11	Yuan 2001 11682363	In addition to age (years) and total energy intake (calories/day), the multivariate Cox proportional hazards model included level of education (primary school or less, middle school or higher), body mass index (<18.5, 18.5–<21, 21–<23.5, 23.5–<26, =26 kg/m2), current smoker at recruitment (no, yes), average no. of cigarettes smoked per day (continuous), no. of alcoholic drinks consumed per week (none, 1–14, 15–28, =29), history of diabetes (no, yes), and history of hypertension (no, yes).	Qt5	g/wk	1.1	mean 1.66	nd
12	de Goede 2010 20335635	age, gender, BMI, total energy intake, ethanol intake, cigarette smoking, social economic status, vitamin/mineral supplement use, use of drugs for hypertension/hypercholesterolemia, family history of CVD, SFA, fruit, and vegetables	Qt1	mg/d		40	<62
13	de Goede 2010 20335635	age, gender, BMI, total energy intake, ethanol intake, cigarette smoking, social economic status, vitamin/mineral supplement use, use of drugs for hypertension/hypercholesterolemia, family history of CVD, SFA, fruit, and vegetables	Qt2	mg/d	62	84	113
14	de Goede 2010 20335635	age, gender, BMI, total energy intake, ethanol intake, cigarette smoking, social economic status, vitamin/mineral supplement use, use of drugs for hypertension/hypercholesterolemia, family history of CVD, SFA, fruit, and vegetables	Qt3	mg/d	114	151	194
15	de Goede 2010 20335635	age, gender, BMI, total energy intake, ethanol intake, cigarette smoking, social economic status, vitamin/mineral supplement use, use of drugs for hypertension/hypercholesterolemia, family history of CVD, SFA, fruit, and vegetables	Qt4	mg/d	>194	234	nd

Appendix F Observational results: death from myocardial infarction

Row	Study PMID	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
2	Yamagishi 2008 18786479	HR	65	11594	735904	Reference group				0.14
3	Yamagishi 2008 18786479	HR	65	11595	735904	0.97	0.67	1.4		
4	Yamagishi 2008 18786479	HR	60	11594	735904	0.81	0.54	1.2		
5	Yamagishi 2008 18786479	HR	60	11595	735904	0.77	0.51	1.18		
6	Yamagishi 2008 18786479	HR	79	11594	735904	0.75	0.47	1.19		
7	Yuan 2001 11682363	RR	33	3789	35583	Reference group			P trend	0.02
8	Yuan 2001 11682363	RR	12	5613	32076	0.39	0.2	0.75		
9	Yuan 2001 11682363	RR	37	3300	54769	0.67	0.42	1.08		
10	Yuan 2001 11682363	RR	16	2606	28613	0.53	0.29	0.97		
11	Yuan 2001 11682363	RR	15	2936	28425	0.43	0.23	0.81		
12	de Goede 2010 20335635	HR	21	5336	nd	Reference group			P trend	0.01
13	de Goede 2010 20335635	HR	13	5335	nd	0.57	0.28	1.14		
14	de Goede 2010 20335635	HR	16	5335	nd	0.56	0.29	1.09		
15	de Goede 2010 20335635	HR	14	5336	nd	0.38	0.19	0.77		

Appendix F
Observational results: death from stroke

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure	Supplement
2	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke death, total	Stroke mortality	Healthy	Healthy age >= 65y	All	130/3941 (3.3)	16y	DHA	Plasma	no
3	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke death, total	Stroke mortality	Healthy	Healthy age >= 65y	All	130/3941 (3.3)	16y	DHA	Plasma	no
4	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke death, total	Stroke mortality	Healthy	Healthy age >= 65y	All	130/3941 (3.3)	16y	DHA	Plasma	no
5	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke death, total	Stroke mortality	Healthy	Healthy age >= 65y	All	130/3941 (3.3)	16y	DHA	Plasma	no
6	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke death, total	Stroke mortality	Healthy	Healthy age >= 65y	All	130/3941 (3.3)	16y	DHA	Plasma	no
7	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke death, total	Stroke mortality	Healthy	Healthy age >= 65y	All	130/3941 (3.3)	16y	DPA	Plasma	no
8	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke death, total	Stroke mortality	Healthy	Healthy age >= 65y	All	130/3941 (3.3)	16y	DPA	Plasma	no
9	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke death, total	Stroke mortality	Healthy	Healthy age >= 65y	All	130/3941 (3.3)	16y	DPA	Plasma	no
10	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke death, total	Stroke mortality	Healthy	Healthy age >= 65y	All	130/3941 (3.3)	16y	DPA	Plasma	no
11	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke death, total	Stroke mortality	Healthy	Healthy age >= 65y	All	130/3941 (3.3)	16y	DPA	Plasma	no
12	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke death, total	Stroke mortality	Healthy	Healthy age >= 65y	All	130/3941 (3.3)	16y	EPA	Plasma	no
13	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke death, total	Stroke mortality	Healthy	Healthy age >= 65y	All	130/3941 (3.3)	16y	EPA	Plasma	no
14	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke death, total	Stroke mortality	Healthy	Healthy age >= 65y	All	130/3941 (3.3)	16y	EPA	Plasma	no
15	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke death, total	Stroke mortality	Healthy	Healthy age >= 65y	All	130/3941 (3.3)	16y	EPA	Plasma	no
16	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke death, total	Stroke mortality	Healthy	Healthy age >= 65y	All	130/3941 (3.3)	16y	EPA	Plasma	no
17	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke death, total	Stroke mortality	Healthy	Healthy age >= 65y	All	130/3941 (3.3)	16y	All n-3	Plasma	no
18	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke death, total	Stroke mortality	Healthy	Healthy age >= 65y	All	130/3941 (3.3)	16y	All n-3	Plasma	no

Appendix F
Observational results: death from stroke

Row	Study PMID	Adjustments	Quantile	n3 units	Quantile low	Quantile median	Quantile high
2	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt1	% FA	nd	1.95	nd
3	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt2	% FA	nd	2.44	nd
4	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt3	% FA	nd	2.87	nd
5	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt4	% FA	nd	3.36	nd
6	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt5	% FA	nd	4.34	nd
7	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt1	% FA	nd	0.63	nd
8	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt2	% FA	nd	0.75	nd
9	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt3	% FA	nd	0.82	nd
10	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt4	% FA	nd	0.91	nd
11	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt5	% FA	nd	1.04	nd
12	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt1	% FA	nd	0.3	nd
13	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt2	% FA	nd	0.41	nd
14	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt3	% FA	nd	0.51	nd
15	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt4	% FA	nd	0.64	nd
16	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt5	% FA	nd	0.92	nd
17	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt1	% FA	nd	3.17	nd
18	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt2	% FA	nd	3.72	nd

Appendix F
Observational results: death from stroke

Row	Study PMID	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
2	Mozaffarian 2013 23546563	HR	nd	nd	nd	Reference group			P trend	0.082
3	Mozaffarian 2013 23546563	HR	nd	nd	nd	1.3	0.76	2.22		
4	Mozaffarian 2013 23546563	HR	nd	nd	nd	1.14	0.66	1.96		
5	Mozaffarian 2013 23546563	HR	nd	nd	nd	1.01	0.57	1.78		
6	Mozaffarian 2013 23546563	HR	nd	nd	nd	0.62	0.32	1.2		
7	Mozaffarian 2013 23546563	HR	nd	nd	nd	Reference group			P trend	0.056
8	Mozaffarian 2013 23546563	HR	nd	nd	nd	0.56	0.33	0.96		
9	Mozaffarian 2013 23546563	HR	nd	nd	nd	0.57	0.33	0.96		
10	Mozaffarian 2013 23546563	HR	nd	nd	nd	0.68	0.41	1.13		
11	Mozaffarian 2013 23546563	HR	nd	nd	nd	0.53	0.31	0.92		
12	Mozaffarian 2013 23546563	HR	nd	nd	nd	Reference group			P trend	0.34
13	Mozaffarian 2013 23546563	HR	nd	nd	nd	1.05	0.63	1.75		
14	Mozaffarian 2013 23546563	HR	nd	nd	nd	0.77	0.44	1.34		
15	Mozaffarian 2013 23546563	HR	nd	nd	nd	0.67	0.38	1.21		
16	Mozaffarian 2013 23546563	HR	nd	nd	nd	0.84	0.47	1.48		
17	Mozaffarian 2013 23546563	HR	nd	nd	nd	Reference group			P trend	0.092
18	Mozaffarian 2013 23546563	HR	nd	nd	nd	0.92	0.53	1.58		

Appendix F
Observational results: death from stroke

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure	Supplement
19	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke death, total	Stroke mortality	Healthy	Healthy age >= 65y	All	130/3941 (3.3)	16y	All n-3	Plasma	no
20	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke death, total	Stroke mortality	Healthy	Healthy age >= 65y	All	130/3941 (3.3)	16y	All n-3	Plasma	no
21	Mozaffarian 2013 23546563	Cardiovascular Health Study	Stroke death, total	Stroke mortality	Healthy	Healthy age >= 65y	All	130/3941 (3.3)	16y	All n-3	Plasma	no
22	Miyagawa 2014 24468152	NIPPON DATA80	Stroke death, total	Stroke	Healthy	healthy individual with mean age of 50	All	417/9190 (4.54)	24 y	EPA+DHA	Intake	no
23	Miyagawa 2014 24468152	NIPPON DATA80	Stroke death, total	Stroke	Healthy	healthy individual with mean age of 50	All	417/9190 (4.54)	24 y	EPA+DHA	Intake	no
24	Miyagawa 2014 24468152	NIPPON DATA80	Stroke death, total	Stroke	Healthy	healthy individual with mean age of 50	All	417/9190 (4.54)	24 y	EPA+DHA	Intake	no
25	Miyagawa 2014 24468152	NIPPON DATA80	Stroke death, total	Stroke	Healthy	healthy individual with mean age of 50	All	417/9190 (4.54)	24 y	EPA+DHA	Intake	no
26	Miyagawa 2014 24468152	NIPPON DATA80	Stroke death, total	Stroke	Healthy	healthy individual with mean age of 50	All	417/9190 (4.54)	24 y	All n-3	Intake	no
27	Miyagawa 2014 24468152	NIPPON DATA80	Stroke death, total	Stroke	Healthy	healthy individual with mean age of 50	All	417/9190 (4.54)	24 y	All n-3	Intake	no
28	Miyagawa 2014 24468152	NIPPON DATA80	Stroke death, total	Stroke	Healthy	healthy individual with mean age of 50	All	417/9190 (4.54)	24 y	All n-3	Intake	no
29	Miyagawa 2014 24468152	NIPPON DATA80	Stroke death, total	Stroke	Healthy	healthy individual with mean age of 50	All	417/9190 (4.54)	24 y	All n-3	Intake	no
30	Miyagawa 2014 24468152	NIPPON DATA80	Stroke death, total	Stroke	Healthy	healthy individual with mean age of 50	All	417/9190 (4.54)	24 y	EPA	Intake	no
31	Miyagawa 2014 24468152	NIPPON DATA80	Stroke death, total	Stroke	Healthy	healthy individual with mean age of 50	All	417/9190 (4.54)	24 y	EPA+DHA	Intake	no
32	Miyagawa 2014 24468152	NIPPON DATA80	Stroke death, total	Stroke	Healthy	healthy individual with mean age of 50	All	417/9190 (4.54)	24 y	EPA+DHA	Intake	no
33	Miyagawa 2014 24468152	NIPPON DATA80	Stroke death, total	Stroke	Healthy	healthy individual with mean age of 50	All	417/9190 (4.54)	24 y	EPA+DHA	Intake	no
34	Miyagawa 2014 24468152	NIPPON DATA80	Stroke death, total	Stroke	Healthy	healthy individual with mean age of 50	All	417/9190 (4.54)	24 y	EPA+DHA	Intake	no
35	Miyagawa 2014 24468152	NIPPON DATA80	Stroke death, total	Stroke	Healthy	healthy individual with mean age of 50	All	417/9190 (4.54)	24 y	All n-3	Intake	no
36	Miyagawa 2014 24468152	NIPPON DATA80	Stroke death, total	Stroke	Healthy	healthy individual with mean age of 50	All	417/9190 (4.54)	24 y	All n-3	Intake	no
37	Miyagawa 2014 24468152	NIPPON DATA80	Stroke death, total	Stroke	Healthy	healthy individual with mean age of 50	All	417/9190 (4.54)	24 y	All n-3	Intake	no
38	Yamagishi 2008 18786479	JACC	Stroke death, total		Healthy	Healthy 40-79 yo	All	417/9190 (4.54)	24 y	All n-3	Intake	no
39	Yamagishi 2008 18786479	JACC	Stroke death, total	nd	Healthy	Healthy 40-79 yo	All	417/9190 (4.54)	24 y	EPA	Intake	no
40	Yamagishi 2008 18786479	JACC	Stroke death, total	nd	Healthy	Healthy 40-79 yo	All	417/9190 (4.54)	24 y	EPA+DHA	Intake	no
41	Yamagishi 2008 18786479	JACC	Stroke death, total	nd	Healthy	Healthy 40-79 yo	All	417/9190 (4.54)	24 y	EPA+DHA	Intake	no
42	Yamagishi 2008 18786479	JACC	Stroke death, total	nd	Healthy	Healthy 40-79 yo	All	417/9190 (4.54)	24 y	EPA+DHA	Intake	no

Appendix F
Observational results: death from stroke

Row	Study PMID	Adjustments	Quantile	n3 units	Quantile low	Quantile median	Quantile high
19	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt3	% FA	nd	4.21	nd
20	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt4	% FA	nd	4.8	nd
21	Mozaffarian 2013 23546563	Adjusted for age (years), sex, race (white, nonwhite), education(<high school, high school, some college, college graduate), enrollment site (4 sites), fatty acid measurement batch (1994–96, 2007–10), smoking (never, former, current), prevalent diabetes (yes, no), prevalent atrial fibrillation (yes, no), prevalent drug-treated hypertension (yes, no), leisure-time physical activity (mcal/week), body mass index (kg/m2), waist circumference (cm), and alcohol use (6 categories).	Qt5	% FA	nd	6.04	nd
22	Miyagawa 2014 24468152	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr1	% kcal	men 0.00, women 0.02	men 0.18, women 0.19	men 0.23, women 0.25
23	Miyagawa 2014 24468152	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr2	% kcal	men 0.24, women 0.26	men 0.29, women 0.32	men 0.35, women 0.38
24	Miyagawa 2014 24468152	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr3	% kcal	men 0.36, women 0.39	men 0.43, women 0.46	men 0.51, women 0.55
25	Miyagawa 2014 24468152	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr4	% kcal	men 0.52, women 0.56	men 0.65, women 0.70	men 2.34 women 2.43
26	Miyagawa 2014 24468152	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr1	% kcal	men 0.20, women 0.21	nd	men 0.85, women 0.93
27	Miyagawa 2014 24468152	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr2	% kcal	men 0.86, women 0.94	nd	men 1.05, women 1.15
28	Miyagawa 2014 24468152	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr3	% kcal	men 1.06, women 1.16	nd	men 1.28, women 1.39
29	Miyagawa 2014 24468152	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr4	% kcal	men 1.29, women 1.40	nd	men 3.92 women 3.66
30	Miyagawa 2014 24468152	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr1	% kcal	men 0.00, women 0.00	nd	men 0.08, women 0.09
31	Miyagawa 2014 24468152	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr1	% kcal	men 0.00, women 0.03	men 0.18, women 0.20	men 0.23, women 0.26
32	Miyagawa 2014 24468152	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr2	% kcal	men 0.24, women 0.27	men 0.29, women 0.33	men 0.35, women 0.39
33	Miyagawa 2014 24468152	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr3	% kcal	men 0.36, women 0.40	men 0.43, women 0.47	men 0.51, women 0.56
34	Miyagawa 2014 24468152	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr4	% kcal	men 0.52, women 0.57	men 0.65, women 0.71	men 2.34 women 2.44
35	Miyagawa 2014 24468152	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr1	% kcal	men 0.20, women 0.22	nd	men 0.85, women 0.94
36	Miyagawa 2014 24468152	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr2	% kcal	men 0.86, women 0.95	nd	men 1.05, women 1.16
37	Miyagawa 2014 24468152	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr3	% kcal	men 1.06, women 1.17	nd	men 1.28, women 1.40
38	Yamagishi 2008 18786479	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr4	% kcal	men 1.29, women 1.41	nd	men 3.92 women 3.67
39	Yamagishi 2008 18786479	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr1	% kcal	men 0.00, women 0.01	nd	men 0.08, women 0.10
40	Yamagishi 2008 18786479	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr1	% kcal	men 0.00, women 0.04	men 0.18, women 0.21	men 0.23, women 0.27
41	Yamagishi 2008 18786479	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr2	% kcal	men 0.24, women 0.28	men 0.29, women 0.34	men 0.35, women 0.40
42	Yamagishi 2008 18786479	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr3	% kcal	men 0.36, women 0.41	men 0.43, women 0.48	men 0.51, women 0.57

Appendix F
Observational results: death from stroke

Row	Study PMID	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
19	Mozaffarian 2013 23546563	HR	nd	nd	nd	1.11	0.66	1.88		
20	Mozaffarian 2013 23546563	HR	nd	nd	nd	0.84	0.48	1.48		
21	Mozaffarian 2013 23546563	HR	nd	nd	nd	0.6	0.32	1.12		
22	Miyagawa 2014 24468152	HR	104	nd	47402	1	nd	nd	overal effect for trend	0.267
23	Miyagawa 2014 24468152	HR	95	nd	50196	0.87	0.62	1.08		
24	Miyagawa 2014 24468152	HR	112	nd	47359	0.99	0.74	1.27		
25	Miyagawa 2014 24468152	HR	106	nd	47940	0.89	0.62	1.06		
26	Miyagawa 2014 24468152	HR	127	nd	45771	1	nd	nd	overal effect for trend	0.449
27	Miyagawa 2014 24468152	HR	107	nd	49814	1.02	0.79	1.32		
28	Miyagawa 2014 24468152	HR	92	nd	48876	0.99	0.75	1.29		
29	Miyagawa 2014 24468152	HR	91	nd	48438	0.91	0.69	1.2		
30	Miyagawa 2014 24468152	HR	102	nd	49312	1	nd	nd	overal effect for trend	0.394
31	Miyagawa 2014 24468152	HR	104	nd	47402	1	nd	nd	overal effect for trend	0.267
32	Miyagawa 2014 24468152	HR	95	nd	50196	0.87	0.62	1.08		
33	Miyagawa 2014 24468152	HR	112	nd	47359	0.99	0.74	1.27		
34	Miyagawa 2014 24468152	HR	106	nd	47940	0.89	0.62	1.06		
35	Miyagawa 2014 24468152	HR	127	nd	45771	1	nd	nd	overal effect for trend	0.449
36	Miyagawa 2014 24468152	HR	107	nd	49814	1.03	0.79	1.32		
37	Miyagawa 2014 24468152	HR	92	nd	48876	0.99	0.75	1.29		
38	Yamagishi 2008 18786479	HR	91	nd	48438	0.91	0.69	1.2		
39	Yamagishi 2008 18786479	HR	102	nd	49312	1	nd	nd	overal effect for trend	0.394
40	Yamagishi 2008 18786479	HR	104	nd	47402	1	nd	nd	overal effect for trend	0.267
41	Yamagishi 2008 18786479	HR	95	nd	50196	0.87	0.62	1.08		
42	Yamagishi 2008 18786479	HR	112	nd	47359	0.99	0.74	1.27		

Appendix F
Observational results: death from stroke

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure	Supplement
43	Yuan 2001 11682363	Shanghai	Stroke death, total	nd	Healthy	Healthy, 45-64 yo	All	417/9190 (4.54)	24 y	EPA+DHA	Intake	no
44	Yuan 2001 11682363	Shanghai	Stroke death, total	nd	Healthy	Healthy, 45-64 yo	All	417/9190 (4.54)	24 y	All n-3	Intake	no
45	Yuan 2001 11682363	Shanghai	Stroke death, total	nd	Healthy	Healthy, 45-64 yo	All	417/9190 (4.54)	24 y	All n-3	Intake	no
46	Yuan 2001 11682363	Shanghai	Stroke death, total	nd	Healthy	Healthy, 45-64 yo	All	417/9190 (4.54)	24 y	All n-3	Intake	no
47	Yuan 2001 11682363	Shanghai	Stroke death, total	nd	Healthy	Healthy, 45-64 yo	All	417/9190 (4.54)	24 y	All n-3	Intake	no
48	Koh_2013_24343844	The Singapore Chinese Health Study	Death_Stroke		Healthy		All	2198/60298 (0.02)	5 y	All n-3	intake	no
49	Koh_2013_24343844	The Singapore Chinese Health Study	Death_Stroke		Healthy		All		5 y	All n-3	intake	no
50	Koh_2013_24343844	The Singapore Chinese Health Study	Death_Stroke		Healthy		All		5 y	All n-3	intake	no
51	Koh_2013_24343844	The Singapore Chinese Health Study	Death_Stroke		Healthy		All		5 y	All n-3	intake	no
52	Koh_2013_24343844	The Singapore Chinese Health Study	Death_Stroke		Healthy		All		5 y	All n-3	intake	no
53	Koh_2013_24343844	The Singapore Chinese Health Study	Death_Stroke		Healthy		All		5 y	All n-3	intake	no
54	Koh_2013_24343844	The Singapore Chinese Health Study	Death_Stroke		Healthy		All		5 y	All n-3	intake	no
55	Koh_2013_24343844	The Singapore Chinese Health Study	Death_Stroke		Healthy		All		5 y	All n-3	intake	no
56	Koh_2013_24343844	The Singapore Chinese Health Study	Death_Stroke		Healthy		All		5 y	All n-3	intake	no
57	Koh_2013_24343844	The Singapore Chinese Health Study	Death_Stroke		Healthy		All		5 y	All n-3	intake	no
58	Koh_2013_24343844	The Singapore Chinese Health Study	Death_Stroke		Healthy		All		5 y	All n-3	intake	no
59	Koh_2013_24343844	The Singapore Chinese Health Study	Death_Stroke		Healthy		All		5 y	All n-3	intake	no

Appendix F
Observational results: death from stroke

Row	Study PMID	Adjustments	Quantile	n3 units	Quantile low	Quantile median	Quantile high
43	Yuan 2001 11682363	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr4	% kcal	men 0.52, women 0.58	men 0.65, women 0.72	men 2.34 women 2.45
44	Yuan 2001 11682363	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr1	% kcal	men 0.20, women 0.23	nd	men 0.85, women 0.95
45	Yuan 2001 11682363	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr2	% kcal	men 0.86, women 0.96	nd	men 1.05, women 1.17
46	Yuan 2001 11682363	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr3	% kcal	men 1.06, women 1.18	nd	men 1.28, women 1.41
47	Yuan 2001 11682363	age, sex, moking status, drinking status, systolic blood pressure, blood glucose, serum total cholesterol, body mass index, antihypertensive medication status and residential area	Qr4	% kcal	men 1.29, women 1.42	nd	men 3.92 women 3.68
48	Koh_2013_24343844	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr1	nd	nd	nd	nd
49	Koh_2013_24343844	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr2	nd	nd	nd	nd
50	Koh_2013_24343844	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr3	nd	nd	nd	nd
51	Koh_2013_24343844	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr4	nd	nd	nd	nd
52	Koh_2013_24343844	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr1	nd	nd	nd	nd
53	Koh_2013_24343844	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr2	nd	nd	nd	nd
54	Koh_2013_24343844	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr3	nd	nd	nd	nd
55	Koh_2013_24343844	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr4	nd	nd	nd	nd
56	Koh_2013_24343844	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr1	nd	nd	nd	nd
57	Koh_2013_24343844	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr2	nd	nd	nd	nd
58	Koh_2013_24343844	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr3	nd	nd	nd	nd
59	Koh_2013_24343844	age, sex, dialect, year of interview, educational level, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, intakes of total energy, protein, dietary fibre, saturated fat, monounsaturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids (in the analysis of EPA/DHA or ALA)	Qr4	nd	nd	nd	nd

Appendix F
Observational results: death from stroke

Row	Study PMID	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
43	Yuan 2001 11682363	HR	106	nd	47940	0.89	0.62	1.06		
44	Yuan 2001 11682363	HR	127	nd	45771	1	nd	nd	overal effect for trend	0.449
45	Yuan 2001 11682363	HR	107	nd	49814	1.04	0.79	1.32		
46	Yuan 2001 11682363	HR	92	nd	48876	0.99	0.75	1.29		
47	Yuan 2001 11682363	HR	91	nd	48438	0.91	0.69	1.2		
48	Koh_2013_24343844	HR	373	15181		Ref			P trend	0.1
49	Koh_2013_24343844	HR	330	15022		0.86	0.72	1.01		
50	Koh_2013_24343844	HR	320	15023		0.84	0.7	1.01		
51	Koh_2013_24343844	HR	275	15072		0.82	0.66	1.01		
52	Koh_2013_24343844	HR	345	15181		Ref			P trend	0.28
53	Koh_2013_24343844	HR	343	15022		0.96	0.82	1.12		
54	Koh_2013_24343844	HR	297	15023		0.82	0.68	0.98		
55	Koh_2013_24343844	HR	313	15072		0.91	0.74	1.12		
56	Koh_2013_24343844	HR	382	15181		Ref			P trend	0.07
57	Koh_2013_24343844	HR	324	15022		0.81	0.68	0.95		
58	Koh_2013_24343844	HR	316	15023		0.81	0.68	0.97		
59	Koh_2013_24343844	HR	276	15072		0.81	0.67	0.99		

Appendix F Observational results: death from hemorrhagic stroke

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure
2	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	Stroke death, hemorrhagic	nd	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	DHA	Intake
3	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	Stroke death, hemorrhagic	nd	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	DHA	Intake
4	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	Stroke death, hemorrhagic	nd	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	DHA	Intake
5	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	Stroke death, hemorrhagic	nd	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	DHA	Intake
6	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	Stroke death, hemorrhagic	nd	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	DHA	Intake
7	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	Stroke death, hemorrhagic	nd	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	EPA	Intake
8	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	Stroke death, hemorrhagic	nd	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	EPA	Intake
9	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	Stroke death, hemorrhagic	nd	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	EPA	Intake
10	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	Stroke death, hemorrhagic	nd	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	EPA	Intake
11	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	Stroke death, hemorrhagic	nd	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	EPA	Intake
12	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	Stroke death, hemorrhagic	nd	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	EPA+DHA	Intake
13	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	Stroke death, hemorrhagic	nd	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	EPA+DHA	Intake
14	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	Stroke death, hemorrhagic	nd	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	EPA+DHA	Intake
15	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	Stroke death, hemorrhagic	nd	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	EPA+DHA	Intake
16	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	Stroke death, hemorrhagic	nd	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	EPA+DHA	Intake

Appendix F Observational results: death from hemorrhagic stroke

Row	Study PMID	Supplement	Adjustments	Quantile	n3 units	Quantile low	Quantile median
2	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt1	g/d	nd	0.009 (men), 0.008 (women)
3	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt2	g/d	nd	0.02 (men), 0.02 (women)
4	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt3	g/d	nd	0.05 (men), 0.04 (women)
5	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt4	g/d	nd	0.08 (men), 0.08 (women)
6	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt5	g/d	nd	0.15 (men), 0.15 (women)
7	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt1	g/d	nd	0.006 (men), 0.005 (women)
8	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt2	g/d	nd	0.01 (men), 0.01 (women)
9	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt3	g/d	nd	0.02 (men), 0.02 (women)
10	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt4	g/d	nd	0.03 (men), 0.03 (women)
11	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt5	g/d	nd	0.07 (men), 0.06 (women)
12	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt1	g/d	nd	nd
13	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt2	g/d	nd	nd
14	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt3	g/d	nd	nd
15	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt4	g/d	nd	nd
16	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt5	g/d	nd	nd

Appendix F Observational results: death from hemorrhagic stroke

Row	Study PMID	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
2	Takata 2013 23788668	nd	HR	162	26860	nd	Reference group			P trend	0.93
3	Takata 2013 23788668	nd	HR	94	nd	nd	0.87	0.67	1.13		
4	Takata 2013 23788668	nd	HR	66	26860	nd	0.76	0.56	1.02		
5	Takata 2013 23788668	nd	HR	76	nd	nd	1.01	0.76	1.36		
6	Takata 2013 23788668	nd	HR	62	26858	nd	0.95	0.5	1.82		
7	Takata 2013 23788668	nd	HR	174	26860	nd	Reference group			P trend	0.39
8	Takata 2013 23788668	nd	HR	87	nd	nd	0.75	0.57	0.97		
9	Takata 2013 23788668	nd	HR	71	26860	nd	0.75	0.56	1.01		
10	Takata 2013 23788668	nd	HR	69	nd	nd	0.88	0.65	1.2		
11	Takata 2013 23788668	nd	HR	59	26858	nd	0.81	0.58	1.12		
12	Takata 2013 23788668	nd	HR	165	26860	nd	Reference group			P trend	0.99
13	Takata 2013 23788668	nd	HR	92	nd	nd	0.85	0.65	1.1		
14	Takata 2013 23788668	nd	HR	69	26860	nd	0.78	0.58	1.05		
15	Takata 2013 23788668	nd	HR	73	nd	nd	1.02	0.55	1.9		
16	Takata 2013 23788668	nd	HR	61	26858	nd	0.88	0.64	1.23		

Appendix F

Observational results: death from ischemic stroke

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure
2	Yamagishi 2008 18786479	JACC	Stroke death, ischemic	nd	Healthy	Healthy 40-79 yo	All	319/57972 (0.55)	12.7 y	All n-3	Intake
3	Yamagishi 2008 18786479	JACC	Stroke death, ischemic	nd	Healthy	Healthy 40-79 yo	All	319/57972 (0.55)	12.7 y	All n-3	Intake
4	Yamagishi 2008 18786479	JACC	Stroke death, ischemic	nd	Healthy	Healthy 40-79 yo	All	319/57972 (0.55)	12.7 y	All n-3	Intake
5	Yamagishi 2008 18786479	JACC	Stroke death, ischemic	nd	Healthy	Healthy 40-79 yo	All	319/57972 (0.55)	12.7 y	All n-3	Intake
6	Yamagishi 2008 18786479	JACC	Stroke death, ischemic	nd	Healthy	Healthy 40-79 yo	All	319/57972 (0.55)	12.7 y	All n-3	Intake
7	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	Stroke death, ischemic	nd	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	DHA	Intake
8	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	Stroke death, ischemic	nd	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	DHA	Intake
9	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	Stroke death, ischemic	nd	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	DHA	Intake
10	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	Stroke death, ischemic	nd	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	DHA	Intake
11	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	Stroke death, ischemic	nd	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	DHA	Intake
12	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	Stroke death, ischemic	nd	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	EPA	Intake
13	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	Stroke death, ischemic	nd	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	EPA	Intake
14	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	Stroke death, ischemic	nd	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	EPA	Intake
15	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	Stroke death, ischemic	nd	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	EPA	Intake
16	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	Stroke death, ischemic	nd	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	EPA	Intake
17	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	Stroke death, ischemic	nd	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	EPA+DHA	Intake
18	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	Stroke death, ischemic	nd	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	EPA+DHA	Intake
19	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	Stroke death, ischemic	nd	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	EPA+DHA	Intake
20	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	Stroke death, ischemic	nd	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	EPA+DHA	Intake
21	Takata 2013 23788668	Shanghai Women's and Men's Health Studies	Stroke death, ischemic	nd	Healthy	Healthy 40-74	All	5836/134296 (4.35)	11.2 y women; 5.6 y men	EPA+DHA	Intake

Appendix F
Observational results: death from ischemic stroke

Row	Study PMID	Supplement	Adjustments	Quantile	n3 units	Quantile low	Quantile median
2	Yamagishi 2008 18786479	No	age, sex, htn and dm history, smoking status, alcohol consumption, BMI, mental stress, walking, sports, education, total energy, dietary intake of cholesterol/saturated and omega-3FA/vegetables/fruit	Qt1	g/d	0.05	nd
3	Yamagishi 2008 18786479	No	age, sex, htn and dm history, smoking status, alcohol consumption, BMI, mental stress, walking, sports, education, total energy, dietary intake of cholesterol/saturated and omega-3FA/vegetables/fruit	Qt2	g/d	1.18	nd
4	Yamagishi 2008 18786479	No	age, sex, htn and dm history, smoking status, alcohol consumption, BMI, mental stress, walking, sports, education, total energy, dietary intake of cholesterol/saturated and omega-3FA/vegetables/fruit	Qt3	g/d	1.47	nd
5	Yamagishi 2008 18786479	No	age, sex, htn and dm history, smoking status, alcohol consumption, BMI, mental stress, walking, sports, education, total energy, dietary intake of cholesterol/saturated and omega-3FA/vegetables/fruit	Qt4	g/d	1.75	nd
6	Yamagishi 2008 18786479	No	age, sex, htn and dm history, smoking status, alcohol consumption, BMI, mental stress, walking, sports, education, total energy, dietary intake of cholesterol/saturated and omega-3FA/vegetables/fruit	Qt5	g/d	2.11	nd
7	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt1	g/d	nd	0.009 (men), 0.008 (women)
8	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt2	g/d	nd	0.02 (men), 0.02 (women)
9	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt3	g/d	nd	0.05 (men), 0.04 (women)
10	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt4	g/d	nd	0.08 (men), 0.08 (women)
11	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt5	g/d	nd	0.15 (men), 0.15 (women)
12	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt1	g/d	nd	0.006 (men), 0.005 (women)
13	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt2	g/d	nd	0.01 (men), 0.01 (women)
14	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt3	g/d	nd	0.02 (men), 0.02 (women)
15	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt4	g/d	nd	0.03 (men), 0.03 (women)
16	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt5	g/d	nd	0.07 (men), 0.06 (women)
17	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt1	g/d	nd	nd
18	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt2	g/d	nd	nd
19	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt3	g/d	nd	nd
20	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt4	g/d	nd	nd
21	Takata 2013 23788668	No	age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).	Qt5	g/d	nd	nd

Appendix F
Observational results: death from ischemic stroke

Row	Study PMID	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
2	Yamagishi 2008 18786479	1.18	HR	360	11594	735904	Reference group				0.01
3	Yamagishi 2008 18786479	1.47	HR	367	11595	735904	0.93	0.8	1.09		
4	Yamagishi 2008 18786479	1.75	HR	412	11594	735904	0.91	0.78	1.07		
5	Yamagishi 2008 18786479	2.11	HR	388	11595	735904	0.81	0.68	0.96		
6	Yamagishi 2008 18786479	5.06	HR	518	11594	735904	0.81	0.67	0.98		
7	Takata 2013 23788668	nd	HR	172	26860	nd	Reference group			P trend	0.02
8	Takata 2013 23788668	nd	HR	80	nd	nd	0.79	0.6	1.04		
9	Takata 2013 23788668	nd	HR	68	26860	nd	0.91	0.68	1.23		
10	Takata 2013 23788668	nd	HR	56	nd	nd	0.93	0.68	1.29		
11	Takata 2013 23788668	nd	HR	28	26858	nd	0.55	0.36	0.83		
12	Takata 2013 23788668	nd	HR	170	26860	nd	Reference group			P trend	0.004
13	Takata 2013 23788668	nd	HR	82	nd	nd	0.88	0.51	1.52		
14	Takata 2013 23788668	nd	HR	74	26860	nd	1.04	0.78	1.39		
15	Takata 2013 23788668	nd	HR	51	nd	nd	0.94	0.67	1.31		
16	Takata 2013 23788668	nd	HR	27	26858	nd	0.56	0.36	0.86		
17	Takata 2013 23788668	nd	HR	169	26860	nd	Reference group			P trend	0.02
18	Takata 2013 23788668	nd	HR	84	nd	nd	0.87	0.67	1.14		
19	Takata 2013 23788668	nd	HR	67	26860	nd	0.94	0.7	1.27		
20	Takata 2013 23788668	nd	HR	58	nd	nd	1.03	0.75	1.41		
21	Takata 2013 23788668	nd	HR	26	26858	nd	0.53	0.34	0.82		

Appendix F
Observational results: death from ischemic stroke

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure
23	**Subgroup analyses**										
24	Bell 2014 24496442	VITAL	Stroke death, ischemic	Death from Ischemic heart disease		Men and women aged 50-76	History of ischemic heart disease at baseline	208/nd	6 y	EPA+DHA	Intake
25	Bell 2014 24496442	VITAL	Stroke death, ischemic	Death from Ischemic heart disease		Men and women aged 50-76	History of ischemic heart disease at baseline	208/nd	6 y	EPA+DHA	Intake
26	Bell 2014 24496442	VITAL	Stroke death, ischemic	Death from Ischemic heart disease		Men and women aged 50-76	History of ischemic heart disease at baseline	208/nd	6 y	EPA+DHA	Intake
27	Bell 2014 24496442	VITAL	Stroke death, ischemic	Death from Ischemic heart disease		Men and women aged 50-76	History of ischemic heart disease at baseline	208/nd	6 y	EPA+DHA	Intake

Appendix F
Observational results: death from ischemic stroke

Row	Study PMID	Supplement	Adjustments	Quantile	n3 units	Quantile low	Quantile median
23	**Subgroup analyses**						
24	Bell 2014 24496442	yes	age (as the time scale), sex, race/ethnicity, marital status (married/living together, never married, separated/divorced, widowed, or missing), education (high school graduate or less, some college, or college/advanced degree), total energy intake (kcal/day; continuous), body mass index (weight (kg)/height (m)2 (none, <1 drink/day, 1–2 drinks/day, >2 drinks/day, or missing), average physical activity in the 10 years before baseline (MET-hours/week; tertiles), self-rated health (excellent, very good, good, fair, or poor), mammogram in the last 2 years (yes/no), prostate-specific antigen test in the last 2 years (yes/no), sigmoidoscopy in the last 10 years (yes/no), current use of cholesterol-lowering medication (yes/no), aspirin use in the past 10 years (none, low, high, or missing), use of nonaspirin nonsteroidal antiinflammatory drugs in the past 10 years (none, low, high, or missing), smoking (never, 1–12.5 pack-years, 12.6–35.0 pack-years, or >35.0 pack-years), morbidity score,c percentage of calories derived from trans fat (quartiles), percentage of calories derived from saturated fat (quartiles), number of servings per day of fruits (quartiles), number of servings per day of vegetables (quartiles), years of estrogen therapy (none, <5, 5–9, ≥10, or missing), years of estrogen + progestin therapy (none, <5, 5–9, ≥10, or missing), age at menopause (≤39 years, 40–44 years, 45–49 years, 50–54 years, ≥55 years, or missing), age at death of father (≤59 years, 60–69 years, 70–79 years, 80–89 years, or ≥90 years), and age at death of mother (≤59 years, 60–69 years, 70–79 years, 80–89 years, or ≥90 years)	Qr1	g/day	0	nd
25	Bell 2014 24496442	yes	age (as the time scale), sex, race/ethnicity, marital status (married/living together, never married, separated/divorced, widowed, or missing), education (high school graduate or less, some college, or college/advanced degree), total energy intake (kcal/day; continuous), body mass index (weight (kg)/height (m)2 (none, <1 drink/day, 1–2 drinks/day, >2 drinks/day, or missing), average physical activity in the 10 years before baseline (MET-hours/week; tertiles), self-rated health (excellent, very good, good, fair, or poor), mammogram in the last 2 years (yes/no), prostate-specific antigen test in the last 2 years (yes/no), sigmoidoscopy in the last 10 years (yes/no), current use of cholesterol-lowering medication (yes/no), aspirin use in the past 10 years (none, low, high, or missing), use of nonaspirin nonsteroidal antiinflammatory drugs in the past 10 years (none, low, high, or missing), smoking (never, 1–12.5 pack-years, 12.6–35.0 pack-years, or >35.0 pack-years), morbidity score,c percentage of calories derived from trans fat (quartiles), percentage of calories derived from saturated fat (quartiles), number of servings per day of fruits (quartiles), number of servings per day of vegetables (quartiles), years of estrogen therapy (none, <5, 5–9, ≥10, or missing), years of estrogen + progestin therapy (none, <5, 5–9, ≥10, or missing), age at menopause (≤39 years, 40–44 years, 45–49 years, 50–54 years, ≥55 years, or missing), age at death of father (≤59 years, 60–69 years, 70–79 years, 80–89 years, or ≥90 years), and age at death of mother (≤59 years, 60–69 years, 70–79 years, 80–89 years, or ≥90 years)	Qr2	g/day	0.082	nd
26	Bell 2014 24496442	yes	age (as the time scale), sex, race/ethnicity, marital status (married/living together, never married, separated/divorced, widowed, or missing), education (high school graduate or less, some college, or college/advanced degree), total energy intake (kcal/day; continuous), body mass index (weight (kg)/height (m)2 (none, <1 drink/day, 1–2 drinks/day, >2 drinks/day, or missing), average physical activity in the 10 years before baseline (MET-hours/week; tertiles), self-rated health (excellent, very good, good, fair, or poor), mammogram in the last 2 years (yes/no), prostate-specific antigen test in the last 2 years (yes/no), sigmoidoscopy in the last 10 years (yes/no), current use of cholesterol-lowering medication (yes/no), aspirin use in the past 10 years (none, low, high, or missing), use of nonaspirin nonsteroidal antiinflammatory drugs in the past 10 years (none, low, high, or missing), smoking (never, 1–12.5 pack-years, 12.6–35.0 pack-years, or >35.0 pack-years), morbidity score,c percentage of calories derived from trans fat (quartiles), percentage of calories derived from saturated fat (quartiles), number of servings per day of fruits (quartiles), number of servings per day of vegetables (quartiles), years of estrogen therapy (none, <5, 5–9, ≥10, or missing), years of estrogen + progestin therapy (none, <5, 5–9, ≥10, or missing), age at menopause (≤39 years, 40–44 years, 45–49 years, 50–54 years, ≥55 years, or missing), age at death of father (≤59 years, 60–69 years, 70–79 years, 80–89 years, or ≥90 years), and age at death of mother (≤59 years, 60–69 years, 70–79 years, 80–89 years, or ≥90 years)	Qr3	g/day	0.174	nd
27	Bell 2014 24496442	yes	age (as the time scale), sex, race/ethnicity, marital status (married/living together, never married, separated/divorced, widowed, or missing), education (high school graduate or less, some college, or college/advanced degree), total energy intake (kcal/day; continuous), body mass index (weight (kg)/height (m)2 (none, <1 drink/day, 1–2 drinks/day, >2 drinks/day, or missing), average physical activity in the 10 years before baseline (MET-hours/week; tertiles), self-rated health (excellent, very good, good, fair, or poor), mammogram in the last 2 years (yes/no), prostate-specific antigen test in the last 2 years (yes/no), sigmoidoscopy in the last 10 years (yes/no), current use of cholesterol-lowering medication (yes/no), aspirin use in the past 10 years (none, low, high, or missing), use of nonaspirin nonsteroidal antiinflammatory drugs in the past 10 years (none, low, high, or missing), smoking (never, 1–12.5 pack-years, 12.6–35.0 pack-years, or >35.0 pack-years), morbidity score,c percentage of calories derived from trans fat (quartiles), percentage of calories derived from saturated fat (quartiles), number of servings per day of fruits (quartiles), number of servings per day of vegetables (quartiles), years of estrogen therapy (none, <5, 5–9, ≥10, or missing), years of estrogen + progestin therapy (none, <5, 5–9, ≥10, or missing), age at menopause (≤39 years, 40–44 years, 45–49 years, 50–54 years, ≥55 years, or missing), age at death of father (≤59 years, 60–69 years, 70–79 years, 80–89 years, or ≥90 years), and age at death of mother (≤59 years, 60–69 years, 70–79 years, 80–89 years, or ≥90 years)	Qr4	g/day	0.322	nd

Appendix F
Observational results: death from ischemic stroke

Row	Study PMID	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
23	**Subgroup analyses**										
24	Bell 2014 24496442	0.082	HR	54	nd	nd	1	nd	nd		0.812
25	Bell 2014 24496442	0.174	HR	45	nd	nd	0.92	0.61	1.4		
26	Bell 2014 24496442	0.322	HR	47	nd	nd	0.86	0.55	1.35		
27	Bell 2014 24496442	nd	HR	62	nd	nd	0.96	0.6	1.52		

Appendix F
Observational results: death from ischemic stroke

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Population	Subgroup	Cases Total/N Total (Rate %)	Followup	n3 FA	n3 measure
28	Bell 2014 24496442	VITAL	Stroke death, ischemic	Death from Ischemic heart disease		Men and women aged 50-76	No history of ischemic heart disease at baseline	233/nd	6 y	EPA+DHA	Intake
29	Bell 2014 24496442	VITAL	Stroke death, ischemic	Death from Ischemic heart disease		Men and women aged 50-76	No history of ischemic heart disease at baseline	233/nd	6 y	EPA+DHA	Intake
30	Bell 2014 24496442	VITAL	Stroke death, ischemic	Death from Ischemic heart disease		Men and women aged 50-76	No history of ischemic heart disease at baseline	233/nd	6 y	EPA+DHA	Intake
31	Bell 2014 24496442	VITAL	Stroke death, ischemic	Death from Ischemic heart disease		Men and women aged 50-76	No history of ischemic heart disease at baseline	233/nd	6 y	EPA+DHA	Intake

Appendix F
Observational results: death from ischemic stroke

Row	Study PMID	Supplement	Adjustments	Quantile	n3 units	Quantile low	Quantile median
28	Bell 2014 24496442	yes	age (as the time scale), sex, race/ethnicity, marital status (married/living together, never married, separated/divorced, widowed, or missing), education (high school graduate or less, some college, or college/advanced degree), total energy intake (kcal/day; continuous), body mass index (weight (kg)/height (m)2 (none, <1 drink/day, 1–2 drinks/day, >2 drinks/day, or missing), average physical activity in the 10 years before baseline (MET-hours/week; tertiles), self-rated health (excellent, very good, good, fair, or poor), mammogram in the last 2 years (yes/no), prostate-specific antigen test in the last 2 years (yes/no), sigmoidoscopy in the last 10 years (yes/no), current use of cholesterol-lowering medication (yes/no), aspirin use in the past 10 years (none, low, high, or missing), use of nonaspirin nonsteroidal antiinflammatory drugs in the past 10 years (none, low, high, or missing), smoking (never, 1–12.5 pack-years, 12.6–35.0 pack-years, or >35.0 pack-years), morbidity score,c percentage of calories derived from trans fat (quartiles), percentage of calories derived from saturated fat (quartiles), number of servings per day of fruits (quartiles), number of servings per day of vegetables (quartiles), years of estrogen therapy (none, <5, 5–9, ≥10, or missing), years of estrogen + progestin therapy (none, <5, 5–9, ≥10, or missing), age at menopause (≤39 years, 40–44 years, 45–49 years, 50–54 years, ≥55 years, or missing), age at death of father (≤59 years, 60–69 years, 70–79 years, 80–89 years, or ≥90 years), and age at death of mother (≤59 years, 60–69 years, 70–79 years, 80–89 years, or ≥90 years)	Qr1	g/day	0	nd
29	Bell 2014 24496442	yes	age (as the time scale), sex, race/ethnicity, marital status (married/living together, never married, separated/divorced, widowed, or missing), education (high school graduate or less, some college, or college/advanced degree), total energy intake (kcal/day; continuous), body mass index (weight (kg)/height (m)2 (none, <1 drink/day, 1–2 drinks/day, >2 drinks/day, or missing), average physical activity in the 10 years before baseline (MET-hours/week; tertiles), self-rated health (excellent, very good, good, fair, or poor), mammogram in the last 2 years (yes/no), prostate-specific antigen test in the last 2 years (yes/no), sigmoidoscopy in the last 10 years (yes/no), current use of cholesterol-lowering medication (yes/no), aspirin use in the past 10 years (none, low, high, or missing), use of nonaspirin nonsteroidal antiinflammatory drugs in the past 10 years (none, low, high, or missing), smoking (never, 1–12.5 pack-years, 12.6–35.0 pack-years, or >35.0 pack-years), morbidity score,c percentage of calories derived from trans fat (quartiles), percentage of calories derived from saturated fat (quartiles), number of servings per day of fruits (quartiles), number of servings per day of vegetables (quartiles), years of estrogen therapy (none, <5, 5–9, ≥10, or missing), years of estrogen + progestin therapy (none, <5, 5–9, ≥10, or missing), age at menopause (≤39 years, 40–44 years, 45–49 years, 50–54 years, ≥55 years, or missing), age at death of father (≤59 years, 60–69 years, 70–79 years, 80–89 years, or ≥90 years), and age at death of mother (≤59 years, 60–69 years, 70–79 years, 80–89 years, or ≥90 years)	Qr2	g/day	0.082	nd
30	Bell 2014 24496442	yes	age (as the time scale), sex, race/ethnicity, marital status (married/living together, never married, separated/divorced, widowed, or missing), education (high school graduate or less, some college, or college/advanced degree), total energy intake (kcal/day; continuous), body mass index (weight (kg)/height (m)2 (none, <1 drink/day, 1–2 drinks/day, >2 drinks/day, or missing), average physical activity in the 10 years before baseline (MET-hours/week; tertiles), self-rated health (excellent, very good, good, fair, or poor), mammogram in the last 2 years (yes/no), prostate-specific antigen test in the last 2 years (yes/no), sigmoidoscopy in the last 10 years (yes/no), current use of cholesterol-lowering medication (yes/no), aspirin use in the past 10 years (none, low, high, or missing), use of nonaspirin nonsteroidal antiinflammatory drugs in the past 10 years (none, low, high, or missing), smoking (never, 1–12.5 pack-years, 12.6–35.0 pack-years, or >35.0 pack-years), morbidity score,c percentage of calories derived from trans fat (quartiles), percentage of calories derived from saturated fat (quartiles), number of servings per day of fruits (quartiles), number of servings per day of vegetables (quartiles), years of estrogen therapy (none, <5, 5–9, ≥10, or missing), years of estrogen + progestin therapy (none, <5, 5–9, ≥10, or missing), age at menopause (≤39 years, 40–44 years, 45–49 years, 50–54 years, ≥55 years, or missing), age at death of father (≤59 years, 60–69 years, 70–79 years, 80–89 years, or ≥90 years), and age at death of mother (≤59 years, 60–69 years, 70–79 years, 80–89 years, or ≥90 years)	Qr3	g/day	0.174	nd
31	Bell 2014 24496442	yes	age (as the time scale), sex, race/ethnicity, marital status (married/living together, never married, separated/divorced, widowed, or missing), education (high school graduate or less, some college, or college/advanced degree), total energy intake (kcal/day; continuous), body mass index (weight (kg)/height (m)2 (none, <1 drink/day, 1–2 drinks/day, >2 drinks/day, or missing), average physical activity in the 10 years before baseline (MET-hours/week; tertiles), self-rated health (excellent, very good, good, fair, or poor), mammogram in the last 2 years (yes/no), prostate-specific antigen test in the last 2 years (yes/no), sigmoidoscopy in the last 10 years (yes/no), current use of cholesterol-lowering medication (yes/no), aspirin use in the past 10 years (none, low, high, or missing), use of nonaspirin nonsteroidal antiinflammatory drugs in the past 10 years (none, low, high, or missing), smoking (never, 1–12.5 pack-years, 12.6–35.0 pack-years, or >35.0 pack-years), morbidity score,c percentage of calories derived from trans fat (quartiles), percentage of calories derived from saturated fat (quartiles), number of servings per day of fruits (quartiles), number of servings per day of vegetables (quartiles), years of estrogen therapy (none, <5, 5–9, ≥10, or missing), years of estrogen + progestin therapy (none, <5, 5–9, ≥10, or missing), age at menopause (≤39 years, 40–44 years, 45–49 years, 50–54 years, ≥55 years, or missing), age at death of father (≤59 years, 60–69 years, 70–79 years, 80–89 years, or ≥90 years), and age at death of mother (≤59 years, 60–69 years, 70–79 years, 80–89 years, or ≥90 years)	Qr4	g/day	0.322	nd

Appendix F
Observational results: death from ischemic stroke

Row	Study PMID	Quantile high	Metric	n Cases	N quantile	Person Years	Estimate	CI low	CI high	Comparison	P value
28	Bell 2014 24496442	0.082	HR	76	nd	nd	1	nd	nd		0.029
29	Bell 2014 24496442	0.174	HR	60	17485	nd	0.87	0.6	1.26		
30	Bell 2014 24496442	0.322	HR	49	17601	nd	0.71	0.47	1.08		
31	Bell 2014 24496442	nd	HR	48	17498	nd	0.62	0.39	0.99		

Appendix F

Observational results: blood pressure

Row	Study PMID	Study Name	Outcome	Outcome Definition	Population Type	Cases Total/N Total (Rate %)	Followup	n3 FA
2	Zeng 2014 24966412	Guangzhou	bp_SBP	Systolic Blood Pressure	Healthy men and women aged 40-75	na/1477	3 y	ALA
3	Zeng 2014 24966412	Guangzhou	bp_SBP	Systolic Blood Pressure	Healthy men and women aged 40-75	na/1477	3 y	ALA
4	Zeng 2014 24966412	Guangzhou	bp_SBP	Systolic Blood Pressure	Healthy men and women aged 40-75	na/1477	3 y	ALA
5	Zeng 2014 24966412	Guangzhou	bp_SBP	Systolic Blood Pressure	Healthy men and women aged 40-75	na/1477	3 y	ALA
6	Zeng 2014 24966412	Guangzhou	bp_SBP	Systolic Blood Pressure	Healthy men and women aged 40-75	na/1477	3 y	EPA
7	Zeng 2014 24966412	Guangzhou	bp_SBP	Systolic Blood Pressure	Healthy men and women aged 40-75	na/1477	3 y	EPA
8	Zeng 2014 24966412	Guangzhou	bp_SBP	Systolic Blood Pressure	Healthy men and women aged 40-75	na/1477	3 y	EPA
9	Zeng 2014 24966412	Guangzhou	bp_SBP	Systolic Blood Pressure	Healthy men and women aged 40-75	na/1477	3 y	EPA
10	Zeng 2014 24966412	Guangzhou	bp_SBP	Systolic Blood Pressure	Healthy men and women aged 40-75	na/1477	3 y	DPA
11	Zeng 2014 24966412	Guangzhou	bp_SBP	Systolic Blood Pressure	Healthy men and women aged 40-75	na/1477	3 y	DPA
12	Zeng 2014 24966412	Guangzhou	bp_SBP	Systolic Blood Pressure	Healthy men and women aged 40-75	na/1477	3 y	DPA
13	Zeng 2014 24966412	Guangzhou	bp_SBP	Systolic Blood Pressure	Healthy men and women aged 40-75	na/1477	3 y	DPA

Appendix F

Observational results: blood pressure

n3 measure	Supplement	Adjustments	Quantile	n3 units	Quantile low	Quantile median	Quantile high	Metric
Biomarker	no	age, gender, marital status, household income, education, smoking, alcohol, tea drinking, physical activity, dietary intake of energy, fat, protein, and fiber	Qr1	% FA	nd	nd	nd	Change
Biomarker	no	age, gender, marital status, household income, education, smoking, alcohol, tea drinking, physical activity, dietary intake of energy, fat, protein, and fiber	Qr2	% FA	nd	nd	nd	Change
Biomarker	no	age, gender, marital status, household income, education, smoking, alcohol, tea drinking, physical activity, dietary intake of energy, fat, protein, and fiber	Qr3	% FA	nd	nd	nd	Change
Biomarker	no	age, gender, marital status, household income, education, smoking, alcohol, tea drinking, physical activity, dietary intake of energy, fat, protein, and fiber	Qr4	% FA	nd	nd	nd	Change
Biomarker	no	age, gender, marital status, household income, education, smoking, alcohol, tea drinking, physical activity, dietary intake of energy, fat, protein, and fiber	Qr1	% FA	nd	nd	nd	Change
Biomarker	no	age, gender, marital status, household income, education, smoking, alcohol, tea drinking, physical activity, dietary intake of energy, fat, protein, and fiber	Qr2	% FA	nd	nd	nd	Change
Biomarker	no	age, gender, marital status, household income, education, smoking, alcohol, tea drinking, physical activity, dietary intake of energy, fat, protein, and fiber	Qr3	% FA	nd	nd	nd	Change
Biomarker	no	age, gender, marital status, household income, education, smoking, alcohol, tea drinking, physical activity, dietary intake of energy, fat, protein, and fiber	Qr4	% FA	nd	nd	nd	Change
Biomarker	no	age, gender, marital status, household income, education, smoking, alcohol, tea drinking, physical activity, dietary intake of energy, fat, protein, and fiber	Qr1	% FA	nd	nd	nd	Change
Biomarker	no	age, gender, marital status, household income, education, smoking, alcohol, tea drinking, physical activity, dietary intake of energy, fat, protein, and fiber	Qr2	% FA	nd	nd	nd	Change
Biomarker	no	age, gender, marital status, household income, education, smoking, alcohol, tea drinking, physical activity, dietary intake of energy, fat, protein, and fiber	Qr3	% FA	nd	nd	nd	Change
Biomarker	no	age, gender, marital status, household income, education, smoking, alcohol, tea drinking, physical activity, dietary intake of energy, fat, protein, and fiber	Qr4	% FA	nd	nd	nd	Change

Appendix F
Observational results: blood pressure

n Cases	N quantile	Person Years	Estimate	SE	CI low	CI high	Comparison	P value
na	368	nd	0.286	0.23	nd	nd	nd	0.26
na	371	nd	0.508	0.226	nd	nd	nd	
na	370	nd	0.381	0.237	nd	nd	nd	
na	368	nd	0.721	0.24	nd	nd	nd	
na	368	nd	0.89	0.234	nd	nd	nd	0.004
na	371	nd	0.685	0.238	nd	nd	nd	
na	370	nd	0.349	0.23	nd	nd	nd	
na	368	nd	-0.015	0.235	nd	nd	nd	
na	368	nd	0.95	0.233	nd	nd	nd	0.004
na	371	nd	0.596	0.233	nd	nd	nd	
na	370	nd	0.306	0.23	nd	nd	nd	
na	368	nd	0.033	0.235	nd	nd	nd	

Appendix F
Observational results: blood pressure

14	Zeng 2014 24966412	Guangzhou	bp_SBP	Systolic Blood Pressure	Healthy men and women aged 40-75	na/1477	3 y	DHA
15	Zeng 2014 24966412	Guangzhou	bp_SBP	Systolic Blood Pressure	Healthy men and women aged 40-75	na/1477	3 y	DHA
16	Zeng 2014 24966412	Guangzhou	bp_SBP	Systolic Blood Pressure	Healthy men and women aged 40-75	na/1477	3 y	DHA
17	Zeng 2014 24966412	Guangzhou	bp_SBP	Systolic Blood Pressure	Healthy men and women aged 40-75	na/1477	3 y	DHA
20	Zeng 2014 24966412	Guangzhou	bp_DBP	Diastolic Blood Pressure	Healthy men and women aged 40-75	na/1477	3 y	ALA
21	Zeng 2014 24966412	Guangzhou	bp_DBP	Diastolic Blood Pressure	Healthy men and women aged 40-75	na/1477	3 y	ALA
22	Zeng 2014 24966412	Guangzhou	bp_DBP	Diastolic Blood Pressure	Healthy men and women aged 40-75	na/1477	3 y	ALA
23	Zeng 2014 24966412	Guangzhou	bp_DBP	Diastolic Blood Pressure	Healthy men and women aged 40-75	na/1477	3 y	ALA
24	Zeng 2014 24966412	Guangzhou	bp_DBP	Diastolic Blood Pressure	Healthy men and women aged 40-75	na/1477	3 y	EPA
25	Zeng 2014 24966412	Guangzhou	bp_DBP	Diastolic Blood Pressure	Healthy men and women aged 40-75	na/1477	3 y	EPA
26	Zeng 2014 24966412	Guangzhou	bp_DBP	Diastolic Blood Pressure	Healthy men and women aged 40-75	na/1477	3 y	EPA
27	Zeng 2014 24966412	Guangzhou	bp_DBP	Diastolic Blood Pressure	Healthy men and women aged 40-75	na/1477	3 y	EPA

Appendix F

Observational results: blood pressure

Biomarker	no	age, gender, marital status, household income, education, smoking, alcohol, tea drinking, physical activity, dietary intake of energy, fat, protein, and fiber	Qr1	% FA	nd	nd	nd	Change
Biomarker	no	age, gender, marital status, household income, education, smoking, alcohol, tea drinking, physical activity, dietary intake of energy, fat, protein, and fiber	Qr2	% FA	nd	nd	nd	Change
Biomarker	no	age, gender, marital status, household income, education, smoking, alcohol, tea drinking, physical activity, dietary intake of energy, fat, protein, and fiber	Qr3	% FA	nd	nd	nd	Change
Biomarker	no	age, gender, marital status, household income, education, smoking, alcohol, tea drinking, physical activity, dietary intake of energy, fat, protein, and fiber	Qr4	% FA	nd	nd	nd	Change
Biomarker	no	age, gender, marital status, household income, education, smoking, alcohol, tea drinking, physical activity, dietary intake of energy, fat, protein, and fiber	Qr1	% FA	nd	nd	nd	Change
Biomarker	no	age, gender, marital status, household income, education, smoking, alcohol, tea drinking, physical activity, dietary intake of energy, fat, protein, and fiber	Qr2	% FA	nd	nd	nd	Change
Biomarker	no	age, gender, marital status, household income, education, smoking, alcohol, tea drinking, physical activity, dietary intake of energy, fat, protein, and fiber	Qr3	% FA	nd	nd	nd	Change
Biomarker	no	age, gender, marital status, household income, education, smoking, alcohol, tea drinking, physical activity, dietary intake of energy, fat, protein, and fiber	Qr4	% FA	nd	nd	nd	Change
Biomarker	no	age, gender, marital status, household income, education, smoking, alcohol, tea drinking, physical activity, dietary intake of energy, fat, protein, and fiber	Qr1	% FA	nd	nd	nd	Change
Biomarker	no	age, gender, marital status, household income, education, smoking, alcohol, tea drinking, physical activity, dietary intake of energy, fat, protein, and fiber	Qr2	% FA	nd	nd	nd	Change
Biomarker	no	age, gender, marital status, household income, education, smoking, alcohol, tea drinking, physical activity, dietary intake of energy, fat, protein, and fiber	Qr3	% FA	nd	nd	nd	Change
Biomarker	no	age, gender, marital status, household income, education, smoking, alcohol, tea drinking, physical activity, dietary intake of energy, fat, protein, and fiber	Qr4	% FA	nd	nd	nd	Change

Appendix F
Observational results: blood pressure

na	368	nd	0.919	0.237	nd	nd	nd	0.005
na	371	nd	0.759	0.234	nd	nd	nd	
na	370	nd	0.066	0.234	nd	nd	nd	
na	368	nd	0.17	0.229	nd	nd	nd	
na	368	nd	-0.803	0.14	nd	nd	nd	0.18
na	371	nd	-0.586	0.138	nd	nd	nd	
na	370	nd	-0.647	0.145	nd	nd	nd	
na	368	nd	-0.495	0.146	nd	nd	nd	
na	368	nd	-0.388	0.142	nd	nd	nd	<0.001
na	371	nd	-0.29	0.14	nd	nd	nd	
na	370	nd	-0.854	0.142	nd	nd	nd	
na	368	nd	-1.019	0.142	nd	nd	nd	

Observational results: blood pressure

28	Zeng 2014 24966412	Guangzhou	bp_DBP	Diastolic Blood Pressure	Healthy men and women aged 40-75	na/1477	3 y	DPA
29	Zeng 2014 24966412	Guangzhou	bp_DBP	Diastolic Blood Pressure	Healthy men and women aged 40-75	na/1477	3 y	DPA
30	Zeng 2014 24966412	Guangzhou	bp_DBP	Diastolic Blood Pressure	Healthy men and women aged 40-75	na/1477	3 y	DPA
31	Zeng 2014 24966412	Guangzhou	bp_DBP	Diastolic Blood Pressure	Healthy men and women aged 40-75	na/1477	3 y	DPA
32	Zeng 2014 24966412	Guangzhou	bp_DBP	Diastolic Blood Pressure	Healthy men and women aged 40-75	na/1477	3 y	DHA
33	Zeng 2014 24966412	Guangzhou	bp_DBP	Diastolic Blood Pressure	Healthy men and women aged 40-75	na/1477	3 y	DHA
34	Zeng 2014 24966412	Guangzhou	bp_DBP	Diastolic Blood Pressure	Healthy men and women aged 40-75	na/1477	3 y	DHA
35	Zeng 2014 24966412	Guangzhou	bp_DBP	Diastolic Blood Pressure	Healthy men and women aged 40-75	na/1477	3 y	DHA

Appendix F
Observational results: blood pressure

Biomarker	no	age, gender, marital status, household income, education, smoking, alcohol, tea drinking, physical activity, dietary intake of energy, fat, protein, and fiber	Qr1	% FA	nd	nd	nd	Change
Biomarker	no	age, gender, marital status, household income, education, smoking, alcohol, tea drinking, physical activity, dietary intake of energy, fat, protein, and fiber	Qr2	% FA	nd	nd	nd	Change
Biomarker	no	age, gender, marital status, household income, education, smoking, alcohol, tea drinking, physical activity, dietary intake of energy, fat, protein, and fiber	Qr3	% FA	nd	nd	nd	Change
Biomarker	no	age, gender, marital status, household income, education, smoking, alcohol, tea drinking, physical activity, dietary intake of energy, fat, protein, and fiber	Qr4	% FA	nd	nd	nd	Change
Biomarker	no	age, gender, marital status, household income, education, smoking, alcohol, tea drinking, physical activity, dietary intake of energy, fat, protein, and fiber	Qr1	% FA	nd	nd	nd	Change
Biomarker	no	age, gender, marital status, household income, education, smoking, alcohol, tea drinking, physical activity, dietary intake of energy, fat, protein, and fiber	Qr2	% FA	nd	nd	nd	Change
Biomarker	no	age, gender, marital status, household income, education, smoking, alcohol, tea drinking, physical activity, dietary intake of energy, fat, protein, and fiber	Qr3	% FA	nd	nd	nd	Change
Biomarker	no	age, gender, marital status, household income, education, smoking, alcohol, tea drinking, physical activity, dietary intake of energy, fat, protein, and fiber	Qr4	% FA	nd	nd	nd	Change

Appendix F
Observational results: blood pressure

na	368	nd	-0.507	0.142	nd	nd	nd	0.044
na	371	nd	-0.54	0.143	nd	nd	nd	
na	370	nd	-0.576	0.14	nd	nd	nd	
na	368	nd	-0.923	0.143	nd	nd	nd	
na	368	nd	-0.504	0.144	nd	nd	nd	0.017
na	371	nd	-0.27	0.142	nd	nd	nd	
na	370	nd	-0.979	0.143	nd	nd	nd	
na	368	nd	-0.777	0.14	nd	nd	nd	

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Study years (study start date)	Country
1	Alpha-Tocopherol, Beta-Carotene Cancer Prevention	1985	Finland
2	Alpha-Tocopherol, Beta-Carotene Cancer Prevention	1985	Finland
3	Alpha-Tocopherol, Beta-Carotene Cancer Prevention	1985	Finland
4	Alpha-Tocopherol, Beta-Carotene Cancer Prevention	1985	Finland
5	CARDIA	1985	US
6	CARDIA	1985	US
7	CARDIA	1985	US
8	Cardiovascular Health Study	1989	US
9	Cardiovascular Health Study	1989	US
10	Cardiovascular Health Study	1989	US
11	Cardiovascular Health Study	1989	US
12	Cardiovascular Health Study	1989	US
13	Cardiovascular Health Study	1989	US
14	Cardiovascular Health Study	1989	US
15	Cardiovascular Health Study	1989	US
16	Cardiovascular Health Study	1989	US
17	Cardiovascular Health Study	1989	US
18	Cardiovascular Health Study	1989	US
19	Cardiovascular Health Study	1989	US
20	Cardiovascular Health Study	1989	US
21	Cardiovascular Health Study	1989	US
22	Cardiovascular Health Study	1989	US
23	Cardiovascular Health Study	1989	US
24	Cardiovascular Health Study	1989	US
25	Cardiovascular Health Study	1989	US
26	Cardiovascular Health Study	1989	US
27	Cardiovascular Health Study	1989	US
28	Cardiovascular Health Study	1989	US

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Population	Risk type
1	Alpha-Tocopherol, Beta-Carotene Cancer Prevention	Primary Prevention, Healthy	na
2	Alpha-Tocopherol, Beta-Carotene Cancer Prevention	Primary Prevention, Healthy	na
3	Alpha-Tocopherol, Beta-Carotene Cancer Prevention	Primary Prevention, Healthy	na
4	Alpha-Tocopherol, Beta-Carotene Cancer Prevention	Primary Prevention, Healthy	na
5	CARDIA	Primary Prevention, Healthy	na
6	CARDIA	Primary Prevention, Healthy	na
7	CARDIA	Primary Prevention, Healthy	na
8	Cardiovascular Health Study	Primary Prevention, Healthy	na
9	Cardiovascular Health Study	Primary Prevention, Healthy	na
10	Cardiovascular Health Study	Primary Prevention, Healthy	na
11	Cardiovascular Health Study	Primary Prevention, Healthy	na
12	Cardiovascular Health Study	Primary Prevention, Healthy	na
13	Cardiovascular Health Study	Primary Prevention, Healthy	na
14	Cardiovascular Health Study	Primary Prevention, Healthy	na
15	Cardiovascular Health Study	Primary Prevention, Healthy	na
16	Cardiovascular Health Study	Primary Prevention, Healthy	na
17	Cardiovascular Health Study	Primary Prevention, Healthy	na
18	Cardiovascular Health Study	Primary Prevention, Healthy	na
19	Cardiovascular Health Study	Primary Prevention, Healthy	na
20	Cardiovascular Health Study	Primary Prevention, Healthy	na
21	Cardiovascular Health Study	Primary Prevention, Healthy	na
22	Cardiovascular Health Study	Primary Prevention, Healthy	na
23	Cardiovascular Health Study	Primary Prevention, Healthy	na
24	Cardiovascular Health Study	Primary Prevention, Healthy	na
25	Cardiovascular Health Study	Primary Prevention, Healthy	na
26	Cardiovascular Health Study	Primary Prevention, Healthy	na
27	Cardiovascular Health Study	Primary Prevention, Healthy	na
28	Cardiovascular Health Study	Primary Prevention, Healthy	na

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Sample size (total)	Age mean (SD) [median]	Sex (% male)
1	Alpha-Tocopherol, Beta-Carotene Cancer Prevention	21930	range 50, 69	100
2	Alpha-Tocopherol, Beta-Carotene Cancer Prevention	21930	range 50, 69	100
3	Alpha-Tocopherol, Beta-Carotene Cancer Prevention	21930	range 50, 69	100
4	Alpha-Tocopherol, Beta-Carotene Cancer Prevention	21930	range 50, 69	100
5	CARDIA	4508	24.9 (3.7)	46.9
6	CARDIA	4508	24.9 (3.7)	46.9
7	CARDIA	4508	24.9 (3.7)	46.9
8	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
9	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
10	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
11	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
12	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
13	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
14	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
15	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
16	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
17	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
18	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
19	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
20	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
21	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
22	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
23	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
24	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
25	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
26	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
27	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
28	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Race	Blood pressure SBP/DBP (mmHg)
1	Alpha-Tocopherol, Beta-Carotene Cancer Prevention	nd	nd
2	Alpha-Tocopherol, Beta-Carotene Cancer Prevention	nd	nd
3	Alpha-Tocopherol, Beta-Carotene Cancer Prevention	nd	nd
4	Alpha-Tocopherol, Beta-Carotene Cancer Prevention	nd	nd
5	CARDIA	50.6 black	110 (10.2)/68.3 (8.8)
6	CARDIA	50.6 black	110 (10.2)/68.3 (8.8)
7	CARDIA	50.6 black	110 (10.2)/68.3 (8.8)
8	Cardiovascular Health Study	87.8 white, 11.7 black	nd
9	Cardiovascular Health Study	87.8 white, 11.7 black	nd
10	Cardiovascular Health Study	87.8 white, 11.7 black	nd
11	Cardiovascular Health Study	87.8 white, 11.7 black	nd
12	Cardiovascular Health Study	87.8 white, 11.7 black	nd
13	Cardiovascular Health Study	87.8 white, 11.7 black	nd
14	Cardiovascular Health Study	87.8 white, 11.7 black	nd
15	Cardiovascular Health Study	87.8 white, 11.7 black	nd
16	Cardiovascular Health Study	87.8 white, 11.7 black	nd
17	Cardiovascular Health Study	87.8 white, 11.7 black	nd
18	Cardiovascular Health Study	87.8 white, 11.7 black	nd
19	Cardiovascular Health Study	87.8 white, 11.7 black	nd
20	Cardiovascular Health Study	87.8 white, 11.7 black	nd
21	Cardiovascular Health Study	87.8 white, 11.7 black	nd
22	Cardiovascular Health Study	87.8 white, 11.7 black	nd
23	Cardiovascular Health Study	87.8 white, 11.7 black	nd
24	Cardiovascular Health Study	87.8 white, 11.7 black	nd
25	Cardiovascular Health Study	87.8 white, 11.7 black	nd
26	Cardiovascular Health Study	87.8 white, 11.7 black	nd
27	Cardiovascular Health Study	87.8 white, 11.7 black	nd
28	Cardiovascular Health Study	87.8 white, 11.7 black	nd

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Lipids: Total cholesterol/LDL/HDL/Triglycerides mean (SD) mg/dL [mmol/L]
1	Alpha-Tocopherol, Beta-Carotene Cancer Prevention	nd
2	Alpha-Tocopherol, Beta-Carotene Cancer Prevention	nd
3	Alpha-Tocopherol, Beta-Carotene Cancer Prevention	nd
4	Alpha-Tocopherol, Beta-Carotene Cancer Prevention	nd
5	CARDIA	nd
6	CARDIA	nd
7	CARDIA	nd
8	Cardiovascular Health Study	nd
9	Cardiovascular Health Study	nd
10	Cardiovascular Health Study	nd
11	Cardiovascular Health Study	nd
12	Cardiovascular Health Study	nd
13	Cardiovascular Health Study	nd
14	Cardiovascular Health Study	nd
15	Cardiovascular Health Study	nd
16	Cardiovascular Health Study	nd
17	Cardiovascular Health Study	nd
18	Cardiovascular Health Study	nd
19	Cardiovascular Health Study	nd
20	Cardiovascular Health Study	nd
21	Cardiovascular Health Study	nd
22	Cardiovascular Health Study	nd
23	Cardiovascular Health Study	nd
24	Cardiovascular Health Study	nd
25	Cardiovascular Health Study	nd
26	Cardiovascular Health Study	nd
27	Cardiovascular Health Study	nd
28	Cardiovascular Health Study	nd

Appendix G.2.
Causality Table: Observational Studies

Row	Study	BMI mean (SD)/weight mean (SD) Kg
1	Alpha-Tocopherol, Beta-Carotene Cancer Prevention	nd
2	Alpha-Tocopherol, Beta-Carotene Cancer Prevention	nd
3	Alpha-Tocopherol, Beta-Carotene Cancer Prevention	nd
4	Alpha-Tocopherol, Beta-Carotene Cancer Prevention	nd
5	CARDIA	24.4 (4.9)
6	CARDIA	24.4 (4.9)
7	CARDIA	24.4 (4.9)
8	Cardiovascular Health Study	nd
9	Cardiovascular Health Study	nd
10	Cardiovascular Health Study	nd
11	Cardiovascular Health Study	nd
12	Cardiovascular Health Study	nd
13	Cardiovascular Health Study	nd
14	Cardiovascular Health Study	nd
15	Cardiovascular Health Study	nd
16	Cardiovascular Health Study	nd
17	Cardiovascular Health Study	nd
18	Cardiovascular Health Study	nd
19	Cardiovascular Health Study	nd
20	Cardiovascular Health Study	nd
21	Cardiovascular Health Study	nd
22	Cardiovascular Health Study	nd
23	Cardiovascular Health Study	nd
24	Cardiovascular Health Study	nd
25	Cardiovascular Health Study	nd
26	Cardiovascular Health Study	nd
27	Cardiovascular Health Study	nd
28	Cardiovascular Health Study	nd

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Baseline n-3 intake/level (median (IQR), unless noted)
1	Alpha-Tocopherol, Beta-Carotene Cancer Prevention	ALA: 1.5 g/d, EPA+DHA+DPA: 0.4 g/d
2	Alpha-Tocopherol, Beta-Carotene Cancer Prevention	ALA: 1.5 g/d, EPA+DHA+DPA: 0.4 g/d
3	Alpha-Tocopherol, Beta-Carotene Cancer Prevention	ALA: 1.5 g/d, EPA+DHA+DPA: 0.4 g/d
4	Alpha-Tocopherol, Beta-Carotene Cancer Prevention	ALA: 1.5 g/d, EPA+DHA+DPA: 0.4 g/d
5	CARDIA	EPA+DHA+DPA: 0.114 g/d
6	CARDIA	EPA+DHA+DPA: 0.114 g/d
7	CARDIA	EPA+DHA+DPA: 0.114 g/d
8	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
9	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
10	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
11	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
12	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
13	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
14	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
15	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
16	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
17	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
18	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
19	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
20	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
21	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
22	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
23	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
24	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
25	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
26	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
27	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
28	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA

Appendix G.2.
Causality Table: Observational Studies

Row	Study	n-3 source	n-3 measure	n-3 type(s)
1	Alpha-Tocopherol, Beta-Carotene Cancer Prevention	intake	g/d	ALA
2	Alpha-Tocopherol, Beta-Carotene Cancer Prevention	intake	g/d	EPA+DHA+DPA
3	Alpha-Tocopherol, Beta-Carotene Cancer Prevention	intake	g/d	ALA
4	Alpha-Tocopherol, Beta-Carotene Cancer Prevention	intake	g/d	EPA+DHA+DPA
5	CARDIA	intake	g/d	EPA + DHA + DPA
6	CARDIA	intake	g/d	EPA
7	CARDIA	intake	g/d	DHA
8	Cardiovascular Health Study	plasma	% of total plasma phospholipid fatty acids	ALA
9	Cardiovascular Health Study	intake	% of total fat intake	ALA
10	Cardiovascular Health Study	plasma	% of total plasma phospholipid fatty acids	EPA
11	Cardiovascular Health Study	plasma	% of total plasma phospholipid fatty acids	DPA
12	Cardiovascular Health Study	plasma	% of total plasma phospholipid fatty acids	DHA
13	Cardiovascular Health Study	plasma	% of total plasma phospholipid fatty acids	ALA
14	Cardiovascular Health Study	intake	% of total fat intake	ALA
15	Cardiovascular Health Study	plasma	% of total plasma phospholipid fatty acids	EPA
16	Cardiovascular Health Study	plasma	% of total plasma phospholipid fatty acids	DPA
17	Cardiovascular Health Study	plasma	% of total plasma phospholipid fatty acids	All n-3
18	Cardiovascular Health Study	plasma	% of total plasma phospholipid fatty acids	ALA
19	Cardiovascular Health Study	intake	% of total fat intake	ALA
20	Cardiovascular Health Study	plasma	% of total plasma phospholipid fatty acids	EPA
21	Cardiovascular Health Study	plasma	% of total plasma phospholipid fatty acids	DPA
22	Cardiovascular Health Study	plasma	% of total plasma phospholipid fatty acids	DHA
23	Cardiovascular Health Study	plasma	% of total plasma phospholipid fatty acids	All n-3
24	Cardiovascular Health Study	plasma	% of total plasma phospholipid fatty acids	ALA
25	Cardiovascular Health Study	intake	% of total fat intake	ALA
26	Cardiovascular Health Study	plasma	% of total plasma phospholipid fatty acids	EPA
27	Cardiovascular Health Study	plasma	% of total plasma phospholipid fatty acids	DPA
28	Cardiovascular Health Study	plasma	% of total plasma phospholipid fatty acids	DHA

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Study design
1	Alpha-Tocopherol, Beta-Carotene Cancer Prevention	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
2	Alpha-Tocopherol, Beta-Carotene Cancer Prevention	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
3	Alpha-Tocopherol, Beta-Carotene Cancer Prevention	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
4	Alpha-Tocopherol, Beta-Carotene Cancer Prevention	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
5	CARDIA	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
6	CARDIA	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
7	CARDIA	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
8	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
9	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
10	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
11	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
12	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
13	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
14	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
15	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
16	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
17	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
18	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
19	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
20	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
21	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
22	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
23	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
24	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
25	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
26	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
27	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
28	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Outcome	Reported effect Size
1	Alpha-Tocopherol, Beta-Carotene Cancer Prevention	Death, cardiac	See appendix F
2	Alpha-Tocopherol, Beta-Carotene Cancer Prevention	Death, cardiac	See appendix F
3	Alpha-Tocopherol, Beta-Carotene Cancer Prevention	Death, CHD	See appendix F
4	Alpha-Tocopherol, Beta-Carotene Cancer Prevention	Death, CHD	See appendix F
5	CARDIA	Hypertension	See appendix F
6	CARDIA	Hypertension	See appendix F
7	CARDIA	Hypertension	See appendix F
8	Cardiovascular Health Study	Atrial fibrillation	See appendix F
9	Cardiovascular Health Study	Atrial fibrillation	See appendix F
10	Cardiovascular Health Study	Atrial fibrillation	See appendix F
11	Cardiovascular Health Study	Atrial fibrillation	See appendix F
12	Cardiovascular Health Study	Atrial fibrillation	See appendix F
13	Cardiovascular Health Study	Congestive heart failure	See appendix F
14	Cardiovascular Health Study	Congestive heart failure	See appendix F
15	Cardiovascular Health Study	Congestive heart failure	See appendix F
16	Cardiovascular Health Study	Congestive heart failure	See appendix F
17	Cardiovascular Health Study	Congestive heart failure	See appendix F
18	Cardiovascular Health Study	Coronary heart disease	See appendix F
19	Cardiovascular Health Study	Coronary heart disease	See appendix F
20	Cardiovascular Health Study	Coronary heart disease	See appendix F
21	Cardiovascular Health Study	Coronary heart disease	See appendix F
22	Cardiovascular Health Study	Coronary heart disease	See appendix F
23	Cardiovascular Health Study	Coronary heart disease	See appendix F
24	Cardiovascular Health Study	Death, all cause	See appendix F
25	Cardiovascular Health Study	Death, all cause	See appendix F
26	Cardiovascular Health Study	Death, all cause	See appendix F
27	Cardiovascular Health Study	Death, all cause	See appendix F
28	Cardiovascular Health Study	Death, all cause	See appendix F

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Study years (study start date)	Country
29	Cardiovascular Health Study	1989	US
30	Cardiovascular Health Study	1989	US
31	Cardiovascular Health Study	1989	US
32	Cardiovascular Health Study	1989	US
33	Cardiovascular Health Study	1989	US
34	Cardiovascular Health Study	1989	US
35	Cardiovascular Health Study	1989	US
36	Cardiovascular Health Study	1989	US
37	Cardiovascular Health Study	1989	US
38	Cardiovascular Health Study	1989	US
39	Cardiovascular Health Study	1989	US
40	Cardiovascular Health Study	1989	US
41	Cardiovascular Health Study	1989	US
42	Cardiovascular Health Study	1989	US
43	Cardiovascular Health Study	1989	US
44	Cardiovascular Health Study	1989	US
45	Cardiovascular Health Study	1989	US
46	Cardiovascular Health Study	1989	US
47	Cardiovascular Health Study	1989	US
48	Cardiovascular Health Study	1989	US
49	Cardiovascular Health Study	1989	US
50	Cardiovascular Health Study	1989	US
51	Cardiovascular Health Study	1989	US
52	Cardiovascular Health Study	1989	US
53	Cardiovascular Health Study	1989	US

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Population	Risk type
29	Cardiovascular Health Study	Primary Prevention, Healthy	na
30	Cardiovascular Health Study	Primary Prevention, Healthy	na
31	Cardiovascular Health Study	Primary Prevention, Healthy	na
32	Cardiovascular Health Study	Primary Prevention, Healthy	na
33	Cardiovascular Health Study	Primary Prevention, Healthy	na
34	Cardiovascular Health Study	Primary Prevention, Healthy	na
35	Cardiovascular Health Study	Primary Prevention, Healthy	na
36	Cardiovascular Health Study	Primary Prevention, Healthy	na
37	Cardiovascular Health Study	Primary Prevention, Healthy	na
38	Cardiovascular Health Study	Primary Prevention, Healthy	na
39	Cardiovascular Health Study	Primary Prevention, Healthy	na
40	Cardiovascular Health Study	Primary Prevention, Healthy	na
41	Cardiovascular Health Study	Primary Prevention, Healthy	na
42	Cardiovascular Health Study	Primary Prevention, Healthy	na
43	Cardiovascular Health Study	Primary Prevention, Healthy	na
44	Cardiovascular Health Study	Primary Prevention, Healthy	na
45	Cardiovascular Health Study	Primary Prevention, Healthy	na
46	Cardiovascular Health Study	Primary Prevention, Healthy	na
47	Cardiovascular Health Study	Primary Prevention, Healthy	na
48	Cardiovascular Health Study	Primary Prevention, Healthy	na
49	Cardiovascular Health Study	Primary Prevention, Healthy	na
50	Cardiovascular Health Study	Primary Prevention, Healthy	na
51	Cardiovascular Health Study	Primary Prevention, Healthy	na
52	Cardiovascular Health Study	Primary Prevention, Healthy	na
53	Cardiovascular Health Study	Primary Prevention, Healthy	na

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Sample size (total)	Age mean (SD) [median]	Sex (% male)
29	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
30	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
31	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
32	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
33	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
34	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
35	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
36	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
37	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
38	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
39	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
40	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
41	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
42	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
43	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
44	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
45	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
46	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
47	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
48	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
49	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
50	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
51	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
52	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
53	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Race	Blood pressure SBP/DBP (mmHg)
29	Cardiovascular Health Study	87.8 white, 11.7 black	nd
30	Cardiovascular Health Study	87.8 white, 11.7 black	nd
31	Cardiovascular Health Study	87.8 white, 11.7 black	nd
32	Cardiovascular Health Study	87.8 white, 11.7 black	nd
33	Cardiovascular Health Study	87.8 white, 11.7 black	nd
34	Cardiovascular Health Study	87.8 white, 11.7 black	nd
35	Cardiovascular Health Study	87.8 white, 11.7 black	nd
36	Cardiovascular Health Study	87.8 white, 11.7 black	nd
37	Cardiovascular Health Study	87.8 white, 11.7 black	nd
38	Cardiovascular Health Study	87.8 white, 11.7 black	nd
39	Cardiovascular Health Study	87.8 white, 11.7 black	nd
40	Cardiovascular Health Study	87.8 white, 11.7 black	nd
41	Cardiovascular Health Study	87.8 white, 11.7 black	nd
42	Cardiovascular Health Study	87.8 white, 11.7 black	nd
43	Cardiovascular Health Study	87.8 white, 11.7 black	nd
44	Cardiovascular Health Study	87.8 white, 11.7 black	nd
45	Cardiovascular Health Study	87.8 white, 11.7 black	nd
46	Cardiovascular Health Study	87.8 white, 11.7 black	nd
47	Cardiovascular Health Study	87.8 white, 11.7 black	nd
48	Cardiovascular Health Study	87.8 white, 11.7 black	nd
49	Cardiovascular Health Study	87.8 white, 11.7 black	nd
50	Cardiovascular Health Study	87.8 white, 11.7 black	nd
51	Cardiovascular Health Study	87.8 white, 11.7 black	nd
52	Cardiovascular Health Study	87.8 white, 11.7 black	nd
53	Cardiovascular Health Study	87.8 white, 11.7 black	nd

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Lipids: Total cholesterol/LDL/HDL/Triglycerides mean (SD) mg/dL [mmol/L]
29	Cardiovascular Health Study	nd
30	Cardiovascular Health Study	nd
31	Cardiovascular Health Study	nd
32	Cardiovascular Health Study	nd
33	Cardiovascular Health Study	nd
34	Cardiovascular Health Study	nd
35	Cardiovascular Health Study	nd
36	Cardiovascular Health Study	nd
37	Cardiovascular Health Study	nd
38	Cardiovascular Health Study	nd
39	Cardiovascular Health Study	nd
40	Cardiovascular Health Study	nd
41	Cardiovascular Health Study	nd
42	Cardiovascular Health Study	nd
43	Cardiovascular Health Study	nd
44	Cardiovascular Health Study	nd
45	Cardiovascular Health Study	nd
46	Cardiovascular Health Study	nd
47	Cardiovascular Health Study	nd
48	Cardiovascular Health Study	nd
49	Cardiovascular Health Study	nd
50	Cardiovascular Health Study	nd
51	Cardiovascular Health Study	nd
52	Cardiovascular Health Study	nd
53	Cardiovascular Health Study	nd

Appendix G.2.
Causality Table: Observational Studies

Row	Study	BMI mean (SD)/weight mean (SD) Kg
29	Cardiovascular Health Study	nd
30	Cardiovascular Health Study	nd
31	Cardiovascular Health Study	nd
32	Cardiovascular Health Study	nd
33	Cardiovascular Health Study	nd
34	Cardiovascular Health Study	nd
35	Cardiovascular Health Study	nd
36	Cardiovascular Health Study	nd
37	Cardiovascular Health Study	nd
38	Cardiovascular Health Study	nd
39	Cardiovascular Health Study	nd
40	Cardiovascular Health Study	nd
41	Cardiovascular Health Study	nd
42	Cardiovascular Health Study	nd
43	Cardiovascular Health Study	nd
44	Cardiovascular Health Study	nd
45	Cardiovascular Health Study	nd
46	Cardiovascular Health Study	nd
47	Cardiovascular Health Study	nd
48	Cardiovascular Health Study	nd
49	Cardiovascular Health Study	nd
50	Cardiovascular Health Study	nd
51	Cardiovascular Health Study	nd
52	Cardiovascular Health Study	nd
53	Cardiovascular Health Study	nd

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Baseline n-3 intake/level (median (IQR), unless noted)
29	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
30	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
31	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
32	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
33	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
34	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
35	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
36	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
37	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
38	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
39	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
40	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
41	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
42	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
43	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
44	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
45	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
46	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
47	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
48	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
49	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
50	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
51	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
52	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
53	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA

Row	Study	n-3 source	n-3 measure	n-3 type(s)
29	Cardiovascular Health Study	plasma	% of total plasma phospholipid fatty acids	All n-3
30	Cardiovascular Health Study	plasma	% of total plasma phospholipid fatty acids	ALA
31	Cardiovascular Health Study	intake	% of total fat intake	ALA
32	Cardiovascular Health Study	plasma	% of total plasma phospholipid fatty acids	EPA
33	Cardiovascular Health Study	plasma	% of total plasma phospholipid fatty acids	DPA
34	Cardiovascular Health Study	plasma	% of total plasma phospholipid fatty acids	DHA
35	Cardiovascular Health Study	plasma	% of total plasma phospholipid fatty acids	All n-3
36	Cardiovascular Health Study	plasma	% of total plasma phospholipid fatty acids	ALA
37	Cardiovascular Health Study	intake	% of total fat intake	ALA
38	Cardiovascular Health Study	plasma	% of total plasma phospholipid fatty acids	EPA
39	Cardiovascular Health Study	plasma	% of total plasma phospholipid fatty acids	DPA
40	Cardiovascular Health Study	plasma	% of total plasma phospholipid fatty acids	DHA
41	Cardiovascular Health Study	plasma	% of total plasma phospholipid fatty acids	All n-3
42	Cardiovascular Health Study	plasma	% of total plasma phospholipid fatty acids	EPA
43	Cardiovascular Health Study	plasma	% of total plasma phospholipid fatty acids	DPA
44	Cardiovascular Health Study	plasma	% of total plasma phospholipid fatty acids	DHA
45	Cardiovascular Health Study	plasma	% of total plasma phospholipid fatty acids	All n-3
46	Cardiovascular Health Study	plasma	% of total plasma phospholipid fatty acids	ALA
47	Cardiovascular Health Study	intake	% of total fat intake	ALA
48	Cardiovascular Health Study	plasma	% of total plasma phospholipid fatty acids	EPA
49	Cardiovascular Health Study	plasma	% of total plasma phospholipid fatty acids	DPA
50	Cardiovascular Health Study	plasma	% of total plasma phospholipid fatty acids	DHA
51	Cardiovascular Health Study	plasma	% of total plasma phospholipid fatty acids	All n-3
52	Cardiovascular Health Study	plasma	% of total plasma phospholipid fatty acids	ALA
53	Cardiovascular Health Study	intake	% of total fat intake	ALA

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Study design
29	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
30	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
31	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
32	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
33	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
34	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
35	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
36	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
37	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
38	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
39	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
40	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
41	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
42	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
43	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
44	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
45	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
46	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
47	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
48	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
49	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
50	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
51	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
52	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
53	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Outcome	Reported effect Size
29	Cardiovascular Health Study	Death, all cause	See appendix F
30	Cardiovascular Health Study	Death, CHD	See appendix F
31	Cardiovascular Health Study	Death, CHD	See appendix F
32	Cardiovascular Health Study	Death, CHD	See appendix F
33	Cardiovascular Health Study	Death, CHD	See appendix F
34	Cardiovascular Health Study	Death, CHD	See appendix F
35	Cardiovascular Health Study	Death, CHD	See appendix F
36	Cardiovascular Health Study	Death, CVD	See appendix F
37	Cardiovascular Health Study	Death, CVD	See appendix F
38	Cardiovascular Health Study	Death, CVD	See appendix F
39	Cardiovascular Health Study	Death, CVD	See appendix F
40	Cardiovascular Health Study	Death, CVD	See appendix F
41	Cardiovascular Health Study	Death, CVD	See appendix F
42	Cardiovascular Health Study	Death, stroke	See appendix F
43	Cardiovascular Health Study	Death, stroke	See appendix F
44	Cardiovascular Health Study	Death, stroke	See appendix F
45	Cardiovascular Health Study	Death, stroke	See appendix F
46	Cardiovascular Health Study	Stroke, hemorrhagic	See appendix F
47	Cardiovascular Health Study	Stroke, hemorrhagic	See appendix F
48	Cardiovascular Health Study	Stroke, hemorrhagic	See appendix F
49	Cardiovascular Health Study	Stroke, hemorrhagic	See appendix F
50	Cardiovascular Health Study	Stroke, hemorrhagic	See appendix F
51	Cardiovascular Health Study	Stroke, hemorrhagic	See appendix F
52	Cardiovascular Health Study	Stroke, ischemic	See appendix F
53	Cardiovascular Health Study	Stroke, ischemic	See appendix F

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Study years (study start date)	Country
54	Cardiovascular Health Study	1989	US
55	Cardiovascular Health Study	1989	US
56	Cardiovascular Health Study	1989	US
57	Cardiovascular Health Study	1989	US
58	Cardiovascular Health Study	1989	US
59	Cardiovascular Health Study	1989	US
60	Cardiovascular Health Study	1989	US
61	Cardiovascular Health Study	1989	US
62	Cardiovascular Health Study	1989	US
63	Cardiovascular Health Study	1989	US
64	Cardiovascular Health Study	1989	US
65	Cardiovascular Health Study	1989	US
66	Cardiovascular Health Study	1989	US
67	Cardiovascular Health Study	1989	US
68	Cardiovascular Health Study	1989	US
69	Cardiovascular Health Study	1989	US
70	Cohort of Swedish Men	1997	Sweden
71	Danish National Birth Cohort	1996	Denmark
72	Diet, Cancer, Health (Danish)	34304	Denmark
73	Diet, Cancer, Health (Danish)	34304	Denmark
74	Diet, Cancer, Health (Danish)	34304	Denmark
75	Diet, Cancer, Health (Danish)	34304	Denmark
76	Diet, Cancer, Health (Danish)	34304	Denmark
77	Diet, Cancer, Health (Danish)	34304	Denmark
78	Diet, Cancer, Health (Danish)	34304	Denmark
79	Diet, Cancer, Health (Danish)	34304	Denmark

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Population	Risk type
54	Cardiovascular Health Study	Primary Prevention, Healthy	na
55	Cardiovascular Health Study	Primary Prevention, Healthy	na
56	Cardiovascular Health Study	Primary Prevention, Healthy	na
57	Cardiovascular Health Study	Primary Prevention, Healthy	na
58	Cardiovascular Health Study	Primary Prevention, Healthy	na
59	Cardiovascular Health Study	Primary Prevention, Healthy	na
60	Cardiovascular Health Study	Primary Prevention, Healthy	na
61	Cardiovascular Health Study	Primary Prevention, Healthy	na
62	Cardiovascular Health Study	Primary Prevention, Healthy	na
63	Cardiovascular Health Study	Primary Prevention, Healthy	na
64	Cardiovascular Health Study	Primary Prevention, Healthy	na
65	Cardiovascular Health Study	Primary Prevention, Healthy	na
66	Cardiovascular Health Study	Primary Prevention, Healthy	na
67	Cardiovascular Health Study	Primary Prevention, Healthy	na
68	Cardiovascular Health Study	Primary Prevention, Healthy	na
69	Cardiovascular Health Study	Primary Prevention, Healthy	na
70	Cohort of Swedish Men	Primary Prevention, Healthy	na
71	Danish National Birth Cohort	Primary Prevention, Healthy	na
72	Diet, Cancer, Health (Danish)	Primary Prevention, Healthy	na
73	Diet, Cancer, Health (Danish)	Primary Prevention, Healthy	na
74	Diet, Cancer, Health (Danish)	Primary Prevention, Healthy	na
75	Diet, Cancer, Health (Danish)	Primary Prevention, Healthy	na
76	Diet, Cancer, Health (Danish)	Primary Prevention, Healthy	na
77	Diet, Cancer, Health (Danish)	Primary Prevention, Healthy	na
78	Diet, Cancer, Health (Danish)	Primary Prevention, Healthy	na
79	Diet, Cancer, Health (Danish)	Primary Prevention, Healthy	na

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Sample size (total)	Age mean (SD) [median]	Sex (% male)
54	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
55	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
56	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
57	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
58	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
59	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
60	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
61	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
62	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
63	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
64	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
65	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
66	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
67	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
68	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
69	Cardiovascular Health Study	3941	74 (5) median 73 IQR 7198	36.1
70	Cohort of Swedish Men	44601	nd	100
71	Danish National Birth Cohort	48627	29.9 range 15.746.9	0
72	Diet, Cancer, Health (Danish)	1708	[men: 55.9, women 56.2]	47.6
73	Diet, Cancer, Health (Danish)	1708	[men: 55.9, women 56.2]	47.6
74	Diet, Cancer, Health (Danish)	1708	[men: 55.9, women 56.2]	47.6
75	Diet, Cancer, Health (Danish)	1708	[men: 55.9, women 56.2]	47.6
76	Diet, Cancer, Health (Danish)	1708	[men: 55.9, women 56.2]	47.6
77	Diet, Cancer, Health (Danish)	1708	[men: 55.9, women 56.2]	47.6
78	Diet, Cancer, Health (Danish)	1708	[men: 55.9, women 56.2]	47.6
79	Diet, Cancer, Health (Danish)	1708	[men: 55.9, women 56.2]	47.6

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Race	Blood pressure SBP/DBP (mmHg)
54	Cardiovascular Health Study	87.8 white, 11.7 black	nd
55	Cardiovascular Health Study	87.8 white, 11.7 black	nd
56	Cardiovascular Health Study	87.8 white, 11.7 black	nd
57	Cardiovascular Health Study	87.8 white, 11.7 black	nd
58	Cardiovascular Health Study	87.8 white, 11.7 black	nd
59	Cardiovascular Health Study	87.8 white, 11.7 black	nd
60	Cardiovascular Health Study	87.8 white, 11.7 black	nd
61	Cardiovascular Health Study	87.8 white, 11.7 black	nd
62	Cardiovascular Health Study	87.8 white, 11.7 black	nd
63	Cardiovascular Health Study	87.8 white, 11.7 black	nd
64	Cardiovascular Health Study	87.8 white, 11.7 black	nd
65	Cardiovascular Health Study	87.8 white, 11.7 black	nd
66	Cardiovascular Health Study	87.8 white, 11.7 black	nd
67	Cardiovascular Health Study	87.8 white, 11.7 black	nd
68	Cardiovascular Health Study	87.8 white, 11.7 black	nd
69	Cardiovascular Health Study	87.8 white, 11.7 black	nd
70	Cohort of Swedish Men	nd	nd
71	Danish National Birth Cohort	nd	nd
72	Diet, Cancer, Health (Danish)	nd	[men: 140, women 136]/
73	Diet, Cancer, Health (Danish)	nd	[men: 140, women 136]/
74	Diet, Cancer, Health (Danish)	nd	[men: 140, women 136]/
75	Diet, Cancer, Health (Danish)	nd	[men: 140, women 136]/
76	Diet, Cancer, Health (Danish)	nd	[men: 140, women 136]/
77	Diet, Cancer, Health (Danish)	nd	[men: 140, women 136]/
78	Diet, Cancer, Health (Danish)	nd	[men: 140, women 136]/
79	Diet, Cancer, Health (Danish)	nd	[men: 140, women 136]/

Row	Study	Lipids: Total cholesterol/LDL/HDL/Triglycerides mean (SD) mg/dL [mmol/L]
54	Cardiovascular Health Study	nd
55	Cardiovascular Health Study	nd
56	Cardiovascular Health Study	nd
57	Cardiovascular Health Study	nd
58	Cardiovascular Health Study	nd
59	Cardiovascular Health Study	nd
60	Cardiovascular Health Study	nd
61	Cardiovascular Health Study	nd
62	Cardiovascular Health Study	nd
63	Cardiovascular Health Study	nd
64	Cardiovascular Health Study	nd
65	Cardiovascular Health Study	nd
66	Cardiovascular Health Study	nd
67	Cardiovascular Health Study	nd
68	Cardiovascular Health Study	nd
69	Cardiovascular Health Study	nd
70	Cohort of Swedish Men	nd
71	Danish National Birth Cohort	nd
72	Diet, Cancer, Health (Danish)	[median men: 5.9, women: 6.2]/nd/nd/nd
73	Diet, Cancer, Health (Danish)	[median men: 5.9, women: 6.2]/nd/nd/nd
74	Diet, Cancer, Health (Danish)	[median men: 5.9, women: 6.2]/nd/nd/nd
75	Diet, Cancer, Health (Danish)	[median men: 5.9, women: 6.2]/nd/nd/nd
76	Diet, Cancer, Health (Danish)	[median men: 5.9, women: 6.2]/nd/nd/nd
77	Diet, Cancer, Health (Danish)	[median men: 5.9, women: 6.2]/nd/nd/nd
78	Diet, Cancer, Health (Danish)	[median men: 5.9, women: 6.2]/nd/nd/nd
79	Diet, Cancer, Health (Danish)	[median men: 5.9, women: 6.2]/nd/nd/nd

Appendix G.2.
Causality Table: Observational Studies

Row	Study	BMI mean (SD)/weight mean (SD) Kg
54	Cardiovascular Health Study	nd
55	Cardiovascular Health Study	nd
56	Cardiovascular Health Study	nd
57	Cardiovascular Health Study	nd
58	Cardiovascular Health Study	nd
59	Cardiovascular Health Study	nd
60	Cardiovascular Health Study	nd
61	Cardiovascular Health Study	nd
62	Cardiovascular Health Study	nd
63	Cardiovascular Health Study	nd
64	Cardiovascular Health Study	nd
65	Cardiovascular Health Study	nd
66	Cardiovascular Health Study	nd
67	Cardiovascular Health Study	nd
68	Cardiovascular Health Study	nd
69	Cardiovascular Health Study	nd
70	Cohort of Swedish Men	nd
71	Danish National Birth Cohort	nd
72	Diet, Cancer, Health (Danish)	25.9 (3.9)
73	Diet, Cancer, Health (Danish)	25.9 (3.9)
74	Diet, Cancer, Health (Danish)	25.9 (3.9)
75	Diet, Cancer, Health (Danish)	25.9 (3.9)
76	Diet, Cancer, Health (Danish)	25.9 (3.9)
77	Diet, Cancer, Health (Danish)	25.9 (3.9)
78	Diet, Cancer, Health (Danish)	25.9 (3.9)
79	Diet, Cancer, Health (Danish)	25.9 (3.9)

Row	Study	Baseline n-3 intake/level (median (IQR), unless noted)
54	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
55	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
56	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
57	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
58	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
59	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
60	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
61	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
62	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
63	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
64	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
65	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
66	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
67	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
68	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
69	Cardiovascular Health Study	ALA: 0.14% FA, EPA: 0.51% FA, DHA: 2.87% FA, DPA: 0.82% FA, Total n-3 FA 4.21% FA
70	Cohort of Swedish Men	Marine oil: 0.36 g/d
71	Danish National Birth Cohort	Total n-3 FA: 0.31 g/d
72	Diet, Cancer, Health (Danish)	EPA: 0.18 g/d, DHA: 0.43 g/d, DPA: 0.08 g/d, EPA+DPA+DHA: 0.7 g/d
73	Diet, Cancer, Health (Danish)	EPA: 0.18 g/d, DHA: 0.43 g/d, DPA: 0.08 g/d, EPA+DPA+DHA: 0.7 g/d
74	Diet, Cancer, Health (Danish)	EPA: 0.18 g/d, DHA: 0.43 g/d, DPA: 0.08 g/d, EPA+DPA+DHA: 0.7 g/d
75	Diet, Cancer, Health (Danish)	EPA: 0.18 g/d, DHA: 0.43 g/d, DPA: 0.08 g/d, EPA+DPA+DHA: 0.7 g/d
76	Diet, Cancer, Health (Danish)	EPA: 0.18 g/d, DHA: 0.43 g/d, DPA: 0.08 g/d, EPA+DPA+DHA: 0.7 g/d
77	Diet, Cancer, Health (Danish)	EPA: 0.18 g/d, DHA: 0.43 g/d, DPA: 0.08 g/d, EPA+DPA+DHA: 0.7 g/d
78	Diet, Cancer, Health (Danish)	EPA: 0.18 g/d, DHA: 0.43 g/d, DPA: 0.08 g/d, EPA+DPA+DHA: 0.7 g/d
79	Diet, Cancer, Health (Danish)	EPA: 0.18 g/d, DHA: 0.43 g/d, DPA: 0.08 g/d, EPA+DPA+DHA: 0.7 g/d

Appendix G.2.
Causality Table: Observational Studies

Row	Study	n-3 source	n-3 measure	n-3 type(s)
54	Cardiovascular Health Study	plasma	% of total plasma phospholipid fatty acids	EPA
55	Cardiovascular Health Study	plasma	% of total plasma phospholipid fatty acids	DPA
56	Cardiovascular Health Study	plasma	% of total plasma phospholipid fatty acids	DHA
57	Cardiovascular Health Study	plasma	% of total plasma phospholipid fatty acids	All n-3
58	Cardiovascular Health Study	plasma	% of total plasma phospholipid fatty acids	ALA
59	Cardiovascular Health Study	intake	% of total fat intake	ALA
60	Cardiovascular Health Study	plasma	% of total plasma phospholipid fatty acids	EPA
61	Cardiovascular Health Study	plasma	% of total plasma phospholipid fatty acids	DPA
62	Cardiovascular Health Study	plasma	% of total plasma phospholipid fatty acids	DHA
63	Cardiovascular Health Study	plasma	% of total plasma phospholipid fatty acids	All n-3
64	Cardiovascular Health Study	plasma	% of total plasma phospholipid fatty acids	ALA
65	Cardiovascular Health Study	intake	% of total fat intake	ALA
66	Cardiovascular Health Study	plasma	% of total plasma phospholipid fatty acids	EPA
67	Cardiovascular Health Study	plasma	% of total plasma phospholipid fatty acids	DPA
68	Cardiovascular Health Study	plasma	% of total plasma phospholipid fatty acids	DHA
69	Cardiovascular Health Study	plasma	% of total plasma phospholipid fatty acids	All n-3
70	Cohort of Swedish Men	intake	g/d	EPA+DHA
71	Danish National Birth Cohort	intake	g/d	Total n-3
72	Diet, Cancer, Health (Danish)	Intake	g/d	EPA+DPA+DHA
73	Diet, Cancer, Health (Danish)	Intake	g/d	EPA
74	Diet, Cancer, Health (Danish)	Intake	g/d	DPA
75	Diet, Cancer, Health (Danish)	Intake	g/d	DHA
76	Diet, Cancer, Health (Danish)	Adipose tissue	%	EPA+DPA+DHA
77	Diet, Cancer, Health (Danish)	Adipose tissue	%	EPA
78	Diet, Cancer, Health (Danish)	Adipose tissue	%	DPA
79	Diet, Cancer, Health (Danish)	Adipose tissue	%	DHA

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Study design
54	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
55	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
56	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
57	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
58	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
59	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
60	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
61	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
62	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
63	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
64	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
65	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
66	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
67	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
68	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
69	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
70	Cohort of Swedish Men	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
71	Danish National Birth Cohort	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
72	Diet, Cancer, Health (Danish)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
73	Diet, Cancer, Health (Danish)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
74	Diet, Cancer, Health (Danish)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
75	Diet, Cancer, Health (Danish)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
76	Diet, Cancer, Health (Danish)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
77	Diet, Cancer, Health (Danish)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
78	Diet, Cancer, Health (Danish)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
79	Diet, Cancer, Health (Danish)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Outcome	Reported effect Size
54	Cardiovascular Health Study	Stroke, ischemic	See appendix F
55	Cardiovascular Health Study	Stroke, ischemic	See appendix F
56	Cardiovascular Health Study	Stroke, ischemic	See appendix F
57	Cardiovascular Health Study	Stroke, ischemic	See appendix F
58	Cardiovascular Health Study	Stroke, total	See appendix F
59	Cardiovascular Health Study	Stroke, total	See appendix F
60	Cardiovascular Health Study	Stroke, total	See appendix F
61	Cardiovascular Health Study	Stroke, total	See appendix F
62	Cardiovascular Health Study	Stroke, total	See appendix F
63	Cardiovascular Health Study	Stroke, total	See appendix F
64	Cardiovascular Health Study	Sudden cardiac death	See appendix F
65	Cardiovascular Health Study	Sudden cardiac death	See appendix F
66	Cardiovascular Health Study	Sudden cardiac death	See appendix F
67	Cardiovascular Health Study	Sudden cardiac death	See appendix F
68	Cardiovascular Health Study	Sudden cardiac death	See appendix F
69	Cardiovascular Health Study	Sudden cardiac death	See appendix F
70	Cohort of Swedish Men	Congestive heart failure	See appendix F
71	Danish National Birth Cohort	CVD, total	See appendix F
72	Diet, Cancer, Health (Danish)	Acute coronary syndrome	See appendix F
73	Diet, Cancer, Health (Danish)	Acute coronary syndrome	See appendix F
74	Diet, Cancer, Health (Danish)	Acute coronary syndrome	See appendix F
75	Diet, Cancer, Health (Danish)	Acute coronary syndrome	See appendix F
76	Diet, Cancer, Health (Danish)	Acute coronary syndrome	See appendix F
77	Diet, Cancer, Health (Danish)	Acute coronary syndrome	See appendix F
78	Diet, Cancer, Health (Danish)	Acute coronary syndrome	See appendix F
79	Diet, Cancer, Health (Danish)	Acute coronary syndrome	See appendix F

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Study years (study start date)	Country
80	Diet, Cancer, Health (Danish)	34304	Denmark
81	EPIC Norfolk	1993	UK
82	EPIC Norfolk	1993	UK
83	EPIC Norfolk	1993	UK
84	EPIC Norfolk	1993	UK
85	EPIC Norfolk	1993	UK
86	EPIC Norfolk	1993	UK
87	Glostrup Population Studies	1964	Denmark
88	Glostrup Population Studies	1964	Denmark
89	Guangzhou	2008	China
90	Guangzhou	2008	China
91	Guangzhou	2008	China
92	Guangzhou	2008	China
93	Guangzhou	2008	China
94	Guangzhou	2008	China
95	Guangzhou	2008	China
96	Guangzhou	2008	China
97	Health Professional Follow-up Study	1986	US
98	Health Professional Follow-up Study	1986	US
99	Health Professional Follow-up Study	1986	US
100	Health Professional Follow-up Study	1986	US
101	Health Professional Follow-up Study	1986	US
102	Health Professional Follow-up Study	1986	US
103	Health Professional Follow-up Study	1986	US
104	Health Professional Follow-up Study	1986	US
105	Health Professional Follow-up Study	1986	US
106	Health Professional Follow-up Study	1986	US
107	Health Professional Follow-up Study	1986	US
108	Health Professional Follow-up Study	1986	US
109	Hisayama	2002	Japan
110	Hisayama	2002	Japan
111	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	1987	US
112	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	1987	US

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Population	Risk type
80	Diet, Cancer, Health (Danish)	Primary Prevention, Healthy	na
81	EPIC Norfolk	Primary Prevention, Healthy	na
82	EPIC Norfolk	Primary Prevention, Healthy	na
83	EPIC Norfolk	Primary Prevention, Healthy	na
84	EPIC Norfolk	Primary Prevention, Healthy	na
85	EPIC Norfolk	Primary Prevention, Healthy	na
86	EPIC Norfolk	Primary Prevention, Healthy	na
87	Glostrup Population Studies	Primary Prevention, Healthy	na
88	Glostrup Population Studies	Primary Prevention, Healthy	na
89	Guangzhou	Primary Prevention, Healthy	na
90	Guangzhou	Primary Prevention, Healthy	na
91	Guangzhou	Primary Prevention, Healthy	na
92	Guangzhou	Primary Prevention, Healthy	na
93	Guangzhou	Primary Prevention, Healthy	na
94	Guangzhou	Primary Prevention, Healthy	na
95	Guangzhou	Primary Prevention, Healthy	na
96	Guangzhou	Primary Prevention, Healthy	na
97	Health Professional Follow-up Study	Primary Prevention, Healthy	na
98	Health Professional Follow-up Study	Primary Prevention, Healthy	na
99	Health Professional Follow-up Study	Primary Prevention, Healthy	na
100	Health Professional Follow-up Study	Primary Prevention, Healthy	na
101	Health Professional Follow-up Study	Primary Prevention, Healthy	na
102	Health Professional Follow-up Study	Primary Prevention, Healthy	na
103	Health Professional Follow-up Study	Primary Prevention, Healthy	na
104	Health Professional Follow-up Study	Primary Prevention, Healthy	na
105	Health Professional Follow-up Study	Primary Prevention, Healthy	na
106	Health Professional Follow-up Study	Primary Prevention, Healthy	na
107	Health Professional Follow-up Study	Primary Prevention, Healthy	na
108	Health Professional Follow-up Study	Primary Prevention, Healthy	na
109	Hisayama	Primary Prevention, Healthy	na
110	Hisayama	Primary Prevention, Healthy	na
111	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Primary Prevention, Healthy	The population is a mixture of people
112	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Primary Prevention, Healthy	The population is a mixture of people

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Sample size (total)	Age mean (SD) [median]	Sex (% male)
80	Diet, Cancer, Health (Danish)	1708	[men: 55.9, women 56.2]	47.6
81	EPIC Norfolk	7364	men: 60 (8), women 59.4 (8.5)	45.6
82	EPIC Norfolk	7364	men: 60 (8), women 59.4 (8.5)	45.6
83	EPIC Norfolk	7364	men: 60 (8), women 59.4 (8.5)	45.6
84	EPIC Norfolk	7364	men: 60 (8), women 59.4 (8.5)	45.6
85	EPIC Norfolk	7364	men: 60 (8), women 59.4 (8.5)	45.6
86	EPIC Norfolk	7364	men: 60 (8), women 59.4 (8.5)	45.6
87	Glostrup Population Studies	3277	50.6 range 30.8, 60.8	49.9
88	Glostrup Population Studies	3277	50.6 range 30.8, 60.8	49.9
89	Guangzhou	1477	nd	25.3
90	Guangzhou	1477	nd	25.3
91	Guangzhou	1477	nd	25.3
92	Guangzhou	1477	nd	25.3
93	Guangzhou	1477	nd	25.3
94	Guangzhou	1477	nd	25.3
95	Guangzhou	1477	nd	25.3
96	Guangzhou	1477	nd	25.3
97	Health Professional Follow-up Study	44895	53 (9.6) range 40,75	100
98	Health Professional Follow-up Study	44895	53 (9.6) range 40,75	100
99	Health Professional Follow-up Study	44895	53 (9.6) range 40,75	100
100	Health Professional Follow-up Study	44895	53 (9.6) range 40,75	100
101	Health Professional Follow-up Study	44895	53 (9.6) range 40,75	100
102	Health Professional Follow-up Study	44895	53 (9.6) range 40,75	100
103	Health Professional Follow-up Study	44895	53 (9.6) range 40,75	100
104	Health Professional Follow-up Study	44895	53 (9.6) range 40,75	100
105	Health Professional Follow-up Study	44895	53 (9.6) range 40,75	100
106	Health Professional Follow-up Study	44895	53 (9.6) range 40,75	100
107	Health Professional Follow-up Study	44895	53 (9.6) range 40,75	100
108	Health Professional Follow-up Study	44895	53 (9.6) range 40,75	100
109	Hisayama	3103	61.3 (12.5)	42
110	Hisayama	3103	61.3 (12.5	42
111	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	3592	men: 54.2 (5.6), women 53.3 (5.5)	46.6
112	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	3592	men: 54.2 (5.6), women 53.3 (5.5)	46.6

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Race	Blood pressure SBP/DBP (mmHg)
80	Diet, Cancer, Health (Danish)	nd	[men: 140, women 136]/
81	EPIC Norfolk	nd	men: 136.1 (16.4), women: 132.6 (18.0)/men: 83.7 (10.6), women: 80 (10.7)
82	EPIC Norfolk	nd	men: 136.1 (16.4), women: 132.6 (18.0)/men: 83.7 (10.6), women: 80 (10.7)
83	EPIC Norfolk	nd	men: 136.1 (16.4), women: 132.6 (18.0)/men: 83.7 (10.6), women: 80 (10.7)
84	EPIC Norfolk	nd	men: 136.1 (16.4), women: 132.6 (18.0)/men: 83.7 (10.6), women: 80 (10.7)
85	EPIC Norfolk	nd	men: 136.1 (16.4), women: 132.6 (18.0)/men: 83.7 (10.6), women: 80 (10.7)
86	EPIC Norfolk	nd	men: 136.1 (16.4), women: 132.6 (18.0)/men: 83.7 (10.6), women: 80 (10.7)
87	Glostrup Population Studies	nd	123 range 104, 152/
88	Glostrup Population Studies	nd	123 range 104, 152/
89	Guangzhou	nd	nd
90	Guangzhou	nd	nd
91	Guangzhou	nd	nd
92	Guangzhou	nd	nd
93	Guangzhou	nd	nd
94	Guangzhou	nd	nd
95	Guangzhou	nd	nd
96	Guangzhou	nd	nd
97	Health Professional Follow-up Study	nd	nd
98	Health Professional Follow-up Study	nd	nd
99	Health Professional Follow-up Study	nd	nd
100	Health Professional Follow-up Study	nd	nd
101	Health Professional Follow-up Study	nd	nd
102	Health Professional Follow-up Study	nd	nd
103	Health Professional Follow-up Study	nd	nd
104	Health Professional Follow-up Study	nd	nd
105	Health Professional Follow-up Study	nd	nd
106	Health Professional Follow-up Study	nd	nd
107	Health Professional Follow-up Study	nd	nd
108	Health Professional Follow-up Study	nd	nd
109	Hisayama	nd	131.8 (21.1)/78.4 (11.9)
110	Hisayama	nd	131.8 (21.1)/78.4 (11.9)
111	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	100 white	men: 120.5 (14.8), women 116.9 (17.0)/men 75.5(9.2); women 72.1 (9.1)
112	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	100 white	men: 120.5 (14.8), women 116.9 (17.0)/men 75.5(9.2); women 72.1 (9.1)

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Lipids: Total cholesterol/LDL/HDL/Triglycerides mean (SD) mg/dL [mmol/L]
80	Diet, Cancer, Health (Danish)	[median men: 5.9, women: 6.2]/nd/nd/nd
81	EPIC Norfolk	[men: 6.03 (1.05) 6.35 (1.20)]/[men: 3.92 (0.95), women: 4.03 (1.06)/men: 1.25 (0.33), women: 1.58 (0.42)/[men: 2.01 (1.15), women: 1.64 (1.07)]
82	EPIC Norfolk	[men: 6.03 (1.05) 6.35 (1.20)]/[men: 3.92 (0.95), women: 4.03 (1.06)/men: 1.25 (0.33), women: 1.58 (0.42)/[men: 2.01 (1.15), women: 1.64 (1.07)]
83	EPIC Norfolk	[men: 6.03 (1.05) 6.35 (1.20)]/[men: 3.92 (0.95), women: 4.03 (1.06)/men: 1.25 (0.33), women: 1.58 (0.42)/[men: 2.01 (1.15), women: 1.64 (1.07)]
84	EPIC Norfolk	[men: 6.03 (1.05) 6.35 (1.20)]/[men: 3.92 (0.95), women: 4.03 (1.06)/men: 1.25 (0.33), women: 1.58 (0.42)/[men: 2.01 (1.15), women: 1.64 (1.07)]
85	EPIC Norfolk	[men: 6.03 (1.05) 6.35 (1.20)]/[men: 3.92 (0.95), women: 4.03 (1.06)/men: 1.25 (0.33), women: 1.58 (0.42)/[men: 2.01 (1.15), women: 1.64 (1.07)]
86	EPIC Norfolk	[men: 6.03 (1.05) 6.35 (1.20)]/[men: 3.92 (0.95), women: 4.03 (1.06)/men: 1.25 (0.33), women: 1.58 (0.42)/[men: 2.01 (1.15), women: 1.64 (1.07)]
87	Glostrup Population Studies	nd
88	Glostrup Population Studies	nd
89	Guangzhou	[5.43 (0.05)/nd/nd/nd]
90	Guangzhou	[5.43 (0.05)/nd/nd/nd]
91	Guangzhou	[5.43 (0.05)/nd/nd/nd]
92	Guangzhou	[5.43 (0.05)/nd/nd/nd]
93	Guangzhou	[5.43 (0.05)/nd/nd/nd]
94	Guangzhou	[5.43 (0.05)/nd/nd/nd]
95	Guangzhou	[5.43 (0.05)/nd/nd/nd]
96	Guangzhou	[5.43 (0.05)/nd/nd/nd]
97	Health Professional Follow-up Study	203/nd/nd/nd
98	Health Professional Follow-up Study	203/nd/nd/nd
99	Health Professional Follow-up Study	203/nd/nd/nd
100	Health Professional Follow-up Study	203/nd/nd/nd
101	Health Professional Follow-up Study	203/nd/nd/nd
102	Health Professional Follow-up Study	203/nd/nd/nd
103	Health Professional Follow-up Study	203/nd/nd/nd
104	Health Professional Follow-up Study	203/nd/nd/nd
105	Health Professional Follow-up Study	203/nd/nd/nd
106	Health Professional Follow-up Study	203/nd/nd/nd
107	Health Professional Follow-up Study	203/nd/nd/nd
108	Health Professional Follow-up Study	203/nd/nd/nd
109	Hisayama	[nd/nd/1.62 (0.42)/Median 1.1 (IQR 0.78, 1.63)]
110	Hisayama	[nd/nd/1.62 (0.42)/Median 1.1 (IQR 0.78, 1.63)]
111	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	men: 212 (39), women 216 (42)/nd/men: 44(12); women: 60(17)/men: 139 (94), women: 116 (73)
112	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	men: 212 (39), women 216 (42)/nd/men: 44(12); women: 60(17)/men: 139 (94), women: 116 (73)

Appendix G.2.
Causality Table: Observational Studies

Row	Study	BMI mean (SD)/weight mean (SD) Kg
80	Diet, Cancer, Health (Danish)	25.9 (3.9)
81	EPIC Norfolk	men: 26.3 (3.1), women: 25.9 (3.9)
82	EPIC Norfolk	men: 26.3 (3.1), women: 25.9 (3.9)
83	EPIC Norfolk	men: 26.3 (3.1), women: 25.9 (3.9)
84	EPIC Norfolk	men: 26.3 (3.1), women: 25.9 (3.9)
85	EPIC Norfolk	men: 26.3 (3.1), women: 25.9 (3.9)
86	EPIC Norfolk	men: 26.3 (3.1), women: 25.9 (3.9)
87	Glostrup Population Studies	23.9 (range 19.7, 29.6)
88	Glostrup Population Studies	23.9 (range 19.7, 29.6)
89	Guangzhou	nd
90	Guangzhou	nd
91	Guangzhou	nd
92	Guangzhou	nd
93	Guangzhou	nd
94	Guangzhou	nd
95	Guangzhou	nd
96	Guangzhou	nd
97	Health Professional Follow-up Study	25.5 (SE 0.02)
98	Health Professional Follow-up Study	25.5 (SE 0.02)
99	Health Professional Follow-up Study	25.5 (SE 0.02)
100	Health Professional Follow-up Study	25.5 (SE 0.02)
101	Health Professional Follow-up Study	25.5 (SE 0.02)
102	Health Professional Follow-up Study	25.5 (SE 0.02)
103	Health Professional Follow-up Study	25.5 (SE 0.02)
104	Health Professional Follow-up Study	25.5 (SE 0.02)
105	Health Professional Follow-up Study	25.5 (SE 0.02)
106	Health Professional Follow-up Study	25.5 (SE 0.02)
107	Health Professional Follow-up Study	25.5 (SE 0.02)
108	Health Professional Follow-up Study	25.5 (SE 0.02)
109	Hisayama	23.1
110	Hisayama	23.1
111	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	men: 27.7 (3.7), women: 26.2 (5)
112	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	men: 27.7 (3.7), women: 26.2 (5)

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Baseline n-3 intake/level (median (IQR), unless noted)
80	Diet, Cancer, Health (Danish)	EPA: 0.18 g/d, DHA: 0.43 g/d, DPA: 0.08 g/d, EPA+DPA+DHA: 0.7 g/d
81	EPIC Norfolk	ALA: mean 11.4 (SD 6.4) mmol/L, EPA: mean 63.1 (SD 45.2) mmol/l, DHA: mean 237.4 (SD 106.2) mmol/l, DPA: mean 65.1 (SD 28) mmol/l, Total n-3 FA: mean 377 (SD 165.7) mmol/l
82	EPIC Norfolk	ALA: mean 11.4 (SD 6.4) mmol/L, EPA: mean 63.1 (SD 45.2) mmol/l, DHA: mean 237.4 (SD 106.2) mmol/l, DPA: mean 65.1 (SD 28) mmol/l, Total n-3 FA: mean 377 (SD 165.7) mmol/l
83	EPIC Norfolk	ALA: mean 11.4 (SD 6.4) mmol/L, EPA: mean 63.1 (SD 45.2) mmol/l, DHA: mean 237.4 (SD 106.2) mmol/l, DPA: mean 65.1 (SD 28) mmol/l, Total n-3 FA: mean 377 (SD 165.7) mmol/l
84	EPIC Norfolk	ALA: mean 11.4 (SD 6.4) mmol/L, EPA: mean 63.1 (SD 45.2) mmol/l, DHA: mean 237.4 (SD 106.2) mmol/l, DPA: mean 65.1 (SD 28) mmol/l, Total n-3 FA: mean 377 (SD 165.7) mmol/l
85	EPIC Norfolk	ALA: mean 11.4 (SD 6.4) mmol/L, EPA: mean 63.1 (SD 45.2) mmol/l, DHA: mean 237.4 (SD 106.2) mmol/l, DPA: mean 65.1 (SD 28) mmol/l, Total n-3 FA: mean 377 (SD 165.7) mmol/l
86	EPIC Norfolk	ALA: mean 11.4 (SD 6.4) mmol/L, EPA: mean 63.1 (SD 45.2) mmol/l, DHA: mean 237.4 (SD 106.2) mmol/l, DPA: mean 65.1 (SD 28) mmol/l, Total n-3 FA: mean 377 (SD 165.7) mmol/l
87	Glostrup Population Studies	ALA: men 1.61, women 1.24, All n-3: men 0.38, women 0.3 g/d
88	Glostrup Population Studies	ALA: men 1.61, women 1.24, All n-3: men 0.38, women 0.3 g/d
89	Guangzhou	nd
90	Guangzhou	nd
91	Guangzhou	nd
92	Guangzhou	nd
93	Guangzhou	nd
94	Guangzhou	nd
95	Guangzhou	nd
96	Guangzhou	nd
97	Health Professional Follow-up Study	Marine oil: 0.24 g/d
98	Health Professional Follow-up Study	Marine oil: 0.24 g/d
99	Health Professional Follow-up Study	EPA+DHA 0.25 g/d
100	Health Professional Follow-up Study	ALA 1.08 g/d
101	Health Professional Follow-up Study	Marine oil: 0.24 g/d
102	Health Professional Follow-up Study	Marine oil: 0.24 g/d
103	Health Professional Follow-up Study	Marine oil: 0.24 g/d
104	Health Professional Follow-up Study	Marine oil: 0.24 g/d
105	Health Professional Follow-up Study	Marine oil: 0.24 g/d
106	Health Professional Follow-up Study	Marine oil: 0.24 g/d
107	Health Professional Follow-up Study	EPA+DHA 0.25 g/d
108	Health Professional Follow-up Study	ALA 1.08 g/d
109	Hisayama	EPA: 0.41
110	Hisayama	DHA: 0.93
111	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	DHA: 0.38% FA, EPA+DHA+DPA: 0.94% FA
112	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	DHA: 0.38% FA, EPA+DHA+DPA: 0.94% FA

Appendix G.2.
Causality Table: Observational Studies

Row	Study	n-3 source	n-3 measure	n-3 type(s)
80	Diet, Cancer, Health (Danish)	Intake	g/d	EPA+DPA+DHA
81	EPIC Norfolk	blood	mmol/l	all n-3
82	EPIC Norfolk	blood	Mol%	all n-3
83	EPIC Norfolk	blood	mmol/l	ALA
84	EPIC Norfolk	blood	mmol/l	EPA
85	EPIC Norfolk	blood	mmol/l	DPA
86	EPIC Norfolk	blood	mmol/l	DHA
87	Glostrup Population Studies	intake	g/d	ALA
88	Glostrup Population Studies	intake	g/d	n-3 LC-PUFA
89	Guangzhou	erythrocyte	% FA	ALA
90	Guangzhou	erythrocyte	% FA	EPA
91	Guangzhou	erythrocyte	% FA	DPA
92	Guangzhou	erythrocyte	% FA	DHA
93	Guangzhou	erythrocyte	% FA	ALA
94	Guangzhou	erythrocyte	% FA	EPA
95	Guangzhou	erythrocyte	% FA	DPA
96	Guangzhou	erythrocyte	% FA	DHA
97	Health Professional Follow-up Study	intake	g/d	EPA+DHA
98	Health Professional Follow-up Study	intake	g/d	EPA+DHA
99	Health Professional Follow-up Study	intake	g/d	EPA+DHA
100	Health Professional Follow-up Study	intake	g/d	ALA
101	Health Professional Follow-up Study	intake	g/d	EPA+DHA
102	Health Professional Follow-up Study	intake	g/d	EPA+DHA
103	Health Professional Follow-up Study	intake	g/d	EPA+DHA
104	Health Professional Follow-up Study	intake	g/d	EPA+DHA
105	Health Professional Follow-up Study	intake	g/d	EPA+DHA
106	Health Professional Follow-up Study	intake	g/d	EPA+DHA
107	Health Professional Follow-up Study	intake	g/d	EPA+DHA
108	Health Professional Follow-up Study	intake	g/d	ALA
109	Hisayama	serum	EPA/AA ratio	EPA
110	Hisayama	serum	DHA/AA ratio	DHA
111	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Intake	grams/day	DHA+EPA
112	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Intake	grams/day	DHA

Row	Study	Study design
80	Diet, Cancer, Health (Danish)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
81	EPIC Norfolk	Nested Case Control
82	EPIC Norfolk	Nested Case Control
83	EPIC Norfolk	Nested Case Control
84	EPIC Norfolk	Nested Case Control
85	EPIC Norfolk	Nested Case Control
86	EPIC Norfolk	Nested Case Control
87	Glostrup Population Studies	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
88	Glostrup Population Studies	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
89	Guangzhou	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
90	Guangzhou	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
91	Guangzhou	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
92	Guangzhou	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
93	Guangzhou	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
94	Guangzhou	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
95	Guangzhou	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
96	Guangzhou	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
97	Health Professional Follow-up Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
98	Health Professional Follow-up Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
99	Health Professional Follow-up Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
100	Health Professional Follow-up Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
101	Health Professional Follow-up Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
102	Health Professional Follow-up Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
103	Health Professional Follow-up Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
104	Health Professional Follow-up Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
105	Health Professional Follow-up Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
106	Health Professional Follow-up Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
107	Health Professional Follow-up Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
108	Health Professional Follow-up Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
109	Hisayama	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
110	Hisayama	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
111	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
112	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Outcome	Reported effect Size
80	Diet, Cancer, Health (Danish)	Atrial fibrillation or flutter	See appendix F
81	EPIC Norfolk	Myocardial infarction	See appendix F
82	EPIC Norfolk	Myocardial infarction	See appendix F
83	EPIC Norfolk	Myocardial infarction	See appendix F
84	EPIC Norfolk	Myocardial infarction	See appendix F
85	EPIC Norfolk	Myocardial infarction	See appendix F
86	EPIC Norfolk	Myocardial infarction	See appendix F
87	Glostrup Population Studies	Coronary heart disease	See appendix F
88	Glostrup Population Studies	Coronary heart disease	See appendix F
89	Guangzhou	SBP	See appendix F
90	Guangzhou	SBP	See appendix F
91	Guangzhou	SBP	See appendix F
92	Guangzhou	SBP	See appendix F
93	Guangzhou	DBP	See appendix F
94	Guangzhou	DBP	See appendix F
95	Guangzhou	DBP	See appendix F
96	Guangzhou	DBP	See appendix F
97	Health Professional Follow-up Study	CABG	See appendix F
98	Health Professional Follow-up Study	Coronary heart disease	See appendix F
99	Health Professional Follow-up Study	Coronary heart disease	See appendix F
100	Health Professional Follow-up Study	Coronary heart disease	See appendix F
101	Health Professional Follow-up Study	Death, CHD	See appendix F
102	Health Professional Follow-up Study	MACE	See appendix F
103	Health Professional Follow-up Study	Myocardial infarction	See appendix F
104	Health Professional Follow-up Study	Stroke, hemorrhagic	See appendix F
105	Health Professional Follow-up Study	Stroke, ischemic	See appendix F
106	Health Professional Follow-up Study	Stroke, total	See appendix F
107	Health Professional Follow-up Study	Sudden cardiac death	See appendix F
108	Health Professional Follow-up Study	Sudden cardiac death	See appendix F
109	Hisayama	CVD, total	See appendix F
110	Hisayama	CVD, total	See appendix F
111	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Atrial fibrillation	See appendix F
112	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Atrial fibrillation	See appendix F

Row	Study	Study years (study start date)	Country
113	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	1987	US
114	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	1987	US
115	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	1987	US
116	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	1987	US
117	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	1987	US
118	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	1987	US
119	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	1987	US
120	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	1987	US
121	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	1987	US
122	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	1987	US
123	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	1987	US
124	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	1987	US
125	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	1988-1990	Japan
126	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	1988-1990	Japan
127	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	1988-1990	Japan
128	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	1988-1990	Japan
129	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	1988-1990	Japan
130	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	1988-1990	Japan
131	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	1988-1990	Japan

Row	Study	Population	Risk type
113	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Primary Prevention, Healthy	The population is a mixture of people
114	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Primary Prevention, Healthy	The population is a mixture of people
115	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Primary Prevention, Healthy	The population is a mixture of people
116	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Primary Prevention, Healthy	The population is a mixture of people
117	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Primary Prevention, Healthy	The population is a mixture of people
118	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Primary Prevention, Healthy	The population is a mixture of people
119	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Primary Prevention, Healthy	The population is a mixture of people
120	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Primary Prevention, Healthy	The population is a mixture of people
121	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Primary Prevention, Healthy	The population is a mixture of people
122	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Primary Prevention, Healthy	The population is a mixture of people
123	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Primary Prevention, Healthy	The population is a mixture of people
124	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Primary Prevention, Healthy	The population is a mixture of people
125	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Primary Prevention, Healthy	na
126	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Primary Prevention, Healthy	na
127	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Primary Prevention, Healthy	na
128	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Primary Prevention, Healthy	na
129	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Primary Prevention, Healthy	na
130	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Primary Prevention, Healthy	na
131	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Primary Prevention, Healthy	na

Row	Study	Sample size (total)	Age mean (SD) [median]	Sex (% male)
113	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	3592	men: 54.2 (5.6), women 53.3 (5.5)	46.6
114	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	3592	men: 54.2 (5.6), women 53.3 (5.5)	46.6
115	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	3592	men: 54.2 (5.6), women 53.3 (5.5)	46.6
116	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	3592	men: 54.2 (5.6), women 53.3 (5.5)	46.6
117	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	3592	men: 54.2 (5.6), women 53.3 (5.5)	46.6
118	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	3592	men: 54.2 (5.6), women 53.3 (5.5)	46.6
119	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	3592	men: 54.2 (5.6), women 53.3 (5.5)	46.6
120	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	3592	men: 54.2 (5.6), women 53.3 (5.5)	46.6
121	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	3592	men: 54.2 (5.6), women 53.3 (5.5)	46.6
122	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	3592	men: 54.2 (5.6), women 53.3 (5.5)	46.6
123	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	3592	men: 54.2 (5.6), women 53.3 (5.5)	46.6
124	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	3592	men: 54.2 (5.6), women 53.3 (5.5)	46.6
125	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	57972	55.7	39.5
126	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	57972	55.7	39.5
127	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	57972	55.7	39.5
128	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	57972	55.7	39.5
129	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	57972	55.7	39.5
130	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	57972	55.7	39.5
131	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	57972	55.7	39.5

Row	Study	Race	Blood pressure SBP/DBP (mmHg)
113	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	100 white	men: 120.5 (14.8), women 116.9 (17.0)/men 75.5(9.2); women 72.1 (9.1)
114	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	100 white	men: 120.5 (14.8), women 116.9 (17.0)/men 75.5(9.2); women 72.1 (9.1)
115	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	100 white	men: 120.5 (14.8), women 116.9 (17.0)/men 75.5(9.2); women 72.1 (9.1)
116	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	100 white	men: 120.5 (14.8), women 116.9 (17.0)/men 75.5(9.2); women 72.1 (9.1)
117	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	100 white	men: 120.5 (14.8), women 116.9 (17.0)/men 75.5(9.2); women 72.1 (9.1)
118	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	100 white	men: 120.5 (14.8), women 116.9 (17.0)/men 75.5(9.2); women 72.1 (9.1)
119	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	100 white	men: 120.5 (14.8), women 116.9 (17.0)/men 75.5(9.2); women 72.1 (9.1)
120	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	100 white	men: 120.5 (14.8), women 116.9 (17.0)/men 75.5(9.2); women 72.1 (9.1)
121	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	100 white	men: 120.5 (14.8), women 116.9 (17.0)/men 75.5(9.2); women 72.1 (9.1)
122	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	100 white	men: 120.5 (14.8), women 116.9 (17.0)/men 75.5(9.2); women 72.1 (9.1)
123	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	100 white	men: 120.5 (14.8), women 116.9 (17.0)/men 75.5(9.2); women 72.1 (9.1)
124	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	100 white	men: 120.5 (14.8), women 116.9 (17.0)/men 75.5(9.2); women 72.1 (9.1)
125	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	100 Asian	nd
126	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	100 Asian	nd
127	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	100 Asian	nd
128	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	100 Asian	nd
129	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	100 Asian	nd
130	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	100 Asian	nd
131	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	100 Asian	nd

Row	Study	Lipids: Total cholesterol/LDL/HDL/Triglycerides mean (SD) mg/dL [mmol/L]
113	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	men: 212 (39), women 216 (42)/nd/men: 44(12); women: 60(17)/men: 139 (94), women: 116 (73)
114	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	men: 212 (39), women 216 (42)/nd/men: 44(12); women: 60(17)/men: 139 (94), women: 116 (73)
115	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	men: 212 (39), women 216 (42)/nd/men: 44(12); women: 60(17)/men: 139 (94), women: 116 (73)
116	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	men: 212 (39), women 216 (42)/nd/men: 44(12); women: 60(17)/men: 139 (94), women: 116 (73)
117	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	men: 212 (39), women 216 (42)/nd/men: 44(12); women: 60(17)/men: 139 (94), women: 116 (73)
118	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	men: 212 (39), women 216 (42)/nd/men: 44(12); women: 60(17)/men: 139 (94), women: 116 (73)
119	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	men: 212 (39), women 216 (42)/nd/men: 44(12); women: 60(17)/men: 139 (94), women: 116 (73)
120	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	men: 212 (39), women 216 (42)/nd/men: 44(12); women: 60(17)/men: 139 (94), women: 116 (73)
121	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	men: 212 (39), women 216 (42)/nd/men: 44(12); women: 60(17)/men: 139 (94), women: 116 (73)
122	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	men: 212 (39), women 216 (42)/nd/men: 44(12); women: 60(17)/men: 139 (94), women: 116 (73)
123	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	men: 212 (39), women 216 (42)/nd/men: 44(12); women: 60(17)/men: 139 (94), women: 116 (73)
124	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	men: 212 (39), women 216 (42)/nd/men: 44(12); women: 60(17)/men: 139 (94), women: 116 (73)
125	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	nd
126	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	nd
127	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	nd
128	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	nd
129	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	nd
130	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	nd
131	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	nd

Appendix G.2.
Causality Table: Observational Studies

Row	Study	BMI mean (SD)/weight mean (SD) Kg
113	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	men: 27.7 (3.7), women: 26.2 (5)
114	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	men: 27.7 (3.7), women: 26.2 (5)
115	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	men: 27.7 (3.7), women: 26.2 (5)
116	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	men: 27.7 (3.7), women: 26.2 (5)
117	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	men: 27.7 (3.7), women: 26.2 (5)
118	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	men: 27.7 (3.7), women: 26.2 (5)
119	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	men: 27.7 (3.7), women: 26.2 (5)
120	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	men: 27.7 (3.7), women: 26.2 (5)
121	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	men: 27.7 (3.7), women: 26.2 (5)
122	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	men: 27.7 (3.7), women: 26.2 (5)
123	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	men: 27.7 (3.7), women: 26.2 (5)
124	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	men: 27.7 (3.7), women: 26.2 (5)
125	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	men: 22.7, women 22.9
126	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	men: 22.7, women 22.9
127	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	men: 22.7, women 22.9
128	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	men: 22.7, women 22.9
129	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	men: 22.7, women 22.9
130	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	men: 22.7, women 22.9
131	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	men: 22.7, women 22.9

Row	Study	Baseline n-3 intake/level (median (IQR), unless noted)
113	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	DHA: 0.38% FA, EPA+DHA+DPA: 0.94% FA
114	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	DHA: 0.38% FA, EPA+DHA+DPA: 0.94% FA
115	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	DHA: 0.38% FA, EPA+DHA+DPA: 0.94% FA
116	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	DHA: 0.38% FA, EPA+DHA+DPA: 0.94% FA
117	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	DHA: 0.38% FA, EPA+DHA+DPA: 0.94% FA
118	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	DHA: 0.38% FA, EPA+DHA+DPA: 0.94% FA
119	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	DHA: 0.38% FA, EPA+DHA+DPA: 0.94% FA
120	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	DHA: 0.38% FA, EPA+DHA+DPA: 0.94% FA
121	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	DHA: 0.38% FA, EPA+DHA+DPA: 0.94% FA
122	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	DHA: 0.38% FA, EPA+DHA+DPA: 0.94% FA
123	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	DHA: 0.38% FA, EPA+DHA+DPA: 0.94% FA
124	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	DHA: 0.38% FA, EPA+DHA+DPA: 0.94% FA
125	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	All n-3 FA: 1.61 g/d
126	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	All n-3 FA: 1.61 g/d
127	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	All n-3 FA: 1.61 g/d
128	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	All n-3 FA: 1.61 g/d
129	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	All n-3 FA: 1.61 g/d
130	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	All n-3 FA: 1.61 g/d
131	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	All n-3 FA: 1.61 g/d

Appendix G.2.
Causality Table: Observational Studies

Row	Study	n-3 source	n-3 measure	n-3 type(s)
113	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Intake	grams/day	EPA
114	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Phospholipid	grams/day	DHA+EPA
115	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Phospholipid	grams/day	DHA
116	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Phospholipid	grams/day	EPA
117	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Cholesterol ester	% of total FA	ALA
118	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Phospholipid	% of total FA	ALA
119	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Cholesterol ester	% of total FA	EPA+DHA+DPA
120	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Phospholipid	% of total FA	EPA+DHA+DPA
121	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Cholesterol ester	% of total FA	EPA
122	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Phospholipid	% of total FA	EPA
123	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Cholesterol ester	% of total FA	DHA
124	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Phospholipid	% of total FA	DHA
125	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	intake	g/d	all n-3
126	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	intake	g/d	all n-3
127	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	intake	g/d	all n-3
128	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	intake	g/d	all n-3
129	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	intake	g/d	all n-3
130	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	intake	g/d	all n-3
131	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	intake	g/d	all n-3

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Study design
113	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
114	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
115	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
116	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
117	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
118	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
119	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
120	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
121	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
122	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
123	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
124	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
125	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
126	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
127	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
128	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
129	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
130	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
131	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Outcome	Reported effect Size
113	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Atrial fibrillation	See appendix F
114	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Atrial fibrillation	See appendix F
115	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Atrial fibrillation	See appendix F
116	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Atrial fibrillation	See appendix F
117	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Congestive heart failure	See appendix F
118	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Congestive heart failure	See appendix F
119	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Congestive heart failure	See appendix F
120	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Congestive heart failure	See appendix F
121	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Congestive heart failure	See appendix F
122	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Congestive heart failure	See appendix F
123	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Congestive heart failure	See appendix F
124	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Congestive heart failure	See appendix F
125	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Death, all cause	See appendix F
126	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Death, cardiac arrest	See appendix F
127	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Death, CHD	See appendix F
128	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Death, CVD	See appendix F
129	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Death, heart failure	See appendix F
130	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Death, MI	See appendix F
131	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Death, stroke	See appendix F

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Study years (study start date)	Country
132	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	1988-1990	Japan
133	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	1987	US
134	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	1987	US
135	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	1987	US
136	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	1987	US
137	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	1987	US
138	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	1987	US
139	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	1987	US
140	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	1987	US
141	Japan Public Health Center-Based (JPHC) Study - Cohort I	1990	Japan
142	Japan Public Health Center-Based (JPHC) Study - Cohort I	1990	Japan
143	Japan Public Health Center-Based (JPHC) Study - Cohort I	1990	Japan
144	Japan Public Health Center-Based (JPHC) Study - Cohort I	1990	Japan
145	JELIS	1996-1999	Japan
146	JELIS	1996-1999	Japan
147	Kuopio Ischemic Heart Disease Risk Factor Study	1984	Finland
148	Kuopio Ischemic Heart Disease Risk Factor Study	1984	Finland
149	Kuopio Ischemic Heart Disease Risk Factor Study	1984	Finland
150	Kuopio Ischemic Heart Disease Risk Factor Study	1984	Finland

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Population	Risk type
132	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Primary Prevention, Healthy	na
133	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Primary Prevention, Healthy	The population is a mixture of people
134	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Primary Prevention, Healthy	The population is a mixture of people
135	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Primary Prevention, Healthy	The population is a mixture of people
136	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Primary Prevention, Healthy	The population is a mixture of people
137	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Primary Prevention, Healthy	The population is a mixture of people
138	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Primary Prevention, Healthy	The population is a mixture of people
139	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Primary Prevention, Healthy	The population is a mixture of people
140	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Primary Prevention, Healthy	The population is a mixture of people
141	Japan Public Health Center-Based (JPHC) Study - Cohort I	Primary Prevention, Healthy	na
142	Japan Public Health Center-Based (JPHC) Study - Cohort I	Primary Prevention, Healthy	na
143	Japan Public Health Center-Based (JPHC) Study - Cohort I	Primary Prevention, Healthy	na
144	Japan Public Health Center-Based (JPHC) Study - Cohort I	Primary Prevention, Healthy	na
145	JELIS	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome, hypertension, dyslipidemia, or chronic kidney disease)	Dyslipidemia (>250mg/dL total cholesterol or >170mg/dL LDL)
146	JELIS	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome, hypertension, dyslipidemia, or chronic kidney disease)	Dyslipidemia (>250mg/dL total cholesterol or >170mg/dL LDL)
147	Kuopio Ischemic Heart Disease Risk Factor Study	Primary Prevention, Healthy	na
148	Kuopio Ischemic Heart Disease Risk Factor Study	Primary Prevention, Healthy	na
149	Kuopio Ischemic Heart Disease Risk Factor Study	Primary Prevention, Healthy	na
150	Kuopio Ischemic Heart Disease Risk Factor Study	Primary Prevention, Healthy	na

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Sample size (total)	Age mean (SD) [median]	Sex (% male)
132	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	57972	55.7	39.5
133	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	3592	men: 54.2 (5.6), women 53.3 (5.5)	46.6
134	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	3592	men: 54.2 (5.6), women 53.3 (5.5)	46.6
135	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	3592	men: 54.2 (5.6), women 53.3 (5.5)	46.6
136	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	3592	men: 54.2 (5.6), women 53.3 (5.5)	46.6
137	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	3592	men: 54.2 (5.6), women 53.3 (5.5)	46.6
138	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	3592	men: 54.2 (5.6), women 53.3 (5.5)	46.6
139	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	3592	men: 54.2 (5.6), women 53.3 (5.5)	46.6
140	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	3592	men: 54.2 (5.6), women 53.3 (5.5)	46.6
141	Japan Public Health Center-Based (JPHC) Study - Cohort I	41578	49	48
142	Japan Public Health Center-Based (JPHC) Study - Cohort I	41578	49	48
143	Japan Public Health Center-Based (JPHC) Study - Cohort I	41578	49	48
144	Japan Public Health Center-Based (JPHC) Study - Cohort I	41578	49	48
145	JELIS	15534	controls: 61 (9), cases: 61 (8)	30.25
146	JELIS	15534	controls: 61 (9), cases: 61 (8)	30.25
147	Kuopio Ischemic Heart Disease Risk Factor Study	1941	52.8 (5.3)	100
148	Kuopio Ischemic Heart Disease Risk Factor Study	1941	52.8 (5.3)	100
149	Kuopio Ischemic Heart Disease Risk Factor Study	1941	52.8 (5.3)	100
150	Kuopio Ischemic Heart Disease Risk Factor Study	1941	52.8 (5.3)	100

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Race	Blood pressure SBP/DBP (mmHg)
132	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	100 Asian	nd
133	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	100 white	men: 120.5 (14.8), women 116.9 (17.0)/men 75.5(9.2); women 72.1 (9.1)
134	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	100 white	men: 120.5 (14.8), women 116.9 (17.0)/men 75.5(9.2); women 72.1 (9.1)
135	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	100 white	men: 120.5 (14.8), women 116.9 (17.0)/men 75.5(9.2); women 72.1 (9.1)
136	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	100 white	men: 120.5 (14.8), women 116.9 (17.0)/men 75.5(9.2); women 72.1 (9.1)
137	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	100 white	men: 120.5 (14.8), women 116.9 (17.0)/men 75.5(9.2); women 72.1 (9.1)
138	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	100 white	men: 120.5 (14.8), women 116.9 (17.0)/men 75.5(9.2); women 72.1 (9.1)
139	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	100 white	men: 120.5 (14.8), women 116.9 (17.0)/men 75.5(9.2); women 72.1 (9.1)
140	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	100 white	men: 120.5 (14.8), women 116.9 (17.0)/men 75.5(9.2); women 72.1 (9.1)
141	Japan Public Health Center-Based (JPHC) Study - Cohort I	nd	nd
142	Japan Public Health Center-Based (JPHC) Study - Cohort I	nd	nd
143	Japan Public Health Center-Based (JPHC) Study - Cohort I	nd	nd
144	Japan Public Health Center-Based (JPHC) Study - Cohort I	nd	nd
145	JELIS	100 Asian	controls: 134.9 (20.9), cases: 134.9 (21.4)/controls 79.2 (12.6), cases: 78.9 (12.6)
146	JELIS	100 Asian	controls: 134.9 (20.9), cases: 134.9 (21.4)/controls 79.2 (12.6), cases: 78.9 (12.6)
147	Kuopio Ischemic Heart Disease Risk Factor Study	nd	nd
148	Kuopio Ischemic Heart Disease Risk Factor Study	nd	nd
149	Kuopio Ischemic Heart Disease Risk Factor Study	nd	nd
150	Kuopio Ischemic Heart Disease Risk Factor Study	nd	nd

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Lipids: Total cholesterol/LDL/HDL/Triglycerides mean (SD) mg/dL [mmol/L]
132	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	nd
133	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	men: 212 (39), women 216 (42)/nd/men: 44(12); women: 60(17)/men: 139 (94), women: 116 (73)
134	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	men: 212 (39), women 216 (42)/nd/men: 44(12); women: 60(17)/men: 139 (94), women: 116 (73)
135	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	men: 212 (39), women 216 (42)/nd/men: 44(12); women: 60(17)/men: 139 (94), women: 116 (73)
136	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	men: 212 (39), women 216 (42)/nd/men: 44(12); women: 60(17)/men: 139 (94), women: 116 (73)
137	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	men: 212 (39), women 216 (42)/nd/men: 44(12); women: 60(17)/men: 139 (94), women: 116 (73)
138	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	men: 212 (39), women 216 (42)/nd/men: 44(12); women: 60(17)/men: 139 (94), women: 116 (73)
139	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	men: 212 (39), women 216 (42)/nd/men: 44(12); women: 60(17)/men: 139 (94), women: 116 (73)
140	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	men: 212 (39), women 216 (42)/nd/men: 44(12); women: 60(17)/men: 139 (94), women: 116 (73)
141	Japan Public Health Center-Based (JPHC) Study - Cohort I	nd
142	Japan Public Health Center-Based (JPHC) Study - Cohort I	nd
143	Japan Public Health Center-Based (JPHC) Study - Cohort I	nd
144	Japan Public Health Center-Based (JPHC) Study - Cohort I	nd
145	JELIS	nd
146	JELIS	nd
147	Kuopio Ischemic Heart Disease Risk Factor Study	nd
148	Kuopio Ischemic Heart Disease Risk Factor Study	nd
149	Kuopio Ischemic Heart Disease Risk Factor Study	nd
150	Kuopio Ischemic Heart Disease Risk Factor Study	nd

Appendix G.2.
Causality Table: Observational Studies

Row	Study	BMI mean (SD)/weight mean (SD) Kg
132	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	men: 22.7, women 22.9
133	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	men: 27.7 (3.7), women: 26.2 (5)
134	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	men: 27.7 (3.7), women: 26.2 (5)
135	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	men: 27.7 (3.7), women: 26.2 (5)
136	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	men: 27.7 (3.7), women: 26.2 (5)
137	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	men: 27.7 (3.7), women: 26.2 (5)
138	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	men: 27.7 (3.7), women: 26.2 (5)
139	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	men: 27.7 (3.7), women: 26.2 (5)
140	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	men: 27.7 (3.7), women: 26.2 (5)
141	Japan Public Health Center-Based (JPHC) Study - Cohort I	nd
142	Japan Public Health Center-Based (JPHC) Study - Cohort I	nd
143	Japan Public Health Center-Based (JPHC) Study - Cohort I	nd
144	Japan Public Health Center-Based (JPHC) Study - Cohort I	nd
145	JELIS	controls: 24.1 (3.3), cases 24.0 (3.2)
146	JELIS	controls: 24.1 (3.3), cases 24.0 (3.2)
147	Kuopio Ischemic Heart Disease Risk Factor Study	nd
148	Kuopio Ischemic Heart Disease Risk Factor Study	nd
149	Kuopio Ischemic Heart Disease Risk Factor Study	nd
150	Kuopio Ischemic Heart Disease Risk Factor Study	nd

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Baseline n-3 intake/level (median (IQR), unless noted)
132	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	All n-3 FA: 1.61 g/d
133	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	DHA: 0.38% FA, EPA+DHA+DPA: 0.94% FA
134	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	DHA: 0.38% FA, EPA+DHA+DPA: 0.94% FA
135	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	DHA: 0.38% FA, EPA+DHA+DPA: 0.94% FA
136	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	DHA: 0.38% FA, EPA+DHA+DPA: 0.94% FA
137	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	DHA: 0.38% FA, EPA+DHA+DPA: 0.94% FA
138	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	DHA: 0.38% FA, EPA+DHA+DPA: 0.94% FA
139	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	DHA: 0.38% FA, EPA+DHA+DPA: 0.94% FA
140	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	DHA: 0.38% FA, EPA+DHA+DPA: 0.94% FA
141	Japan Public Health Center-Based (JPHC) Study - Cohort I	EPA+DHA: mean 0.9
142	Japan Public Health Center-Based (JPHC) Study - Cohort I	EPA+DHA: mean 0.9
143	Japan Public Health Center-Based (JPHC) Study - Cohort I	EPA+DHA: mean 0.9
144	Japan Public Health Center-Based (JPHC) Study - Cohort I	EPA+DHA: mean 0.9
145	JELIS	EPA: 133 mcg/mL, DHA: 160 mcg/mL
146	JELIS	EPA: 133 mcg/mL, DHA: 160 mcg/mL
147	Kuopio Ischemic Heart Disease Risk Factor Study	EPA: 1.48% FA, DPA: 0.55% FA, DHA: 2.37% FA, EPA+DPA+DHA: 4.36% FA
148	Kuopio Ischemic Heart Disease Risk Factor Study	EPA: 1.48% FA, DPA: 0.55% FA, DHA: 2.37% FA, EPA+DPA+DHA: 4.36% FA
149	Kuopio Ischemic Heart Disease Risk Factor Study	EPA: 1.48% FA, DPA: 0.55% FA, DHA: 2.37% FA, EPA+DPA+DHA: 4.36% FA
150	Kuopio Ischemic Heart Disease Risk Factor Study	EPA: 1.48% FA, DPA: 0.55% FA, DHA: 2.37% FA, EPA+DPA+DHA: 4.36% FA

Appendix G.2.
Causality Table: Observational Studies

Row	Study	n-3 source	n-3 measure	n-3 type(s)
132	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	intake	g/d	all n-3
133	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Cholesterol ester	% plasma LC n-3 FA	EPA+DHA+DPA
134	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Phospholipid	% plasma LC n-3 FA	EPA+DHA+DPA
135	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Cholesterol ester	% plasma LC n-3 FA	ALA
136	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Phospholipid	% plasma LC n-3 FA	ALA
137	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Cholesterol ester	% plasma LC n-3 FA	EPA
138	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Phospholipid	% plasma LC n-3 FA	EPA
139	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Cholesterol ester	% plasma LC n-3 FA	DHA
140	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Phospholipid	% plasma LC n-3 FA	DHA
141	Japan Public Health Center-Based (JPHC) Study - Cohort I	intake	g/d	EPA + DHA
142	Japan Public Health Center-Based (JPHC) Study - Cohort I	intake	g/d	EPA + DHA
143	Japan Public Health Center-Based (JPHC) Study - Cohort I	intake	g/d	EPA + DHA
144	Japan Public Health Center-Based (JPHC) Study - Cohort I	intake	g/d	EPA + DHA
145	JELIS	plasma	mcg/mL	EPA
146	JELIS	plasma	mcg/mL	DHA
147	Kuopio Ischemic Heart Disease Risk Factor Study	serum	% of serum FA	EPA+DPA+DHA
148	Kuopio Ischemic Heart Disease Risk Factor Study	serum	% of serum FA	EPA
149	Kuopio Ischemic Heart Disease Risk Factor Study	serum	% of serum FA	DPA
150	Kuopio Ischemic Heart Disease Risk Factor Study	serum	% of serum FA	DHA

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Study design
132	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
133	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
134	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
135	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
136	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
137	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
138	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
139	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
140	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
141	Japan Public Health Center-Based (JPHC) Study - Cohort I	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
142	Japan Public Health Center-Based (JPHC) Study - Cohort I	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
143	Japan Public Health Center-Based (JPHC) Study - Cohort I	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
144	Japan Public Health Center-Based (JPHC) Study - Cohort I	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
145	JELIS	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
146	JELIS	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
147	Kuopio Ischemic Heart Disease Risk Factor Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
148	Kuopio Ischemic Heart Disease Risk Factor Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
149	Kuopio Ischemic Heart Disease Risk Factor Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
150	Kuopio Ischemic Heart Disease Risk Factor Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Outcome	Reported effect Size
132	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Death, stroke, ischemic	See appendix F
133	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Stroke, ischemic	See appendix F
134	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Stroke, ischemic	See appendix F
135	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Stroke, ischemic	See appendix F
136	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Stroke, ischemic	See appendix F
137	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Stroke, ischemic	See appendix F
138	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Stroke, ischemic	See appendix F
139	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Stroke, ischemic	See appendix F
140	JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk)	Stroke, ischemic	See appendix F
141	Japan Public Health Center-Based (JPHC) Study - Cohort I	Coronary heart disease	See appendix F
142	Japan Public Health Center-Based (JPHC) Study - Cohort I	Death, cardiac	See appendix F
143	Japan Public Health Center-Based (JPHC) Study - Cohort I	Myocardial infarction	See appendix F
144	Japan Public Health Center-Based (JPHC) Study - Cohort I	Sudden cardiac death	See appendix F
145	JELIS	MACE	See appendix F
146	JELIS	MACE	See appendix F
147	Kuopio Ischemic Heart Disease Risk Factor Study	Atrial fibrillation	See appendix F
148	Kuopio Ischemic Heart Disease Risk Factor Study	Atrial fibrillation	See appendix F
149	Kuopio Ischemic Heart Disease Risk Factor Study	Atrial fibrillation	See appendix F
150	Kuopio Ischemic Heart Disease Risk Factor Study	Atrial fibrillation	See appendix F

Appendix G.2.

Causality Table: Observational Studies

Row	Study	Study years (study start date)	Country
151	MDC (Malmo Diet and Cancer)	1991	Sweden
152	MDC (Malmo Diet and Cancer)	1991	Sweden
153	MDC (Malmo Diet and Cancer)	1991	Sweden
154	MDC (Malmo Diet and Cancer)	1991	Sweden
155	MDC (Malmo Diet and Cancer)	1991	Sweden
156	MDC (Malmo Diet and Cancer)	1991	Sweden
157	MESA	2000	US
158	MESA	2000	US
159	MESA	2000	US
160	MESA	2000	US
161	MESA	2000	US
162	MESA	2000	US
163	MESA	2000	US
164	MESA	2000	US
165	MESA	2000	US
166	MESA	2000	US
167	MESA	2000	US
168	MESA	2000	US
169	MESA	2000	US
170	MESA	2000	US
171	MESA	2000	US
172	MESA	2000	US
173	MESA	2000	US

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Population	Risk type
151	MDC (Malmo Diet and Cancer)	Primary Prevention, Healthy	na
152	MDC (Malmo Diet and Cancer)	Primary Prevention, Healthy	na
153	MDC (Malmo Diet and Cancer)	Primary Prevention, Healthy	na
154	MDC (Malmo Diet and Cancer)	Primary Prevention, Healthy	na
155	MDC (Malmo Diet and Cancer)	Primary Prevention, Healthy	na
156	MDC (Malmo Diet and Cancer)	Primary Prevention, Healthy	na
157	MESA	Primary Prevention, Healthy	na
158	MESA	Primary Prevention, Healthy	na
159	MESA	Primary Prevention, Healthy	na
160	MESA	Primary Prevention, Healthy	na
161	MESA	Primary Prevention, Healthy	na
162	MESA	Primary Prevention, Healthy	na
163	MESA	Primary Prevention, Healthy	na
164	MESA	Primary Prevention, Healthy	na
165	MESA	Primary Prevention, Healthy	na
166	MESA	Primary Prevention, Healthy	na
167	MESA	Primary Prevention, Healthy	na
168	MESA	Primary Prevention, Healthy	na
169	MESA	Primary Prevention, Healthy	na
170	MESA	Primary Prevention, Healthy	na
171	MESA	Primary Prevention, Healthy	na
172	MESA	Primary Prevention, Healthy	na
173	MESA	Primary Prevention, Healthy	na

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Sample size (total)	Age mean (SD) [median]	Sex (% male)
151	MDC (Malmo Diet and Cancer)	24032	range 44, 74	37
152	MDC (Malmo Diet and Cancer)	24032	range 44, 74	37
153	MDC (Malmo Diet and Cancer)	24032	range 44, 74	37
154	MDC (Malmo Diet and Cancer)	24032	range 44, 74	37
155	MDC (Malmo Diet and Cancer)	24032	range 44, 74	37
156	MDC (Malmo Diet and Cancer)	24032	range 44, 74	37
157	MESA	2837	61.5 (10.2)	46.8
158	MESA	2837	61.5 (10.2)	46.8
159	MESA	2837	61.5 (10.2)	46.8
160	MESA	2837	61.5 (10.2)	46.8
161	MESA	2837	61.5 (10.2)	46.8
162	MESA	2837	61.5 (10.2)	46.8
163	MESA	2837	61.5 (10.2)	46.8
164	MESA	2837	61.5 (10.2)	46.8
165	MESA	2837	61.5 (10.2)	46.8
166	MESA	2837	61.5 (10.2)	46.8
167	MESA	2837	61.5 (10.2)	46.8
168	MESA	2837	61.5 (10.2)	46.8
169	MESA	2837	61.5 (10.2)	46.8
170	MESA	2837	61.5 (10.2)	46.8
171	MESA	2837	61.5 (10.2)	46.8
172	MESA	2837	61.5 (10.2)	46.8
173	MESA	2837	61.5 (10.2)	46.8

Row	Study	Race	Blood pressure SBP/DBP (mmHg)
151	MDC (Malmo Diet and Cancer)	nd	nd
152	MDC (Malmo Diet and Cancer)	nd	nd
153	MDC (Malmo Diet and Cancer)	nd	nd
154	MDC (Malmo Diet and Cancer)	nd	nd
155	MDC (Malmo Diet and Cancer)	nd	nd
156	MDC (Malmo Diet and Cancer)	nd	nd
157	MESA	26 white, 25 black, 25 Asian, 25 Hispanic	nd
158	MESA	26 white, 25 black, 25 Asian, 25 Hispanic	nd
159	MESA	26 white, 25 black, 25 Asian, 25 Hispanic	nd
160	MESA	26 white, 25 black, 25 Asian, 25 Hispanic	nd
161	MESA	26 white, 25 black, 25 Asian, 25 Hispanic	nd
162	MESA	26 white, 25 black, 25 Asian, 25 Hispanic	nd
163	MESA	26 white, 25 black, 25 Asian, 25 Hispanic	nd
164	MESA	26 white, 25 black, 25 Asian, 25 Hispanic	nd
165	MESA	26 white, 25 black, 25 Asian, 25 Hispanic	nd
166	MESA	26 white, 25 black, 25 Asian, 25 Hispanic	nd
167	MESA	26 white, 25 black, 25 Asian, 25 Hispanic	nd
168	MESA	26 white, 25 black, 25 Asian, 25 Hispanic	nd
169	MESA	26 white, 25 black, 25 Asian, 25 Hispanic	nd
170	MESA	26 white, 25 black, 25 Asian, 25 Hispanic	nd
171	MESA	26 white, 25 black, 25 Asian, 25 Hispanic	nd
172	MESA	26 white, 25 black, 25 Asian, 25 Hispanic	nd
173	MESA	26 white, 25 black, 25 Asian, 25 Hispanic	nd

Row	Study	Lipids: Total cholesterol/LDL/HDL/Triglycerides mean (SD) mg/dL [mmol/L]
151	MDC (Malmo Diet and Cancer)	nd
152	MDC (Malmo Diet and Cancer)	nd
153	MDC (Malmo Diet and Cancer)	nd
154	MDC (Malmo Diet and Cancer)	nd
155	MDC (Malmo Diet and Cancer)	nd
156	MDC (Malmo Diet and Cancer)	nd
157	MESA	nd
158	MESA	nd
159	MESA	nd
160	MESA	nd
161	MESA	nd
162	MESA	nd
163	MESA	nd
164	MESA	nd
165	MESA	nd
166	MESA	nd
167	MESA	nd
168	MESA	nd
169	MESA	nd
170	MESA	nd
171	MESA	nd
172	MESA	nd
173	MESA	nd

Appendix G.2.
Causality Table: Observational Studies

Row	Study	BMI mean (SD)/weight mean (SD) Kg
151	MDC (Malmo Diet and Cancer)	25.6
152	MDC (Malmo Diet and Cancer)	25.6
153	MDC (Malmo Diet and Cancer)	25.6
154	MDC (Malmo Diet and Cancer)	25.6
155	MDC (Malmo Diet and Cancer)	25.6
156	MDC (Malmo Diet and Cancer)	25.6
157	MESA	27.9 (5.5)
158	MESA	27.9 (5.5)
159	MESA	27.9 (5.5)
160	MESA	27.9 (5.5)
161	MESA	27.9 (5.5)
162	MESA	27.9 (5.5)
163	MESA	27.9 (5.5)
164	MESA	27.9 (5.5)
165	MESA	27.9 (5.5)
166	MESA	27.9 (5.5)
167	MESA	27.9 (5.5)
168	MESA	27.9 (5.5)
169	MESA	27.9 (5.5)
170	MESA	27.9 (5.5)
171	MESA	27.9 (5.5)
172	MESA	27.9 (5.5)
173	MESA	27.9 (5.5)

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Baseline n-3 intake/level (median (IQR), unless noted)
151	MDC (Malmo Diet and Cancer)	ALA 0.72% energy, EPA+DPA+DHA: 0.19% energy, Total n-3 FA: 0.96% energy
152	MDC (Malmo Diet and Cancer)	ALA 0.72% energy, EPA+DPA+DHA: 0.19% energy, Total n-3 FA: 0.96% energy
153	MDC (Malmo Diet and Cancer)	ALA 0.72% energy, EPA+DPA+DHA: 0.19% energy, Total n-3 FA: 0.96% energy
154	MDC (Malmo Diet and Cancer)	ALA 0.72% energy, EPA+DPA+DHA: 0.19% energy, Total n-3 FA: 0.96% energy
155	MDC (Malmo Diet and Cancer)	ALA 0.72% energy, EPA+DPA+DHA: 0.19% energy, Total n-3 FA: 0.96% energy
156	MDC (Malmo Diet and Cancer)	ALA 0.72% energy, EPA+DPA+DHA: 0.19% energy, Total n-3 FA: 0.96% energy
157	MESA	ALA: mean 1.0 (SD 0.6) g/d, EPA: mean 45 (SD 50) mg/d, DHA: mean 82 (SD 73) mg/d, DPA: mean 20 (SD 20) mg/d
158	MESA	ALA: mean 1.0 (SD 0.6) g/d, EPA: mean 45 (SD 50) mg/d, DHA: mean 82 (SD 73) mg/d, DPA: mean 20 (SD 20) mg/d
159	MESA	ALA: mean 1.0 (SD 0.6) g/d, EPA: mean 45 (SD 50) mg/d, DHA: mean 82 (SD 73) mg/d, DPA: mean 20 (SD 20) mg/d
160	MESA	ALA: mean 1.0 (SD 0.6) g/d, EPA: mean 45 (SD 50) mg/d, DHA: mean 82 (SD 73) mg/d, DPA: mean 20 (SD 20) mg/d
161	MESA	ALA: mean 1.0 (SD 0.6) g/d, EPA: mean 45 (SD 50) mg/d, DHA: mean 82 (SD 73) mg/d, DPA: mean 20 (SD 20) mg/d
162	MESA	ALA: mean 1.0 (SD 0.6) g/d, EPA: mean 45 (SD 50) mg/d, DHA: mean 82 (SD 73) mg/d, DPA: mean 20 (SD 20) mg/d
163	MESA	ALA: mean 1.0 (SD 0.6) g/d, EPA: mean 45 (SD 50) mg/d, DHA: mean 82 (SD 73) mg/d, DPA: mean 20 (SD 20) mg/d
164	MESA	ALA: mean 1.0 (SD 0.6) g/d, EPA: mean 45 (SD 50) mg/d, DHA: mean 82 (SD 73) mg/d, DPA: mean 20 (SD 20) mg/d
165	MESA	ALA: mean 1.0 (SD 0.6) g/d, EPA: mean 45 (SD 50) mg/d, DHA: mean 82 (SD 73) mg/d, DPA: mean 20 (SD 20) mg/d
166	MESA	ALA: mean 1.0 (SD 0.6) g/d, EPA: mean 45 (SD 50) mg/d, DHA: mean 82 (SD 73) mg/d, DPA: mean 20 (SD 20) mg/d
167	MESA	ALA: mean 1.0 (SD 0.6) g/d, EPA: mean 45 (SD 50) mg/d, DHA: mean 82 (SD 73) mg/d, DPA: mean 20 (SD 20) mg/d
168	MESA	ALA: mean 1.0 (SD 0.6) g/d, EPA: mean 45 (SD 50) mg/d, DHA: mean 82 (SD 73) mg/d, DPA: mean 20 (SD 20) mg/d
169	MESA	ALA: mean 1.0 (SD 0.6) g/d, EPA: mean 45 (SD 50) mg/d, DHA: mean 82 (SD 73) mg/d, DPA: mean 20 (SD 20) mg/d
170	MESA	ALA: mean 1.0 (SD 0.6) g/d, EPA: mean 45 (SD 50) mg/d, DHA: mean 82 (SD 73) mg/d, DPA: mean 20 (SD 20) mg/d
171	MESA	ALA: mean 1.0 (SD 0.6) g/d, EPA: mean 45 (SD 50) mg/d, DHA: mean 82 (SD 73) mg/d, DPA: mean 20 (SD 20) mg/d
172	MESA	ALA: mean 1.0 (SD 0.6) g/d, EPA: mean 45 (SD 50) mg/d, DHA: mean 82 (SD 73) mg/d, DPA: mean 20 (SD 20) mg/d
173	MESA	ALA: mean 1.0 (SD 0.6) g/d, EPA: mean 45 (SD 50) mg/d, DHA: mean 82 (SD 73) mg/d, DPA: mean 20 (SD 20) mg/d

Row	Study	n-3 source	n-3 measure	n-3 type(s)
151	MDC (Malmo Diet and Cancer)	intake	energy %	ALA
152	MDC (Malmo Diet and Cancer)	intake	energy %	long-chain n-3 PUFA (EPA, DPA, DHA)
153	MDC (Malmo Diet and Cancer)	intake	energy %	Total n-3 PUFA (ALA, EPA, DPA, and DHA)
154	MDC (Malmo Diet and Cancer)	intake	Per 1 E% increase of PUFA intake	ALA
155	MDC (Malmo Diet and Cancer)	intake	Per 1 E% increase of PUFA intake	long-chain n-3 PUFA (EPA, DPA, DHA)
156	MDC (Malmo Diet and Cancer)	intake	Per 1 E% increase of PUFA intake	Total n-3 PUFA (ALA, EPA, DPA, and DHA)
157	MESA	Phospholipid	% total FA	EPA
158	MESA	Phospholipid	% total FA	DPA
159	MESA	Phospholipid	% total FA	DHA
160	MESA	Phospholipid	% total FA	EPA+DPA+DHA
161	MESA	intake	mg/d	EPA
162	MESA	intake	mg/d	DPA
163	MESA	intake	mg/d	DHA
164	MESA	intake	mg/d	EPA+DPA+DHA
165	MESA	Phospholipid	% total FA	ALA
166	MESA	intake	mg/d	ALA
167	MESA	phospholipid	mg/d	EPA
168	MESA	phospholipid	mg/d	DPA
169	MESA	phospholipid	mg/d	DHA
170	MESA	phospholipid	mg/d	EPA+DPA+DHA
171	MESA	Phospholipid	% total FA	EPA
172	MESA	Phospholipid	% total FA	DPA
173	MESA	Phospholipid	% total FA	DHA

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Study design
151	MDC (Malmo Diet and Cancer)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
152	MDC (Malmo Diet and Cancer)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
153	MDC (Malmo Diet and Cancer)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
154	MDC (Malmo Diet and Cancer)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
155	MDC (Malmo Diet and Cancer)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
156	MDC (Malmo Diet and Cancer)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
157	MESA	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
158	MESA	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
159	MESA	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
160	MESA	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
161	MESA	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
162	MESA	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
163	MESA	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
164	MESA	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
165	MESA	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
166	MESA	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
167	MESA	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
168	MESA	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
169	MESA	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
170	MESA	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
171	MESA	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
172	MESA	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
173	MESA	Prospective, longitudinal study of intake (eg, FFQ, biomarker)

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Outcome	Reported effect Size
151	MDC (Malmo Diet and Cancer)	CVD, total	See appendix F
152	MDC (Malmo Diet and Cancer)	CVD, total	See appendix F
153	MDC (Malmo Diet and Cancer)	CVD, total	See appendix F
154	MDC (Malmo Diet and Cancer)	CVD, total	See appendix F
155	MDC (Malmo Diet and Cancer)	CVD, total	See appendix F
156	MDC (Malmo Diet and Cancer)	CVD, total	See appendix F
157	MESA	CVD, total	See appendix F
158	MESA	CVD, total	See appendix F
159	MESA	CVD, total	See appendix F
160	MESA	CVD, total	See appendix F
161	MESA	CVD, total	See appendix F
162	MESA	CVD, total	See appendix F
163	MESA	CVD, total	See appendix F
164	MESA	CVD, total	See appendix F
165	MESA	CVD, total	See appendix F
166	MESA	CVD, total	See appendix F
167	MESA	CVD, total	See appendix F
168	MESA	CVD, total	See appendix F
169	MESA	CVD, total	See appendix F
170	MESA	CVD, total	See appendix F
171	MESA	MACE	See appendix F
172	MESA	MACE	See appendix F
173	MESA	MACE	See appendix F

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Study years (study start date)	Country
174	MESA	2000	US
175	MESA	2000	US
176	MESA	2000	US
177	MESA	2000	US
178	MESA	2000	US
179	MESA	2000	US
180	MESA	2000	US
181	MORGEN	1993	Netherlands
182	MORGEN	1993	Netherlands
183	MORGEN	1993	Netherlands
184	MORGEN	1993	Netherlands
185	MORGEN	1993	Netherlands
186	MORGEN	1993	Netherlands
187	MORGEN	1993	Netherlands
188	MORGEN	1993	Netherlands
189	Multiple Risk Factor Intervention Trial	1973	US
190	Multiple Risk Factor Intervention Trial	1973	US
191	Multiple Risk Factor Intervention Trial	1973	US
192	Multiple Risk Factor Intervention Trial	1973	US
193	Multiple Risk Factor Intervention Trial	1973	US

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Population	Risk type
174	MESA	Primary Prevention, Healthy	na
175	MESA	Primary Prevention, Healthy	na
176	MESA	Primary Prevention, Healthy	na
177	MESA	Primary Prevention, Healthy	na
178	MESA	Primary Prevention, Healthy	na
179	MESA	Primary Prevention, Healthy	na
180	MESA	Primary Prevention, Healthy	na
181	MORGEN	Primary Prevention, Healthy	na
182	MORGEN	Primary Prevention, Healthy	na
183	MORGEN	Primary Prevention, Healthy	na
184	MORGEN	Primary Prevention, Healthy	na
185	MORGEN	Primary Prevention, Healthy	na
186	MORGEN	Primary Prevention, Healthy	na
187	MORGEN	Primary Prevention, Healthy	na
188	MORGEN	Primary Prevention, Healthy	na
189	Multiple Risk Factor Intervention Trial	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome, hypertension, dyslipidemia, or chronic kidney disease)	nd
190	Multiple Risk Factor Intervention Trial	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome, hypertension, dyslipidemia, or chronic kidney disease)	nd
191	Multiple Risk Factor Intervention Trial	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome, hypertension, dyslipidemia, or chronic kidney disease)	nd
192	Multiple Risk Factor Intervention Trial	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome, hypertension, dyslipidemia, or chronic kidney disease)	nd
193	Multiple Risk Factor Intervention Trial	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome, hypertension, dyslipidemia, or chronic kidney disease)	nd

Row	Study	Sample size (total)	Age mean (SD) [median]	Sex (% male)
174	MESA	2837	61.5 (10.2)	46.8
175	MESA	2837	61.5 (10.2)	46.8
176	MESA	2837	61.5 (10.2)	46.8
177	MESA	2837	61.5 (10.2)	46.8
178	MESA	2837	61.5 (10.2)	46.8
179	MESA	2837	61.5 (10.2)	46.8
180	MESA	2837	61.5 (10.2)	46.8
181	MORGEN	21055	41.8	45
182	MORGEN	21055	41.8	45
183	MORGEN	358	Cases: 50.1 (9.5), Controls: 50.0 (9.5)	53
184	MORGEN	358	Cases: 50.1 (9.5), Controls: 50.0 (9.5)	53
185	MORGEN	358	Cases: 50.1 (9.5), Controls: 50.0 (9.5)	53
186	MORGEN	358	Cases: 50.1 (9.5), Controls: 50.0 (9.5)	53
187	MORGEN	358	Cases: 50.1 (9.5), Controls: 50.0 (9.5)	53
188	MORGEN	358	Cases: 50.1 (9.5), Controls: 50.0 (9.5)	53
189	Multiple Risk Factor Intervention Trial	6258	range 35, 57	100
190	Multiple Risk Factor Intervention Trial	6258	range 35, 57	100
191	Multiple Risk Factor Intervention Trial	6258	range 35, 57	100
192	Multiple Risk Factor Intervention Trial	6258	range 35, 57	100
193	Multiple Risk Factor Intervention Trial	6258	range 35, 57	100

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Race	Blood pressure SBP/DBP (mmHg)
174	MESA	26 white, 25 black, 25 Asian, 25 Hispanic	nd
175	MESA	26 white, 25 black, 25 Asian, 25 Hispanic	nd
176	MESA	26 white, 25 black, 25 Asian, 25 Hispanic	nd
177	MESA	26 white, 25 black, 25 Asian, 25 Hispanic	nd
178	MESA	26 white, 25 black, 25 Asian, 25 Hispanic	nd
179	MESA	26 white, 25 black, 25 Asian, 25 Hispanic	nd
180	MESA	26 white, 25 black, 25 Asian, 25 Hispanic	nd
181	MORGEN	nd	120.4 (15.9)/76.6 (10.5)
182	MORGEN	nd	120.4 (15.9)/76.6 (10.5)
183	MORGEN	nd	Cases: 132.1 (20.2), Controls: 126.1 (16.1)/Cases: 82.9 (12.0), Controls: 80.9 (11.3)
184	MORGEN	nd	Cases: 132.1 (20.2), Controls: 126.1 (16.1)/Cases: 82.9 (12.0), Controls: 80.9 (11.3)
185	MORGEN	nd	Cases: 132.1 (20.2), Controls: 126.1 (16.1)/Cases: 82.9 (12.0), Controls: 80.9 (11.3)
186	MORGEN	nd	Cases: 132.1 (20.2), Controls: 126.1 (16.1)/Cases: 82.9 (12.0), Controls: 80.9 (11.3)
187	MORGEN	nd	Cases: 132.1 (20.2), Controls: 126.1 (16.1)/Cases: 82.9 (12.0), Controls: 80.9 (11.3)
188	MORGEN	nd	Cases: 132.1 (20.2), Controls: 126.1 (16.1)/Cases: 82.9 (12.0), Controls: 80.9 (11.3)
189	Multiple Risk Factor Intervention Trial	nd	nd
190	Multiple Risk Factor Intervention Trial	nd	nd
191	Multiple Risk Factor Intervention Trial	nd	nd
192	Multiple Risk Factor Intervention Trial	nd	nd
193	Multiple Risk Factor Intervention Trial	nd	nd

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Lipids: Total cholesterol/LDL/HDL/Triglycerides mean (SD) mg/dL [mmol/L]
174	MESA	nd
175	MESA	nd
176	MESA	nd
177	MESA	nd
178	MESA	nd
179	MESA	nd
180	MESA	nd
181	MORGEN	[5.2 (1.0)]/nd/[1.4 (0.4)]/nd
182	MORGEN	[5.2 (1.0)]/nd/[1.4 (0.4)]/nd
183	MORGEN	[Cases: 5.7 (1.1), Controls: 5.6 (1.1)]/nd/[Cases: 1.3 (0.4), Controls: 1.3 (0.3)/nd
184	MORGEN	[Cases: 5.7 (1.1), Controls: 5.6 (1.1)]/nd/[Cases: 1.3 (0.4), Controls: 1.3 (0.3)/nd
185	MORGEN	[Cases: 5.7 (1.1), Controls: 5.6 (1.1)]/nd/[Cases: 1.3 (0.4), Controls: 1.3 (0.3)/nd
186	MORGEN	[Cases: 5.7 (1.1), Controls: 5.6 (1.1)]/nd/[Cases: 1.3 (0.4), Controls: 1.3 (0.3)/nd
187	MORGEN	[Cases: 5.7 (1.1), Controls: 5.6 (1.1)]/nd/[Cases: 1.3 (0.4), Controls: 1.3 (0.3)/nd
188	MORGEN	[Cases: 5.7 (1.1), Controls: 5.6 (1.1)]/nd/[Cases: 1.3 (0.4), Controls: 1.3 (0.3)/nd
189	Multiple Risk Factor Intervention Trial	nd
190	Multiple Risk Factor Intervention Trial	nd
191	Multiple Risk Factor Intervention Trial	nd
192	Multiple Risk Factor Intervention Trial	nd
193	Multiple Risk Factor Intervention Trial	nd

Appendix G.2.
Causality Table: Observational Studies

Row	Study	BMI mean (SD)/weight mean (SD) Kg
174	MESA	27.9 (5.5)
175	MESA	27.9 (5.5)
176	MESA	27.9 (5.5)
177	MESA	27.9 (5.5)
178	MESA	27.9 (5.5)
179	MESA	27.9 (5.5)
180	MESA	27.9 (5.5)
181	MORGEN	25.0 (3.9)
182	MORGEN	25.0 (3.9)
183	MORGEN	Cases: 25.8 (4.1), Controls: 25.9 (4.3)
184	MORGEN	Cases: 25.8 (4.1), Controls: 25.9 (4.3)
185	MORGEN	Cases: 25.8 (4.1), Controls: 25.9 (4.3)
186	MORGEN	Cases: 25.8 (4.1), Controls: 25.9 (4.3)
187	MORGEN	Cases: 25.8 (4.1), Controls: 25.9 (4.3)
188	MORGEN	Cases: 25.8 (4.1), Controls: 25.9 (4.3)
189	Multiple Risk Factor Intervention Trial	nd
190	Multiple Risk Factor Intervention Trial	nd
191	Multiple Risk Factor Intervention Trial	nd
192	Multiple Risk Factor Intervention Trial	nd
193	Multiple Risk Factor Intervention Trial	nd

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Baseline n-3 intake/level (median (IQR), unless noted)
174	MESA	ALA: mean 1.0 (SD 0.6) g/d, EPA: mean 45 (SD 50) mg/d, DHA: mean 82 (SD 73) mg/d, DPA: mean 20 (SD 20) mg/d
175	MESA	ALA: mean 1.0 (SD 0.6) g/d, EPA: mean 45 (SD 50) mg/d, DHA: mean 82 (SD 73) mg/d, DPA: mean 20 (SD 20) mg/d
176	MESA	ALA: mean 1.0 (SD 0.6) g/d, EPA: mean 45 (SD 50) mg/d, DHA: mean 82 (SD 73) mg/d, DPA: mean 20 (SD 20) mg/d
177	MESA	ALA: mean 1.0 (SD 0.6) g/d, EPA: mean 45 (SD 50) mg/d, DHA: mean 82 (SD 73) mg/d, DPA: mean 20 (SD 20) mg/d
178	MESA	ALA: mean 1.0 (SD 0.6) g/d, EPA: mean 45 (SD 50) mg/d, DHA: mean 82 (SD 73) mg/d, DPA: mean 20 (SD 20) mg/d
179	MESA	ALA: mean 1.0 (SD 0.6) g/d, EPA: mean 45 (SD 50) mg/d, DHA: mean 82 (SD 73) mg/d, DPA: mean 20 (SD 20) mg/d
180	MESA	ALA: mean 1.0 (SD 0.6) g/d, EPA: mean 45 (SD 50) mg/d, DHA: mean 82 (SD 73) mg/d, DPA: mean 20 (SD 20) mg/d
181	MORGEN	ALA: 1.3 g/d, EPA+DHA: 114 mg/d
182	MORGEN	ALA: 1.3 g/d, EPA+DHA: 114 mg/d
183	MORGEN	ALA: cases mean 0.53 (SD 0.14)% FA, controls mean 0.52 (SD 0.15)% FA, EPA+DHA: cases mean 1.43 (SD 1.04)% FA, controls man 1.23 (SD 0.56)% FA
184	MORGEN	ALA: cases mean 0.53 (SD 0.14)% FA, controls mean 0.52 (SD 0.15)% FA, EPA+DHA: cases mean 1.43 (SD 1.04)% FA, controls man 1.23 (SD 0.56)% FA
185	MORGEN	ALA: cases mean 0.53 (SD 0.14)% FA, controls mean 0.52 (SD 0.15)% FA, EPA+DHA: cases mean 1.43 (SD 1.04)% FA, controls man 1.23 (SD 0.56)% FA
186	MORGEN	ALA: cases mean 0.53 (SD 0.14)% FA, controls mean 0.52 (SD 0.15)% FA, EPA+DHA: cases mean 1.43 (SD 1.04)% FA, controls man 1.23 (SD 0.56)% FA
187	MORGEN	ALA: cases mean 0.53 (SD 0.14)% FA, controls mean 0.52 (SD 0.15)% FA, EPA+DHA: cases mean 1.43 (SD 1.04)% FA, controls man 1.23 (SD 0.56)% FA
188	MORGEN	ALA: cases mean 0.53 (SD 0.14)% FA, controls mean 0.52 (SD 0.15)% FA, EPA+DHA: cases mean 1.43 (SD 1.04)% FA, controls man 1.23 (SD 0.56)% FA
189	Multiple Risk Factor Intervention Trial	ALA: mean 1.577 g/d, EPA+DHA+DPA: mean 0.046 g/d
190	Multiple Risk Factor Intervention Trial	ALA: mean 1.577 g/d, EPA+DHA+DPA: mean 0.046 g/d
191	Multiple Risk Factor Intervention Trial	ALA: mean 1.577 g/d, EPA+DHA+DPA: mean 0.046 g/d
192	Multiple Risk Factor Intervention Trial	ALA: mean 1.577 g/d, EPA+DHA+DPA: mean 0.046 g/d
193	Multiple Risk Factor Intervention Trial	ALA: mean 1.577 g/d, EPA+DHA+DPA: mean 0.046 g/d

Row	Study	n-3 source	n-3 measure	n-3 type(s)
174	MESA	Phospholipid	% total FA	EPA+DPA+DHA
175	MESA	intake	mg/d	EPA
176	MESA	intake	mg/d	DPA
177	MESA	intake	mg/d	DHA
178	MESA	intake	mg/d	EPA+DPA+DHA
179	MESA	Phospholipid	% total FA	ALA
180	MESA	intake	mg/d	ALA
181	MORGEN	intake	mg/d	EPA+DHA
182	MORGEN	intake	mg/d	EPA+DHA
183	MORGEN	plasma	% FA	ALA
184	MORGEN	plasma	% FA	EPA+DHA
185	MORGEN	plasma	% FA	ALA
186	MORGEN	plasma	% FA	EPA-DHA
187	MORGEN	plasma	% FA	ALA
188	MORGEN	plasma	% FA	EPA-DHA
189	Multiple Risk Factor Intervention Trial	intake	g	ALA
190	Multiple Risk Factor Intervention Trial	intake	% of total kilocalories	ALA
191	Multiple Risk Factor Intervention Trial	intake	g	EPA+DHA+DPA
192	Multiple Risk Factor Intervention Trial	intake	% of total kilocalories	EPA+DHA+DPA
193	Multiple Risk Factor Intervention Trial	intake	g	ALA

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Study design
174	MESA	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
175	MESA	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
176	MESA	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
177	MESA	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
178	MESA	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
179	MESA	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
180	MESA	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
181	MORGEN	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
182	MORGEN	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
183	MORGEN	Nested Case Control
184	MORGEN	Nested Case Control
185	MORGEN	Nested Case Control
186	MORGEN	Nested Case Control
187	MORGEN	Nested Case Control
188	MORGEN	Nested Case Control
189	Multiple Risk Factor Intervention Trial	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
190	Multiple Risk Factor Intervention Trial	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
191	Multiple Risk Factor Intervention Trial	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
192	Multiple Risk Factor Intervention Trial	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
193	Multiple Risk Factor Intervention Trial	Prospective, longitudinal study of intake (eg, FFQ, biomarker)

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Outcome	Reported effect Size
174	MESA	MACE	See appendix F
175	MESA	MACE	See appendix F
176	MESA	MACE	See appendix F
177	MESA	MACE	See appendix F
178	MESA	MACE	See appendix F
179	MESA	MACE	See appendix F
180	MESA	MACE	See appendix F
181	MORGEN	Death, CVD	See appendix F
182	MORGEN	Myocardial infarction	See appendix F
183	MORGEN	Stroke, hemorrhagic	See appendix F
184	MORGEN	Stroke, hemorrhagic	See appendix F
185	MORGEN	Stroke, ischemic	See appendix F
186	MORGEN	Stroke, ischemic	See appendix F
187	MORGEN	Stroke, total	See appendix F
188	MORGEN	Stroke, total	See appendix F
189	Multiple Risk Factor Intervention Trial	Death, all cause	See appendix F
190	Multiple Risk Factor Intervention Trial	Death, all cause	See appendix F
191	Multiple Risk Factor Intervention Trial	Death, all cause	See appendix F
192	Multiple Risk Factor Intervention Trial	Death, all cause	See appendix F
193	Multiple Risk Factor Intervention Trial	Death, all cause	See appendix F

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Study years (study start date)	Country
194	Multiple Risk Factor Intervention Trial	1973	US
195	Multiple Risk Factor Intervention Trial	1973	US
196	Multiple Risk Factor Intervention Trial	1973	US
197	Multiple Risk Factor Intervention Trial	1973	US
198	Multiple Risk Factor Intervention Trial	1973	US
199	Multiple Risk Factor Intervention Trial	1973	US
200	Multiple Risk Factor Intervention Trial	1973	US
201	Multiple Risk Factor Intervention Trial	1973	US
202	Multiple Risk Factor Intervention Trial	1973	US
203	Multiple Risk Factor Intervention Trial	1973	US
204	Multiple Risk Factor Intervention Trial	1973	US
205	Multiple Risk Factor Intervention Trial	1973	US
206	Multiple Risk Factor Intervention Trial	1973	US
207	Multiple Risk Factor Intervention Trial	1973	US
208	Multiple Risk Factor Intervention Trial	1973	US
209	Multiple Risk Factor Intervention Trial	1973	US

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Population	Risk type
194	Multiple Risk Factor Intervention Trial	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome, hypertension, dyslipidemia, or chronic kidney disease)	nd
195	Multiple Risk Factor Intervention Trial	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome, hypertension, dyslipidemia, or chronic kidney disease)	nd
196	Multiple Risk Factor Intervention Trial	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome, hypertension, dyslipidemia, or chronic kidney disease)	nd
197	Multiple Risk Factor Intervention Trial	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome, hypertension, dyslipidemia, or chronic kidney disease)	nd
198	Multiple Risk Factor Intervention Trial	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome, hypertension, dyslipidemia, or chronic kidney disease)	nd
199	Multiple Risk Factor Intervention Trial	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome, hypertension, dyslipidemia, or chronic kidney disease)	nd
200	Multiple Risk Factor Intervention Trial	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome, hypertension, dyslipidemia, or chronic kidney disease)	nd
201	Multiple Risk Factor Intervention Trial	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome, hypertension, dyslipidemia, or chronic kidney disease)	nd
202	Multiple Risk Factor Intervention Trial	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome, hypertension, dyslipidemia, or chronic kidney disease)	nd
203	Multiple Risk Factor Intervention Trial	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome, hypertension, dyslipidemia, or chronic kidney disease)	nd
204	Multiple Risk Factor Intervention Trial	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome, hypertension, dyslipidemia, or chronic kidney disease)	nd
205	Multiple Risk Factor Intervention Trial	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome, hypertension, dyslipidemia, or chronic kidney disease)	nd
206	Multiple Risk Factor Intervention Trial	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome, hypertension, dyslipidemia, or chronic kidney disease)	nd
207	Multiple Risk Factor Intervention Trial	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome, hypertension, dyslipidemia, or chronic kidney disease)	nd
208	Multiple Risk Factor Intervention Trial	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome, hypertension, dyslipidemia, or chronic kidney disease)	nd
209	Multiple Risk Factor Intervention Trial	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome, hypertension, dyslipidemia, or chronic kidney disease)	nd

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Sample size (total)	Age mean (SD) [median]	Sex (% male)
194	Multiple Risk Factor Intervention Trial	6258	range 35, 57	100
195	Multiple Risk Factor Intervention Trial	6258	range 35, 57	100
196	Multiple Risk Factor Intervention Trial	6258	range 35, 57	100
197	Multiple Risk Factor Intervention Trial	6258	range 35, 57	100
198	Multiple Risk Factor Intervention Trial	6258	range 35, 57	100
199	Multiple Risk Factor Intervention Trial	6258	range 35, 57	100
200	Multiple Risk Factor Intervention Trial	6258	range 35, 57	100
201	Multiple Risk Factor Intervention Trial	6258	range 35, 57	100
202	Multiple Risk Factor Intervention Trial	6258	range 35, 57	100
203	Multiple Risk Factor Intervention Trial	6258	range 35, 57	100
204	Multiple Risk Factor Intervention Trial	6258	range 35, 57	100
205	Multiple Risk Factor Intervention Trial	6258	range 35, 57	100
206	Multiple Risk Factor Intervention Trial	6258	range 35, 57	100
207	Multiple Risk Factor Intervention Trial	6258	range 35, 57	100
208	Multiple Risk Factor Intervention Trial	6258	range 35, 57	100
209	Multiple Risk Factor Intervention Trial	6258	range 35, 57	100

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Race	Blood pressure SBP/DBP (mmHg)
194	Multiple Risk Factor Intervention Trial	nd	nd
195	Multiple Risk Factor Intervention Trial	nd	nd
196	Multiple Risk Factor Intervention Trial	nd	nd
197	Multiple Risk Factor Intervention Trial	nd	nd
198	Multiple Risk Factor Intervention Trial	nd	nd
199	Multiple Risk Factor Intervention Trial	nd	nd
200	Multiple Risk Factor Intervention Trial	nd	nd
201	Multiple Risk Factor Intervention Trial	nd	nd
202	Multiple Risk Factor Intervention Trial	nd	nd
203	Multiple Risk Factor Intervention Trial	nd	nd
204	Multiple Risk Factor Intervention Trial	nd	nd
205	Multiple Risk Factor Intervention Trial	nd	nd
206	Multiple Risk Factor Intervention Trial	nd	nd
207	Multiple Risk Factor Intervention Trial	nd	nd
208	Multiple Risk Factor Intervention Trial	nd	nd
209	Multiple Risk Factor Intervention Trial	nd	nd

Row	Study	Lipids: Total cholesterol/LDL/HDL/Triglycerides mean (SD) mg/dL [mmol/L]
194	Multiple Risk Factor Intervention Trial	nd
195	Multiple Risk Factor Intervention Trial	nd
196	Multiple Risk Factor Intervention Trial	nd
197	Multiple Risk Factor Intervention Trial	nd
198	Multiple Risk Factor Intervention Trial	nd
199	Multiple Risk Factor Intervention Trial	nd
200	Multiple Risk Factor Intervention Trial	nd
201	Multiple Risk Factor Intervention Trial	nd
202	Multiple Risk Factor Intervention Trial	nd
203	Multiple Risk Factor Intervention Trial	nd
204	Multiple Risk Factor Intervention Trial	nd
205	Multiple Risk Factor Intervention Trial	nd
206	Multiple Risk Factor Intervention Trial	nd
207	Multiple Risk Factor Intervention Trial	nd
208	Multiple Risk Factor Intervention Trial	nd
209	Multiple Risk Factor Intervention Trial	nd

Appendix G.2.
Causality Table: Observational Studies

Row	Study	BMI mean (SD)/weight mean (SD) Kg
194	Multiple Risk Factor Intervention Trial	nd
195	Multiple Risk Factor Intervention Trial	nd
196	Multiple Risk Factor Intervention Trial	nd
197	Multiple Risk Factor Intervention Trial	nd
198	Multiple Risk Factor Intervention Trial	nd
199	Multiple Risk Factor Intervention Trial	nd
200	Multiple Risk Factor Intervention Trial	nd
201	Multiple Risk Factor Intervention Trial	nd
202	Multiple Risk Factor Intervention Trial	nd
203	Multiple Risk Factor Intervention Trial	nd
204	Multiple Risk Factor Intervention Trial	nd
205	Multiple Risk Factor Intervention Trial	nd
206	Multiple Risk Factor Intervention Trial	nd
207	Multiple Risk Factor Intervention Trial	nd
208	Multiple Risk Factor Intervention Trial	nd
209	Multiple Risk Factor Intervention Trial	nd

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Baseline n-3 intake/level (median (IQR), unless noted)
194	Multiple Risk Factor Intervention Trial	ALA: mean 1.577 g/d, EPA+DHA+DPA: mean 0.046 g/d
195	Multiple Risk Factor Intervention Trial	ALA: mean 1.577 g/d, EPA+DHA+DPA: mean 0.046 g/d
196	Multiple Risk Factor Intervention Trial	ALA: mean 1.577 g/d, EPA+DHA+DPA: mean 0.046 g/d
197	Multiple Risk Factor Intervention Trial	ALA: mean 1.577 g/d, EPA+DHA+DPA: mean 0.046 g/d
198	Multiple Risk Factor Intervention Trial	ALA: mean 1.577 g/d, EPA+DHA+DPA: mean 0.046 g/d
199	Multiple Risk Factor Intervention Trial	ALA: mean 1.577 g/d, EPA+DHA+DPA: mean 0.046 g/d
200	Multiple Risk Factor Intervention Trial	ALA: mean 1.577 g/d, EPA+DHA+DPA: mean 0.046 g/d
201	Multiple Risk Factor Intervention Trial	ALA: mean 1.577 g/d, EPA+DHA+DPA: mean 0.046 g/d
202	Multiple Risk Factor Intervention Trial	ALA: mean 1.577 g/d, EPA+DHA+DPA: mean 0.046 g/d
203	Multiple Risk Factor Intervention Trial	ALA: mean 1.577 g/d, EPA+DHA+DPA: mean 0.046 g/d
204	Multiple Risk Factor Intervention Trial	ALA: mean 1.577 g/d, EPA+DHA+DPA: mean 0.046 g/d
205	Multiple Risk Factor Intervention Trial	ALA: mean 1.577 g/d, EPA+DHA+DPA: mean 0.046 g/d
206	Multiple Risk Factor Intervention Trial	ALA: mean 1.577 g/d, EPA+DHA+DPA: mean 0.046 g/d
207	Multiple Risk Factor Intervention Trial	ALA: mean 1.577 g/d, EPA+DHA+DPA: mean 0.046 g/d
208	Multiple Risk Factor Intervention Trial	ALA: mean 1.577 g/d, EPA+DHA+DPA: mean 0.046 g/d
209	Multiple Risk Factor Intervention Trial	ALA: mean 1.577 g/d, EPA+DHA+DPA: mean 0.046 g/d

Appendix G.2.
Causality Table: Observational Studies

Row	Study	n-3 source	n-3 measure	n-3 type(s)
194	Multiple Risk Factor Intervention Trial	intake	% of total kilocalories	ALA
195	Multiple Risk Factor Intervention Trial	intake	g	ALA
196	Multiple Risk Factor Intervention Trial	intake	% of total kilocalories	ALA
197	Multiple Risk Factor Intervention Trial	intake	g	EPA+DHA+DPA
198	Multiple Risk Factor Intervention Trial	intake	% of total kilocalories	EPA+DHA+DPA
199	Multiple Risk Factor Intervention Trial	intake	g	EPA+DHA+DPA
200	Multiple Risk Factor Intervention Trial	intake	% of total kilocalories	EPA+DHA+DPA
201	Multiple Risk Factor Intervention Trial	intake	g	ALA
202	Multiple Risk Factor Intervention Trial	intake	% of total kilocalories	ALA
203	Multiple Risk Factor Intervention Trial	intake	g	ALA
204	Multiple Risk Factor Intervention Trial	intake	% of total kilocalories	ALA
205	Multiple Risk Factor Intervention Trial	intake	g	EPA+DHA+DPA
206	Multiple Risk Factor Intervention Trial	intake	% of total kilocalories	EPA+DHA+DPA
207	Multiple Risk Factor Intervention Trial	intake	g	EPA+DHA+DPA
208	Multiple Risk Factor Intervention Trial	intake	% of total kilocalories	EPA+DHA+DPA
209	Multiple Risk Factor Intervention Trial	intake	g	EPA+DHA+DPA

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Study design
194	Multiple Risk Factor Intervention Trial	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
195	Multiple Risk Factor Intervention Trial	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
196	Multiple Risk Factor Intervention Trial	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
197	Multiple Risk Factor Intervention Trial	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
198	Multiple Risk Factor Intervention Trial	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
199	Multiple Risk Factor Intervention Trial	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
200	Multiple Risk Factor Intervention Trial	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
201	Multiple Risk Factor Intervention Trial	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
202	Multiple Risk Factor Intervention Trial	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
203	Multiple Risk Factor Intervention Trial	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
204	Multiple Risk Factor Intervention Trial	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
205	Multiple Risk Factor Intervention Trial	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
206	Multiple Risk Factor Intervention Trial	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
207	Multiple Risk Factor Intervention Trial	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
208	Multiple Risk Factor Intervention Trial	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
209	Multiple Risk Factor Intervention Trial	Prospective, longitudinal study of intake (eg, FFQ, biomarker)

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Outcome	Reported effect Size
194	Multiple Risk Factor Intervention Trial	Death, all cause	See appendix F
195	Multiple Risk Factor Intervention Trial	Death, CHD	See appendix F
196	Multiple Risk Factor Intervention Trial	Death, CHD	See appendix F
197	Multiple Risk Factor Intervention Trial	Death, CHD	See appendix F
198	Multiple Risk Factor Intervention Trial	Death, CHD	See appendix F
199	Multiple Risk Factor Intervention Trial	Death, CHD	See appendix F
200	Multiple Risk Factor Intervention Trial	Death, CHD	See appendix F
201	Multiple Risk Factor Intervention Trial	Death, CHD	See appendix F
202	Multiple Risk Factor Intervention Trial	Death, CHD	See appendix F
203	Multiple Risk Factor Intervention Trial	Death, CVD	See appendix F
204	Multiple Risk Factor Intervention Trial	Death, CVD	See appendix F
205	Multiple Risk Factor Intervention Trial	Death, CVD	See appendix F
206	Multiple Risk Factor Intervention Trial	Death, CVD	See appendix F
207	Multiple Risk Factor Intervention Trial	Death, CVD	See appendix F
208	Multiple Risk Factor Intervention Trial	Death, CVD	See appendix F
209	Multiple Risk Factor Intervention Trial	Death, CVD	See appendix F

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Study years (study start date)	Country
210	Multiple Risk Factor Intervention Trial	1973	US
211	Multiple Risk Factor Intervention Trial	1973	US
212	Multiple Risk Factor Intervention Trial	1973	US
213	NIPPON DATA80	1980	Japan
214	NIPPON DATA80	1980	Japan
215	NIPPON DATA80	1980	Japan
216	NIPPON DATA80	1980	Japan
217	NIPPON DATA80	1980	Japan
218	NIPPON DATA80	1980	Japan
219	NIPPON DATA80	1980	Japan
220	NIPPON DATA80	1980	Japan
221	NIPPON DATA80	1980	Japan
222	NIPPON DATA80	1980	Japan
223	NIPPON DATA80	1980	Japan
224	NIPPON DATA80	1980	Japan
225	Nurses' Health Study (NHS)	1980	US
226	Nurses' Health Study (NHS)	1980	US
227	Nurses' Health Study (NHS)	1980	US
228	Nurses' Health Study (NHS)	1980	US
229	Nurses' Health Study (NHS)	1980	US

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Population	Risk type
210	Multiple Risk Factor Intervention Trial	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome, hypertension, dyslipidemia, or chronic kidney disease)	nd
211	Multiple Risk Factor Intervention Trial	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome, hypertension, dyslipidemia, or chronic kidney disease)	nd
212	Multiple Risk Factor Intervention Trial	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome, hypertension, dyslipidemia, or chronic kidney disease)	nd
213	NIPPON DATA80	Primary Prevention, Healthy	na
214	NIPPON DATA80	Primary Prevention, Healthy	na
215	NIPPON DATA80	Primary Prevention, Healthy	na
216	NIPPON DATA80	Primary Prevention, Healthy	na
217	NIPPON DATA80	Primary Prevention, Healthy	na
218	NIPPON DATA80	Primary Prevention, Healthy	na
219	NIPPON DATA80	Primary Prevention, Healthy	na
220	NIPPON DATA80	Primary Prevention, Healthy	na
221	NIPPON DATA80	Primary Prevention, Healthy	na
222	NIPPON DATA80	Primary Prevention, Healthy	na
223	NIPPON DATA80	Primary Prevention, Healthy	na
224	NIPPON DATA80	Primary Prevention, Healthy	na
225	Nurses' Health Study (NHS)	Primary Prevention, Healthy	na
226	Nurses' Health Study (NHS)	Primary Prevention, Healthy	na
227	Nurses' Health Study (NHS)	Primary Prevention, Healthy	na
228	Nurses' Health Study (NHS)	Primary Prevention, Healthy	na
229	Nurses' Health Study (NHS)	Primary Prevention, Healthy	na

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Sample size (total)	Age mean (SD) [median]	Sex (% male)
210	Multiple Risk Factor Intervention Trial	6258	range 35, 57	100
211	Multiple Risk Factor Intervention Trial	6258	range 35, 57	100
212	Multiple Risk Factor Intervention Trial	6258	range 35, 57	100
213	NIPPON DATA80	9190	49.4 (13) (Q2)	43.8
214	NIPPON DATA80	9190	49.4 (13) (Q2)	43.8
215	NIPPON DATA80	9190	49.4 (13) (Q2)	43.8
216	NIPPON DATA80	9190	49.4 (13) (Q2)	43.8
217	NIPPON DATA80	9190	49.4 (13) (Q2)	43.8
218	NIPPON DATA80	9190	49.4 (13) (Q2)	43.8
219	NIPPON DATA80	9190	49.4 (13) (Q2)	43.8
220	NIPPON DATA80	9190	49.4 (13) (Q2)	43.8
221	NIPPON DATA80	9190	49.4 (13) (Q2)	43.8
222	NIPPON DATA80	9190	49.4 (13) (Q2)	43.8
223	NIPPON DATA80	9190	49.4 (13) (Q2)	43.8
224	NIPPON DATA80	9190	49.4 (13) (Q2)	43.8
225	Nurses' Health Study (NHS)	79839	range 34, 59	0
226	Nurses' Health Study (NHS)	79839	range 34, 59	0
227	Nurses' Health Study (NHS)	79839	range 34, 59	0
228	Nurses' Health Study (NHS)	79839	range 34, 59	0
229	Nurses' Health Study (NHS)	79839	range 34, 59	0

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Race	Blood pressure SBP/DBP (mmHg)
210	Multiple Risk Factor Intervention Trial	nd	nd
211	Multiple Risk Factor Intervention Trial	nd	nd
212	Multiple Risk Factor Intervention Trial	nd	nd
213	NIPPON DATA80	nd	Q2: 135.5 (21.5)/Q2: 81.1 (12.1)
214	NIPPON DATA80	nd	Q2: 135.5 (21.5)/Q2: 81.1 (12.1)
215	NIPPON DATA80	nd	Q2: 135.5 (21.5)/Q2: 81.1 (12.1)
216	NIPPON DATA80	nd	Q2: 135.5 (21.5)/Q2: 81.1 (12.1)
217	NIPPON DATA80	nd	Q2: 135.5 (21.5)/Q2: 81.1 (12.1)
218	NIPPON DATA80	nd	Q2: 135.5 (21.5)/Q2: 81.1 (12.1)
219	NIPPON DATA80	nd	Q2: 135.5 (21.5)/Q2: 81.1 (12.1)
220	NIPPON DATA80	nd	Q2: 135.5 (21.5)/Q2: 81.1 (12.1)
221	NIPPON DATA80	nd	Q2: 135.5 (21.5)/Q2: 81.1 (12.1)
222	NIPPON DATA80	nd	Q2: 135.5 (21.5)/Q2: 81.1 (12.1)
223	NIPPON DATA80	nd	Q2: 135.5 (21.5)/Q2: 81.1 (12.1)
224	NIPPON DATA80	nd	Q2: 135.5 (21.5)/Q2: 81.1 (12.1)
225	Nurses' Health Study (NHS)	98 white	nd
226	Nurses' Health Study (NHS)	98 white	nd
227	Nurses' Health Study (NHS)	98 white	nd
228	Nurses' Health Study (NHS)	98 white	nd
229	Nurses' Health Study (NHS)	98 white	nd

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Lipids: Total cholesterol/LDL/HDL/Triglycerides mean (SD) mg/dL [mmol/L]
210	Multiple Risk Factor Intervention Trial	nd
211	Multiple Risk Factor Intervention Trial	nd
212	Multiple Risk Factor Intervention Trial	nd
213	NIPPON DATA80	Q2: 188.7 (33.8)/nd/nd/nd
214	NIPPON DATA80	Q2: 188.7 (33.8)/nd/nd/nd
215	NIPPON DATA80	Q2: 188.7 (33.8)/nd/nd/nd
216	NIPPON DATA80	Q2: 188.7 (33.8)/nd/nd/nd
217	NIPPON DATA80	Q2: 188.7 (33.8)/nd/nd/nd
218	NIPPON DATA80	Q2: 188.7 (33.8)/nd/nd/nd
219	NIPPON DATA80	Q2: 188.7 (33.8)/nd/nd/nd
220	NIPPON DATA80	Q2: 188.7 (33.8)/nd/nd/nd
221	NIPPON DATA80	Q2: 188.7 (33.8)/nd/nd/nd
222	NIPPON DATA80	Q2: 188.7 (33.8)/nd/nd/nd
223	NIPPON DATA80	Q2: 188.7 (33.8)/nd/nd/nd
224	NIPPON DATA80	Q2: 188.7 (33.8)/nd/nd/nd
225	Nurses' Health Study (NHS)	nd
226	Nurses' Health Study (NHS)	nd
227	Nurses' Health Study (NHS)	nd
228	Nurses' Health Study (NHS)	nd
229	Nurses' Health Study (NHS)	nd

Appendix G.2.
Causality Table: Observational Studies

Row	Study	BMI mean (SD)/weight mean (SD) Kg
210	Multiple Risk Factor Intervention Trial	nd
211	Multiple Risk Factor Intervention Trial	nd
212	Multiple Risk Factor Intervention Trial	nd
213	NIPPON DATA80	Q2: 22.7 (3.1)
214	NIPPON DATA80	Q2: 22.7 (3.1)
215	NIPPON DATA80	Q2: 22.7 (3.1)
216	NIPPON DATA80	Q2: 22.7 (3.1)
217	NIPPON DATA80	Q2: 22.7 (3.1)
218	NIPPON DATA80	Q2: 22.7 (3.1)
219	NIPPON DATA80	Q2: 22.7 (3.1)
220	NIPPON DATA80	Q2: 22.7 (3.1)
221	NIPPON DATA80	Q2: 22.7 (3.1)
222	NIPPON DATA80	Q2: 22.7 (3.1)
223	NIPPON DATA80	Q2: 22.7 (3.1)
224	NIPPON DATA80	Q2: 22.7 (3.1)
225	Nurses' Health Study (NHS)	nd
226	Nurses' Health Study (NHS)	nd
227	Nurses' Health Study (NHS)	nd
228	Nurses' Health Study (NHS)	nd
229	Nurses' Health Study (NHS)	nd

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Baseline n-3 intake/level (median (IQR), unless noted)
210	Multiple Risk Factor Intervention Trial	ALA: mean 1.577 g/d, EPA+DHA+DPA: mean 0.046 g/d
211	Multiple Risk Factor Intervention Trial	ALA: mean 1.577 g/d, EPA+DHA+DPA: mean 0.046 g/d
212	Multiple Risk Factor Intervention Trial	ALA: mean 1.577 g/d, EPA+DHA+DPA: mean 0.046 g/d
213	NIPPON DATA80	EPA: men 0.14, women 0.15% kcal, DHA: men 0.23, women 0.24% kcal, EPA+DHA: men 0.36, women 0.39% kcal, Total n-3 FA: men 1.06, women 1.16% kcal
214	NIPPON DATA80	EPA: men 0.14, women 0.15% kcal, DHA: men 0.23, women 0.24% kcal, EPA+DHA: men 0.36, women 0.39% kcal, Total n-3 FA: men 1.06, women 1.16% kcal
215	NIPPON DATA80	EPA: men 0.14, women 0.15% kcal, DHA: men 0.23, women 0.24% kcal, EPA+DHA: men 0.36, women 0.39% kcal, Total n-3 FA: men 1.06, women 1.16% kcal
216	NIPPON DATA80	EPA: men 0.14, women 0.15% kcal, DHA: men 0.23, women 0.24% kcal, EPA+DHA: men 0.36, women 0.39% kcal, Total n-3 FA: men 1.06, women 1.16% kcal
217	NIPPON DATA80	EPA: men 0.14, women 0.15% kcal, DHA: men 0.23, women 0.24% kcal, EPA+DHA: men 0.36, women 0.39% kcal, Total n-3 FA: men 1.06, women 1.16% kcal
218	NIPPON DATA80	EPA: men 0.14, women 0.15% kcal, DHA: men 0.23, women 0.24% kcal, EPA+DHA: men 0.36, women 0.39% kcal, Total n-3 FA: men 1.06, women 1.16% kcal
219	NIPPON DATA80	EPA: men 0.14, women 0.15% kcal, DHA: men 0.23, women 0.24% kcal, EPA+DHA: men 0.36, women 0.39% kcal, Total n-3 FA: men 1.06, women 1.16% kcal
220	NIPPON DATA80	EPA: men 0.14, women 0.15% kcal, DHA: men 0.23, women 0.24% kcal, EPA+DHA: men 0.36, women 0.39% kcal, Total n-3 FA: men 1.06, women 1.16% kcal
221	NIPPON DATA80	EPA: men 0.14, women 0.15% kcal, DHA: men 0.23, women 0.24% kcal, EPA+DHA: men 0.36, women 0.39% kcal, Total n-3 FA: men 1.06, women 1.16% kcal
222	NIPPON DATA80	EPA: men 0.14, women 0.15% kcal, DHA: men 0.23, women 0.24% kcal, EPA+DHA: men 0.36, women 0.39% kcal, Total n-3 FA: men 1.06, women 1.16% kcal
223	NIPPON DATA80	EPA: men 0.14, women 0.15% kcal, DHA: men 0.23, women 0.24% kcal, EPA+DHA: men 0.36, women 0.39% kcal, Total n-3 FA: men 1.06, women 1.16% kcal
224	NIPPON DATA80	EPA: men 0.14, women 0.15% kcal, DHA: men 0.23, women 0.24% kcal, EPA+DHA: men 0.36, women 0.39% kcal, Total n-3 FA: men 1.06, women 1.16% kcal
225	Nurses' Health Study (NHS)	ALA: 0.52% energy, EPA+DHA 0.08% energy
226	Nurses' Health Study (NHS)	ALA: 0.52% energy, EPA+DHA 0.08% energy
227	Nurses' Health Study (NHS)	ALA: 0.52% energy, EPA+DHA 0.08% energy
228	Nurses' Health Study (NHS)	ALA: 0.52% energy, EPA+DHA 0.08% energy
229	Nurses' Health Study (NHS)	ALA: 0.52% energy, EPA+DHA 0.08% energy

Appendix G.2.
Causality Table: Observational Studies

Row	Study	n-3 source	n-3 measure	n-3 type(s)
210	Multiple Risk Factor Intervention Trial	intake	% of total kilocalories	EPA+DHA+DPA
211	Multiple Risk Factor Intervention Trial	intake	g	ALA
212	Multiple Risk Factor Intervention Trial	intake	% of total kilocalories	ALA
213	NIPPON DATA80	intake	% kcal	EPA+DHA
214	NIPPON DATA80	intake	% kcal	Total n-3
215	NIPPON DATA80	intake	% kcal	EPA
216	NIPPON DATA80	intake	% kcal	DHA
217	NIPPON DATA80	intake	% kcal	EPA+DHA
218	NIPPON DATA80	intake	% kcal	Total n-3
219	NIPPON DATA80	intake	% kcal	EPA
220	NIPPON DATA80	intake	% kcal	DHA
221	NIPPON DATA80	intake	% kcal	EPA+DHA
222	NIPPON DATA80	intake	% kcal	Total n-3
223	NIPPON DATA80	intake	% kcal	EPA
224	NIPPON DATA80	intake	% kcal	DHA
225	Nurses' Health Study (NHS)	intake	% energy	EPA + DHA
226	Nurses' Health Study (NHS)	intake	% energy	EPA + DHA
227	Nurses' Health Study (NHS)	intake	g/d	EPA + DHA
228	Nurses' Health Study (NHS)	intake	g/d	EPA + DHA
229	Nurses' Health Study (NHS)	intake	g/d	EPA + DHA

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Study design
210	Multiple Risk Factor Intervention Trial	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
211	Multiple Risk Factor Intervention Trial	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
212	Multiple Risk Factor Intervention Trial	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
213	NIPPON DATA80	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
214	NIPPON DATA80	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
215	NIPPON DATA80	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
216	NIPPON DATA80	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
217	NIPPON DATA80	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
218	NIPPON DATA80	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
219	NIPPON DATA80	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
220	NIPPON DATA80	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
221	NIPPON DATA80	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
222	NIPPON DATA80	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
223	NIPPON DATA80	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
224	NIPPON DATA80	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
225	Nurses' Health Study (NHS)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
226	Nurses' Health Study (NHS)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
227	Nurses' Health Study (NHS)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
228	Nurses' Health Study (NHS)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
229	Nurses' Health Study (NHS)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Outcome	Reported effect Size
210	Multiple Risk Factor Intervention Trial	Death, CVD	See appendix F
211	Multiple Risk Factor Intervention Trial	Death, CVD	See appendix F
212	Multiple Risk Factor Intervention Trial	Death, CVD	See appendix F
213	NIPPON DATA80	Death, CHD	See appendix F
214	NIPPON DATA80	Death, CHD	See appendix F
215	NIPPON DATA80	Death, CHD	See appendix F
216	NIPPON DATA80	Death, CHD	See appendix F
217	NIPPON DATA80	Death, CVD	See appendix F
218	NIPPON DATA80	Death, CVD	See appendix F
219	NIPPON DATA80	Death, CVD	See appendix F
220	NIPPON DATA80	Death, CVD	See appendix F
221	NIPPON DATA80	Death, stroke	See appendix F
222	NIPPON DATA80	Death, stroke	See appendix F
223	NIPPON DATA80	Death, stroke	See appendix F
224	NIPPON DATA80	Death, stroke	See appendix F
225	Nurses' Health Study (NHS)	Coronary heart disease	See appendix F
226	Nurses' Health Study (NHS)	Death, CHD	See appendix F
227	Nurses' Health Study (NHS)	Stroke, hemorrhagic	See appendix F
228	Nurses' Health Study (NHS)	Stroke, ischemic	See appendix F
229	Nurses' Health Study (NHS)	Stroke, total	See appendix F

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Study years (study start date)	Country
230	Nurses' Health Study (NHS)	1980	US
231	Osaka Acute Coronary Insufficiency Study	2006	Japan
232	Osaka Acute Coronary Insufficiency Study	2006	Japan
233	Osaka Acute Coronary Insufficiency Study	2006	Japan
234	Osaka Acute Coronary Insufficiency Study	2006	Japan
235	Physician's Health Study	1995-2001	US
236	Physician's Health Study	1995-2001	US
237	Physician's Health Study	1995-2001	US
238	Physician's Health Study	1995-2001	US
239	Physician's Health Study	1995-2001	US
240	Physician's Health Study	1995-2001	US
241	Physician's Health Study	1982-1983	US
242	Physician's Health Study	1982-1983	US
243	Physician's Health Study	1982-1983	US
244	Physician's Health Study	1982-1983	US
245	Physician's Health Study	1982-1983	US
246	Physician's Health Study	1982-1983	US
247	Physician's Health Study	1995-2001	US
248	Physician's Health Study	1995-2001	US
249	Physician's Health Study	1995-2001	US
250	Physician's Health Study	1995-2001	US
251	Physician's Health Study	1995-2001	US
252	Physician's Health Study	1995-2001	US
253	Physician's Health Study	1982-1983	US
254	Physician's Health Study	1982-1983	US
255	Physician's Health Study	1982-1983	US
256	Physician's Health Study	1982-1983	US
257	Physician's Health Study	1982-1983	US
258	Physician's Health Study	1982-1983	US
259	Physician's Health Study	1982-1983	US
260	Physician's Health Study	1982-1983	US
261	Physician's Health Study	1982-1983	US
262	Pooling Project of Cohort Studies on Diet and Coronary Disease	various across cohorts: 1966-1992	US, Finland, Sweden
263	Pooling Project of Cohort Studies on Diet and Coronary Disease	various across cohorts: 1966-1992	US, Finland, Sweden
264	Rotterdam	1990	Netherlands
265	Rotterdam	1990	Netherlands
266	Rotterdam	1990	Netherlands

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Population	Risk type
230	Nurses' Health Study (NHS)	Primary Prevention, Healthy	na
231	Osaka Acute Coronary Insufficiency Study	Secondary Prevention (history of CVD event)	Acute MI
232	Osaka Acute Coronary Insufficiency Study	Secondary Prevention (history of CVD event)	Acute MI
233	Osaka Acute Coronary Insufficiency Study	Secondary Prevention (history of CVD event)	Acute MI
234	Osaka Acute Coronary Insufficiency Study	Secondary Prevention (history of CVD event)	Acute MI
235	Physician's Health Study	Primary Prevention, Healthy	na
236	Physician's Health Study	Primary Prevention, Healthy	na
237	Physician's Health Study	Primary Prevention, Healthy	na
238	Physician's Health Study	Primary Prevention, Healthy	na
239	Physician's Health Study	Primary Prevention, Healthy	na
240	Physician's Health Study	Primary Prevention, Healthy	na
241	Physician's Health Study	Primary Prevention, Healthy	na
242	Physician's Health Study	Primary Prevention, Healthy	na
243	Physician's Health Study	Primary Prevention, Healthy	na
244	Physician's Health Study	Primary Prevention, Healthy	na
245	Physician's Health Study	Primary Prevention, Healthy	na
246	Physician's Health Study	Primary Prevention, Healthy	na
247	Physician's Health Study	Primary Prevention, Healthy	na
248	Physician's Health Study	Primary Prevention, Healthy	na
249	Physician's Health Study	Primary Prevention, Healthy	na
250	Physician's Health Study	Primary Prevention, Healthy	na
251	Physician's Health Study	Primary Prevention, Healthy	na
252	Physician's Health Study	Primary Prevention, Healthy	na
253	Physician's Health Study	Primary Prevention, Healthy	na
254	Physician's Health Study	Primary Prevention, Healthy	na
255	Physician's Health Study	Primary Prevention, Healthy	na
256	Physician's Health Study	Primary Prevention, Healthy	na
257	Physician's Health Study	Primary Prevention, Healthy	na
258	Physician's Health Study	Primary Prevention, Healthy	na
259	Physician's Health Study	Primary Prevention, Healthy	na
260	Physician's Health Study	Primary Prevention, Healthy	na
261	Physician's Health Study	Primary Prevention, Healthy	na
262	Pooling Project of Cohort Studies on Diet and Coronary Disease	Primary Prevention, Healthy	na
263	Pooling Project of Cohort Studies on Diet and Coronary Disease	Primary Prevention, Healthy	na
264	Rotterdam	Primary Prevention, Healthy	No AF at baseline
265	Rotterdam	Primary Prevention, Healthy	No previous MI
266	Rotterdam	Primary Prevention, Healthy	No heart failure at baseline

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Sample size (total)	Age mean (SD) [median]	Sex (% male)
230	Nurses' Health Study (NHS)	79839	range 34, 59	0
231	Osaka Acute Coronary Insufficiency Study	671	65 range 57, 73	77.8
232	Osaka Acute Coronary Insufficiency Study	671	65 range 57, 73	77.8
233	Osaka Acute Coronary Insufficiency Study	671	65 range 57, 73	77.8
234	Osaka Acute Coronary Insufficiency Study	671	65 range 57, 73	77.8
235	Physician's Health Study	2000	68.7 (8.7)	100
236	Physician's Health Study	2000	68.7 (8.7)	100
237	Physician's Health Study	2000	68.7 (8.7)	100
238	Physician's Health Study	2000	68.7 (8.7)	100
239	Physician's Health Study	2000	68.7 (8.7)	100
240	Physician's Health Study	2000	68.7 (8.7)	100
241	Physician's Health Study	19097	53.2	100
242	Physician's Health Study	19097	53.2	100
243	Physician's Health Study	19097	53.2	100
244	Physician's Health Study	19097	53.2	100
245	Physician's Health Study	19097	53.2	100
246	Physician's Health Study	19097	53.2	100
247	Physician's Health Study	2000	68.7 (8.7)	100
248	Physician's Health Study	2000	68.7 (8.7)	100
249	Physician's Health Study	2000	68.7 (8.7)	100
250	Physician's Health Study	2000	68.7 (8.7)	100
251	Physician's Health Study	2000	68.7 (8.7)	100
252	Physician's Health Study	2000	68.7 (8.7)	100
253	Physician's Health Study	19097	53.2	100
254	Physician's Health Study	19097	53.2	100
255	Physician's Health Study	19097	53.2	100
256	Physician's Health Study	19097	53.2	100
257	Physician's Health Study	19097	53.2	100
258	Physician's Health Study	19097	53.2	100
259	Physician's Health Study	19097	53.2	100
260	Physician's Health Study	19097	53.2	100
261	Physician's Health Study	19097	53.2	100
262	Pooling Project of Cohort Studies on Diet and Coronary Disease	229043	range 49, 61	35.1
263	Pooling Project of Cohort Studies on Diet and Coronary Disease	229043	range 49, 61	35.1
264	Rotterdam	5184	67.3 (7.6)	41% in Q3 (secondary study)
265	Rotterdam	5184	67.3 (7.6)	41% in Q3 (secondary study)
266	Rotterdam	5184	67.3 (7.6)	41% in Q3 (secondary study)

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Race	Blood pressure SBP/DBP (mmHg)
230	Nurses' Health Study (NHS)	98 white	nd
231	Osaka Acute Coronary Insufficiency Study	nd	nd
232	Osaka Acute Coronary Insufficiency Study	nd	nd
233	Osaka Acute Coronary Insufficiency Study	nd	nd
234	Osaka Acute Coronary Insufficiency Study	nd	nd
235	Physician's Health Study	nd	nd
236	Physician's Health Study	nd	nd
237	Physician's Health Study	nd	nd
238	Physician's Health Study	nd	nd
239	Physician's Health Study	nd	nd
240	Physician's Health Study	nd	nd
241	Physician's Health Study	nd	nd
242	Physician's Health Study	nd	nd
243	Physician's Health Study	nd	nd
244	Physician's Health Study	nd	nd
245	Physician's Health Study	nd	nd
246	Physician's Health Study	nd	nd
247	Physician's Health Study	nd	nd
248	Physician's Health Study	nd	nd
249	Physician's Health Study	nd	nd
250	Physician's Health Study	nd	nd
251	Physician's Health Study	nd	nd
252	Physician's Health Study	nd	nd
253	Physician's Health Study	nd	nd
254	Physician's Health Study	nd	nd
255	Physician's Health Study	nd	nd
256	Physician's Health Study	nd	nd
257	Physician's Health Study	nd	nd
258	Physician's Health Study	nd	nd
259	Physician's Health Study	nd	nd
260	Physician's Health Study	nd	nd
261	Physician's Health Study	nd	nd
262	Pooling Project of Cohort Studies on Diet and Coronary Disease	nd	nd
263	Pooling Project of Cohort Studies on Diet and Coronary Disease	nd	nd
264	Rotterdam		138 (21)/73 (11)
265	Rotterdam		138 (21)/73 (11)
266	Rotterdam		138 (21)/73 (11)

Row	Study	Lipids: Total cholesterol/LDL/HDL/Triglycerides mean (SD) mg/dL [mmol/L]
230	Nurses' Health Study (NHS)	nd
231	Osaka Acute Coronary Insufficiency Study	191 (range 163, 222)/122 (range 100, 147)/44 (range 38, 52)/98 (range 60, 153)
232	Osaka Acute Coronary Insufficiency Study	191 (range 163, 222)/122 (range 100, 147)/44 (range 38, 52)/98 (range 60, 153)
233	Osaka Acute Coronary Insufficiency Study	191 (range 163, 222)/122 (range 100, 147)/44 (range 38, 52)/98 (range 60, 153)
234	Osaka Acute Coronary Insufficiency Study	191 (range 163, 222)/122 (range 100, 147)/44 (range 38, 52)/98 (range 60, 153)
235	Physician's Health Study	nd
236	Physician's Health Study	nd
237	Physician's Health Study	nd
238	Physician's Health Study	nd
239	Physician's Health Study	nd
240	Physician's Health Study	nd
241	Physician's Health Study	nd
242	Physician's Health Study	nd
243	Physician's Health Study	nd
244	Physician's Health Study	nd
245	Physician's Health Study	nd
246	Physician's Health Study	nd
247	Physician's Health Study	nd
248	Physician's Health Study	nd
249	Physician's Health Study	nd
250	Physician's Health Study	nd
251	Physician's Health Study	nd
252	Physician's Health Study	nd
253	Physician's Health Study	nd
254	Physician's Health Study	nd
255	Physician's Health Study	nd
256	Physician's Health Study	nd
257	Physician's Health Study	nd
258	Physician's Health Study	nd
259	Physician's Health Study	nd
260	Physician's Health Study	nd
261	Physician's Health Study	nd
262	Pooling Project of Cohort Studies on Diet and Coronary Disease	nd
263	Pooling Project of Cohort Studies on Diet and Coronary Disease	nd
264	Rotterdam	[6.6 (1.2)]/nd/[1.3 (0.4)]/nd
265	Rotterdam	[6.6 (1.2)]/nd/[1.3 (0.4)]/nd
266	Rotterdam	[6.6 (1.2)]/nd/[1.3 (0.4)]/nd

Appendix G.2.
Causality Table: Observational Studies

Row	Study	BMI mean (SD)/weight mean (SD) Kg
230	Nurses' Health Study (NHS)	nd
231	Osaka Acute Coronary Insufficiency Study	23.9 (range 22.1, 26.1)
232	Osaka Acute Coronary Insufficiency Study	23.9 (range 22.1, 26.1)
233	Osaka Acute Coronary Insufficiency Study	23.9 (range 22.1, 26.1)
234	Osaka Acute Coronary Insufficiency Study	23.9 (range 22.1, 26.1)
235	Physician's Health Study	25.8 (3.4)
236	Physician's Health Study	25.8 (3.4)
237	Physician's Health Study	25.8 (3.4)
238	Physician's Health Study	25.8 (3.4)
239	Physician's Health Study	25.8 (3.4)
240	Physician's Health Study	25.8 (3.4)
241	Physician's Health Study	24.9
242	Physician's Health Study	24.9
243	Physician's Health Study	24.9
244	Physician's Health Study	24.9
245	Physician's Health Study	24.9
246	Physician's Health Study	24.9
247	Physician's Health Study	25.8 (3.4)
248	Physician's Health Study	25.8 (3.4)
249	Physician's Health Study	25.8 (3.4)
250	Physician's Health Study	25.8 (3.4)
251	Physician's Health Study	25.8 (3.4)
252	Physician's Health Study	25.8 (3.4)
253	Physician's Health Study	24.9
254	Physician's Health Study	24.9
255	Physician's Health Study	24.9
256	Physician's Health Study	24.9
257	Physician's Health Study	24.9
258	Physician's Health Study	24.9
259	Physician's Health Study	24.9
260	Physician's Health Study	24.9
261	Physician's Health Study	24.9
262	Pooling Project of Cohort Studies on Diet and Coronary Disease	nd
263	Pooling Project of Cohort Studies on Diet and Coronary Disease	nd
264	Rotterdam	26.4 (3.6)
265	Rotterdam	26.4 (3.6)
266	Rotterdam	26.4 (3.6)

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Baseline n-3 intake/level (median (IQR), unless noted)
230	Nurses' Health Study (NHS)	ALA: 0.52% energy, EPA+DHA 0.08% energy
231	Osaka Acute Coronary Insufficiency Study	EPA: 31.7 µg/mL, DHA: 72.5 µg/mL
232	Osaka Acute Coronary Insufficiency Study	EPA: 31.7 µg/mL, DHA: 72.5 µg/mL
233	Osaka Acute Coronary Insufficiency Study	EPA: 31.7 µg/mL, DHA: 72.5 µg/mL
234	Osaka Acute Coronary Insufficiency Study	EPA: 31.7 µg/mL, DHA: 72.5 µg/mL
235	Physician's Health Study	nd
236	Physician's Health Study	nd
237	Physician's Health Study	nd
238	Physician's Health Study	nd
239	Physician's Health Study	nd
240	Physician's Health Study	nd
241	Physician's Health Study	ALA: 0.765 g/d, EPA+DPA+DHA: 0.152 g/d,
242	Physician's Health Study	ALA: 0.765 g/d, EPA+DPA+DHA: 0.152 g/d,
243	Physician's Health Study	ALA: 0.765 g/d, EPA+DPA+DHA: 0.152 g/d,
244	Physician's Health Study	ALA: 0.765 g/d, EPA+DPA+DHA: 0.152 g/d,
245	Physician's Health Study	ALA: 0.765 g/d, EPA+DPA+DHA: 0.152 g/d,
246	Physician's Health Study	ALA: 0.765 g/d, EPA+DPA+DHA: 0.152 g/d,
247	Physician's Health Study	nd
248	Physician's Health Study	nd
249	Physician's Health Study	nd
250	Physician's Health Study	nd
251	Physician's Health Study	nd
252	Physician's Health Study	nd
253	Physician's Health Study	ALA: 0.765 g/d, EPA+DPA+DHA: 0.152 g/d,
254	Physician's Health Study	ALA: 0.765 g/d, EPA+DPA+DHA: 0.152 g/d,
255	Physician's Health Study	ALA: 0.765 g/d, EPA+DPA+DHA: 0.152 g/d,
256	Physician's Health Study	ALA: 0.765 g/d, EPA+DPA+DHA: 0.152 g/d,
257	Physician's Health Study	ALA: 0.765 g/d, EPA+DPA+DHA: 0.152 g/d,
258	Physician's Health Study	ALA: 0.765 g/d, EPA+DPA+DHA: 0.152 g/d,
259	Physician's Health Study	ALA: 0.765 g/d, EPA+DPA+DHA: 0.152 g/d,
260	Physician's Health Study	ALA: 0.765 g/d, EPA+DPA+DHA: 0.152 g/d,
261	Physician's Health Study	ALA: 0.765 g/d, EPA+DPA+DHA: 0.152 g/d,
262	Pooling Project of Cohort Studies on Diet and Coronary Disease	ALA: 1.06 (80% central range 0.60, 1.06) g/d, EPA+DHA: 0.19 (80% central range 0.05, 0.50) g/d
263	Pooling Project of Cohort Studies on Diet and Coronary Disease	ALA: 1.06 (80% central range 0.60, 1.06) g/d, EPA+DHA: 0.19 (80% central range 0.05, 0.50) g/d
264	Rotterdam	EPA+DHA: 89 mg/d
265	Rotterdam	EPA+DHA: 89 mg/d
266	Rotterdam	EPA+DHA: 89 mg/d

Appendix G.2.
Causality Table: Observational Studies

Row	Study	n-3 source	n-3 measure	n-3 type(s)
230	Nurses' Health Study (NHS)	intake	% energy	ALA
231	Osaka Acute Coronary Insufficiency Study	blood	μg/mL	DHA
232	Osaka Acute Coronary Insufficiency Study	blood	μg/mL	EPA
233	Osaka Acute Coronary Insufficiency Study	blood	μg/mL	DHA
234	Osaka Acute Coronary Insufficiency Study	blood	μg/mL	EPA
235	Physician's Health Study	RBC	Per SD increase	SDA
236	Physician's Health Study	RBC	Per SD increase	ALA
237	Physician's Health Study	RBC	Per SD increase	EPA+DPA+DHA
238	Physician's Health Study	RBC	Per SD increase	EPA
239	Physician's Health Study	RBC	Per SD increase	DPA
240	Physician's Health Study	RBC	Per SD increase	DHA
241	Physician's Health Study	intake	g/d	Marine (EPA+DHA+DPA)
242	Physician's Health Study	intake	g/d	ALA
243	Physician's Health Study	plasma	% of total Fas	Marine (EPA+DHA+DPA)
244	Physician's Health Study	plasma	% of total Fas	ALA
245	Physician's Health Study	intake	g/week	Total n-3
246	Physician's Health Study	intake	g/month	Total n-3
247	Physician's Health Study	RBC	Per SD increase	SDA
248	Physician's Health Study	RBC	Per SD increase	ALA
249	Physician's Health Study	RBC	Per SD increase	EPA+DPA+DHA
250	Physician's Health Study	RBC	Per SD increase	EPA
251	Physician's Health Study	RBC	Per SD increase	DPA
252	Physician's Health Study	RBC	Per SD increase	DHA
253	Physician's Health Study	intake	g/week	Total n-3
254	Physician's Health Study	intake	g/week	Total n-3
255	Physician's Health Study	cholesterol esters	% U	EPA
256	Physician's Health Study	cholesterol esters	% U	DHA
257	Physician's Health Study	cholesterol esters	% U	EPA+DHA
258	Physician's Health Study	phospholipids	% U	EPA
259	Physician's Health Study	phospholipids	% U	DHA
260	Physician's Health Study	phospholipids	% U	EPA+DHA
261	Physician's Health Study	intake	g/week	Total n-3
262	Pooling Project of Cohort Studies on Diet and Coronary Disease	intake	g/d	ALA
263	Pooling Project of Cohort Studies on Diet and Coronary Disease	intake	g/d	ALA
264	Rotterdam	intake	mg/d	EPA+DHA
265	Rotterdam	intake	mg/d	EPA+DHA
266	Rotterdam	intake	mg/d	EPA+DHA

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Study design
230	Nurses' Health Study (NHS)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
231	Osaka Acute Coronary Insufficiency Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
232	Osaka Acute Coronary Insufficiency Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
233	Osaka Acute Coronary Insufficiency Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
234	Osaka Acute Coronary Insufficiency Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
235	Physician's Health Study	Nested Case Control
236	Physician's Health Study	Nested Case Control
237	Physician's Health Study	Nested Case Control
238	Physician's Health Study	Nested Case Control
239	Physician's Health Study	Nested Case Control
240	Physician's Health Study	Nested Case Control
241	Physician's Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
242	Physician's Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
243	Physician's Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
244	Physician's Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
245	Physician's Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
246	Physician's Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
247	Physician's Health Study	Nested Case Control
248	Physician's Health Study	Nested Case Control
249	Physician's Health Study	Nested Case Control
250	Physician's Health Study	Nested Case Control
251	Physician's Health Study	Nested Case Control
252	Physician's Health Study	Nested Case Control
253	Physician's Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
254	Physician's Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
255	Physician's Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
256	Physician's Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
257	Physician's Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
258	Physician's Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
259	Physician's Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
260	Physician's Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
261	Physician's Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
262	Pooling Project of Cohort Studies on Diet and Coronary Disease	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
263	Pooling Project of Cohort Studies on Diet and Coronary Disease	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
264	Rotterdam	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
265	Rotterdam	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
266	Rotterdam	Prospective, longitudinal study of intake (eg, FFQ, biomarker)

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Outcome	Reported effect Size
230	Nurses' Health Study (NHS)	Sudden cardiac death	See appendix F
231	Osaka Acute Coronary Insufficiency Study	Congestive heart failure	See appendix F
232	Osaka Acute Coronary Insufficiency Study	Congestive heart failure	See appendix F
233	Osaka Acute Coronary Insufficiency Study	Death, all cause	See appendix F
234	Osaka Acute Coronary Insufficiency Study	Death, all cause	See appendix F
235	Physician's Health Study	CHD	See appendix F
236	Physician's Health Study	CHD	See appendix F
237	Physician's Health Study	CHD	See appendix F
238	Physician's Health Study	CHD	See appendix F
239	Physician's Health Study	CHD	See appendix F
240	Physician's Health Study	CHD	See appendix F
241	Physician's Health Study	Congestive heart failure	See appendix F
242	Physician's Health Study	Congestive heart failure	See appendix F
243	Physician's Health Study	Congestive heart failure	See appendix F
244	Physician's Health Study	Congestive heart failure	See appendix F
245	Physician's Health Study	CVD, total	See appendix F
246	Physician's Health Study	Death, cardiac	See appendix F
247	Physician's Health Study	Death, CHD	See appendix F
248	Physician's Health Study	Death, CHD	See appendix F
249	Physician's Health Study	Death, CHD	See appendix F
250	Physician's Health Study	Death, CHD	See appendix F
251	Physician's Health Study	Death, CHD	See appendix F
252	Physician's Health Study	Death, CHD	See appendix F
253	Physician's Health Study	Death, CVD	See appendix F
254	Physician's Health Study	Myocardial infarction	See appendix F
255	Physician's Health Study	Myocardial infarction	See appendix F
256	Physician's Health Study	Myocardial infarction	See appendix F
257	Physician's Health Study	Myocardial infarction	See appendix F
258	Physician's Health Study	Myocardial infarction	See appendix F
259	Physician's Health Study	Myocardial infarction	See appendix F
260	Physician's Health Study	Myocardial infarction	See appendix F
261	Physician's Health Study	Stroke, total	See appendix F
262	Pooling Project of Cohort Studies on Diet and Coronary Disease	Coronary heart disease	See appendix F
263	Pooling Project of Cohort Studies on Diet and Coronary Disease	Death, cardiac	See appendix F
264	Rotterdam	Atrial fibrillation	See appendix F
265	Rotterdam	Atrial fibrillation	See appendix F
266	Rotterdam	Congestive heart failure	See appendix F

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Study years (study start date)	Country
267	Scottish Heart Health Extended Cohort Study	1984	UK
268	Scottish Heart Health Extended Cohort Study	1984	UK
269	Shanghai	1986	China
270	Shanghai	1986	China
271	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	1997	China
272	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	1997	China
273	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	1997	China
274	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	1997	China
275	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	1997	China
276	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	1997	China
277	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	1997	China
278	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	1997	China
279	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	1997	China
280	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	1997	China
281	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	1997	China
282	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	1997	China
283	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	1997	China
284	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	1997	China
285	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	1997	China
286	Spanish EPIC	1992	Spain
287	Spanish EPIC	1992	Spain
288	Spanish EPIC	1992	Spain
289	Spanish EPIC	1992	Spain
290	Spanish EPIC	1992	Spain

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Population	Risk type
267	Scottish Heart Health Extended Cohort Study	Primary Prevention, Healthy	na
268	Scottish Heart Health Extended Cohort Study	Primary Prevention, Healthy	na
269	Shanghai	Primary Prevention, Healthy	na
270	Shanghai	Primary Prevention, Healthy	na
271	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	Primary Prevention, Healthy	na
272	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	Primary Prevention, Healthy	na
273	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	Primary Prevention, Healthy	na
274	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	Primary Prevention, Healthy	na
275	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	Primary Prevention, Healthy	na
276	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	Primary Prevention, Healthy	na
277	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	Primary Prevention, Healthy	na
278	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	Primary Prevention, Healthy	na
279	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	Primary Prevention, Healthy	na
280	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	Primary Prevention, Healthy	na
281	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	Primary Prevention, Healthy	na
282	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	Primary Prevention, Healthy	na
283	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	Primary Prevention, Healthy	na
284	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	Primary Prevention, Healthy	na
285	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	Primary Prevention, Healthy	na
286	Spanish EPIC	Primary Prevention, Healthy	na
287	Spanish EPIC	Primary Prevention, Healthy	na
288	Spanish EPIC	Primary Prevention, Healthy	na
289	Spanish EPIC	Primary Prevention, Healthy	na
290	Spanish EPIC	Primary Prevention, Healthy	na

Row	Study	Sample size (total)	Age mean (SD) [median]	Sex (% male)
267	Scottish Heart Health Extended Cohort Study	3944	men: 49.0 (6.9), women: 48.9(6.6)	53
268	Scottish Heart Health Extended Cohort Study	3944	men: 49.0 (6.9), women: 48.9(6.6)	53
269	Shanghai	18244	55.8	100
270	Shanghai	18244	55.8	100
271	Shanghai Women’s Health Study (SWHS) Shanghai Men’s Health Study (SMHS)	134296	men: 55.1 (9.54), women: 51.8 (8.76)	45.5
272	Shanghai Women’s Health Study (SWHS) Shanghai Men’s Health Study (SMHS)	134296	men: 55.1 (9.54), women: 51.8 (8.76)	45.5
273	Shanghai Women’s Health Study (SWHS) Shanghai Men’s Health Study (SMHS)	134296	men: 55.1 (9.54), women: 51.8 (8.76)	45.5
274	Shanghai Women’s Health Study (SWHS) Shanghai Men’s Health Study (SMHS)	134296	men: 55.1 (9.54), women: 51.8 (8.76)	45.5
275	Shanghai Women’s Health Study (SWHS) Shanghai Men’s Health Study (SMHS)	134296	men: 55.1 (9.54), women: 51.8 (8.76)	45.5
276	Shanghai Women’s Health Study (SWHS) Shanghai Men’s Health Study (SMHS)	134296	men: 55.1 (9.54), women: 51.8 (8.76)	45.5
277	Shanghai Women’s Health Study (SWHS) Shanghai Men’s Health Study (SMHS)	134296	men: 55.1 (9.54), women: 51.8 (8.76)	45.5
278	Shanghai Women’s Health Study (SWHS) Shanghai Men’s Health Study (SMHS)	134296	men: 55.1 (9.54), women: 51.8 (8.76)	45.5
279	Shanghai Women’s Health Study (SWHS) Shanghai Men’s Health Study (SMHS)	134296	men: 55.1 (9.54), women: 51.8 (8.76)	45.5
280	Shanghai Women’s Health Study (SWHS) Shanghai Men’s Health Study (SMHS)	134296	men: 55.1 (9.54), women: 51.8 (8.76)	45.5
281	Shanghai Women’s Health Study (SWHS) Shanghai Men’s Health Study (SMHS)	134296	men: 55.1 (9.54), women: 51.8 (8.76)	45.5
282	Shanghai Women’s Health Study (SWHS) Shanghai Men’s Health Study (SMHS)	134296	men: 55.1 (9.54), women: 51.8 (8.76)	45.5
283	Shanghai Women’s Health Study (SWHS) Shanghai Men’s Health Study (SMHS)	134296	men: 55.1 (9.54), women: 51.8 (8.76)	45.5
284	Shanghai Women’s Health Study (SWHS) Shanghai Men’s Health Study (SMHS)	134296	men: 55.1 (9.54), women: 51.8 (8.76)	45.5
285	Shanghai Women’s Health Study (SWHS) Shanghai Men’s Health Study (SMHS)	134296	men: 55.1 (9.54), women: 51.8 (8.76)	45.5
286	Spanish EPIC	41091	49.2 (8)	37.6
287	Spanish EPIC	41091	49.2 (8)	37.6
288	Spanish EPIC	41091	49.2 (8)	37.6
289	Spanish EPIC	41091	49.2 (8)	37.6
290	Spanish EPIC	41091	49.2 (8)	37.6

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Race	Blood pressure SBP/DBP (mmHg)
267	Scottish Heart Health Extended Cohort Study	nd	men: 133.2 (18.5), women: 130.0(20.0)/
268	Scottish Heart Health Extended Cohort Study	nd	men: 133.2 (18.5), women: 130.0(20.0)/
269	Shanghai	nd	nd
270	Shanghai	nd	nd
271	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	nd	nd
272	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	nd	nd
273	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	nd	nd
274	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	nd	nd
275	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	nd	nd
276	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	nd	nd
277	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	nd	nd
278	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	nd	nd
279	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	nd	nd
280	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	nd	nd
281	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	nd	nd
282	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	nd	nd
283	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	nd	nd
284	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	nd	nd
285	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	nd	nd
286	Spanish EPIC	nd	nd
287	Spanish EPIC	nd	nd
288	Spanish EPIC	nd	nd
289	Spanish EPIC	nd	nd
290	Spanish EPIC	nd	nd

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Lipids: Total cholesterol/LDL/HDL/Triglycerides mean (SD) mg/dL [mmol/L]
267	Scottish Heart Health Extended Cohort Study	[men: 6.29(1.13), women: 6.49(1.31)/nd/[men: 1.38(0.37), women: 1.68(0.42)]/nd
268	Scottish Heart Health Extended Cohort Study	[men: 6.29(1.13), women: 6.49(1.31)/nd/[men: 1.38(0.37), women: 1.68(0.42)]/nd
269	Shanghai	nd
270	Shanghai	nd
271	Shanghai Women’s Health Study (SWHS) Shanghai Men’s Health Study (SMHS)	nd
272	Shanghai Women’s Health Study (SWHS) Shanghai Men’s Health Study (SMHS)	nd
273	Shanghai Women’s Health Study (SWHS) Shanghai Men’s Health Study (SMHS)	nd
274	Shanghai Women’s Health Study (SWHS) Shanghai Men’s Health Study (SMHS)	nd
275	Shanghai Women’s Health Study (SWHS) Shanghai Men’s Health Study (SMHS)	nd
276	Shanghai Women’s Health Study (SWHS) Shanghai Men’s Health Study (SMHS)	nd
277	Shanghai Women’s Health Study (SWHS) Shanghai Men’s Health Study (SMHS)	nd
278	Shanghai Women’s Health Study (SWHS) Shanghai Men’s Health Study (SMHS)	nd
279	Shanghai Women’s Health Study (SWHS) Shanghai Men’s Health Study (SMHS)	nd
280	Shanghai Women’s Health Study (SWHS) Shanghai Men’s Health Study (SMHS)	nd
281	Shanghai Women’s Health Study (SWHS) Shanghai Men’s Health Study (SMHS)	nd
282	Shanghai Women’s Health Study (SWHS) Shanghai Men’s Health Study (SMHS)	nd
283	Shanghai Women’s Health Study (SWHS) Shanghai Men’s Health Study (SMHS)	nd
284	Shanghai Women’s Health Study (SWHS) Shanghai Men’s Health Study (SMHS)	nd
285	Shanghai Women’s Health Study (SWHS) Shanghai Men’s Health Study (SMHS)	nd
286	Spanish EPIC	nd
287	Spanish EPIC	nd
288	Spanish EPIC	nd
289	Spanish EPIC	nd
290	Spanish EPIC	nd

Appendix G.2.
Causality Table: Observational Studies

Row	Study	BMI mean (SD)/weight mean (SD) Kg
267	Scottish Heart Health Extended Cohort Study	nd
268	Scottish Heart Health Extended Cohort Study	nd
269	Shanghai	22.2
270	Shanghai	22.2
271	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	nd
272	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	nd
273	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	nd
274	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	nd
275	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	nd
276	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	nd
277	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	nd
278	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	nd
279	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	nd
280	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	nd
281	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	nd
282	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	nd
283	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	nd
284	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	nd
285	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	nd
286	Spanish EPIC	73.7 (12.6)
287	Spanish EPIC	73.7 (12.6)
288	Spanish EPIC	73.7 (12.6)
289	Spanish EPIC	73.7 (12.6)
290	Spanish EPIC	73.7 (12.6)

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Baseline n-3 intake/level (median (IQR), unless noted)
267	Scottish Heart Health Extended Cohort Study	DPA: men 0.25 (0.20, 0.30)% FA, women 0.26 (0.21, 0.32)% FA, DHA: men 0.17 (0.13, 0.22)% FA, women 0.19 (0.15, 0.26)% FA, DPA+DHA: men 0.42 (0.33, 0.52)% FA, women 0.46 (0.36, 0.58)% FA
268	Scottish Heart Health Extended Cohort Study	DPA: men 0.25 (0.20, 0.30)% FA, women 0.26 (0.21, 0.32)% FA, DHA: men 0.17 (0.13, 0.22)% FA, women 0.19 (0.15, 0.26)% FA, DPA+DHA: men 0.42 (0.33, 0.52)% FA, women 0.46 (0.36, 0.58)% FA
269	Shanghai	All n-3 FA: 0.65 g/week
270	Shanghai	All n-3 FA: 0.65 g/week
271	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	EPA: men and women 0.02 g/d, DHA: men 0.05 g/d, women 0.04 g/d
272	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	EPA: men and women 0.02 g/d, DHA: men 0.05 g/d, women 0.04 g/d
273	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	EPA: men and women 0.02 g/d, DHA: men 0.05 g/d, women 0.04 g/d
274	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	EPA: men and women 0.02 g/d, DHA: men 0.05 g/d, women 0.04 g/d
275	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	EPA: men and women 0.02 g/d, DHA: men 0.05 g/d, women 0.04 g/d
276	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	EPA: men and women 0.02 g/d, DHA: men 0.05 g/d, women 0.04 g/d
277	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	EPA: men and women 0.02 g/d, DHA: men 0.05 g/d, women 0.04 g/d
278	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	EPA: men and women 0.02 g/d, DHA: men 0.05 g/d, women 0.04 g/d
279	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	EPA: men and women 0.02 g/d, DHA: men 0.05 g/d, women 0.04 g/d
280	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	EPA: men and women 0.02 g/d, DHA: men 0.05 g/d, women 0.04 g/d
281	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	EPA: men and women 0.02 g/d, DHA: men 0.05 g/d, women 0.04 g/d
282	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	EPA: men and women 0.02 g/d, DHA: men 0.05 g/d, women 0.04 g/d
283	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	EPA: men and women 0.02 g/d, DHA: men 0.05 g/d, women 0.04 g/d
284	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	EPA: men and women 0.02 g/d, DHA: men 0.05 g/d, women 0.04 g/d
285	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	EPA: men and women 0.02 g/d, DHA: men 0.05 g/d, women 0.04 g/d
286	Spanish EPIC	EPA: mean 0.2 (SD 0.2) g/d, DHA: mean 0.4 (SD 0.3) g/d, Total n-3 FA: mean 1.4 (SD 0.7) g/d
287	Spanish EPIC	EPA: mean 0.2 (SD 0.2) g/d, DHA: mean 0.4 (SD 0.3) g/d, Total n-3 FA: mean 1.4 (SD 0.7) g/d
288	Spanish EPIC	EPA: mean 0.2 (SD 0.2) g/d, DHA: mean 0.4 (SD 0.3) g/d, Total n-3 FA: mean 1.4 (SD 0.7) g/d
289	Spanish EPIC	EPA: mean 0.2 (SD 0.2) g/d, DHA: mean 0.4 (SD 0.3) g/d, Total n-3 FA: mean 1.4 (SD 0.7) g/d
290	Spanish EPIC	EPA: mean 0.2 (SD 0.2) g/d, DHA: mean 0.4 (SD 0.3) g/d, Total n-3 FA: mean 1.4 (SD 0.7) g/d

Appendix G.2.
Causality Table: Observational Studies

Row	Study	n-3 source	n-3 measure	n-3 type(s)
267	Scottish Heart Health Extended Cohort Study	adipose tissue	mmol/L	DPA
268	Scottish Heart Health Extended Cohort Study	adipose tissue	mmol/L	DHA
269	Shanghai	intake	g/week	all_n3
270	Shanghai	intake	g/week	all_n3
271	Shanghai Women’s Health Study (SWHS) Shanghai Men’s Health Study (SMHS)	intake	g/d	EPA
272	Shanghai Women’s Health Study (SWHS) Shanghai Men’s Health Study (SMHS)	intake	g/d	DHA
273	Shanghai Women’s Health Study (SWHS) Shanghai Men’s Health Study (SMHS)	intake	g/d	EPA + DHA
274	Shanghai Women’s Health Study (SWHS) Shanghai Men’s Health Study (SMHS)	intake	g/d	EPA
275	Shanghai Women’s Health Study (SWHS) Shanghai Men’s Health Study (SMHS)	intake	g/d	DHA
276	Shanghai Women’s Health Study (SWHS) Shanghai Men’s Health Study (SMHS)	intake	g/d	EPA + DHA
277	Shanghai Women’s Health Study (SWHS) Shanghai Men’s Health Study (SMHS)	intake	g/d	EPA
278	Shanghai Women’s Health Study (SWHS) Shanghai Men’s Health Study (SMHS)	intake	g/d	DHA
279	Shanghai Women’s Health Study (SWHS) Shanghai Men’s Health Study (SMHS)	intake	g/d	EPA + DHA
280	Shanghai Women’s Health Study (SWHS) Shanghai Men’s Health Study (SMHS)	intake	g/d	EPA
281	Shanghai Women’s Health Study (SWHS) Shanghai Men’s Health Study (SMHS)	intake	g/d	DHA
282	Shanghai Women’s Health Study (SWHS) Shanghai Men’s Health Study (SMHS)	intake	g/d	EPA + DHA
283	Shanghai Women’s Health Study (SWHS) Shanghai Men’s Health Study (SMHS)	intake	g/d	EPA
284	Shanghai Women’s Health Study (SWHS) Shanghai Men’s Health Study (SMHS)	intake	g/d	DHA
285	Shanghai Women’s Health Study (SWHS) Shanghai Men’s Health Study (SMHS)	intake	g/d	EPA + DHA
286	Spanish EPIC	intake	g/d	EPA + DHA
287	Spanish EPIC	intake	g/d	EPA + DHA
288	Spanish EPIC	intake	g/d	EPA
289	Spanish EPIC	intake	g/d	EPA
290	Spanish EPIC	intake	g/d	DHA

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Study design
267	Scottish Heart Health Extended Cohort Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
268	Scottish Heart Health Extended Cohort Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
269	Shanghai	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
270	Shanghai	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
271	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
272	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
273	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
274	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
275	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
276	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
277	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
278	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
279	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
280	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
281	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
282	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
283	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
284	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
285	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
286	Spanish EPIC	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
287	Spanish EPIC	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
288	Spanish EPIC	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
289	Spanish EPIC	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
290	Spanish EPIC	Prospective, longitudinal study of intake (eg, FFQ, biomarker)

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Outcome	Reported effect Size
267	Scottish Heart Health Extended Cohort Study	CVD, total	See appendix F
268	Scottish Heart Health Extended Cohort Study	CVD, total	See appendix F
269	Shanghai	Death, CHD	See appendix F
270	Shanghai	Death, stroke	See appendix F
271	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	Death, all cause	See appendix F
272	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	Death, all cause	See appendix F
273	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	Death, all cause	See appendix F
274	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	Death, CHD	See appendix F
275	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	Death, CHD	See appendix F
276	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	Death, CHD	See appendix F
277	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	Death, CVD	See appendix F
278	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	Death, CVD	See appendix F
279	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	Death, CVD	See appendix F
280	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	Death, stroke, hemorrhagic	See appendix F
281	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	Death, stroke, hemorrhagic	See appendix F
282	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	Death, stroke, hemorrhagic	See appendix F
283	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	Death, stroke, ischemic	See appendix F
284	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	Death, stroke, ischemic	See appendix F
285	Shanghai Women's Health Study (SWHS) Shanghai Men's Health Study (SMHS)	Death, stroke, ischemic	See appendix F
286	Spanish EPIC	Myocardial infarction	See appendix F
287	Spanish EPIC	Myocardial infarction	See appendix F
288	Spanish EPIC	Myocardial infarction	See appendix F
289	Spanish EPIC	Myocardial infarction	See appendix F
290	Spanish EPIC	Myocardial infarction	See appendix F

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Study years (study start date)	Country
291	Spanish EPIC	1992	Spain
292	Swedish Mammography Study	1997	Sweden
293	Swedish Mammography Study	1997	Sweden
294	Swedish Mammography Study	1997	Sweden
295	Swedish Mammography Study	1997	Sweden
296	Swedish Mammography Study	1997	Sweden
297	Swedish Mammography Study	1997	Sweden
298	Swedish Mammography Study	1997	Sweden
299	Takayama	1992	Japan
300	Takayama	1992	Japan
301	The Singapore Chinese Health Study	1993	China
302	The Singapore Chinese Health Study	1993	China
303	The Singapore Chinese Health Study	1993	China
304	The Singapore Chinese Health Study	1993	China
305	The Singapore Chinese Health Study	1993	China
306	The Singapore Chinese Health Study	1993	China
307	The Singapore Chinese Health Study	1993	China
308	The Singapore Chinese Health Study	1993	China
309	The Singapore Chinese Health Study	1993	China
310	The Singapore Chinese Health Study	1993	China
311	The Singapore Chinese Health Study	1993	China
312	The Singapore Chinese Health Study	1993	China
313	ULSAM	1970	Sweden
314	ULSAM	1970	Sweden
315	ULSAM	1970	Sweden
316	ULSAM	1970	Sweden
317	ULSAM	1970	Sweden
318	ULSAM	1970	Sweden
319	VITAL	2000	US
320	VITAL	2000	US
321	VITAL	2000	US
322	Women's Health Initiative	nd	US

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Population	Risk type
291	Spanish EPIC	Primary Prevention, Healthy	na
292	Swedish Mammography Study	Primary Prevention, Healthy	na
293	Swedish Mammography Study	Primary Prevention, Healthy	na
294	Swedish Mammography Study	Primary Prevention, Healthy	na
295	Swedish Mammography Study	Primary Prevention, Healthy	na
296	Swedish Mammography Study	Primary Prevention, Healthy	na
297	Swedish Mammography Study	Primary Prevention, Healthy	na
298	Swedish Mammography Study	Primary Prevention, Healthy	na
299	Takayama	Primary Prevention, Healthy	na
300	Takayama	Primary Prevention, Healthy	na
301	The Singapore Chinese Health Study	Primary Prevention, Healthy	na
302	The Singapore Chinese Health Study	Primary Prevention, Healthy	na
303	The Singapore Chinese Health Study	Primary Prevention, Healthy	na
304	The Singapore Chinese Health Study	Primary Prevention, Healthy	na
305	The Singapore Chinese Health Study	Primary Prevention, Healthy	na
306	The Singapore Chinese Health Study	Primary Prevention, Healthy	na
307	The Singapore Chinese Health Study	CVD	history of CHD or stroke
308	The Singapore Chinese Health Study	CVD	history of CHD or stroke
309	The Singapore Chinese Health Study	CVD	history of CHD or stroke
310	The Singapore Chinese Health Study	Primary Prevention, Healthy	na
311	The Singapore Chinese Health Study	Primary Prevention, Healthy	na
312	The Singapore Chinese Health Study	Primary Prevention, Healthy	na
313	ULSAM	Primary Prevention, Healthy	na
314	ULSAM	Primary Prevention, Healthy	na
315	ULSAM	Primary Prevention, Healthy	na
316	ULSAM	Primary Prevention, Healthy	na
317	ULSAM	Primary Prevention, Healthy	na
318	ULSAM	Primary Prevention, Healthy	na
319	VITAL	Primary Prevention, Healthy	na
320	VITAL	Primary Prevention, Healthy	na
321	VITAL	Primary Prevention, Healthy	na
322	Women's Health Initiative	Primary Prevention, Healthy	na

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Sample size (total)	Age mean (SD) [median]	Sex (% male)
291	Spanish EPIC	41091	49.2 (8)	37.6
292	Swedish Mammography Study	34670	62	0
293	Swedish Mammography Study	34670	62	0
294	Swedish Mammography Study	34670	62	0
295	Swedish Mammography Study	34670	62	0
296	Swedish Mammography Study	34670	62	0
297	Swedish Mammography Study	34670	62	0
298	Swedish Mammography Study	34670	62	0
299	Takayama	30480	men: 54.0 (12.1), women: 55.1 (13.0)	nd
300	Takayama	30480	men: 54.0 (12.1), women: 55.1 (13.0)	nd
301	The Singapore Chinese Health Study	60298	56 (8)	44.2
302	The Singapore Chinese Health Study	60298	56 (8)	44.2
303	The Singapore Chinese Health Study	60298	56 (8)	44.2
304	The Singapore Chinese Health Study	60298	56 (8)	44.2
305	The Singapore Chinese Health Study	60298	56 (8)	44.2
306	The Singapore Chinese Health Study	60298	56 (8)	44.2
307	The Singapore Chinese Health Study	nd	nd	nd
308	The Singapore Chinese Health Study	nd	nd	nd
309	The Singapore Chinese Health Study	nd	nd	nd
310	The Singapore Chinese Health Study	60298	56 (8)	44.2
311	The Singapore Chinese Health Study	60298	56 (8)	44.2
312	The Singapore Chinese Health Study	60298	56 (8)	44.2
313	ULSAM	1012	nd	100
314	ULSAM	1012	nd	100
315	ULSAM	1012	nd	100
316	ULSAM	1012	nd	100
317	ULSAM	1012	nd	100
318	ULSAM	1012	nd	100
319	VITAL	70.287	range 50, 76	49
320	VITAL	70.287	range 50, 76	49
321	VITAL	70.287	range 50, 76	49
322	Women's Health Initiative	84493	range 50, 79	0

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Race	Blood pressure SBP/DBP (mmHg)
291	Spanish EPIC	nd	nd
292	Swedish Mammography Study	nd	nd
293	Swedish Mammography Study	nd	nd
294	Swedish Mammography Study	nd	nd
295	Swedish Mammography Study	nd	nd
296	Swedish Mammography Study	nd	nd
297	Swedish Mammography Study	nd	nd
298	Swedish Mammography Study	nd	nd
299	Takayama	nd	nd
300	Takayama	nd	nd
301	The Singapore Chinese Health Study	100 Asian	nd
302	The Singapore Chinese Health Study	100 Asian	nd
303	The Singapore Chinese Health Study	100 Asian	nd
304	The Singapore Chinese Health Study	100 Asian	nd
305	The Singapore Chinese Health Study	100 Asian	nd
306	The Singapore Chinese Health Study	100 Asian	nd
307	The Singapore Chinese Health Study	100 Asian	nd
308	The Singapore Chinese Health Study	100 Asian	nd
309	The Singapore Chinese Health Study	100 Asian	nd
310	The Singapore Chinese Health Study	100 Asian	nd
311	The Singapore Chinese Health Study	100 Asian	nd
312	The Singapore Chinese Health Study	100 Asian	nd
313	ULSAM	nd	nd
314	ULSAM	nd	nd
315	ULSAM	nd	nd
316	ULSAM	nd	nd
317	ULSAM	nd	nd
318	ULSAM	nd	nd
319	VITAL	93% white, 1% black, 2% Asian, 1% Hispanic, 1.5% Inuit.Eskimo, 1.5% other/missing	nd
320	VITAL	93% white, 1% black, 2% Asian, 1% Hispanic, 1.5% Inuit.Eskimo, 1.5% other/missing	nd
321	VITAL	93% white, 1% black, 2% Asian, 1% Hispanic, 1.5% Inuit.Eskimo, 1.5% other/missing	nd
322	Women's Health Initiative	~84 white, ~7% black, ~3% Asian, ~5% Hispanic, ~0.4% American Indian/Alaskan Native, ~1% unknown	127 (18)/nd

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Lipids: Total cholesterol/LDL/HDL/Triglycerides mean (SD) mg/dL [mmol/L]
291	Spanish EPIC	nd
292	Swedish Mammography Study	nd
293	Swedish Mammography Study	nd
294	Swedish Mammography Study	nd
295	Swedish Mammography Study	nd
296	Swedish Mammography Study	nd
297	Swedish Mammography Study	nd
298	Swedish Mammography Study	nd
299	Takayama	nd
300	Takayama	nd
301	The Singapore Chinese Health Study	nd
302	The Singapore Chinese Health Study	nd
303	The Singapore Chinese Health Study	nd
304	The Singapore Chinese Health Study	nd
305	The Singapore Chinese Health Study	nd
306	The Singapore Chinese Health Study	nd
307	The Singapore Chinese Health Study	nd
308	The Singapore Chinese Health Study	nd
309	The Singapore Chinese Health Study	nd
310	The Singapore Chinese Health Study	nd
311	The Singapore Chinese Health Study	nd
312	The Singapore Chinese Health Study	nd
313	ULSAM	6.9 (1.3)/nd/nd/nd
314	ULSAM	6.9 (1.3)/nd/nd/nd
315	ULSAM	6.9 (1.3)/nd/nd/nd
316	ULSAM	6.9 (1.3)/nd/nd/nd
317	ULSAM	6.9 (1.3)/nd/nd/nd
318	ULSAM	6.9 (1.3)/nd/nd/nd
319	VITAL	nd
320	VITAL	nd
321	VITAL	nd
322	Women's Health Initiative	nd/nd/64 (17)/nd

Appendix G.2.
Causality Table: Observational Studies

Row	Study	BMI mean (SD)/weight mean (SD) Kg
291	Spanish EPIC	73.7 (12.6)
292	Swedish Mammography Study	25
293	Swedish Mammography Study	25
294	Swedish Mammography Study	25
295	Swedish Mammography Study	25
296	Swedish Mammography Study	25
297	Swedish Mammography Study	25
298	Swedish Mammography Study	25
299	Takayama	men: 22.5 (2.8), women: 22.0 (2.9)
300	Takayama	men: 22.5 (2.8), women: 22.0 (2.9)
301	The Singapore Chinese Health Study	23.2 (3.3)
302	The Singapore Chinese Health Study	23.2 (3.3)
303	The Singapore Chinese Health Study	23.2 (3.3)
304	The Singapore Chinese Health Study	23.2 (3.3)
305	The Singapore Chinese Health Study	23.2 (3.3)
306	The Singapore Chinese Health Study	23.2 (3.3)
307	The Singapore Chinese Health Study	nd
308	The Singapore Chinese Health Study	nd
309	The Singapore Chinese Health Study	nd
310	The Singapore Chinese Health Study	23.2 (3.3)
311	The Singapore Chinese Health Study	23.2 (3.3)
312	The Singapore Chinese Health Study	23.2 (3.3)
313	ULSAM	25.0 (3.2)
314	ULSAM	25.0 (3.2)
315	ULSAM	25.0 (3.2)
316	ULSAM	25.0 (3.2)
317	ULSAM	25.0 (3.2)
318	ULSAM	25.0 (3.2)
319	VITAL	nd
320	VITAL	nd
321	VITAL	nd
322	Women's Health Initiative	28 (6)

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Baseline n-3 intake/level (median (IQR), unless noted)
291	Spanish EPIC	EPA: mean 0.2 (SD 0.2) g/d, DHA: mean 0.4 (SD 0.3) g/d, Total n-3 FA: mean 1.4 (SD 0.7) g/d
292	Swedish Mammography Study	ALA: 1.1 g/d, EPA+DHA 289 mg/d
293	Swedish Mammography Study	ALA: 1.1 g/d, EPA+DHA 289 mg/d
294	Swedish Mammography Study	ALA: 1.1 g/d, EPA+DHA 289 mg/d
295	Swedish Mammography Study	ALA: 1.1 g/d, EPA+DHA 289 mg/d
296	Swedish Mammography Study	ALA: 1.1 g/d, EPA+DHA 289 mg/d
297	Swedish Mammography Study	ALA: 1.1 g/d, EPA+DHA 289 mg/d
298	Swedish Mammography Study	ALA: 1.1 g/d, EPA+DHA 289 mg/d
299	Takayama	Fish oil: men 788 mg/d, women 635 mg/d
300	Takayama	Fish oil: men 788 mg/d, women 635 mg/d
301	The Singapore Chinese Health Study	nd
302	The Singapore Chinese Health Study	nd
303	The Singapore Chinese Health Study	nd
304	The Singapore Chinese Health Study	nd
305	The Singapore Chinese Health Study	nd
306	The Singapore Chinese Health Study	nd
307	The Singapore Chinese Health Study	nd
308	The Singapore Chinese Health Study	nd
309	The Singapore Chinese Health Study	nd
310	The Singapore Chinese Health Study	nd
311	The Singapore Chinese Health Study	nd
312	The Singapore Chinese Health Study	nd
313	ULSAM	ALA: 0.66% FA, EPA: 1.3% FA, DHA 0.68% FA
314	ULSAM	ALA: 0.66% FA, EPA: 1.3% FA, DHA 0.68% FA
315	ULSAM	ALA: 0.66% FA, EPA: 1.3% FA, DHA 0.68% FA
316	ULSAM	ALA: 0.66% FA, EPA: 1.3% FA, DHA 0.68% FA
317	ULSAM	ALA: 0.66% FA, EPA: 1.3% FA, DHA 0.68% FA
318	ULSAM	ALA: 0.66% FA, EPA: 1.3% FA, DHA 0.68% FA
319	VITAL	EPA+DHA: 0.174 g/d; EPA 0.058 g/d; DHA 0.113 g/d
320	VITAL	EPA+DHA: 0.174 g/d; EPA 0.058 g/d; DHA 0.113 g/d
321	VITAL	EPA+DHA: 0.174 g/d; EPA 0.058 g/d; DHA 0.113 g/d
322	Women's Health Initiative	ALA: 1.02 g/d, DHA+EPA: 0.093

Appendix G.2.
Causality Table: Observational Studies

Row	Study	n-3 source	n-3 measure	n-3 type(s)
291	Spanish EPIC	intake	g/d	DHA
292	Swedish Mammography Study	intake	g/d	ALA
293	Swedish Mammography Study	intake	g/d	EPA + DHA
294	Swedish Mammography Study	intake	g/d	EPA + DHA
295	Swedish Mammography Study	intake	g/d	ALA
296	Swedish Mammography Study	intake	mg/d	EPA + DHA
297	Swedish Mammography Study	intake	g/d	ALA
298	Swedish Mammography Study	intake	mg/d	EPA + DHA
299	Takayama	intake	mg/d	FO
300	Takayama	intake	mg/d	FO
301	The Singapore Chinese Health Study	intake	nd	Total n-3
302	The Singapore Chinese Health Study	intake	nd	EPA+DHA
303	The Singapore Chinese Health Study	intake	nd	ALA
304	The Singapore Chinese Health Study	intake	nd	Total n-3
305	The Singapore Chinese Health Study	intake	nd	EPA+DHA
306	The Singapore Chinese Health Study	intake	nd	ALA
307	The Singapore Chinese Health Study	intake	nd	Total n-3
308	The Singapore Chinese Health Study	intake	nd	EPA+DHA
309	The Singapore Chinese Health Study	intake	nd	ALA
310	The Singapore Chinese Health Study	intake	nd	Total n-3
311	The Singapore Chinese Health Study	intake	nd	EPA+DHA
312	The Singapore Chinese Health Study	intake	nd	ALA
313	ULSAM	serum	% FA	ALA
314	ULSAM	serum	% FA	EPA
315	ULSAM	serum	% FA	DHA
316	ULSAM	serum	% FA	ALA
317	ULSAM	serum	% FA	EPA
318	ULSAM	serum	% FA	DHA
319	VITAL	intake	g/d	EPA+DHA
320	VITAL	intake	g/d	EPA+DHA
321	VITAL	intake	g/d	EPA+DHA
322	Women's Health Initiative	intake	g/d	Fish Intake

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Study design
291	Spanish EPIC	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
292	Swedish Mammography Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
293	Swedish Mammography Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
294	Swedish Mammography Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
295	Swedish Mammography Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
296	Swedish Mammography Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
297	Swedish Mammography Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
298	Swedish Mammography Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
299	Takayama	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
300	Takayama	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
301	The Singapore Chinese Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
302	The Singapore Chinese Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
303	The Singapore Chinese Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
304	The Singapore Chinese Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
305	The Singapore Chinese Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
306	The Singapore Chinese Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
307	The Singapore Chinese Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
308	The Singapore Chinese Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
309	The Singapore Chinese Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
310	The Singapore Chinese Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
311	The Singapore Chinese Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
312	The Singapore Chinese Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
313	ULSAM	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
314	ULSAM	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
315	ULSAM	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
316	ULSAM	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
317	ULSAM	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
318	ULSAM	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
319	VITAL	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
320	VITAL	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
321	VITAL	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
322	Women's Health Initiative	Prospective, longitudinal study of intake (eg, FFQ, biomarker)

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Outcome	Reported effect Size
291	Spanish EPIC	Myocardial infarction	See appendix F
292	Swedish Mammography Study	Myocardial infarction	See appendix F
293	Swedish Mammography Study	Myocardial infarction	See appendix F
294	Swedish Mammography Study	Myocardial infarction	See appendix F
295	Swedish Mammography Study	Stroke, hemorrhagic	See appendix F
296	Swedish Mammography Study	Stroke, hemorrhagic	See appendix F
297	Swedish Mammography Study	Stroke, total	See appendix F
298	Swedish Mammography Study	Stroke, total	See appendix F
299	Takayama	Coronary heart disease	See appendix F
300	Takayama	Death, all cause	See appendix F
301	The Singapore Chinese Health Study	Death, CHD	See appendix F
302	The Singapore Chinese Health Study	Death, CHD	See appendix F
303	The Singapore Chinese Health Study	Death, CHD	See appendix F
304	The Singapore Chinese Health Study	Death, CVD	See appendix F
305	The Singapore Chinese Health Study	Death, CVD	See appendix F
306	The Singapore Chinese Health Study	Death, CVD	See appendix F
307	The Singapore Chinese Health Study	Death, CVD	See appendix F
308	The Singapore Chinese Health Study	Death, CVD	See appendix F
309	The Singapore Chinese Health Study	Death, CVD	See appendix F
310	The Singapore Chinese Health Study	Death, stroke	See appendix F
311	The Singapore Chinese Health Study	Death, stroke	See appendix F
312	The Singapore Chinese Health Study	Death, stroke	See appendix F
313	ULSAM	Death, all cause	See appendix F
314	ULSAM	Death, all cause	See appendix F
315	ULSAM	Death, all cause	See appendix F
316	ULSAM	Death, cardiac	See appendix F
317	ULSAM	Death, cardiac	See appendix F
318	ULSAM	Death, cardiac	See appendix F
319	VITAL	Death, all cause	See appendix F
320	VITAL	Death, CHD	See appendix F
321	VITAL	Death, CVD	See appendix F
322	Women's Health Initiative	Atrial fibrillation	See appendix F

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Study years (study start date)	Country
323	Women's Health Initiative	nd	US
324	Women's Health Initiative	nd	US
325	Women's Health Study	1992	US
326	Women's Health Study	1992	US
327	Women's Health Study	1992	US
328	Women's Health Study	1992	US
329	Women's Health Study	1992	US

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Population	Risk type
323	Women's Health Initiative	Primary Prevention, Healthy	na
324	Women's Health Initiative	Primary Prevention, Healthy	na
325	Women's Health Study	Primary Prevention, Healthy	na
326	Women's Health Study	Primary Prevention, Healthy	na
327	Women's Health Study	Primary Prevention, Healthy	na
328	Women's Health Study	Primary Prevention, Healthy	na
329	Women's Health Study	Primary Prevention, Healthy	na

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Sample size (total)	Age mean (SD) [median]	Sex (% male)
323	Women's Health Initiative	84493	range 50, 79	0
324	Women's Health Initiative	84493	range 50, 79	0
325	Women's Health Study	28100	54	0
326	Women's Health Study	28100	54	0
327	Women's Health Study	28100	54	0
328	Women's Health Study	28100	54	0
329	Women's Health Study	1032	54 (6.3)	0

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Race	Blood pressure SBP/DBP (mmHg)
323	Women's Health Initiative	~84 white, ~7% black, ~3% Asian, ~5% Hispanic, ~0.4% American Indian/Alaskan Native, ~1% unknown	127 (18)/nd
324	Women's Health Initiative	~84 white, ~7% black, ~3% Asian, ~5% Hispanic, ~0.4% American Indian/Alaskan Native, ~1% unknown	127 (18)/nd
325	Women's Health Study	95 white	nd
326	Women's Health Study	95 white	nd
327	Women's Health Study	95 white	nd
328	Women's Health Study	95 white	nd
329	Women's Health Study	71.6 white, 14.1 black, 13.25 Asian	nd

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Lipids: Total cholesterol/LDL/HDL/Triglycerides mean (SD) mg/dL [mmol/L]
323	Women's Health Initiative	nd/nd/64 (17)/nd
324	Women's Health Initiative	nd/nd/64 (17)/nd
325	Women's Health Study	nd
326	Women's Health Study	nd
327	Women's Health Study	nd
328	Women's Health Study	nd
329	Women's Health Study	208.45/122/54.1/nd

Appendix G.2.
Causality Table: Observational Studies

Row	Study	BMI mean (SD)/weight mean (SD) Kg
323	Women's Health Initiative	28 (6)
324	Women's Health Initiative	28 (6)
325	Women's Health Study	25
326	Women's Health Study	25
327	Women's Health Study	25
328	Women's Health Study	25
329	Women's Health Study	25.5

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Baseline n-3 intake/level (median (IQR), unless noted)
323	Women's Health Initiative	ALA: 1.02 g/d, DHA+EPA: 0.093
324	Women's Health Initiative	ALA: 1.02 g/d, DHA+EPA: 0.093
325	Women's Health Study	All n-3 FA: 10.4 g/d
326	Women's Health Study	All n-3 FA: 10.4 g/d
327	Women's Health Study	All n-3 FA: 10.4 g/d
328	Women's Health Study	All n-3 FA: 10.4 g/d
329	Women's Health Study	All n-3 FA: 6.05% FA

Appendix G.2.
Causality Table: Observational Studies

Row	Study	n-3 source	n-3 measure	n-3 type(s)
323	Women's Health Initiative	intake	g/d	DHA + EPA
324	Women's Health Initiative	intake	g/d	ALA
325	Women's Health Study	intake	g/d	all n-3
326	Women's Health Study	intake	g/d	ALA
327	Women's Health Study	intake	g/d	EPA
328	Women's Health Study	intake	g/d	DHA
329	Women's Health Study	erythrocyte	% of total FA	cis n-3 PUFA

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Study design
323	Women's Health Initiative	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
324	Women's Health Initiative	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
325	Women's Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
326	Women's Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
327	Women's Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
328	Women's Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)
329	Women's Health Study	Nested Case Control

Appendix G.2.
Causality Table: Observational Studies

Row	Study	Outcome	Reported effect Size
323	Women's Health Initiative	Congestive heart failure	See appendix F
324	Women's Health Initiative	Congestive heart failure	See appendix F
325	Women's Health Study	Hypertension	See appendix F
326	Women's Health Study	Hypertension	See appendix F
327	Women's Health Study	Hypertension	See appendix F
328	Women's Health Study	Hypertension	See appendix F
329	Women's Health Study	Hypertension	See appendix F