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

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| **Nutraceutical Intervention Type** | **Study**  **Design Country**  **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 20161  United States  RCT  High | 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% Female  Race: NR  Education: NR  Mean 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)  RCT  Multinational  Medium (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% female  59% white  Education:  35% <8 years  27% 9-12 years  38% >12 years Mean 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 20143  Iran  RCT  High | 199 | Individuals ≥65 with normal or mild to moderate cognitive impairment.  Mean age (SD): 74.63 (5.4)  54.75% Female  Race: NR  68.35% Illiterate  16.6% Primary education  10.55% Secondary education  4.5% Higher education  Mean MMSE (SD): 18.70 (5.25)  28.6% with normal MMSE  41.7% with mild MMSE  29.6% 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, 20144  RCT  Germany  Medium | 80 | Healthy adults aged 50-75 years  Mean age (SD): 64 (± 6.5) years  46 % female  Race not reported Mean 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, 20135  RCT  New Zealand  High | 176 | Healthy adults with normal cognition aged 18-45 years & low DHA intake  Mean age (SD): 33.3 (7.8) years  64% female  80% European  28% secondary education 72% tertiary education  Baseline 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, 20126  RCT subset  Netherlands  Medium | 2911 | Coronary patients aged 60-80 years  Mean age (SD): 69 (5.5) years  22% female  Race not reported  22% elementary ed  66% secondary or higher vocational education  12% 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, 20117  RCT followup  France  Medium | 1748 | Adults with normal cognition aged 45-80 with a history of ischemic heart disease  Mean age (SD): 61 (8.8) years  20% female  Race not reported  10% foreign-born  58% < 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, 20108  RCT  UK  Medium | 867 | Cognitively healthy adults aged 70-79 years, MMSE >24  Mean age (SD): 75 (2.6) years  58% aged 70-74  42% aged 75-79  45% female  Race not reported  Education:  33% no qualifications  26% O level, clerical  18% A level, college  23% 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, 20109 RCT  US  Low/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 adults  Mean age (SD): 70 (9) years  58% female  84% white  Logical 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, 200810  RCT  Netherlands  Low | 302 | Cognitively healthy (MMSE ≥21) adults aged 65+  Mean age (SD): 70 (3.5) years  45% female  Race not reported  Education:  9% low  54% medium  37% high  Median 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, 201411  RCT  USA  High | 97 | English-speaking, nonsmoking, healthy older adults aged 60+ with an MMSE score ≥ 23  Mean age (SD): 69 (7) years  72% female  83% white  Education:  12% ≤ high school  35% some post-high school training  25% college grad  28% ≥ 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, 201212 France  RCT Medium | 2854 | Adults aged 70+ who spontaneously reported memory complaints to their primary care physician; screened and excluded diagnosed dementia, major memory impairment  Mean age (SD): 76 (4.4) years  67% female  Race not reported  Education:  14% no formal educ  37% primary school  24% 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, 200913  DeKosky, 200814  RCT USA  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) years  46% female  95% white  Education mean (SD): 14.4 (3) years  Mean 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 reported  Other 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, 200815  RCT  USA  Medium | 118 | Cognitively intact subjects aged 85+  Mean age (SD): 87.5 (2) years 60% female  Race not reported  Mean education (SD): 14 (2.5) years  Mean 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 16  United Kingdom  RCT  Low | 27 | Non-ill community dwelling females ≥60 who could walk ≥50 m and negotiate stairs  Mean age (SD): 66.8 (9.3)  100% Female  Race: NR  Education: NR  Mean 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, 201411  RCT  USA  High | 97 | Healthy older adults aged 60+ with an MMSE score ≥23  Mean age (SD): 69 (7) years  72% female  83% white  Education:  12% ≤ high school 35% some post-high school training  25% college grad  28% ≥ 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, 201417  RCT  Germany  Medium | 46 | Healthy overweight older adults aged 50-80 years  Mean age (SD): 64 (6) years  64% female  Race not reported  Mean education (SD): 17 (3) years  Mean 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, 200918  RCT Netherlands  Medium | 57 | People aged 43-69 years taking statins  Mean age (SD): 60 (7) years  42% female  Race not reported  39% low education  Baseline 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, 20117  RCT  France  Medium | 1748 | People with normal cognition aged 45-80 with a history of ischemic heart disease  Mean age (SD): 61 (8.8) years  20% female  10% foreign-born  58% < high school diploma  Mean 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, 201519  RCT  USA  High | 3501 | Adults at risk for developing macular degeneration  Mean age (SD): 72.7 (± 7.7) years  57.5% female  97% white  29% ≤ high school  49% ≥ some college  22% postgraduate  Mean 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, 201519  RCT  USA  High | 3501 | Adults at risk for developing age-related macular degeneration  Mean age (SD): 72.7 (± 7.7) years  57.5% female  97% white  29% ≤ high school  49% ≥ some college  22% postgraduate  Mean TICS (SD): 33 (3.4) | Lutein (10mg)/ zeaxanthin (2mg) daily  5 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, 201520  Open label intervention study (observational)  Japan  High | 825 | People aged 65+  Mean age (SD): 72 (5) years  42% female  Race not reported  Mean education (SD): 10 (2.5) years  Baseline 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