**Appendix Table H1. Characteristics of eligible studies: nutraceutical interventions in adults with normal cognition**

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| **Nutraceutical Intervention Type** | **Study****DesignCountry****RoB** | **N=** | **Population****Inclusion****Age (mean)****Sex (% female)****Race (% White)****Education (mean years)** **Baseline Cognition** | **Intervention****Mode****Components****Frequency****Duration** | **Comparison****Mode****Components****Frequency****Duration** | **Outcome** **Timing** | **Outcome** **Domain [Instrument]** |
| **Omega 3 fatty acids efficacy** | Boespflug 20161United StatesRCTHigh | 21 | Individuals without dementia, diabetes, kidney disease, liver disease, serious psychiatric condition, substance abuse, or taking supplements that might affect outcome measures or interact with fish oil.Mean age (SD): 68.3 (4.94)62.3% FemaleRace: NREducation: NRMean Clinical Dementia Rating Score (SD): 0.2 (0.37) | Fish oil 2.4g daily [1.6g EPA and 0.8g DHA] and either whole fruit or freeze-dried blueberry powered for 6 months | Matching placebo for 6 months | 6 months | Biomarker [fMRI]Memory [Sequential Letter N-back Working Memory] |
| Cukierman-Yaffe, 20142(Substudy of ORIGIN trial)RCTMultinationalMedium (High for outcomes at t5 for MMSE and t6 for DSS) | 11,685 | Adults older than 50 with dysglycaemia, with additional risk factors for cardiovascular events, not taking insulin, and taking no more than 1 oral glucose drug. Mean age (SD): 63 (7.75)35% female59% whiteEducation:35% <8 years27% 9-12 years38% >12 yearsMean MMSE (SD): 28 (2.75) | Omega 3 (EPA 465 mg+ DHA 375 mg) daily for 6 years | Placebo daily for 6 years | Median 6.2 years | Diagnosis [Incident Probable Cognitive Impairment = Reported Dementia or an MMSE score of <24]Brief Cognitive Test Performance [MMSE] Executive/Attention/Processing Speed [DSST] |
| Mahmoudi 20143IranRCTHigh | 199 | Individuals ≥65 with normal or mild to moderate cognitive impairment. Mean age (SD): 74.63 (5.4)54.75% FemaleRace: NR68.35% Illiterate16.6% Primary education10.55% Secondary education4.5% Higher educationMean MMSE (SD): 18.70 (5.25)28.6% with normal MMSE41.7% with mild MMSE29.6% with moderate MMSE | Fish oil 1g daily [180mg DHA plus 120mg EPA | Matching-placebo | 180 days | Brief Cognitive Test Performance [MMSE]Memory [Abbreviated Mental Test] |
| Witte, 20144RCTGermanyMedium | 80 | Healthy adults aged 50-75 yearsMean age (SD): 64 (± 6.5) years46 % femaleRace not reportedMean education (SD) (range 0=no educ - 5=college): 4.2 (1.2) Mean MMSE (SD): 29.3 (1) | Omega 3 (fish oil, 2.2 g) daily for 6 months | Placebo capsules (sunflower oil) daily for 6 months (26 weeks) | 6 months | Biomarker [MRI: Gray Matter Changes And White Matter Integrity]Executive/Attention/Processing Speed [Executive Function Composite] [Attention Composite] [Sensorimotor Speed Composite] Memory [Memory Composite] |
| Stonehouse, 20135RCTNew ZealandHigh | 176 | Healthy adults with normal cognition aged 18-45 years & low DHA intake Mean age (SD): 33.3 (7.8) years64% female80% European28% secondary education72% tertiary educationBaseline global cog not reported | Omega 3 (DHA 1.16 g) daily for 6 months | Placebo daily for 6 months | 6 months | Executive/Attention/Processing Speed [Composite Attention] [Reaction Time Attention] [Finding As Task] [Reaction Time Episodic Memory] [Reaction Time Working Memory] Memory [Composite Episodic Memory] [Composite Working Memory] |
| Geleijnse, 20126RCT subsetNetherlandsMedium | 2911 | Coronary patients aged 60-80 years Mean age (SD): 69 (5.5) years22% femaleRace not reported22% elementary ed66% secondary or higher vocational education12% college Mean MMSE (SD): 28.2 (1.7) | Omega 3 (EPA-DHA 400 mg or ALA 200 mg) daily for 40 months(There is also an EPA-DHA + ALA arm; however, 2X2 factorial design was collapsed into combined group analysis of all EPA-DHA vs placebo and all ALA versus placebo) | Placebo daily for 40 months | 40 months | Brief Cognitive Test Performance [MMSE] [Risk of Cognitive Decline based on MMSE Score] |
| Andreeva, 20117RCT followupFranceMedium | 1748 | Adults with normal cognition aged 45-80 with a history of ischemic heart diseaseMean age (SD): 61 (8.8) years20% femaleRace not reported10% foreign-born58% < high school Mean Isaacs Set Test (SD): 35.8 (7.5) | Omega 3 (EPA + DHA 600 mg in a 2:1 ratio) daily for 4 years or Omega 3 + Vitamin B for 4 years | Placebo for 4 years | 4 years | Brief Cognitive Test Performance [F-TICS]Memory [F-TICS Memory Subscore] [F-TICS Recall Subscore] |
| Dangour, 20108RCTUKMedium | 867 | Cognitively healthy adults aged 70-79 years, MMSE >24Mean age (SD): 75 (2.6) years58% aged 70-7442% aged 75-7945% femaleRace not reportedEducation:33% no qualifications 26% O level, clerical 18% A level, college23% other Median MMSE (IQR): 29 (28, 30) | Omega 3 (EPA 200 mg + DHA 500 mg) daily for 2 years | Olive oil capsules for 2 years | 2 years | Multidomain Neuropsychological Test Performance [Composite]Executive/Attention/Processing Speed [Executive Composite] [Processing Composite] [Letter Search/Cancellation - # Correct, % of Total Attempts] [Symbol Letter Modality - # Correct] [RT, Simple] [RT, Choice] [DS Forward] [DS Backward]Memory [Memory Composite] [Global Delay Composite] [CVLT] [Story Recall, Immediate] [Story Recall, Delayed] [Spatial Memory, Correct Images - Immediate] [Spatial Memory, Correct Images - Delayed]Language [Verbal Fluency, Animals Named] |
| Yurko-Mauro, 20109RCTUSLow/Medium | 485 | Healthy adults aged 55+ with MMSE scores >26 and a Logical Memory (WMS III) baseline score of at least 1 SD below younger adultsMean age (SD): 70 (9) years58% female84% whiteLogical memory – immediate recall (SD): 25 (6.8)Logical memory – delayed recall (SD): 11.3 (4.1) | Omega 3 (DHA 900 mg) daily for 6 months | Placebo daily for 6 months | 6 months | Brief Cognitive Test Performance [MMSE] Executive/Attention/Processing Speed [CANTAB Stockings of Cambridge]Memory [CANTAB PAL] [CANTAB VRM – Free Recall] [CANTAB VRM - Immediate Recall] [CANTAB VRM - Delayed Recall] [CANTAB SWM] [CANTAB PRM - Delayed] |
| Van de Rest, 200810RCTNetherlandsLow | 302 | Cognitively healthy (MMSE ≥21) adults aged 65+Mean age (SD): 70 (3.5) years45% femaleRace not reportedEducation:9% low54% medium37% highMedian MMSE (IQR): 28 (27-29)  | Omega 3 (EPA-DHA 400 mg or 1800 mg) daily for 6 months | Placebo capsules for 6 months | 6 months | Executive/Attention/Processing Speed [Executive Function Composite] [Attention Composite] [Sensorimotor Speed Composite] [TMT A] [TMT B] [Stroop Part 1] [Stroop Part 2] [Stroop Part 3 – (Part 1 + Part 2/2)] Memory [Memory Composite]Language [Word Fluency-Animals] [Word Fluency-Letter] |
| **Ginkgo biloba efficacy** | Lewis, 201411RCTUSAHigh | 97 | English-speaking, nonsmoking, healthy older adults aged 60+ with an MMSE score ≥ 23Mean age (SD): 69 (7) years72% female83% whiteEducation:12% ≤ high school35% some post-high school training25% college grad28% ≥ master’s degree No baseline cognition reported other than inclusion criteria | Ginkgo Synergy for 6 months(2 capsules/day providing 120 mg/d Ginkgo biloba leaf, 80 mg/d Gingko biloba whole extract, plus various other extracts) | Placebo (cellulose, lactose, and beet powder) for 6 months | 6 months | Brief Cognitive Test Performance [MMSE]Executive/Attention/Processing Speed [SCWT] [TMT A] [TMT B] [DSST]Memory [HVLT]Language [COWAT] |
| Vellas, 201212FranceRCTMedium | 2854 | Adults aged 70+ who spontaneously reported memory complaints to their primary care physician; screened and excluded diagnosed dementia, major memory impairmentMean age (SD): 76 (4.4) years67% femaleRace not reportedEducation:14% no formal educ37% primary school24% some secondary educ 24% high school diploma Mean MMSE (SD): 27.6 (1.9) | Ginkgo biloba extract (EGb761) 120 mg twice daily for at least 4 years | Matched placebo for at least 4 years | 5 years | Diagnosis [Incidence Of Probable AD According to DSM-IV and NINCDS-ADRDA Criteria at 5 years] |
| Snitz, 200913DeKosky, 200814RCTUSA Low | 3069 (normal cog & MCI)2587 normal cog | Community-dwelling participants aged 72 to 96 years; 15% baseline MCI Mean age (SD): 79.1 (3.3) years46% female95% whiteEducation mean (SD): 14.4 (3) yearsMean 3MSE (SD): 93.4 (4.7) | Ginkgo biloba extract 120 mg twice daily for a median of 6.1 years | Identical appearing placebo for a median of 6.1 years | Global cognition: average annual change reportedOther cognitive outcomes at year 4 | Diagnosis [Incident Dementia & AD (5 categories)]Multidomain Neuropsychological Test Performance [Global Composite]Executive/Attention/Processing Speed [Executive Composite [Attention and Psychomotor Speed Composite] [TMT B] [SCWT] [TMT A] [Digit Span]Memory [Memory Compositet] [CVLT] [RCFT]Visuospatial [Visuospatial Composite] [Copy Condition Of The Rey Osterrieth Figure Test] [WAIS-R Block Design] Language [Language Composite] [BNT][Semantic Verbal Fluency] |
| Dodge, 200815RCTUSAMedium | 118 | Cognitively intact subjects aged 85+Mean age (SD): 87.5 (2) years60% femaleRace not reportedMean education (SD): 14 (2.5) yearsMean MMSE (SD): 28.25 (1.4) | Ginkgo biloba extract 80 mg three times daily (240 mg/d) for 3 years 6 months |  Placebo | 3 years 6 months | Diagnosis (estimate): [Mild Cognitive Decline Defined As Progress from CDR = 0 to 0.5]Memory [CERAD Word List Delayed Recall] |
| **Multi-nutraceutical supplement**  | Strike 2016 16United KingdomRCTLow | 27 | Non-ill community dwelling females ≥60 who could walk ≥50 m and negotiate stairsMean age (SD): 66.8 (9.3)100% FemaleRace: NREducation: NRMean Number errors National Adult Reading Score (SD): 8.1 (4.8) | Efalex Active 50+ per day [1g DHA, 160mg EPA, 240mg Ginkgo biloba, 60mg phosphatidylserine, 20mg a-tocopherol, 1mg folic acid, and 20ug B12] for 6 months | Matching-placebo for 6 months | 6 months | Executive/Attention/Processing Speed [Stockings of Cambridge, Motor Screening Task] Memory [PALS] |
| Lewis, 201411RCTUSAHigh | 97 | Healthy older adults aged 60+ with an MMSE score ≥23Mean age (SD): 69 (7) years72% female83% whiteEducation:12% ≤ high school 35% some post-high school training25% college grad28% ≥ master’s No baseline cognition reported other than inclusion criteria | OPC Synergy for 6 months(2 capsules/d providing 100 mg/d grape seed extract, 50 mg/d green tea extract, 50 mg/d bilberry fruit, dried buckwheat leaf and juice, green tea leaf powder, and dried carrot root plus Catalyn (4 tablets/d providing 312 IU/d vitamin D, 1600 IU/d vitamin A, 5.3 mg/d vitamin C, 0.3 mg/d thiamine, 0.3 mg/d riboflavin, 1.3 mg/d vitamin B6, defatted wheat germ, carrot (root), and various other ingredients) for 6 months | Placebo (cellulose, lactose, and beet powder) for 6 months | 6 months | Brief Cognitive Test Performance [MMSE]Executive/Attention/Processing Speed [SCWT] [TMT A] [TMT B] [DSST]Memory [HVLT-R]Language [COWAT] |
| **Resveratrol efficacy** | Witte, 201417RCTGermanyMedium | 46 | Healthy overweight older adults aged 50-80 yearsMean age (SD): 64 (6) years64% femaleRace not reportedMean education (SD): 17 (3) yearsMean MMSE (SD): 29 (1) | Resveratrol (200 mg/d) for 6 months | Placebo for 6 months | 6 months | Biomarker [MRI: Volume, Microstructure, and Functional Connectivity of the Hippocampus]Memory [AVLT Retention] [AVLT Delayed Recall] [AVLT Recognition] [AVLT Learning Ability] [AVLT 5th Learning Trial] |
| **Plant sterols/ plant stanols efficacy** | Schiepers, 200918RCTNetherlandsMedium | 57 | People aged 43-69 years taking statinsMean age (SD): 60 (7) years42% femaleRace not reported39% low educationBaseline cognition not reported | Margarines enriched with plant sterol esters (2.5 g/d) or plant stanol esters (2.5 g/d) for 7 years (85 weeks) | Control margarine for 7 years (85 weeks) | 7 years (85 weeks) | Executive/Attention/Processing Speed [Simple Information Processing Speed Composite] [Complex Speed Composite]Memory [Memory Composite] |
| **Omega 3 comparative effectiveness** | Andreeva, 20117RCTFranceMedium | 1748 | People with normal cognition aged 45-80 with a history of ischemic heart diseaseMean age (SD): 61 (8.8) years20% female10% foreign-born58% < high school diplomaMean F-TICS-m (SD): 28.5 (4.8) | Omega 3 (EPA + DHA 600 mg in a 2:1 ratio) daily for 4 years or Omega 3 + Vitamin B for 4 years | Omega 3 + Vitamin B for 4 years or Vitamin B for 4 years | 4 years | Brief Cognitive Test Performance [F-TICS]Memory [F-TICS-m Subscore] [F-TICS-m Recall Subscore] |
| Chew, 201519RCTUSAHigh | 3501 | Adults at risk for developing macular degenerationMean age (SD): 72.7 (± 7.7) years57.5% female97% white29% ≤ high school 49% ≥ some college22% postgraduateMean TICS (SD): 33 (3.4) | Long-chain polyunsaturated fatty acids (1 g, specifically DHA 350 mg and EPA 650 mg) for 5 years | No long-chain polyunsaturated fatty acids (other groups) for 5 years | Yearly for 5 years | Brief Cognitive Test Performance [TICS Total Score]Multidomain Neuropsychological Test Performance [Composite]Executive/Attention/Processing Speed [Backwards Counting] [Verbal Fluency – Animal, Letter & Alternating]Memory [Wechsler Logical Memory I & II] [TICS Word List Recall]Language [Verbal Fluency – Animal] [Verbal Fluency – Letter] [Verbal Fluency – Category] |
| **Lutein/Zeaxanthin** | Chew, 201519RCTUSAHigh | 3501 | Adults at risk for developing age-related macular degenerationMean age (SD): 72.7 (± 7.7) years57.5% female97% white29% ≤ high school 49% ≥ some college22% postgraduateMean TICS (SD): 33 (3.4) | Lutein (10mg)/ zeaxanthin (2mg) daily5 years | No Lutein/zeaxanthin (other groups) for 5 years | Yearly for 5 years | Brief Cognitive Test Performance [TICS Total Score]Multidomain Neuropsychological Test Performance [Composite]Executive/Attention/Processing Speed [Backwards Counting] [Verbal Fluency – Animal, Letter & Alternating]Memory [Wechsler Logical Memory I & II] [TICS Word List Recall]Language [Verbal Fluency – Animal] [Verbal Fluency – Letter] [Verbal Fluency – Category] |
| **Multi-nutraceutical supplement** | Bun, 201520Open label intervention study (observational)JapanHigh | 825 | People aged 65+Mean age (SD): 72 (5) years42% femaleRace not reportedMean education (SD): 10 (2.5) yearsBaseline cog exclusion score < 1.5 SD on ≥ 1 domain of the 5-cog test after adjustment  | Nutritional supplementation (n-3 polyunsaturated fatty acid, Ginkgo biloba, leaf dry extracts, and lycopene) for 3 years | No nutritional supplementation (exercise and inactive control groups) | 3 years | Diagnosis [Diagnosis of AD] |

 3MS=Modified Mini Mental Status Examination; AD=Alzheimer’s disease; ADAS=Cog-Alzheimer’s Disease Assessment Scale-Cognitive; ALA=alpha-linolenic acid; AVLT=Auditory Verbal Learning Test; BNT=Boston Naming Test; BVMT=Breif Visuospatial Memory Test; BVRT=Benton Visual Retention Test; CAMCOG=Cambridge Cognition Examination; CDR=Clinical Dementia Rating; CERAD=Consortium to Establish a Registry for Alzheimer's Disease; CLOX-1=Clock Drawing Test; COWAT=Controlled Oral Word Association Test; CVFT=Category Verbal Fluency Test; CVLT=California Verbal Learning Test; DHA=docosahexaenoic acid; DS=Digit Span (Forward and/or Backward); DSM=Diagnostic Statistical Manual of Mental Disorders; DSST=Digit Symbol Substition Test; DVT=Digit Vigilance Test; EBMT=East Boston Memory Test; EPA=eicosapentaenoic acid; FCSRT=Free and Cued Selective Reminding Test; F-TICS=French Version, Telephone Interview Cognitive Status; HVLT=Hopkins Verbal Learning Test; MCI=mild cognitive impairment; MMSE=Mini-Mental Status Examination; MRI=magnetic resonance imaging; n=sample size; NINCDS-ADRDA=National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer’s Disease; NR=PALS=Paired Association Learning Test; PRM=Pattern Recognition Memory; RAVLT=Rey’s Auditory Verbal Learning Test; RBANS=Repeatable Battery for Neuropsychological Status; RBMT= Rivermead Behavioral Memory Test; RCFT=Rey-Osterrieth Complex Figure Test; RCPM=Raven’s Colored Progressive Matrices; RCT=Randomized Controlled Trial; RoB=Risk of Bias; SCWT=Stroop Color Word Test; SD=Standard Deviation; SDMT=Symbol Digit Modalities Test; SOE=Strength of Evidence; SWM=Spatial Working Memory; TICS=Telephone Interview for Cognitive Status (TICS-M=Modified); TMT=Trail Making Test (Part A and/or B); VP=Verbal Proficiency; VR=Visual Reproduuction; VRM=Verbal Recognition Memory; WAIS=Wechsler Adult Intelligence Scale; WMS=Wechsler Memory Scale