Appendix A. Search Strategies

Database: Ovid MEDLINE(R) <1946 to January Week 4 2016> Search Strategy: RCTs

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1 exp Tertiary Prevention/ or exp Secondary Prevention/ or exp Primary Prevention/ (141964)

2 prevent*.ti. (216549)

3 protect*.ti. (118660)

4 delay*.ti. (51184)

5 ((reduc* or decreas* or effect* or lower* or modif* or change* or stop* or improv* or increas* or enhanc* or rais*) and risk*).ti. (43135)

6 1 or 2 or 3 or 4 or 5 (545854)

7 lifestyle*.ti. (8489)

8 life style.ti. (1355)

9 exp Health Behavior/ (133222)

10 exp Motor Activity/ (216634)

11 ((physical or aerobic* or leisure) and (activit* or fitness)).ti. (25122)

12 exercis*.ti. (84377)

13 exp Diet/ (218815)

14 diet*.ti. (134912)

15 fruit*.ti. (16048)

16 vegetable*.ti. (7963)

17 nutrition*.ti. (74518)

18 fat*.ti. (181033)

19 caffeine.ti. (9030)

20 sodium.ti. (73002)

21 salt*.ti. (34028)

22 alcohol*.ti. (103760)

23 ((smok* or tobacco) and (quit or cessation or stop*)).ti. (9709)

24 ((metacognitive or cognitive or mental or brain or memory or social or perceptual or computer) and (activit* or train* or stimulat* or intervention or engag* or rehab*)).ti. (36862)

25 exp *Pharmacology, Clinical/ (1700)

26 exp Pharmaceutical Preparations/ (674904)

27 drug*.ti. (298706)

28 medication*.ti. (29416)

29 pharmacopsychiatry.ti. (51)

30 exp Psychopharmacology/ (5429)

31 lovastatin/ or simvastatin/ or pravastatin/ (11705)
32 statin*.ti. (9993)
33 exp Antihypertensive Agents/ (234730)
34 anti-hypertensive*.ti. (541)
35 antihypertensive*.ti. (10665)
36 exp Cholinesterase Inhibitors/ (44525)
37 Acetylcholinesterase inhibitor*.ti. (815)
38 (Donepezil or Aricept or Memantine or Namenda or Rivastigmine or Exelon or Galantamine or razadyne or Quetiapine or seroquel).ti. (4354)
39 cholinesterase inhibitor*.ti. (1161)
40 exp Antibodies, Monoclonal/ or exp Antibodies, Monoclonal, Humanized/ (190958)
41 anti amyloid*.ti. (125)
42 antiamyloid*.ti. (26)
43 Solanezumab.ti. (15)
44 crenezumab.ti. (0)
45 gantenerumab.ti. (6)
46 crenezumab.ab. (4)
47 antiplatlet.ti. (0)
48 anti-platelet.ti. (782)
49 (Triflusal or Ticlid or plavix or brilinta or persantine or Ticlopidine or Dipyridomole or Clopidogrel).ti. (4606)
50 exp Hypoglycemic Agents/ (206876)
51 (Pioglitazone or actos or Glucophage or metformin).ti. (6739)
52 ((gonadal or sex) adj steroid*).ti. (3910)
53 exp Hormone Replacement Therapy/ (21950)
54 estrogen*.ti. (46056)
55 progest*.ti. (27523)
56 medroxyprogesterone*.ti. (1983)
57 estradiol.ti. (17656)
58 raloxifene.ti. (1169)
59 exp Cyclooxygenase 2 Inhibitors/ (10161)
60 (Celecoxib or Rofecoxib).ti. (2498)
61 exp Anti-Inflammatory Agents, Non-Steroidal/ (170835)
62 (Ibuprofen or Tarenflurbil or flurbiprofen or Flurizan or Naproxen or Aspirin).ti. (19958)
63 exp Dietary Supplements/ (49171)
64 supplement*.ti. (42004)
65 nutraceutical*.ti. (625)

66 exp Nootropic Agents/ (28153)
67 nootropic*.ti. (444)
68 exp Vitamins/ (279374)
69 exp Minerals/ (129537)
70 omega.ti. (7082)
71 ginkgo biloba.ti. (1700)
72 ginko biloba.ti. (6)
73 folate.ti. (7866)
74 fish oil.ti. (2892)
75 saffron.ti. (288)
76 crocus sativus.ti. (206)
77 fuzhisan.ti. (7)
78 melissa.ti. (155)
79 beta carotene.ti. (2945)
80 vitamin*.ti. (79987)
81 ((manag* or control* or lower* or reduc* or decreas* or loss or lose) and (weight or BMI or body mass index or overweight or obes* or diabetes or depress* or cardio* or vascular or blood pressure or hypertension or cholesterol or hypercholesterolemia or homocysteine)).ti. (84346)
82 or/6-81 (3655158)
83 dementia/ or alzheimer disease/ (104784)
84 dement*.ti. (33084)
85 exp Cognition/ (119536)
86 exp Mild Cognitive Impairment/ or exp Cognition Disorders/ (68412)
87 memory disorders/ (16505)
88 executive funtion/ (0)
89 exp memory/ (107625)
90 cognition.ti. (7518)
91 ((cognit* or neurocognit* or memory or neuropsy* or neuro*) adj (impair* or disorder* or dysfunction* or function* ag?ing or declin* or status or perform* or diabil* or disable* or maint* or enhanc*)).ti. (31889)
92 ((maint* or impair* or disorder* or declin* or enhanc*) adj (cognit* or neurocognit* or memory or neuropsy* or neuro*)).ti. (1900)
93 (amyloid or tau or plasticity).ti. (44515)
94 ((brain or grey matter or gray matter) adj3 (function* or scan* or mri or volume or chang* or imag*)).ti. (15993)
95 exp Biological Markers/ (681977)
96 (83 or 86) and 95 (6502)

97 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 96 (403150)
98 82 and 97 (65610)
99 *Alzheimer Disease/pc [Prevention & Control] (1256)
100 *Mild Cognitive Impairment/pc [Prevention & Control] (48)
101 Cognition Disorders/pc [Preventions & Control] (2341)
102 or/98-101 (66756)
103 98 or 102 (66756)
104 randomized controlled trials as topic/ (100210)
105 randomized controlled trial/ (404260)
106 random allocation/ (85128)
107 double blind method/ (132506)
108 single blind method/ (21176)
109 clinical trial/ (495811)
110 clinical trial, phase i.pt. (15460)
111 clinical trial, phase ii.pt. (25039)
112 clinical trial, phase iii.pt. (10500)
113 clinical trial, phase iv.pt. (1099)
114 controlled clinical trial.pt. (89967)
115 randomized controlled trial.pt. (404260)
116 multicenter study.pt. (192213)
117 clinical trial.pt. (495811)
118 exp Clinical trials as topic/ (286404)
119 or/104-118 (1096584)
120 (clinical adj trial$).tw. (219796)
121 ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw. (129617)
122 placebos/ (32961)
123 placebo$.tw. (159399)
124 randomly allocated.tw. (17236)
125 (allocated adj2 random$).tw. (19800)
126 120 or 121 or 122 or 123 or 124 or 125 (425064)
127 119 or 126 (1229155)
128 103 and 127 (13446)
129 limit 128 to humans (12721)
130 limit 129 to (addresses or autobiography or bibliography or biography or case reports or classical article or clinical conference or comment or congresses or consensus development conference or consensus development conference, nih or "corrected and republished article" or dataset or dictionary or directory or editorial or evaluation studies or historical article or in vitro or interactive

tutorial or interview or lectures or legal cases or legislation or letter or news or newspaper article or observational study or patient education handout or periodical index or portraits or validation studies or video-audio media or webcasts) (838)

131 129 not 130 (11883)

132 limit 131 to yr="2009 -Current" (4830)

Database: Ovid MEDLINE(R) <1946 to January Week 4 2016> Search Strategy: Observational Studies

Database: Ovid MEDLINE(R) <1946 to January Week 4 2016>

Search Strategy:

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1 exp Tertiary Prevention/ or exp Secondary Prevention/ or exp Primary Prevention/ (141964)

2 prevent*.ti. (216549)

3 protect*.ti. (118660)

4 delay*.ti. (51184)

5 ((reduc* or decreas* or effect* or lower* or modif* or change* or stop* or improv* or increas* or enhanc* or rais*) and risk*).ti. (43135)

6 (biomarker* adj2 enrich*).ti. (11)

7 intervention*.ti. (83501)

8 program*.ti. (139255)

9 multidomain*.ti. (421)

10 multi-domain*.ti. (143)

11 multicomponent*.ti. (1987)

12 multi-component*.ti. (561)

13 multifactoral*.ti. (15)

14 multi-factoral*.ti. (2)

15 approach*.ti. (175606)

16 lifestyle*.ti. (8489)

17 life style.ti. (1355)

18 exp Health Behavior/ (133222)

19 exp Motor Activity/ (216634)

20 ((physical or aerobic* or leisure) and (activit* or fitness)).ti. (25122)

21 exercis*.ti. (84377)

22 exp Diet/ (218815)

23 diet*.ti. (134912)

24 fruit*.ti. (16048)

25 vegetable*.ti. (7963)

26 nutrition*.ti. (74518)

27 fat*.ti. (181033)

28 caffeine.ti. (9030)

29 sodium.ti. (73002)

30 salt*.ti. (34028)

31 alcohol*.ti. (103760)
32 ((smok* or tobacco) and (quit or cessation or stop*)).ti. (9709)
33 ((metacognitive or cognitive or mental or brain or memory or social or perceptual or computer) and (activit* or train* or stimulat* or intervention or engag* or rehab*)).ti. (36862)
34 exp *Pharmacology, Clinical/ (1700)
35 exp Pharmaceutical Preparations/ (674904)
36 drug*.ti. (298706)
37 medication*.ti. (29416)
38 pharmacopsychiatry.ti. (51)
39 exp Psychopharmacology/ (5429)
40 lovastatin/ or simvastatin/ or pravastatin/ (11705)
41 statin*.ti. (9993)
42 exp Antihypertensive Agents/ (234730)
43 anti-hypertensive*.ti. (541)
44 antihypertensive*.ti. (10665)
45 exp Cholinesterase Inhibitors/ (44525)
46 Acetylcholinesterase inhibitor*.ti. (815)
47 (Donepezil or Aricept or Memantine or Namenda or Rivastigmine or Exelon or Galantamine or razadyne or Quetiapine or seroquel).ti. (4354)
48 cholinesterase inhibitor*.ti. (1161)
49 exp Antibodies, Monoclonal/ or exp Antibodies, Monoclonal, Humanized/ (190958)
50 anti amyloid*.ti. (125)
51 antiamyloid*.ti. (26)
52 Solanezumab.ti. (15)
53 crenezumab.ti. (0)
54 gantenerumab.ti. (6)
55 crenezumab.ab. (4)
56 antiplatlet.ti. (0)
57 anti-platelet.ti. (782)
58 (Triflusal or Ticlid or plavix or brilinta or persantine or Ticlopidine or Dipyridomole or Clopidogrel).ti. (4606)
59 exp Hypoglycemic Agents/ (206876)
60 (Pioglitazone or actos or Glucophage or metformin).ti. (6739)
61 ((gonadal or sex) adj steroid*).ti. (3910)
62 exp Hormone Replacement Therapy/ (21950)
63 estrogen*.ti. (46056)
64 progest*.ti. (27523)

65 medroxyprogesterone*.ti. (1983)
66 estradiol.ti. (17656)
67 raloxifene.ti. (1169)
68 exp Cyclooxygenase 2 Inhibitors/ (10161)
69 (Celecoxib or Rofecoxib).ti. (2498)
70 exp Anti-Inflammatory Agents, Non-Steroidal/ (170835)
71 (Ibuprofen or Tarenflurbil or flurbiprofen or Flurizan or Naproxen or Aspirin).ti. (19958)
72 exp Dietary Supplements/ (49171)
73 supplement*.ti. (42004)
74 nutraceutical*.ti. (625)
75 exp Nootropic Agents/ (28153)
76 nootropic*.ti. (444)
77 exp Vitamins/ (279374)
78 exp Minerals/ (129537)
79 omega.ti. (7082)
80 ginkgo biloba.ti. (1700)
81 ginko biloba.ti. (6)
82 folate.ti. (7866)
83 fish oil.ti. (2892)
84 saffron.ti. (288)
85 crocus sativus.ti. (206)
86 fuzhisan.ti. (7)
87 melissa.ti. (155)
88 beta carotene.ti. (2945)
89 vitamin*.ti. (79987)
90 ((manag* or control* or lower* or reduc* or decreas* or loss or lose) and (weight or BMI or body mass index or overweight or obes* or diabetes or depress* or cardio* or vascular or blood pressure or hypertension or cholesterol or hypercholesterolemia or homocysteine)).ti. (84346)
91 or/1-90 (3967512)
92 dementia/ or alzheimer disease/ (104784)
93 dement*.ti. (33084)
94 exp Mild Cognitive Impairment/ or exp Cognition Disorders/ (68412)
95 ((cognit* or neurocognit* or memory or neuropsy* or neuro*) adj (impair* or disorder* or dysfunction* or diabil* or disable*)).ti. (23706)
96 ((impair* or disorder*) adj (cognit* or neurocognit* or memory)).ti. (576)
97 or/92-96 (175046)
98 *Alzheimer Disease/pc [Prevention & Control] (1256)

99 *Mild Cognitive Impairment/pc [Prevention & Control] (48)
100 Cognition Disorders/pc [Preventions & Control] (2341)
101 or/98-100 (3558)
102 (91 and 97) or 101 (34439)
103 exp cohort studies/ (1486668)
104 cohort$.tw. (295133)
105 controlled clinical trial.pt. (89967)
106 epidemiologic studies/ (6963)
107 (follow up adj stud$).tw. (37939)
108 longitudinal.tw. (142385)
109 (observational adj stud$).tw. (48091)
110 Comparative Study/ (1720170)
111 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 (3175113)
112 102 and 111 (7550)
113 limit 112 to humans (7069)
114 limit 113 to "all child (0 to 18 years)" (691)
115 limit 114 to "all adult (19 plus years)" (372)
116 113 not 114 (6378)
117 115 or 116 (6750)
118 limit 117 to (addresses or autobiography or bibliography or biography or case reports or clinical conference or comment or congresses or consensus development conference or consensus development conference, nih or dataset or dictionary or directory or editorial or in vitro or interactive tutorial or interview or lectures or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or portraits or validation studies or video-audio media or webcasts) (360)
119 117 not 118 (6390)
120 limit 119 to yr="2009 - 2016" (2812)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <February 09, 2016>
Search Strategy: RCTs

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1 exp Tertiary Prevention/ or exp Secondary Prevention/ or exp Primary Prevention/ (0)

2 prevent*.ti. (16727)

3 protect*.ti. (9964)

4 delay*.ti. (5679)

5 ((reduc* or decreas* or effect* or lower* or modif* or change* or stop* or improv* or increas* or enhanc* or rais*) and risk*).ti. (5717)

6 1 or 2 or 3 or 4 or 5 (37733)

7 lifestyle*.ti. (1346)

8 life style.ti. (73)

9 exp Health Behavior/ (0)

10 exp Motor Activity/ (0)

11 ((physical or aerobic* or leisure) and (activit* or fitness)).ti. (3604)

12 exercis*.ti. (7474)

13 exp Diet/ (0)

14 diet*.ti. (11652)

15 fruit*.ti. (2919)

16 vegetable*.ti. (892)

17 nutrition*.ti. (6266)

18 fat*.ti. (15032)

19 caffeine.ti. (503)

20 sodium.ti. (5610)

21 salt*.ti. (5744)

22 alcohol*.ti. (9093)

23 ((smok* or tobacco) and (quit or cessation or stop*)).ti. (976)

24 ((metacognitive or cognitive or mental or brain or memory or social or perceptual or computer) and (activit* or train* or stimulat* or intervention or engag* or rehab*)).ti. (3677)

25 exp *Pharmacology, Clinical/ (0)

26 exp Pharmaceutical Preparations/ (0)

27 drug*.ti. (21843)

28 medication*.ti. (3542)

29 pharmacopsychiatry.ti. (2)

30 exp Psychopharmacology/ (0)

31 lovastatin/ or simvastatin/ or pravastatin/ (0)
32 statin*.ti. (1193)
33 exp Antihypertensive Agents/ (0)
34 anti-hypertensive*.ti. (46)
35 antihypertensive*.ti. (505)
36 exp Cholinesterase Inhibitors/ (0)
37 Acetylcholinesterase inhibitor*.ti. (84)
38 (Donepezil or Aricept or Memantine or Namenda or Rivastigmine or Exelon or Galantamine or razadyne or Quetiapine or seroquel).ti. (565)
39 cholinesterase inhibitor*.ti. (89)
40 exp Antibodies, Monoclonal/ or exp Antibodies, Monoclonal, Humanized/ (0)
41 anti amyloid*.ti. (18)
42 antiamyloid*.ti. (3)
43 Solanezumab.ti. (3)
44 crenezumab.ti. (1)
45 gantenerumab.ti. (0)
46 crenezumab.ab. (5)
47 antiplatlet.ti. (1)
48 anti-platelet.ti. (74)
49 (Triflusal or Ticlid or plavix or brilinta or persantine or Ticlopidine or Dipyridomole or Clopidogrel).ti. (515)
50 exp Hypoglycemic Agents/ (0)
51 (Pioglitazone or actos or Glucophage or metformin).ti. (1160)
52 ((gonadal or sex) adj steroid*).ti. (134)
53 exp Hormone Replacement Therapy/ (0)
54 estrogen*.ti. (1884)
55 progest*.ti. (985)
56 medroxyprogesterone*.ti. (51)
57 estradiol.ti. (676)
58 raloxifene.ti. (78)
59 exp Cyclooxygenase 2 Inhibitors/ (0)
60 (Celecoxib or Rofecoxib).ti. (207)
61 exp Anti-Inflammatory Agents, Non-Steroidal/ (0)
62 (Ibuprofen or Tarenflurbil or flurbiprofen or Flurizan or Naproxen or Aspirin).ti. (1397)
63 exp Dietary Supplements/ (0)
64 supplement*.ti. (4634)
65 nutraceutical*.ti. (127)

66 exp Nootropic Agents/ (0)
67 nootropic*.ti. (28)
68 exp Vitamins/ (0)
69 exp Minerals/ (0)
70 omega.ti. (1008)
71 ginkgo biloba.ti. (149)
72 ginko biloba.ti. (1)
73 folate.ti. (495)
74 fish oil.ti. (242)
75 saffron.ti. (81)
76 crocus sativus.ti. (55)
77 fuzhisan.ti. (1)
78 melissa.ti. (40)
79 beta carotene.ti. (163)
80 vitamin*.ti. (6567)
81 ((manag* or control* or lower* or reduc* or decreas* or loss or lose) and (weight or BMI or body mass index or overweight or obes* or diabetes or depress* or cardio* or vascular or blood pressure or hypertension or cholesterol or hypercholesterolemia or homocysteine)).ti. (9325)
82 or/6-81 (152409)
83 dementia/ or alzheimer disease/ (0)
84 dement*.ti. (3196)
85 exp Cognition/ (0)
86 exp Mild Cognitive Impairment/ or exp Cognition Disorders/ (0)
87 memory disorders/ (0)
88 executive funtion/ (0)
89 exp memory/ (0)
90 cognition.ti. (1391)
91 ((cognit* or neurocognit* or memory or neuropsy* or neuro*) adj (impair* or disorder* or dysfunction* or function* ag?ing or declin* or status or perform* or diabil* or disable* or maint* or enhanc*)).ti. (4103)
92 ((maint* or impair* or disorder* or declin* or enhanc*) adj (cognit* or neurocognit* or memory or neuropsy* or neuro*)).ti. (216)
93 (amyloid or tau or plasticity).ti. (4251)
94 ((brain or grey matter or gray matter) adj3 (function* or scan* or mri or volume or chang* or imag*)).ti. (1579)
95 exp Biological Markers/ (0)
96 (83 or 86) and 95 (0)

97 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 96 (12603)
98 82 and 97 (1485)
99 *Alzheimer Disease/pc [Prevention & Control] (0)
100 *Mild Cognitive Impairment/pc [Prevention & Control] (0)
101 Cognition Disorders/pc [Preventions & Control] (0)
102 or/98-101 (1485)
103 98 or 102 (1485)
104 randomized controlled trials as topic/ (0)
105 randomized controlled trial/ (759)
106 random allocation/ (0)
107 double blind method/ (0)
108 single blind method/ (0)
109 clinical trial/ (472)
110 clinical trial, phase i.pt. (29)
111 clinical trial, phase ii.pt. (42)
112 clinical trial, phase iii.pt. (35)
113 clinical trial, phase iv.pt. (2)
114 controlled clinical trial.pt. (55)
115 randomized controlled trial.pt. (759)
116 multicenter study.pt. (399)
117 clinical trial.pt. (472)
118 exp Clinical trials as topic/ (0)
119 or/104-118 (1245)
120 (clinical adj trial$).tw. (26676)
121 ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw. (9179)
122 placebos/ (0)
123 placebo$.tw. (11961)
124 randomly allocated.tw. (2339)
125 (allocated adj2 random$).tw. (2515)
126 120 or 121 or 122 or 123 or 124 or 125 (40573)
127 119 or 126 (41429)
128 103 and 127 (147)

Database: Embase Classic+Embase <1947 to 2016 February 10>
Search Strategy: RCTs

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1 prevention/ or "prevention and control"/ or primary prevention/ or prophylaxis/ or protection/ (388002)
2 prevent*.ti. (292863)
3 protect*.ti. (166106)
4 delay*.ti. (70519)
5 ((reduc* or decreas* or effect* or lower* or modif* or change* or stop* or improv* or increas* or enhanc* or rais*) and risk*).ti. (68778)
6 (biomarker* adj2 enrich*).ti. (29)
7 intervention*.ti. (128336)
8 program*.ti. (190084)
9 multidomain*.ti. (482)
10 multi-domain*.ti. (196)
11 multicomponent*.ti. (3473)
12 multi-component*.ti. (1062)
13 multifactoral*.ti. (25)
14 multi-factoral*.ti. (2)
15 approach*.ti. (256521)
16 lifestyle*.ti. (13016)
17 life style.ti. (1723)
18 exp physical activity/ (295154)
19 exp exercise/ (263840)
20 ((physical or aerobic* or leisure) and (activit* or fitness)).ti. (35810)
21 exercis*.ti. (118665)
22 exp Diet/ (271531)
23 diet*.ti. (181510)
24 fruit*.ti. (23508)
25 vegetable*.ti. (11437)
26 nutrition*.ti. (103074)
27 fat*.ti. (247795)
28 caffeine.ti. (12266)
29 sodium.ti. (99989)
30 salt*.ti. (48776)
31 alcohol*.ti. (151585)
32 ((smok* or tobacco) and (quit or cessation or stop*)).ti. (13072)

33 ((metacognitive or cognitive or mental or brain or memory or social or perceptual or computer) and (activit* or train* or stimulat* or intervention or engag* or rehab*)).ti. (53741)
34 exp *drug therapy/ (652263)
35 drug*.ti. (450662)
36 medication*.ti. (48020)
37 pharmacopsychiatry.ti. (90)
38 exp Psychopharmacology/ (27649)
39 lovastatin/ or simvastatin/ or pravastatin/ (44198)
40 statin*.ti. (16827)
41 exp Antihypertensive Agents/ (628950)
42 anti-hypertensive*.ti. (972)
43 antihypertensive*.ti. (16198)
44 exp Cholinesterase Inhibitors/ (83861)
45 Acetylcholinesterase inhibitor*.ti. (1226)
46 (Donepezil or Aricept or Memantine or Namenda or Rivastigmine or Exelon or Galantamine or razadyne or Quetiapine or seroquel).ti. (7323)
47 cholinesterase inhibitor*.ti. (1672)
48 exp Antibodies, Monoclonal/ or exp Antibodies, Monoclonal, Humanized/ (394269)
49 anti amyloid*.ti. (214)
50 antiamyloid*.ti. (40)
51 Solanezumab.ti. (43)
52 crenezumab.ti. (2)
53 gantenerumab.ti. (9)
54 crenezumab.ab. (14)
55 antiplatlet.ti. (8)
56 anti-platelet.ti. (1311)
57 (Triflusal or Ticlid or plavix or brilinta or persantine or Ticlopidine or Dipyridomole or Clopidogrel).ti. (8156)
58 exp Hypoglycemic Agents/ (408843)
59 (Pioglitazone or actos or Glucophage or metformin).ti. (12917)
60 ((gonadal or sex) adj steroid*).ti. (4750)
61 exp Hormone Replacement Therapy/ (52856)
62 estrogen*.ti. (59100)
63 progest*.ti. (35701)
64 medroxyprogesterone*.ti. (2555)
65 estradiol.ti. (22509)
66 raloxifene.ti. (1622)

67 exp Cyclooxygenase 2 Inhibitors/ (42579)
68 (Celecoxib or Rofecoxib).ti. (3619)
69 exp Anti-Inflammatory Agents, Non-Steroidal/ (490780)
70 (Ibuprofen or Tarenflurbil or flurbiprofen or Flurizan or Naproxen or Aspirin).ti. (30083)
71 exp Dietary Supplements/ (72740)
72 supplement*.ti. (59036)
73 nutraceutical*.ti. (1163)
74 exp Nootropic Agents/ (98194)
75 nootropic*.ti. (693)
76 exp Vitamins/ (573824)
77 exp Minerals/ (36345)
78 omega.ti. (10406)
79 ginkgo biloba.ti. (2538)
80 ginko biloba.ti. (20)
81 folate.ti. (10490)
82 fish oil.ti. (3894)
83 saffron.ti. (625)
84 crocus sativus.ti. (434)
85 fuzhisan.ti. (12)
86 melissa.ti. (356)
87 beta carotene.ti. (3702)
88 vitamin*.ti. (113036)
89 ((manag* or control* or lower* or reduc* or decreas* or loss or lose) and (weight or BMI or body mass index or overweight or obes* or diabetes or depress* or cardio* or vascular or blood pressure or hypertension or cholesterol or hypercholesterolemia or homocysteine)).ti. (127982)
90 or/1-89 (6007082)
91 *dementia/ or *alzheimer disease/ (122973)
92 (dementia or cognitive impair*).ti. (60302)
93 *Cognition/ (57927)
94 *Mild Cognitive Impairment/ (5955)
95 *memory disorders/ (2392)
96 *executive funtion/ (0)
97 exp *memory/ (86144)
98 cognition.ti. (12039)
99 ((cognit* or neurocognit* or memory or neuropsy* or neuro*) adj (impair* or disorder* or dysfunction* or function* ag?ing or declin* or status or perform* or diabil* or disable* or maint* or enhanc*)).ti. (50252)

100 ((maint* or impair* or disorder* or declin* or enhanc*) adj (cognit* or neurocognit* or memory or neuropsy* or neuro*)).ti. (2750)
101 (amyloid or tau or plasticity).ti. (59657)
102 ((brain or grey matter or gray matter) adj3 (function* or scan* or mri or volume or chang* or imag*)).ti. (23708)
103 exp Biological Markers/ (172233)
104 (91 or 94) and 103 (4462)
105 91 or 92 or 94 or 95 or 96 or 97 or 101 or 104 (274389)
106 *Alzheimer Disease/pc [Prevention & Control] (2840)
107 *Mild Cognitive Impairment/pc [Prevention & Control] (42)
108 106 or 107 (2870)
109 90 and 105 (57490)
110 108 or 109 (58108)
111 limit 110 to human (41595)
112 limit 111 to (embryo <first trimester> or infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>) (1366)
113 limit 112 to (adult <18 to 64 years> or aged <65+ years>) (596)
114 (111 not 112) or 113 (40825)
115 Clinical trial/ (861651)
116 Randomized controlled trial/ (394622)
117 Randomization/ (69534)
118 Single blind procedure/ (21500)
119 Double blind procedure/ (130682)
120 Crossover procedure/ (46320)
121 Placebo/ (286985)
122 Randomi?ed controlled trial$.tw. (129567)
123 Rct.tw. (19484)
124 Random allocation.tw. (1561)
125 Randomly allocated.tw. (24259)
126 Allocated randomly.tw. (2119)
127 (allocated adj2 random).tw. (905)
128 (waitlist or wait list).tw. (4382)
129 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 (1271460)
130 Case study/ (45524)
131 Case report.tw. (324413)
132 Abstract report/ or letter/ (967648)

133 130 or 131 or 132 (1330767)

134 129 not 133 (1236125)

135 114 and 134 (9013)

136 limit 135 to (book or book series or conference abstract or conference paper or conference proceeding or "conference review" or editorial or letter or note or short survey or trade journal) (2271)

137 135 not 136 (6742)

138 limit 137 to yr="2009 -Current" (2443)

Database: Embase Classic+Embase <1947 to 2016 February 10>
Search Strategy: Observational Studies

Database: Embase Classic+Embase <1947 to 2016 February 10>
Search Strategy:

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1 prevention/ or "prevention and control"/ or primary prevention/ or prophylaxis/ or protection/ (388002)
2 prevent*.ti. (292863)
3 protect*.ti. (166106)
4 delay*.ti. (70519)
5 ((reduc* or decreas* or effect* or lower* or modif* or change* or stop* or improv* or increas* or enhanc* or rais*) and risk*).ti. (68778)
6 (biomarker* adj2 enrich*).ti. (29)
7 intervention*.ti. (128336)
8 program*.ti. (190084)
9 multidomain*.ti. (482)
10 multi-domain*.ti. (196)
11 multicomponent*.ti. (3473)
12 multi-component*.ti. (1062)
13 multifactoral*.ti. (25)
14 multi-factoral*.ti. (2)
15 approach*.ti. (256521)
16 lifestyle*.ti. (13016)
17 life style.ti. (1723)
18 exp physical activity/ (295154)
19 exp exercise/ (263840)
20 ((physical or aerobic* or leisure) and (activit* or fitness)).ti. (35810)
21 exercis*.ti. (118665)
22 exp Diet/ (271531)
23 diet*.ti. (181510)
24 fruit*.ti. (23508)
25 vegetable*.ti. (11437)
26 nutrition*.ti. (103074)
27 fat*.ti. (247795)
28 caffeine.ti. (12266)

29 sodium.ti. (99989)
30 salt*.ti. (48776)
31 alcohol*.ti. (151585)
32 ((smok* or tobacco) and (quit or cessation or stop*)).ti. (13072)
33 ((metacognitive or cognitive or mental or brain or memory or social or perceptual or computer) and (activit* or train* or stimulat* or intervention or engag* or rehab*)).ti. (53741)
34 exp *drug therapy/ (652263)
35 drug*.ti. (450662)
36 medication*.ti. (48020)
37 pharmacopsychiatry.ti. (90)
38 exp Psychopharmacology/ (27649)
39 lovastatin/ or simvastatin/ or pravastatin/ (44198)
40 statin*.ti. (16827)
41 exp Antihypertensive Agents/ (628950)
42 anti-hypertensive*.ti. (972)
43 antihypertensive*.ti. (16198)
44 exp Cholinesterase Inhibitors/ (83861)
45 Acetylcholinesterase inhibitor*.ti. (1226)
46 (Donepezil or Aricept or Memantine or Namenda or Rivastigmine or Exelon or Galantamine or razadyne or Quetiapine or seroquel).ti. (7323)
47 cholinesterase inhibitor*.ti. (1672)
48 exp Antibodies, Monoclonal/ or exp Antibodies, Monoclonal, Humanized/ (394269)
49 anti amyloid*.ti. (214)
50 antiamyloid*.ti. (40)
51 Solanezumab.ti. (43)
52 crenezumab.ti. (2)
53 gantenerumab.ti. (9)
54 crenezumab.ab. (14)
55 antiplatlet.ti. (8)
56 anti-platelet.ti. (1311)
57 (Triflusal or Ticlid or plavix or brilinta or persantine or Ticlopidine or Dipyridomole or Clopidogrel).ti. (8156)
58 exp Hypoglycemic Agents/ (408843)
59 (Pioglitazone or actos or Glucophage or metformin).ti. (12917)
60 ((gonadal or sex) adj steroid*).ti. (4750)
61 exp Hormone Replacement Therapy/ (52856)
62 estrogen*.ti. (59100)

63 progest*.ti. (35701)
64 medroxyprogesterone*.ti. (2555)
65 estradiol.ti. (22509)
66 raloxifene.ti. (1622)
67 exp Cyclooxygenase 2 Inhibitors/ (42579)
68 (Celecoxib or Rofecoxib).ti. (3619)
69 exp Anti-Inflammatory Agents, Non-Steroidal/ (490780)
70 (Ibuprofen or Tarenflurbil or flurbiprofen or Flurizan or Naproxen or Aspirin).ti. (30083)
71 exp Dietary Supplements/ (72740)
72 supplement*.ti. (59036)
73 nutraceutical*.ti. (1163)
74 exp Nootropic Agents/ (98194)
75 nootropic*.ti. (693)
76 exp Vitamins/ (573824)
77 exp Minerals/ (36345)
78 omega.ti. (10406)
79 ginkgo biloba.ti. (2538)
80 ginko biloba.ti. (20)
81 folate.ti. (10490)
82 fish oil.ti. (3894)
83 saffron.ti. (625)
84 crocus sativus.ti. (434)
85 fuzhisan.ti. (12)
86 melissa.ti. (356)
87 beta carotene.ti. (3702)
88 vitamin*.ti. (113036)
89 ((manag* or control* or lower* or reduc* or decreas* or loss or lose) and (weight or BMI or body mass index or overweight or obes* or diabetes or depress* or cardio* or vascular or blood pressure or hypertension or cholesterol or hypercholesterolemia or homocysteine)).ti. (127982)
90 or/1-89 (6007082)
91 *dementia/ or *alzheimer disease/ (122973)
92 (dementia or cognitive impair*).ti. (60302)
93 *Cognition/ (57927)
94 *Mild Cognitive Impairment/ (5955)
95 *memory disorders/ (2392)
96 *executive funtion/ (0)
97 exp *memory/ (86144)

98 cognition.ti. (12039)

99 ((cognit* or neurocognit* or memory or neuropsy* or neuro*) adj (impair* or disorder* or dysfunction* or function* ag?ing or declin* or status or perform* or diabil* or disable* or maint* or enhanc*)).ti. (50252)

100 ((maint* or impair* or disorder* or declin* or enhanc*) adj (cognit* or neurocognit* or memory or neuropsy* or neuro*)).ti. (2750)

101 (amyloid or tau or plasticity).ti. (59657)

102 ((brain or grey matter or gray matter) adj3 (function* or scan* or mri or volume or chang* or imag*)).ti. (23708)

103 exp Biological Markers/ (172233)

104 91 or 92 or 94 or 99 or 100 (177159)

105 *Alzheimer Disease/pc [Prevention & Control] (2840)

106 *Mild Cognitive Impairment/pc [Prevention & Control] (42)

107 105 or 106 (2870)

108 90 and 104 (46186)

109 107 or 108 (46804)

110 limit 109 to human (37668)

111 limit 110 to (embryo <first trimester> or infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>) (928)

112 limit 111 to (adult <18 to 64 years> or aged <65+ years>) (353)

113 (110 not 111) or 112 (37093)

114 Clinical study/ (132584)

115 longitudinal study/ (85243)

116 prospective study/ (322344)

117 cohort analysis/ (230562)

118 (cohort adj stud*).mp. (158158)

119 (observational adj stud*).mp. (119842)

120 (follow up adj stud*).mp. (57729)

121 (epidemiologic* adj stud*).mp. (88591)

122 (cross sectional adj stud*).mp. (205524)

123 or/114-122 (1136620)

124 113 and 123 (4143)

125 limit 124 to (book or book series or chapter or conference abstract or conference paper or conference proceeding or "conference review" or editorial or erratum or letter or note or "review" or short survey or trade journal) (1652)

126 124 not 125 (2491)

127 limit 126 to yr="2009 -Current" (1644)

Database: PsycINFO <2002 to February Week 1 2016>
Search Strategy: RCTs

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1 prophylaxis/ or prevention/ (14810)
2 prevent*.ti. (21271)
3 protect*.ti. (8537)
4 delay*.ti. (5830)
5 ((reduc* or decreas* or effect* or lower* or modif* or change* or stop* or improv* or increas* or enhanc* or rais*) and risk*).ti. (7006)
6 intervention*.ti. (36138)
7 program*.ti. (35798)
8 multidomain*.ti. (22)
9 multi-domain*.ti. (34)
10 multicomponent*.ti. (176)
11 multi-component*.ti. (101)
12 lifestyle*.ti. (2645)
13 ((metacognitive or cognitive or mental or brain or memory or social or perceptual or computer) and (activit* or train* or stimulat* or intervention or engag* or rehab*)).ti. (16817)
14 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (126101)
15 *dementia/ or *alzheimer disease/ (35185)
16 *mild cognitive impairment/ (0)
17 ((cognit* or neurocognit* or memory or neuropsy* or neuro*) adj (impair* or disorder* or dysfunction* or function* ag?ing or declin* or status or perform* or diabil* or disable* or maint* or enhanc*)).ti. (15609)
18 ((maint* or impair* or disorder* or declin* or enhanc*) adj (cognit* or neurocognit* or memory or neuropsy* or neuro*)).ti. (990)
19 (amyloid or tau or plasticity).ti. (9730)
20 ((brain or grey matter or gray matter) adj3 (function* or scan* or mri or volume or chang* or imag*)).ti. (4219)
21 biological marker/ (6893)
22 dementia/ or alzheimer disease/ (39250)
23 21 and 22 (1529)
24 15 or 16 or 17 or 18 or 19 or 20 or 23 (58609)
25 14 and 24 (4017)
26 limit 25 to human (3317)

27 limit 26 to (embryo <first trimester> or infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>) [Limit not valid in PsycINFO; records were retained] (72)

28 limit 27 to (adult <18 to 64 years> or aged <65+ years>) [Limit not valid in PsycINFO; records were retained] (12)

29 (26 not 27) or 28 (3257)

30 limit 29 to (clinical trial or randomized controlled trial or controlled clinical trial or multicenter study or phase 1 clinical trial or phase 2 clinical trial or phase 3 clinical trial or phase 4 clinical trial) [Limit not valid in PsycINFO; records were retained] (3257)

31 limit 30 to (book or book series or conference abstract or conference paper or conference proceeding or "conference review" or editorial or letter or note or "review" or short survey or trade journal) [Limit not valid in PsycINFO; records were retained] (283)

32 30 not 31 (2974)

33 limit 32 to yr="2009 -Current" (2013)

Database: PsycINFO <2002 to February Week 1 2016>
Search Strategy: Observational Studies

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1 prophylaxis/ or prevention/ (14810)
2 prevent*.ti. (21271)
3 protect*.ti. (8537)
4 delay*.ti. (5830)
5 ((reduc* or decreas* or effect* or lower* or modif* or change* or stop* or improv* or increas* or enhanc* or rais*) and risk*).ti. (7006)
6 intervention*.ti. (36138)
7 program*.ti. (35798)
8 multidomain*.ti. (22)
9 multi-domain*.ti. (34)
10 multicomponent*.ti. (176)
11 multi-component*.ti. (101)
12 lifestyle*.ti. (2645)
13 ((metacognitive or cognitive or mental or brain or memory or social or perceptual or computer) and (activit* or train* or stimulat* or intervention or engag* or rehab*)).ti. (16817)
14 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (126101)
15 *dementia/ or *alzheimer disease/ (35185)
16 *mild cognitive impairment/ (0)
17 ((cognit* or neurocognit* or neuropsy* or neuro*) adj (impair* or disorder* or dysfunction*)).ti. (9474)
18 15 or 16 or 17 (41904)
19 14 and 18 (2846)
20 limit 19 to human (2537)
21 (cohort or longitudinal or prospective).ti,ab. (115078)
22 exp Longitudinal Studies/ (1595)
23 Prospective Studies/ (216)
24 21 or 22 or 23 (115252)
25 limit 24 to "reviews (best balance of sensitivity and specificity)" (53066)
26 24 not 25 (62186)
27 20 and 26 (85)
28 limit 27 to yr="2009 -Current" (55)

Cochrane Central Register of Controlled Trials

Precise search on dementia, cognitive impairment terms

Database: Ovid MEDLINE(R) <1946 to March Week 1 2016>
Search Strategy:

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1 exp Memory Disorders/ or exp Neuropsychological Tests/ or exp Alzheimer Disease/ or exp Cognition/ or exp Cognition Disorders/ (298451)

2 exp Alzheimer Disease/ (73521)

3 ((cognit* or memory) adj2 (impair* or declin*)).ti,ab. (58569)

4 exp Mild Cognitive Impairment/ (3643)

5 cognition.ti,ab. (34845)

6 (cognitive adj (performan* or test*)).ti,ab. (15238)

7 1 or 2 or 3 or 4 or 5 or 6 (329242)

8 exp Cardiovascular Diseases/dh, dt, rh, su, th [Diet Therapy, Drug Therapy, Rehabilitation, Surgery, Therapy] (766074)

9 exp Depression/dh, dt, th [Diet Therapy, Drug Therapy, Therapy] (21954)

10 exp Sleep Wake Disorders/dh, dt, th [Diet Therapy, Drug Therapy, Therapy] (19655)

11 (sleep adj (quality or duration or time)).ti. (2355)

12 exp Diabetes Mellitus, Type 2/dh, dt, th [Diet Therapy, Drug Therapy, Therapy] (32195)

13 8 or 9 or 10 or 11 or 12 (837027)

14 7 and 13 (8871)

15 limit 14 to (clinical study or clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or observational study or pragmatic clinical trial or randomized controlled trial or systematic reviews) (2669)

16 limit 15 to yr="2009 -Current" (1210)

Appendix B. Risk of Bias Assessment Tool

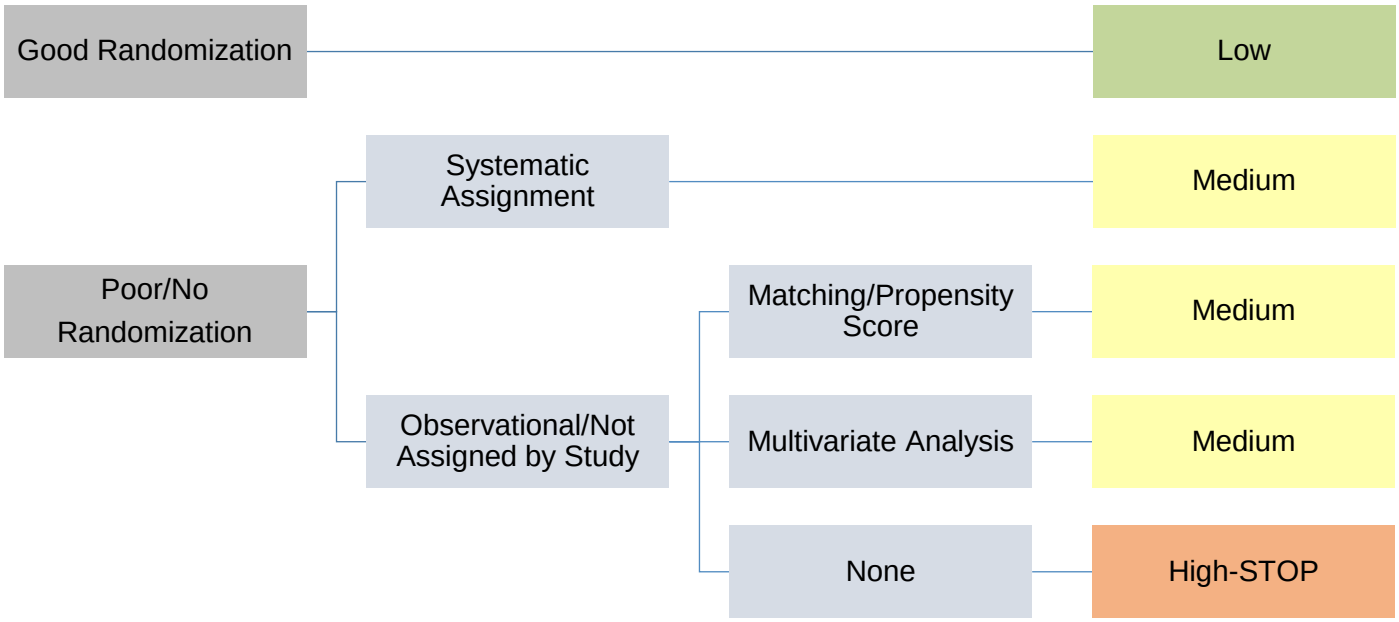
Review the methods of each trial and assess each risk of bias component as described in these instructions. You may need to have separate assessments for different outcomes (i.e. different measures; different time points may have different attrition rates). Remember, this tool is not an algorithm. Discretion must be applied.

1) Selection Bias

Systematic differences between baseline characteristics of the groups that arise from self-selection of treatments, physician-directed selection of treatments, or association of treatment assignments with demographic, clinical, or social characteristics.

- Did method of randomization create biased allocation to interventions (inadequate randomization)?
- "Good" Randomization: Random numbers table, computer random number generator
- "Poor" Randomization: Randomized based on week of the month of birthday
- No Randomization: Non-randomized clinical trial, observational study

Figure B1



2) Attrition

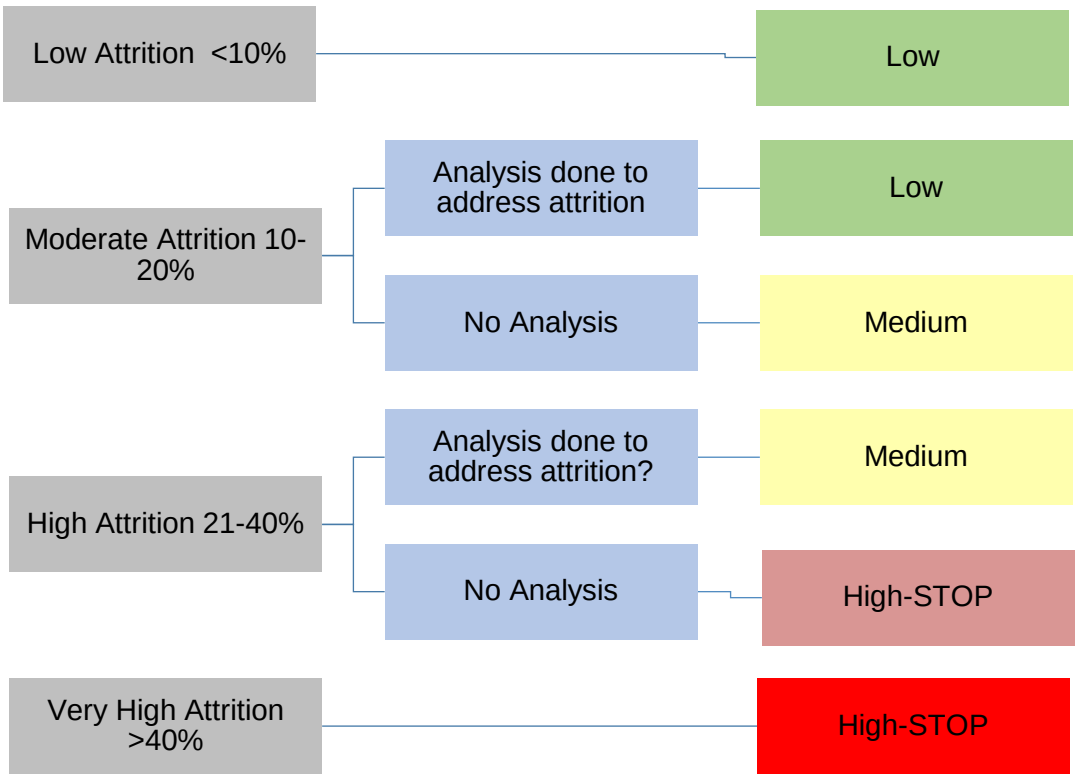
Systematic differences in the loss of participants from the study and how they were accounted for in the results (e.g., incomplete followup, differential attrition). Those who drop out of the study or who are lost to followup may be systematically different from those who remain in the study. Attrition bias can potentially change the collective (group) characteristics of the relevant groups and their observed outcomes in ways that affect study results by confounding and spurious associations.

- Reasons for incomplete/missing data adequately explained?
- Do the author's attempt to address attrition in the analysis?

Notes

- Report attrition rate in spreadsheet.
- If a study reports outcomes at multiple intervals (e.g., 6 months, 12 months, 18 months) assess attrition at each time-point and record separately.
- Analysis should be done with appropriate method (i.e., sensitivity analysis with various scenarios; last value forward would only be appropriate for interventions that are supposed to improve the outcomes (i.e., memory training that intends to improve memory).

Figure B2



3) Selection and Attrition Bias Overall

Assess joint selection and attrition bias. If either selection or attrition bias is high, the risk of bias is HIGH.

Selection Bias	Low	Low	Medium	Low	Medium	Medium	High
Attrition Bias	Low	Medium	Low	High	Medium	High	X
Action	Assess other biases	Assess other biases	Assess other biases	STOP	Assess other biases	STOP	STOP

4) Other Biases

A. Detection Bias

Systematic differences in outcomes assessment among groups being compared, including systematic misclassification of the exposure or intervention, covariates, or outcomes because of variable definitions and timings, diagnostic thresholds, recall from memory, inadequate assessor blinding, and faulty measurement techniques. Erroneous statistical analysis might also affect the validity of effect estimates.

- Were the outcome assessors blinded to the intervention ("outcome assessor blinded")?
- Was the timing of the outcome assessment similar in all groups ("comparable timing outcomes assessment")?
- Was the scale used to measure outcomes validated, reliable?
- Were outcomes measured in clinically meaningful ways?

Domain	**Options**		**Overall Rating**
Outcome assessor blinded	Yes	No	All 4 Yes =Low 2 or 3 Yes = Medium 3+ No=High
Outcome assessor independent	Yes	No	
Comparable timing outcomes assessment	Yes	No	
Outcome assessment instrument/measurement quality	Yes (Adequate)	No (Inadequate)	

B. Performance Bias

Systematic differences in the care provided to participants and protocol deviation. Examples include contamination of the control group with the exposure or intervention, unbalanced provision of additional interventions or co-interventions, difference in co-interventions, and inadequate blinding of providers and participants.

Notes

- Intention-to-Treat (ITT): Includes every subject according to randomized treatment assignment. Ignores noncompliance, protocol deviations, withdrawal, and anything that happens after randomization.
- Concurrent Intervention: Study participants are receiving another intervention (i.e., treatment) that is not part of the intervention being tested. Example: Participants are randomized to a physical activity intervention (or no intervention), but are also dieting.

Domain	Options	Rating	Overall Rating
1a. RCTs-ITT	Yes	Low	*Low* All Low=Low 1-Low, 2-Low, 3-N/A=Low *Medium* 1-Low, 2-Low, 3-High=Medium 1-Low, 2-Medium, 3-Low=Medium 1-Low, 2-Medium, 3-N/A=Medium 1-Medium, 2-Medium, 3-N/A=Medium 1-Medium, 2-High, 3-Low=Medium 1-Medium, 2-Medium, 3-High=Medium *High* 1-High + Anything Else=High 2+ High=High
	No/Not reported	High	
1b. Obs-Adjustment for known confounders	Adequate	Low	
	Inadequate	High	
2. Concurrent intervention	Yes-Adjusted	Medium	
	Yes-Unadjusted	High	
	No	Low	
	Unclear/Not Reported	NR	
3. Participant Blinding	Yes	Low	
	No	Medium	
	N/A	N/A	

C. Reporting Bias

Systematic differences between reported and unreported findings (e.g., differential reporting of outcomes or harms, incomplete reporting of study findings, potential for bias in reporting through source of funding).

- Was a select group of outcomes reported?

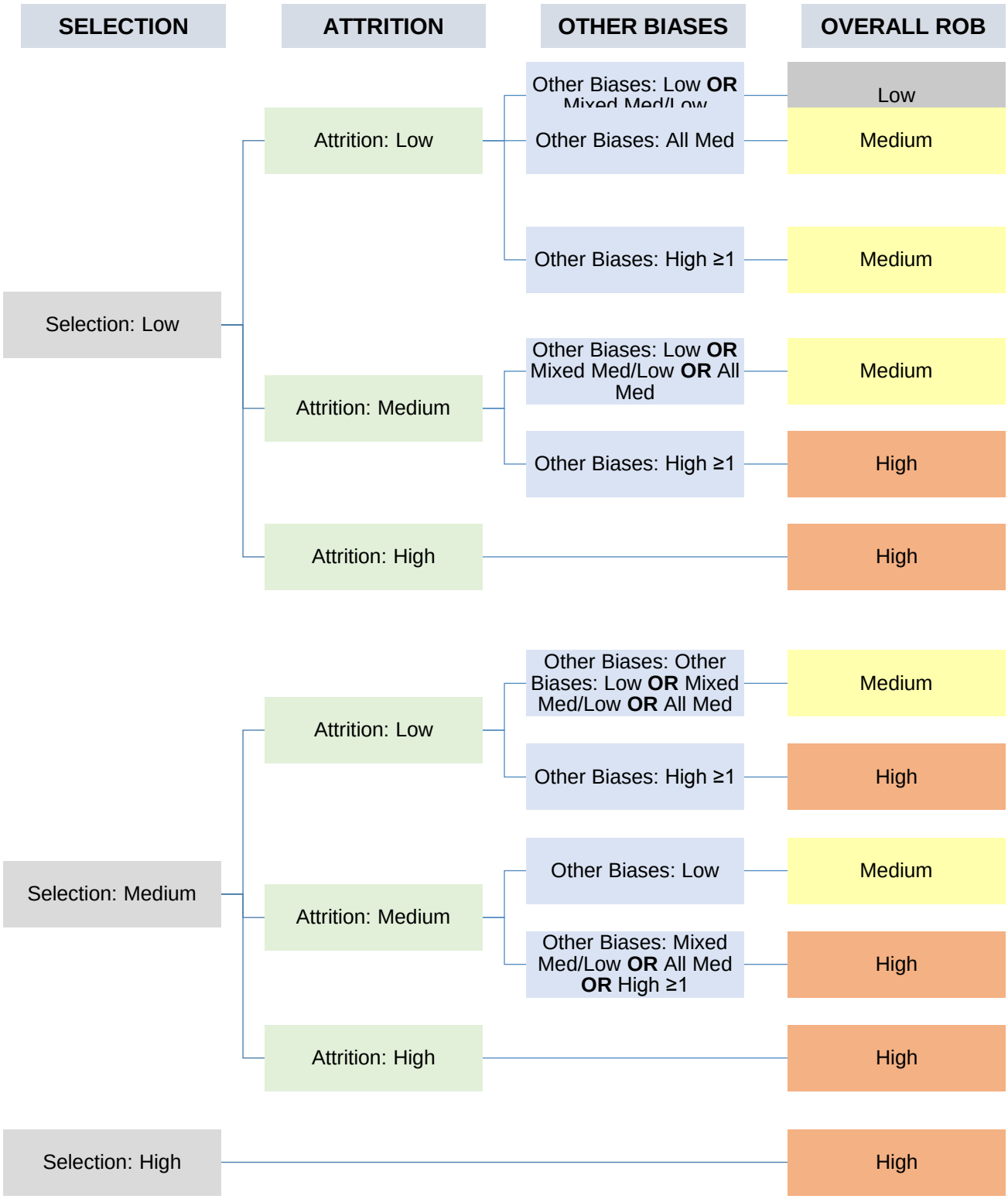
Notes

- Compare results to methods section and/ or protocol.
- Check if some results are reported in a different publication.

Domain	Options	Rating
All outcomes reported	Yes	Low
	No	Medium
	Not Reported	Medium

5) Overall Rob

Figure B3



Appendix C. Cognitive Performance Outcomes

Appendix Table C1. Cognitive outcomes categorization

Test Names	Common Abbreviations	Cognitive Outcome Categorization
Abstraction (Shipley Inst. of Living Scales subtest)		Executive/Attention/Processing Speed
AD Cooperative Studies AD Assessment Scale - Cognitive Subscale	ADAS-Cog, ADCS-Cog	Multidomain neuropsychological performance
AD Cooperative Studies ADL in MCI Scale	ADCS-MCI-ADL	Multidomain neuropsychological performance
AD Cooperative Studies Activities of Daily Living Scale	ADCS-ADL	Multidomain neuropsychological performance
Babcock Story Recall		Memory
Benton Visual Retention Test	BVRT	Memory
Blessed Dementia Rating Scale: Blessed Information Memory Concentration	BIMC	Brief cognitive test performance
Blessed Dementia Rating Scale: Blessed Rating Scale	BRS, DRS, BDS, Dementia score	Brief cognitive test performance
Block Design (WAIS subtest)	BD	Visuospatial
Boston Naming Test - multiple versions: 15, 30, 60-items	BNT	Language
Brief Visuospatial Memory Test	BVMT, BVMT-R	Memory
Brixton Spatial Anticipation Test	Brixton	Executive/Attention/Processing Speed
Buschke Selective Reminding Test	SRT	Memory
California Verbal Learning Test - multiple versions	CVLT, CVLT-II	Memory
Cancellation Tests (several versions: bell, star, letter, ...)		Visuospatial
Cambridge Neuropsychological Test Automated Battery (part of the CAMDEX)	CANTAB	Multidomain neuropsychological performance
CERAD word list / list learning subtest	CERAD	Memory
Clock Drawing Tests (many versions & featured in screening tools)	CDT, CLOX	Visuospatial
Cognitive Abilities Screening Instrument	CASI	Brief cognitive test performance
Consortium to Establish a Registry for Alzheimer's Disease (cognitive battery)	CERAD	Multidomain neuropsychological performance
Continuous Performance Test	CPT	Executive/Attention/Processing Speed

Corsi Block Tapping - fowards & backwards (similar to Spatial Span)		Executive/Attention/Processing Speed
Delis–Kaplan Executive Function System	D-KEFS	Executive/Attention/Processing Speed
Digit Span - forwards & backwards (WAIS/WMS subtest)	DS, DSp	Executive/Attention/Processing Speed
Digit Symbol Coding (WAIS subtest; inverse of Symbol Digit Modalities)	DSy	Executive/Attention/Processing Speed
East Boston Story or East Boston Memory Test	EBMT	Memory
Faces - parts I & II (WMS subtest)		Memory
Finger Tapping Test	FTT	Motor
Grip Strength / Hand Dynamometer		Motor
Grooved Pegboard		Motor
Hopkins Verbal Learning Test	HVLT, HVLT-R	Memory
Judgement of Line Orientation	JLO	Visuospatial
Letter Digit Substitution (Coding) Test	LDST	Executive/Attention/Processing Speed
Letter-Number Sequencing (most commonly a WAIS subtest)	LNS	Executive/Attention/Processing Speed
Letter Sets		Executive/Attention/Processing Speed
Logical Memory - parts I & II (WMS subtest)	LM, LMI, LMII	Memory
Matrix Reasoning (WAIS subtest)		Executive/Attention/Processing Speed
Mattis Dementia Rating Scale	MDRS, DRS	Multidomain neuropsychological performance
Maze Tracing (including Porteus Maze Test)		Executive/Attention/Processing Speed
Mini-Mental State Examination	MMSE	Brief cognitive test performance
Modified Mini-Mental State Examination	3MS, 3MSE	Brief cognitive test performance
Montreal Cognitive Assessment	MoCA	Brief cognitive test performance
N-Back		Executive/Attention/Processing Speed
National Adult Reading Test	NART	Language
Neurobehavioral Cognitive Status Examination (original Cognistat paper test)	NCSE	Multidomain neuropsychological performance
New York University Paragraph Recall		Memory
Number Series		Executive/Attention/Processing Speed
Picture Completion (many versions, most commonly a WAIS subtest)	PC	Executive/Attention/Processing Speed; Visualspatial
Purdue Pegboard	PPT, PPBT	Motor
Raven's Progressive Matrices (several versions	RPM, RCPM	Executive/Attention/Processing Speed

including Colored & Advanced)		
Reaction Time Tests (many versions: simple, choice, auditory, visual...)	RT, SRT	Executive/Attention/Processing Speed
Repeatable Battery for the Assessment of Neuropsychological Status	RBANS	Multidomain neuropsychological performance
Rey Auditory Verbal Learning Test	RAVLT (may see AVLT or RVLT)	Memory
Rey-Osterrieth Complex Figure Test	CFT, RCFT, Rey-O, Rey	Memory; Visuospatial
Rivermead Behavioral Memory Test - multiple versions	RBMT, RBMT-II, RBMT-3	Memory
Self-Ordered Pointing Task(Test)	SOPT	Executive/Attention/Processing Speed
Short Portable Mental Status Questionnaire	SPMSQ	Brief cognitive test performance
Short Test of Mental Status	STMS	Brief cognitive test performance
Syndrom Kurztest - SKT (German)	SKT	Executive/Attention/Processing Speed; Memory
Spatial Span - forwards & backwards (WMS subtest; similar to Corsi Block Tapping)		Executive/Attention/Processing Speed
Stroop - color, word, interference (there are many versions of the Stroop)		Executive/Attention/Processing Speed
Symbol Digit Modalities Test (inverse of Digit Symbol)	SDMT	Executive/Attention/Processing Speed
Taylor Complex Figure		Memory; Visuospatial
Telephone Interview for Cognitive Status	TICS	Brief cognitive test performance
Telephone Interview for Cognitive Status, modified	TICS-M, mTICS	Brief cognitive test performance
Token Test		Language
Trail Making Test - part A	TMT A	Executive/Attention/Processing Speed
Trail Making Test - part B (or B-A, B/A, etc.)	TMT B	Executive/Attention/Processing Speed
Verbal Fluency, Phonemic/Phonological or Letter	VF, PVF, FAS, CFL, COWAT, COWA	Executive/Attention/Processing Speed; Language
Verbal Fluency, Semantic or Category	VF, SVF, animals, names, fruits/vegetables	Language
Visual Reproduction (WMS subtest)	VR, VRI, VRII, Vis Rep	Memory
Useful Field of View	UFOV	Executive/Attention/Processing Speed
Walter Reed performance assessment battery		Multidomain neuropsychological performance
Wechsler Adult Intelligence Scale - multiple versions	WAIS, WAIS-R, WAIS-III, WAIS-IV	Multidomain neuropsychological performance
Wechsler Memory Scale - multiple versions	WMS, WMS-R, WMS-III,	Memory

	WMS-IV	
Wisconsin Card Sorting Test	WCST	Executive/Attention/Processing Speed

Appendix Table C2. Neuropsychological tests and reliable change indices

Cognitive Domain	Instrument	Measurement Properties	Reliable Change Indices
Global Cognitive Function	Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog)	Used to measure cognitive impairment in the assessment of Alzheimer's disease. Tests several cognitive domains, including memory, language, and praxis. Range: 0-70; higher scores indicate worse cognition[17]	4 pts (6 months); considered to be clinically important, but not meaningful; no established RCI's[17]
	Mini-Mental State Examination (MMSE)	11 items assessing cognitive function: orientation, registration, attention and calculation, recall, language (range 0-30) Range: 0-30; higher scores indicate better[18]	2.73 pts (3 months) 3.60 pts (5 years)[19]
	Modified Mini-Mental State Examination (3MS)	15 items: 11 from MMSE plus 4 additional items assessing long-term memory, abstract thinking, category fluency, delayed recall Range: 0-100; higher scores indicate better cognition[18]	5 pts [20] 7.41 pts (3 months) 9.82 pts (5 years)[19]
	Telephone Interview for Cognitive Status (TICS)	11 items assessing word list memory, orientation, attention, repetition, conceptual knowledge, nonverbal praxis Range: 0-41; higher scores indicate better cognition[18]	None identified
Executive, Attention, Processing Speed	Tower Test	Varying number of items assessing spatial planning, rule learning, inhibition of impulsive and perseverative responding, and the ability to establish and maintain instructional set. Subjects must construct towers using 5 circular pieces, placed onto one of 3 pegs. Towers constructed must be identical to a picture shown. Subjects are not allowed to place a larger piece on a smaller piece, and must move one piece at a time. Range: 0-30[21]	None identified
	Digit Span Forward*†	Varying number of items assessing attention efficiency and capacity: subjects asked to listen to a sequence of numbers read and then recite back in order (reported as either subscore or summary score with Digit Span Backward)	None identified; part of WAIS-III WMI and VIQ
	Digit Span Backward*†	Varying number of items assessing executive function and especially working memory: sequence of numbers read, participants asked to read sequence back in reverse order (reported as either subscore or summary score with Digit Span Forward)	None identified; part of WAIS-III WMI and VIQ

Cognitive Domain	Instrument	Measurement Properties	Reliable Change Indices
	Digit Symbol Substitution Test*	Varying number of items assessing psychomotor ability, sustained attention, processing speed and working memory: participants asked to use a key to substitute certain items within rows of numbers (Digit Symbol) or symbols (Symbol Digit Modalities) (score comprised of items completed within the specified time).	None identified; part of WAIS-III PSI and PIQ
	Stroop Interference Test	3 to 4 parts (depending on the version). Original version has 4 parts. Part 1: rows of written color names written in black ink, and the subject must say the written word. Part 2: the subject reads color names printed in colored ink, ignoring the printed color. Part 3: Subject names the colors of squares. Part 4: the subject uses the printed words from part 2, but must say the color of the ink each word is printed in instead of saying the word. Range: Time to completion and number of errors. Higher raw time and raw errors indicate worse cognition.[18]	None identified
	Trail Making Test Part A (Trails A)	Assesses visual attention and processing speed: subject asked to draw lines connecting circled numbers in sequence (score comprised of both time to complete task and number of errors made; higher score indicates lower function, unless age-scaled score is presented) Range: Time, in seconds, required for completion; higher raw scores indicate worse cognition while higher scaled scores indicate better cognition. Additionally, if error rate is reported, then higher error rates indicate worse cognition.[18]	Scores to calculate RCI: T2-T1 mean, SD: -0.96, 7.54[22]
	Vigil/Continuous Performance Task (CPT)	Varying number of items assessing sustained and selective attention. Letters flash by one at a time on a computer screen. Subject must press the spacebar after they see an 'A' followed immediately by a 'K.[18]	None identified
	Wisconsin Card Sorting Test (WCST)	Cards are presented to the subject. Subject is told to match the cards, but not how to match; however, he or she is told whether a particular match is right or wrong.[18]	None identified
Intelligence Quotient (Verbal Comprehension, Perceptual Reasoning, Working Memory, Processing Speed)	Wechsler Adult Intelligence Scale (WAIS)	Published battery of neuropsychological tests with varying numbers of core and optional subtests. WAIS-III assesses Verbal Comprehension (Similarities, Vocabulary, Information); Working Memory (Digit Span, Arithmetic, [Letter-Number Sequencing], [Comprehension]); Perceptual Organization (Picture Completion, Block Design, Matrix Reasoning); and Processing Speed (Digit Symbol, [Symbol Search], [Picture Arrangement], [Object Assembly]). [Bracketed] subtests are optional.[18]	VIQ: 9 pts PIQ: 11 pts FSIQ: 9 pts VCI: 11 pts POI: 13 pts WMI: 1 2pts PSI: 14 pts (WAIS-III)[23]
Memory	Wechsler Memory Scale (WMS)	Published battery of neuropsychological tests with varying numbers of core and optional tests. WMS-III assesses auditory presentation (Logical Memory I and II, Verbal Paired Associates I and II, [Letter-Number Sequencing], [Information and Orientation], [Word Lists I and II], [Mental Control], [Digit Span]) and visual presentation (Faces I and II, Family Pictures I and II, [Spatial Span], [Visual Reproduction I and II]).[18]	None identified

Cognitive Domain	Instrument	Measurement Properties	Reliable Change Indices
	Benton Visual Retention Test (BVRT)	10 items (designs) assessing visual memory and perception: subjects are shown one design at a time and asked to draw it from memory (score based on either correctness of drawing or number of errors made; higher error scores indicate lower function) Range: 0-10; higher scores indicate better cognition[18]	None identified
	Rey-Osterrich Complex Figure	3 part test assessing visuospatial abilities, memory, attention, planning, and working memory (executive functions). Subject asked to reproduce a complicated line drawing 3 times: first by copying it while looking at the figure, second by reproducing it immediately afterwards from memory, and third by reproducing the figure again after a 20 to 30-minute delay[18]	Scores to calculate RCI: Copy T2-T1 mean, SD: -0.03, 1.76 Immediate Recall T2-T1 mean, SD: 2.48, 4.51 Delayed Recall T2-T1 mean, SD: 2.30, 4.32[24]
	Buschke Selective Reminding Test	12 items in one list assessing verbal recall and recognition, with a possible 12 trials. List is read aloud until subject recalls all 12 words three times in a row, or until items are read 12 total times (whichever occurs first). After a 20 to 30-minute delay, subjects are asked to recall the 12 words again. Then a recognition trial may be given, which consists of a longer list of words that is read one word at a time; subjects respond 'yes' or 'no' if the word was on the original list of 12. Range: 0-12 for each trial and the recognition score, with higher scores indicating better cognition. Also an intrusion score for the recognition portion, counting each incorrect 'yes' given; higher scores indicate worse cognition[18]	None identified
	California Verbal Learning Test (CVLT)	32 items in two lists (A & B) of 16 words assessing verbal recall and recognition: List A is presented five times for learning and List B is presented once as a distractor Range: Total Recall Score is 20-80; all other scores are z-scores -5 to +5; higher error and recency-recall index scores indicate worse cognition; all other higher scores indicate better cognition[18]	None identified
	Rey Auditory Verbal Learning Test (RAVLT)	30 items in two lists assessing verbal recall and recognition. First a list of 15 words is read aloud and subjects are asked to recall as many as possible (over 5 trials, with the list repeated each time). Then subjects are read a 15 word distractor list and asked to recall as many of the distractor words as possible (1 trial). Afterwards subjects are asked to recall as many of the original 15 words as possible (without being read the list). After a 20-minute delay period, subjects are asked to recall the original list of 15-words again (1 trial). Then a recognition trial may be given, which consists of a longer list of words that is read one word at a time; subjects respond 'yes' or 'no' if the word was on the original list of 15. Range: 0-15 for each trial (1-5, the distractor, delayed recall, and recognition) with higher scores indicating better cognition. Also an intrusion score for the recognition portion, counting each incorrect 'yes' given; higher scores indicate worse cognition.[18]	(decline; improvement) Trial 1:-2.77; 2.65 Trial 5: -3.51; 2.63 Sum 1–5: -11.64; 9.36 Interference: -3.03; 3.11 Trial 7: -4.73; 3.57 Delay: -4.96; 3.60 Recognition: -3.47; 3.69 (12 months)[25]

Cognitive Domain	Instrument	Measurement Properties	Reliable Change Indices
	Wechsler Adult Intelligence Scale (WAIS)	Published battery of neuropsychological tests with varying numbers of core and optional subtests. WAIS-III assesses Verbal Comprehension (Similarities, Vocabulary, Information); Working Memory (Digit Span, Arithmetic, [Letter-Number Sequencing], [Comprehension]); Perceptual Organization (Picture Completion, Block Design, Matrix Reasoning); and Processing Speed (Digit Symbol, [Symbol Search], [Picture Arrangement], [Object Assembly]). [Bracketed] subtests are optional.[18]	VIQ: 9 pts PIQ: 11 pts FSIQ: 9 pts VCI: 11 pts POI: 13 pts WMI: 1 2pts PSI: 14 pts (WAIS-III)[23]
Language	Boston Naming Test (BNT)	60 items assessing word retrieval. Subjects are shown pictures and asked to name what they are pictures of, and receive semantic cues if needed Range: 0-60; higher scores indicate better cognition[18]	4 pts (9-15 months); 6 pts (16-24 months)Sachs, 2012 #618}
	Verbal Fluency Test	Varying number of items assessing spontaneous verbal production: subjects asked to produce as many words beginning with a specific letter (phonemic/letter fluency) or as many words in a specific category such as “animals” (semantic/category fluency) as is possible in one minute Range (phonemic fluency): sum of all admissible words for the three letters; higher scores indicate better cognition Range (semantic fluency): sum of all admissible words for the semantic categories; higher scores indicate better cognition[18]	(Decline; improvement) Letter ‘S’: -5.5; 9.8 Animals: -7.6; 10.5 (1 month)[26]

*Subtest of WAIS; †Subtest of WMS

Abbreviations: 3MS=Modified Mini-Mental State Examination; BNT=Boston Naming Test; BVRT=Benton Visual Retention Test; CERAD=Consortium to Establish a Registry for Alzheimer’s Disease; CPT=Continuous Performance Task; CVLT=California Verbal Learning Test; DKEFS=Delis-Kaplan Executive Function System; FSIQ=Full Scale IQ; MMSE=Mini-Mental State Examination; PIQ=Performance IQ; POI=Perceptual Organization Index; PSI=Processing Speed Index; RCI=Reliable Change Index; RVLT=Rey Verbal Learning Test; SDMT=Symbol Digit Modalities Test; TICS=Telephone Interview for Cognitive Status; Trails A= Trail Making Test Part A; Trails B=Trail Making Test Part B; VCI=Verbal Comprehension Index; VIQ=Verbal IQ; WAIS=Wechsler Adult Intelligence Scale; WMI=Working Memory Index; WMS=Wechsler Memory Scale

Appendix D. Excluded Studies

1. [Public title] Disease-modifying properties of lithium in the neurobiology of Alzheimer's disease; [Scientific title] Disease-modifying properties of lithium in the neurobiology of Alzheimer's disease: a double-blind, placebo-controlled prevention study in elderly patients with mild cognitive impairment. 2010. http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/416/CN-00738416/frame.html. *Ineligible population*
2. Nourishing Xin and Shen method improved mild cognitive impairment due to subcortical small vessel disease: a clinical study. [Chinese]. Zhongguo Zhong xi yi jie he za zhi Zhongguo Zhongxiyi jiehe zazhi = Chinese journal of integrated traditional and Western medicine / Zhongguo Zhong xi yi jie he xue hui, Zhongguo Zhong yi yan jiu yuan zhu ban. 2015 01 Jan;35(1):41-5. PMID 25790673. *Inadequate follow up time*
3. Abbatecola AM, Lattanzio F, Molinari AM, et al. Rosiglitazone and cognitive stability in older individuals with type 2 diabetes and mild cognitive impairment. Diabetes Care. 2010 Aug;33(8):1706-11. PMID 20435794. *Not cognitive decline prevention intervention*
4. Abdullah L, Luis C, Paris D, et al. Serum Abeta levels as predictors of conversion to mild cognitive impairment/Alzheimer disease in an ADAPT subcohort. Molecular Medicine. 2009 November-December;15(11-12):432-7. PMID 2010010064. *Not cognitive decline prevention intervention*
5. Abelson JL, Khan S, Young EA, et al. Cognitive modulation of endocrine responses to CRH stimulation in healthy subjects. Psychoneuroendocrinology. 2010 Apr;35(3):451-9. PMID 19758763. *Inadequate follow up time*
6. Abizanda P, Leon M, Dominguez-Martin L, et al. Effects of a short-term occupational therapy intervention in an acute geriatric unit. A randomized clinical trial. Maturitas. 2011 Jul;69(3):273-8. PMID 21600709. *Inadequate follow up time*
7. Ablin JN, Clauw DJ, Lyden AK, et al. Effects of sleep restriction and exercise deprivation on somatic symptoms and mood in healthy adults. Clinical & Experimental Rheumatology. 2013 Nov-Dec;31(6 Suppl 79):S53-9. PMID 24373363. *Inadequate follow up time*
8. Abner E, Schmitt F, Caban AH, et al. Dual cognitive screening for dementia: Preliminary case ascertainment in the antioxidant Alzheimer's prevention (Preadvise) trial [Journal: Conference Abstract]. 2012. http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/737/CN-01004737/frame.htmlhttp://ac.els-cdn.com/S1552526012005171/1-s2.0-S1552526012005171-main.pdf?_tid=ae514dc0-c392-11e5-9470-00000aacb35f&acdnat=1453747226_8f943887053a7c81bbe29ad13ae1155d. Accessed on 4 suppl. 1 8. *Not cognitive decline prevention intervention*
9. Afzal S, Bojesen SE, Nordestgaard Bo G. Reduced 25-hydroxyvitamin D and risk of Alzheimer's disease and vascular dementia. Alzheimer's and Dementia. 2014 May;10(3):296-302. PMID 2014293602. *Not cognitive decline prevention intervention*
10. Agnew-Blais JC, Wassertheil-Smoller S, Kang JH, et al. Folate, vitamin B-6, and vitamin B-12 intake and mild cognitive impairment and probable dementia in the Women's Health Initiative Memory Study. Journal of the Academy of Nutrition & Dietetics. 2015 Feb;115(2):231-41. PMID 25201007. *Not cognitive decline prevention intervention*
11. Aguiar P, Monteiro L, Feres A, et al. Rivastigmine transdermal patch and physical exercises for Alzheimer's disease: a randomized clinical trial. Current Alzheimer Research. 2014;11(6):532-7. PMID 24938502. *Ineligible population*
12. Aguirre E, Spector A, Hoe J, et al. Maintenance Cognitive Stimulation Therapy (CST) for dementia: a single-blind, multi-centre, randomized controlled trial of Maintenance CST vs. CST for dementia. Trials [Electronic Resource]. 2010;11:46. PMID 20426866. *Ineligible population*

13. Aisen PS, Gauthier S, Ferris SH, et al. Tramiprosate in mild-to-moderate Alzheimer's disease - A randomized, double-blind, placebo-controlled, multi-centre study (the alphase study). Archives of Medical Science. 2011 February;7(1):102-11. PMID 2011142367. *Ineligible population*

14. Akbaraly TN, Portet F, Fustinoni S, et al. Leisure activities and the risk of dementia in the elderly: results from the Three-City Study. Neurology. 2009 Sep 15;73(11):854-61. PMID 19752452. *Not cognitive decline prevention intervention*

15. Akbaraly TN, Singh-Manoux A, Marmot MG, et al. Education attenuates the association between dietary patterns and cognition. Dementia & Geriatric Cognitive Disorders. 2009;27(2):147-54. PMID 19182482. *Not cognitive decline prevention intervention*

16. Akhondzadeh S, Sabet MS, Harirchian MH, et al. Saffron in the treatment of patients with mild to moderate Alzheimer's disease: a 16-week, randomized and placebo-controlled trial. Journal of Clinical Pharmacy & Therapeutics. 2010 Oct;35(5):581-8. PMID 20831681. *Ineligible population*

17. Almaraz AC, Driver-Dunckley ED, Woodruff BK, et al. Efficacy of rivastigmine for cognitive symptoms in Parkinson disease with dementia. The neurologist. 2009 Jul;15(4):234-7. PMID 19590387. *Ineligible study design*

18. Almeida OP, Yeap BB, Alfonso H, et al. Older men who use computers have lower risk of dementia. PLoS ONE [Electronic Resource]. 2012;7(8):e44239. PMID 22937167. *Not cognitive decline prevention intervention*

19. Alosco ML, Spitznagel MB, Cohen R, et al. Decreases in body mass index after cardiac rehabilitation predict improved cognitive function in older adults with heart failure. Journal of the American Geriatrics Society. 2014 Nov;62(11):2215-6. PMID 25413196. *Ineligible study design*

20. Altmann A, Tian L, Henderson VW, et al. Sex modifies the APOE-related risk of developing Alzheimer disease. Annals of Neurology. 2014 Apr;75(4):563-73. PMID 24623176. *Ineligible study design*

21. Alvarez XA, Cacabelos R, Sampedro C, et al. Combination treatment in Alzheimer's disease: results of a randomized, controlled trial with cerebrolysin and donepezil. Current Alzheimer Research. 2011 Aug;8(5):583-91. PMID 21679156. *Ineligible population*

22. Alvarez XA, Sampedro C, Cacabelos R, et al. Reduced TNF-alpha and increased IGF-I levels in the serum of Alzheimer's disease patients treated with the neurotrophic agent cerebrolysin. International Journal of Neuropsychopharmacology. 2009 Aug;12(7):867-72. PMID 19531281. *Ineligible population*

23. Alves J, Alves-Costa F, Magalhaes R, et al. Cognitive stimulation for Portuguese older adults with cognitive impairment: a randomized controlled trial of efficacy, comparative duration, feasibility, and experiential relevance. American Journal of Alzheimer's Disease & Other Dementias. 2014 Sep;29(6):503-12. PMID 24526760. *Inadequate follow up time*

24. Amagase H, Sun B, Nance DM. Immunomodulatory effects of a standardized Lycium barbarum fruit juice in Chinese older healthy human subjects. Journal of Medicinal Food. 2009 Oct;12(5):1159-65. PMID 19857084. *Inadequate follow up time*

25. Ambrosius WT, Sink KM, Foy CG, et al. The design and rationale of a multicenter clinical trial comparing two strategies for control of systolic blood pressure: the Systolic Blood Pressure Intervention Trial (SPRINT). Clinical Trials. 2014 Oct;11(5):532-46. PMID 24902920. *Ineligible study design*

26. Amenta F, Carotenuto A, Fasanaro AM, et al. The ASCOMALVA trial: association between the cholinesterase inhibitor donepezil and the cholinergic precursor choline alphoscerate in Alzheimer's disease with cerebrovascular injury: interim results. Journal of the Neurological Sciences. 2012 Nov 15;322(1-2):96-101. PMID 22959283. *Ineligible population*

27. Amenta F, Carotenuto A, Fasanaro AM, et al. The ASCOMALVA (Association between the Cholinesterase Inhibitor Donepezil and the Cholinergic Precursor Choline Alphoscerate in Alzheimer's Disease) Trial: interim results after two years of treatment. Journal of Alzheimer's Disease. 2014;42 Suppl 3:S281-8. PMID 24898643. *Ineligible population*

28. Amenta F, Carotenuto A, Fasanaro G, et al. Preliminary results of ASCOMALVA trial on the association of donepezil and choline alphoscerate in Alzheimer's disease with associated cerebrovascular injury. [Italian]. Studio sull'effetto dell'associazione tra l'inibitore delle colinesterasi donepezil e il precursore colinergico colina alfoscerato sui sintomi della malattia di Alzheimer con danno vascolare associato (ASCOMALVA). primi risultati. Giornale di Gerontologia. 2011 April;59(2):89-98. PMID 2011290156. *Ineligible population*

29. Amieva H, Stoykova R, Matharan F, et al. What aspects of social network are protective for dementia? Not the quantity but the quality of social interactions is protective up to 15 years later. Psychosomatic Medicine. 2010 Nov;72(9):905-11. PMID 20807876. *Not cognitive decline prevention intervention*

30. Ancelin ML, Carriere I, Barberger-Gateau P, et al. Lipid lowering agents, cognitive decline, and dementia: The three-city study. Journal of Alzheimer's Disease. 2012;30(3):629-37. PMID 2012367868. *Not cognitive decline prevention intervention*

31. Ancelin ML, Carriere I, Helmer C, et al. Steroid and nonsteroidal anti-inflammatory drugs, cognitive decline, and dementia. Neurobiology of Aging. 2012 Sep;33(9):2082-90. PMID 22071123. *Not cognitive decline prevention intervention*

32. Andel R, Crowe M, Hahn EA, et al. Work-related stress may increase the risk of vascular dementia. Journal of the American Geriatrics Society. 2012 Jan;60(1):60-7. PMID 22175444. *Ineligible population*

33. Andersen F, Viitanen M, Halvorsen DS, et al. The effect of stimulation therapy and donepezil on cognitive function in Alzheimer's disease. A community based RCT with a two-by-two factorial design. BMC Neurology. 2012;12:59. PMID 22813231. *Ineligible population*

34. Anderson-Hanley C, Arciero PJ, Brickman AM, et al. Exergaming and older adult cognition: a cluster randomized clinical trial. American Journal of Preventive Medicine. 2012 Feb;42(2):109-19. PMID 22261206. *Inadequate follow up time*

35. Andreasen N, Simeoni M, Ostlund H, et al. First administration of the Fc-attenuated anti-beta amyloid antibody GSK933776 to patients with mild Alzheimer's disease: A randomized, placebo-controlled study. PLoS ONE. 2015 19 Mar;10(3)PMID 2015879759. *Ineligible population*

36. Andreeva VA, Whegang-Youdom S, Touvier M, et al. Midlife dietary vitamin D intake and subsequent performance in different cognitive domains. Annals of Nutrition & Metabolism. 2014;65(1):81-9. PMID 25227981. *No relevant outcomes reported*

37. Annweiler C, Ferland G, Barberger-Gateau P, et al. Vitamin K antagonists and cognitive impairment: results from a cross-sectional pilot study among geriatric patients. Journals of Gerontology Series A-Biological Sciences & Medical Sciences. 2015 Jan;70(1):97-101. PMID 25151653. *Ineligible study design*

38. Annweiler C, Rolland Y, Schott AM, et al. Higher vitamin D dietary intake is associated with lower risk of alzheimer's disease: a 7-year follow-up. Journals of Gerontology Series A-Biological Sciences & Medical Sciences. 2012 Nov;67(11):1205-11. PMID 22503994. *Cohort study with inadequate sample size*

39. Anstey KJ, Bahar-Fuchs A, Herath P, et al. Body brain life: A randomized controlled trial of an online dementia risk reduction intervention in middle-aged adults at risk of Alzheimer's disease. Alzheimer's and Dementia: Translational Research and Clinical Interventions. 2015 14 Oct;1(1):72-80. PMID 2015440238. *No relevant outcomes reported*

40. Anstey KJ, Byles JE, Luszcz MA, et al. Cohort profile: The Dynamic Analyses to Optimize Ageing (DYNOPTA) project. International Journal of Epidemiology. 2010 Feb;39(1):44-51. PMID 19151373. *Not cognitive decline prevention intervention*

41. Anton Alvarez X, Sampedro C, Cacabelos R, et al. Reduced TNF- and increased IGF-I levels in the serum of Alzheimer's disease patients treated with the neurotrophic agent Cerebrolysin. International Journal of Neuropsychopharmacology. 2009 August;12(7):867-72. PMID 2009469772. *Ineligible population*

42. Apostolo JL, Cardoso DF, Rosa AI, et al. The effect of cognitive stimulation on nursing home elders: a randomized controlled trial. Journal of Nursing Scholarship. 2014 May;46(3):157-66. PMID 24597922. *Ineligible population*

43. Apostolova LG, Babakchanian S, Hwang KS, et al. Ventricular enlargement and its clinical correlates in the imaging cohort from the ADCS MCI donepezil/vitamin E study. Alzheimer Disease & Associated Disorders. 2013 Apr-Jun;27(2):174-81. PMID 23694947. *Cohort study with inadequate sample size*

44. Arab L, Biggs ML, O'Meara ES, et al. Gender differences in tea, coffee, and cognitive decline in the elderly: the Cardiovascular Health Study. Journal of Alzheimer's Disease. 2011;27(3):553-66. PMID 21841254. *Not cognitive decline prevention intervention*

45. Araki A, Iimuro S, Sakurai T, et al. Long-term multiple risk factor interventions in Japanese elderly diabetic patients: the Japanese Elderly Diabetes Intervention Trial--study design, baseline characteristics and effects of intervention. Geriatrics & gerontology international. 2012 Apr;12 Suppl 1:7-17. PMID 22435936. *No relevant outcomes reported*

46. Araki T, Wake R, Miyaoka T, et al. The effects of combine treatment of memantine and donepezil on Alzheimer's disease patients and its relationship with cerebral blood flow in the prefrontal area. International Journal of Geriatric Psychiatry. 2014 Sep;29(9):881-9. PMID 24436135. *Ineligible population*

47. Arntzen KA, Schirmer H, Wilsgaard T, et al. Moderate wine consumption is associated with better cognitive test results: a 7 year follow up of 5033 subjects in the Tromso Study. Acta Neurologica Scandinavica. 2010;Supplementum.(190):23-9. PMID 20586731. *Not cognitive decline prevention intervention*

48. Articus K, Baier M, Tracik F, et al. A 24-week, multicentre, open evaluation of the clinical effectiveness of the rivastigmine patch in patients with probable Alzheimer's disease. International Journal of Clinical Practice. 2011 Jul;65(7):790-6. PMID 21645184. *Ineligible population*

49. Athilingam P, Edwards JD, Valdes EG, et al. Computerized auditory cognitive training to improve cognition and functional outcomes in patients with heart failure: Results of a pilot study. Heart & Lung. 2015 Mar-Apr;44(2):120-8. PMID 25592205. *Inadequate follow up time*

50. Au R, Seshadri S, Knox K, et al. The Framingham Brain Donation Program: neuropathology along the cognitive continuum. Current Alzheimer Research. 2012 Jul;9(6):673-86. PMID 22471865. *Not cognitive decline prevention intervention*

51. Azhar ZM, Zubaidah JO, Norjan KO, et al. A pilot placebo-controlled, double-blind, and randomized study on the cognition-enhancing benefits of a proprietary chicken meat ingredient in healthy subjects. Nutrition Journal. 2013;12:121. PMID 23945213. *Inadequate follow up time*

52. Bachinskaya N, Hoerr R, Ihl R. Alleviating neuropsychiatric symptoms in dementia: The effects of Ginkgo biloba extract EGb 761. Findings from a randomized controlled trial. Neuropsychiatric Disease and Treatment. 2011;7(1):209-15. PMID 2011559394. *Ineligible population*

53. Baker LD, Asthana S, Cholerton BA, et al. Cognitive response to estradiol in postmenopausal women is modified by high cortisol. Neurobiology of Aging. 2012 Apr;33(4):829.e9-20. PMID 21855173. *Inadequate follow up time*

54. Baker LD, Cross DJ, Minoshima S, et al. Insulin resistance and Alzheimer-like reductions in regional cerebral glucose metabolism for cognitively normal adults with prediabetes or early type 2 diabetes. Archives of Neurology. 2011 Jan;68(1):51-7. PMID 20837822. *Inadequate follow up time*

55. Bakker A, Albert MS, Krauss G, et al. Response of the medial temporal lobe network in amnestic mild cognitive impairment to therapeutic intervention assessed by fMRI and memory task performance. NeuroImage: Clinical. 2015;7:688-98. PMID 2015830727. *Inadequate follow up time*

56. Barnes DE, Mehling W, Wu E, et al. Preventing Loss of Independence through Exercise (PLIE): A pilot clinical trial in older adults with dementia. PLoS ONE. 2015 11 Feb;10(2)PMID 2015767557. *Ineligible population*

57. Barnes DE, Santos-Modesitt W, Poelke G, et al. The Mental Activity and eXercise (MAX) trial: a randomized controlled trial to enhance cognitive function in older adults. JAMA Internal Medicine. 2013 May 13;173(9):797-804. PMID 23545598. *Inadequate follow up time*

58. Barnes DE, Yaffe K, Belfor N, et al. Computer-based cognitive training for mild cognitive impairment: results from a pilot randomized, controlled trial. Alzheimer Disease & Associated Disorders. 2009 Jul-Sep;23(3):205-10. PMID 19812460. *Inadequate follow up time*

59. Barnes DE, Yaffe K, Byers AL, et al. Midlife vs late-life depressive symptoms and risk of dementia: differential effects for Alzheimer disease and vascular dementia. Archives of General Psychiatry. 2012 May;69(5):493-8. PMID 22566581. *Not cognitive decline prevention intervention*

60. Barone P, Santangelo G, Morgante L, et al. A randomized clinical trial to evaluate the effects of rasagiline on depressive symptoms in non-demented Parkinson's disease patients. European Journal of Neurology. 2015 Aug;22(8):1184-91. PMID 25962410. *Inadequate follow up time*

61. Barrett DW, Gonzalez-Lima F. Transcranial infrared laser stimulation produces beneficial cognitive and emotional effects in humans. Neuroscience. 2013 Jan 29;230:13-23. PMID 23200785. *Inadequate follow up time*

62. Barton DL, Burger K, Novotny PJ, et al. The use of Ginkgo biloba for the prevention of chemotherapy-related cognitive dysfunction in women receiving adjuvant treatment for breast cancer, N00C9. Supportive Care in Cancer. 2013 Apr;21(4):1185-92. PMID 23150188. *Ineligible population*

63. Batty GD, Li Q, Huxley R, et al. Oral disease in relation to future risk of dementia and cognitive decline: prospective cohort study based on the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation (ADVANCE) trial. European Psychiatry: the Journal of the Association of European Psychiatrists. 2013 Jan;28(1):49-52. PMID 21964484. *Not cognitive decline prevention intervention*

64. Bauer I, Hughes M, Rowsell R, et al. Omega-3 supplementation improves cognition and modifies brain activation in young adults. Human Psychopharmacology. 2014 Mar;29(2):133-44. PMID 24470182. *Inadequate follow up time*

65. Baurle P, Suter A, Wormstall H. Safety and effectiveness of a traditional ginkgo fresh plant extract - results from a clinical trial. Forschende Komplementarmedizin (2006). 2009 Jun;16(3):156-61. PMID 19657199. *Inadequate follow up time*

66. Bayer-Carter JL, Green PS, Montine TJ, et al. Diet intervention and cerebrospinal fluid biomarkers in amnestic mild cognitive impairment. Archives of Neurology. 2011 Jun;68(6):743-52. PMID 21670398. *Inadequate follow up time*

67. Beck C, Fausett JK, Krukowski RA, et al. A randomized trial of a community-based cognitive intervention for obese senior adults. Journal of Aging & Health. 2013 Feb;25(1):97-118. PMID 23248351. *Inadequate follow up time*

68. Bentley P, Driver J, Dolan RJ. Modulation of fusiform cortex activity by cholinesterase inhibition predicts effects on subsequent memory. Brain. 2009 Sep;132(Pt 9):2356-71. PMID 19605530. *Not cognitive decline prevention intervention*

69. Bergamaschi S, Arcara G, Calza A, et al. One-year repeated cycles of cognitive training (CT) for Alzheimer's disease. Aging-Clinical & Experimental Research. 2013 Aug;25(4):421-6. PMID 23784727. *Ineligible population*

70. Bernick C, Cummings J, Raman R, et al. Age and rate of cognitive decline in Alzheimer disease: Implications for clinical trials. Archives of Neurology. 2012 July;69(7):901-5. PMID 2012409204. *Ineligible population*

71. Berr C, Portet F, Carriere I, et al. Olive oil and cognition: results from the three-city study. Dementia & Geriatric Cognitive Disorders. 2009;28(4):357-64. PMID 19887798. *Not cognitive decline prevention intervention*

72. Bettermann K, Arnold AM, Williamson J, et al. Statins, risk of dementia, and cognitive function: secondary analysis of the ginkgo evaluation of memory study. Journal of Stroke & Cerebrovascular Diseases. 2012 Aug;21(6):436-44. PMID 21236699. *Not cognitive decline prevention intervention*

73. Beydoun MA, Beason-Held LL, Kitner-Triolo MH, et al. Statins and serum cholesterol's associations with incident dementia and mild cognitive impairment. Journal of Epidemiology & Community Health. 2011 Nov;65(11):949-57. PMID 20841372. *Not cognitive decline prevention intervention*

74. Bickel H, Ander KH, Bronner M, et al. Reduction of long-term care dependence after an 8-year primary care prevention program for stroke and dementia: The INVADE trial. Journal of the American Heart Association. 2012 August;1(4)PMID 2013312020. *Ineligible population*

75. Bielak AA, Anstey KJ, Christensen H, et al. Activity engagement is related to level, but not change in cognitive ability across adulthood. Psychology & Aging. 2012 Mar;27(1):219-28. PMID 21806303. *Not cognitive decline prevention intervention*

76. Biemans E, Hart HE, Rutten GE, et al. Cobalamin status and its relation with depression, cognition and neuropathy in patients with type 2 diabetes mellitus using metformin. Acta Diabetologica. 2015 Apr;52(2):383-93. PMID 25315630. *Ineligible study design*

77. Bisby JA, King JA, Brewin CR, et al. Acute effects of alcohol on intrusive memory development and viewpoint dependence in spatial memory support a dual representation model. Biological Psychiatry. 2010 Aug 1;68(3):280-6. PMID 20202625. *Inadequate follow up time*

78. Bjerke M, Kern S, Blennow K, et al. Cerebrospinal fluid fatty acid-binding protein 3 is related to dementia development in a population-based sample of older adult women followed for 8 years. Journal of Alzheimer's Disease. 2016;49(3):733-41. PMID 20151037428. *Ineligible study design*

79. Blackburn DJ, Krishnan K, Fox L, et al. Prevention of Decline in Cognition after Stroke Trial (PODCAST): a study protocol for a factorial randomised controlled trial of intensive versus guideline lowering of blood pressure and lipids. Trials [Electronic Resource]. 2013;14:401. PMID 24266960. *Ineligible population*

80. Blackwell T, Yaffe K, Laffan A, et al. Associations of objectively and subjectively measured sleep quality with subsequent cognitive decline in older community-dwelling men: the MrOS sleep study. Sleep. 2014;37(4):655-63. PMID 24899757. *Ineligible study design*

81. Blasko I, Hinterberger M, Kemmler G, et al. Conversion from mild cognitive impairment to dementia: influence of folic acid and vitamin B12 use in the VITA cohort. Journal of Nutrition, Health & Aging. 2012 Aug;16(8):687-94. PMID 23076510. *Not cognitive decline prevention intervention*

82. Blennow K, Zetterberg H, Rinne JO, et al. Effect of immunotherapy with bapineuzumab on cerebrospinal fluid biomarker levels in patients with mild to moderate Alzheimer disease. Archives of Neurology. 2012 Aug;69(8):1002-10. PMID 22473769. *Ineligible population*

83. Blumenthal JA, Smith PJ, Welsh-Bohmer K, et al. Can lifestyle modification improve neurocognition? Rationale and design of the ENLIGHTEN clinical trial. Contemporary Clinical Trials. 2013 Jan;34(1):60-9. PMID 23000080. *Ineligible study design*

84. Boche D, Donald J, Love S, et al. Reduction of aggregated Tau in neuronal processes but not in the cell bodies after Abeta42 immunisation in Alzheimer's disease. Acta Neuropathologica. 2010 Jul;120(1):13-20. PMID 20532897. *Ineligible population*

85. Bohm M, Schumacher H, Leong D, et al. Systolic blood pressure variation and mean heart rate is associated with cognitive dysfunction in patients with high cardiovascular risk. Hypertension. 2015 Mar;65(3):651-61. PMID 25583157. *Not cognitive decline prevention intervention*

86. Boissoneault J, Sklar A, Prather R, et al. Acute effects of moderate alcohol on psychomotor, set shifting, and working memory function in older and younger social drinkers. Journal of Studies on Alcohol & Drugs. 2014 Sep;75(5):870-9. PMID 25208205. *Inadequate follow up time*

87. Boss HM, Van Schaik SM, Deijle IA, et al. A randomised controlled trial of aerobic exercise after transient ischaemic attack or minor stroke to prevent cognitive decline: the MoveIT study protocol. BMJ Open. 2014;4(12):e007065. PMID 25552615. *Ineligible population*

88. Bossers WJ, Scherder EJ, Boersma F, et al. Feasibility of a combined aerobic and strength training program and its effects on cognitive and physical function in institutionalized dementia patients. A pilot study. PLoS ONE [Electronic Resource]. 2014;9(5):e97577. PMID 24844772. *Inadequate follow up time*

89. Bouchard P. [Cognitive risks and HRT]. Revue du Praticien. 2010 Oct 20;60(8):1137-8. PMID 21197753. *Not available in English*

90. Bowen ME. A prospective examination of the relationship between physical activity and dementia risk in later life. American Journal of Health Promotion. 2012 Jul-Aug;26(6):333-40. PMID 22747314. *Not cognitive decline prevention intervention*

91. Bowen RL, Perry G, Xiong C, et al. A clinical study of lupron depot in the treatment of women with Alzheimer's disease: preservation of cognitive function in patients taking an acetylcholinesterase inhibitor and treated with high dose lupron over 48 weeks. Journal of Alzheimer's Disease. 2015;44(2):549-60. PMID 25310993. *Ineligible population*

92. Boyle PA, Buchman AS, Barnes LL, et al. Effect of a purpose in life on risk of incident Alzheimer disease and mild cognitive impairment in community-dwelling older persons. Archives of General Psychiatry. 2010 Mar;67(3):304-10. PMID 20194831. *Not cognitive decline prevention intervention*

93. Boyle PA, Buchman AS, Wilson RS, et al. Association of muscle strength with the risk of Alzheimer disease and the rate of cognitive decline in community-dwelling older persons. Archives of Neurology. 2009 November;66(11):1339-44. PMID 2009598988. *Not cognitive decline prevention intervention*

94. Bozoki A, Radovanovic M, Winn B, et al. Effects of a computer-based cognitive exercise program on age-related cognitive decline. Archives of Gerontology & Geriatrics. 2013 Jul-Aug;57(1):1-7. PMID 23542053. *Inadequate follow up time*

95. Brainin M, Matz K, Nemec M, et al. Prevention of poststroke cognitive decline: ASPIS - a multicenter, randomized, observer-blind, parallel group clinical trial to evaluate multiple lifestyle interventions - study design and baseline characteristics. International Journal of Stroke. 2015 01 Jun;10(4):627-35. PMID 2014768731. *Ineligible population*

96. Braun AK, Kubiak T, Kuntsche J, et al. SGS: a structured treatment and teaching programme for older patients with diabetes mellitus--a prospective randomised controlled multi-centre trial. Age & Ageing. 2009 Jul;38(4):390-6. PMID 19454403. *No relevant outcomes reported*

97. Breitner JCS, Haneuse SJPA, Walker R, et al. Risk of dementia and AD with prior exposure to NSAIDs in an elderly community-based cohort. Neurology. 2009 02 Jun;72(22):1899-905. PMID 2009338455. *Not cognitive decline prevention intervention*

98. Brown AK, Liu-Ambrose T, Tate R, et al. The effect of group-based exercise on cognitive performance and mood in seniors residing in intermediate care and self-care retirement facilities: a randomised controlled trial. British Journal of Sports Medicine. 2009 Aug;43(8):608-14. PMID 18927162. *Ineligible population*

99. Brown D, Spanjers K, Atherton N, et al. Development of an exercise intervention to improve cognition in people with mild to moderate dementia: Dementia And Physical Activity (DAPA) Trial, registration ISRCTN32612072. Physiotherapy (United Kingdom). 2015 01 Jun;101(2):126-34. PMID 2015778040. *Ineligible population*

100. Brown ES, Zaidel L, Allen G, et al. Effects of lamotrigine on hippocampal activation in corticosteroid-treated patients. Journal of Affective Disorders. 2010 November;126(3):415-9. PMID 2010547628. *Ineligible population*

101. Brown PD, Pugh S, Laack NN, et al. Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: a randomized, double-blind, placebo-controlled trial. Neuro-Oncology. 2013 Oct;15(10):1429-37. PMID 23956241. *Ineligible population*

102. Bruce J, Hancock L, Roberg B, et al. Impact of armodafinil on cognition in multiple sclerosis: a randomized, double-blind crossover pilot study. Cognitive & Behavioral Neurology. 2012 Sep;25(3):107-14. PMID 22960434. *Ineligible population*

103. Brunetti V, Losurdo A, Testani E, et al. Rivastigmine for refractory REM behavior disorder in mild cognitive impairment. Current Alzheimer Research. 2014 Mar;11(3):267-73. PMID 24597506. *No relevant outcomes reported*

104. Buchman AS, Boyle PA, Yu L, et al. Total daily physical activity and the risk of AD and cognitive decline in older adults. Neurology. 2012 Apr 24;78(17):1323-9. PMID 22517108. *Not cognitive decline prevention intervention*

105. Buecking B, Struewer J, Waldermann A, et al. What determines health-related quality of life in hip fracture patients at the end of acute care?--a prospective observational study. Osteoporosis International. 2014 Feb;25(2):475-84. PMID 23783644. *Ineligible population*

106. Burstein AH, Grimes I, Galasko DR, et al. Effect of TTP488 in patients with mild to moderate Alzheimer's disease. BMC Neurology. 2014 January 15;14(1)PMID 2015890655. *Ineligible population*

107. Buschert VC, Friese U, Teipel SJ, et al. Effects of a newly developed cognitive intervention in amnestic mild cognitive impairment and mild Alzheimer's disease: a pilot study. Journal of Alzheimer's Disease. 2011;25(4):679-94. PMID 21483095. *Ineligible population*

108. Byeon H, Lee Y, Lee SY, et al. Association of alcohol drinking with verbal and visuospatial memory impairment in older adults: Clinical Research Center for Dementia of South Korea (CREDOS) study. International Psychogeriatrics. 2015 Mar;27(3):455-61. PMID 25119654. *Inadequate follow up time*

109. Cadar D, Pikhart H, Mishra G, et al. The role of lifestyle behaviors on 20-year cognitive decline. Journal of Aging Research. 2012;2012 (no pagination)(304014)PMID 2012621473. *Not cognitive decline prevention intervention*

110. Cao C, Loewenstein DA, Lin X, et al. High Blood caffeine levels in MCI linked to lack of progression to dementia. Journal of Alzheimer's Disease. 2012;30(3):559-72. PMID 22430531. *Not cognitive decline prevention intervention*

111. Caramelli P, Laks J, Palmini AL, et al. Effects of galantamine and galantamine combined with nimodipine on cognitive speed and quality of life in mixed dementia: a 24-week, randomized, placebo-controlled exploratory trial (the REMIX study). Arquivos de Neuro-Psiquiatria. 2014 Jun;72(6):411-7. PMID 24964105. *Ineligible population*

112. Carlson MC, Erickson KI, Kramer AF, et al. Evidence for neurocognitive plasticity in at-risk older adults: the experience corps program. The journals of gerontology. 2009 Dec;Series A, Biological sciences and medical sciences. 64(12):1275-82. PMID 19692672. *No relevant outcomes reported*

113. Carlsson CM, Nondahl DM, Klein BE, et al. Increased atherogenic lipoproteins are associated with cognitive impairment: effects of statins and subclinical atherosclerosis. Alzheimer Disease & Associated Disorders. 2009 Jan-Mar;23(1):11-7. PMID 19266697. *Ineligible study design*

114. Carretti B, Borella E, Fostinelli S, et al. Benefits of training working memory in amnestic mild cognitive impairment: specific and transfer effects. International Psychogeriatrics. 2013 Apr;25(4):617-26. PMID 23253363. *Inadequate follow up time*

115. Carriere I, Fourrier-Reglat A, Dartigues JF, et al. Drugs with anticholinergic properties, cognitive decline, and dementia in an elderly general population: the 3-city study. Archives of Internal Medicine. 2009 Jul 27;169(14):1317-24. PMID 19636034. *Not cognitive decline prevention intervention*

116. Casoli T, Giuli C, Balietti M, et al. Effect of cognitive training on the expression of brain-derived neurotrophic factor in lymphocytes of mild cognitive impairment patients. Rejuvenation Research. 2014 Apr;17(2):235-8. PMID 24127698. *Inadequate follow up time*

117. Cereda E, Sacchi MC, Malavazos AE. Central obesity and increased risk of dementia more than three decades later. Neurology. 2009 Mar 17;72(11):1030-1; author reply 1. PMID 19289749. *Not cognitive decline prevention intervention*

118. Cervellati C, Trentini A, Romani A, et al. Serum paraoxonase and arylesterase activities of paraoxonase-1 (PON-1), mild cognitive impairment, and 2-year conversion to dementia: A pilot study. Journal of Neurochemistry. 2015 Oct;135(2):395-401. PMID 26178739. *Not cognitive decline prevention intervention*

119. Chan A, Paskavitz J, Remington R, et al. Efficacy of a vitamin/nutriceutical formulation for early-stage Alzheimer's disease: A 1-year, open-label pilot study with an 16-month caregiver extension. American Journal of Alzheimer's Disease and other Dementias. 2009 December-January;23(6):571-85. PMID 2009009400. *Ineligible population*

120. Chang M, Jonsson PV, Snaedal J, et al. The effect of midlife physical activity on cognitive function among older adults: AGES--Reykjavik Study. Journals of Gerontology Series A-Biological Sciences & Medical Sciences. 2010 Dec;65(12):1369-74. PMID 20805238. *Ineligible study design*

121. Chang SL, Tsai AC. Gender differences in the longitudinal associations of depressive symptoms and leisure-time physical activity with cognitive decline in > 57 year-old Taiwanese. Preventive Medicine. 2015 August 01;77:68-73. PMID 2015071830. *Not cognitive decline prevention intervention*

122. Chang YK, Etnier JL. Exploring the dose-response relationship between resistance exercise intensity and cognitive function. Journal of Sport & Exercise Psychology. 2009 Oct;31(5):640-56. PMID 20016113. *Inadequate follow up time*

123. Chao TF, Liu CJ, Chen SJ, et al. Statins and the risk of dementia in patients with atrial fibrillation: A nationwide population-based cohort study. International Journal of Cardiology. 2015 23 Jul;196:91-7. PMID 2015217508. *Not cognitive decline prevention intervention*

124. Chen CL, Ikram K, Anqi Q, et al. The NeuroAiD II (MLC901) in vascular cognitive impairment study (NEURITES). Cerebrovascular Diseases. 2013;35 Suppl 1:23-9. PMID 23548916. *Ineligible population*

125. Chen PY, Liu SK, Chen CL, et al. Long-term statin use and dementia risk in Taiwan. Journal of Geriatric Psychiatry & Neurology. 2014 Sep;27(3):165-71. PMID 24578458. *Not cognitive decline prevention intervention*

126. Chen S, Yao X, Liang Y, et al. Alzheimer's disease treated with combined therapy based on nourishing marrow and reinforcing Qi. Journal of Traditional Chinese Medicine. 2015 Jun;35(3):255-9. PMID 26237827. *Ineligible population*

127. Cheng Y, Wang YJ, Yan JC, et al. Effects of carotid artery stenting on cognitive function in patients with mild cognitive impairment and carotid stenosis. Experimental and Therapeutic Medicine. 2013 April;5(4):1019-24. PMID 2013144752. *Cohort study with inadequate sample size*

128. Cheng Y, Wu W, Feng W, et al. The effects of multi-domain versus single-domain cognitive training in non-demented older people: a randomized controlled trial. BMC Medicine. 2012;10:30. PMID 22453114. *Inadequate follow up time*

129. Cherbuin N, Anstey KJ. The Mediterranean diet is not related to cognitive change in a large prospective investigation: the PATH Through Life study. American Journal of Geriatric Psychiatry. 2012 Jul;20(7):635-9. PMID 21937919. *Not cognitive decline prevention intervention*

130. Cherrier MM, Anderson K, David D, et al. A randomized trial of cognitive rehabilitation in cancer survivors. Life Sciences. 2013 Oct 17;93(17):617-22. PMID 24012579. *Ineligible population*

131. Chiu WC, Ho WC, Lin MH, et al. Angiotension receptor blockers reduce the risk of dementia. Journal of Hypertension. 2014 Apr;32(4):938-47. PMID 24406780. *Not cognitive decline prevention intervention*

132. Choi SH, Park KW, Na DL, et al. Tolerability and efficacy of memantine add-on therapy to rivastigmine transdermal patches in mild to moderate Alzheimer's disease: a multicenter, randomized, open-label, parallel-group study. Current Medical Research & Opinion. 2011 Jul;27(7):1375-83. PMID 21561398. *Ineligible population*

133. Chou CY, Chou YC, Chou YJ, et al. Statin use and incident dementia: a nationwide cohort study of Taiwan. International Journal of Cardiology. 2014 May 1;173(2):305-10. PMID 24681022. *Ineligible study design*

134. Choudhary P, Lonnen K, Emery CJ, et al. Comparing hormonal and symptomatic responses to experimental hypoglycaemia in insulin- and sulphonylurea-treated Type 2 diabetes. Diabetic Medicine. 2009 Jul;26(7):665-72. PMID 19573114. *No relevant outcomes reported*

135. Christopher MS, Jacob KL, Neuhaus EC, et al. Cognitive and behavioral changes related to symptom improvement among patients with a mood disorder receiving intensive cognitive-behavioral therapy. Journal of Psychiatric Practice. 2009 Mar;15(2):95-102. PMID 19339843. *Inadequate follow up time*

136. Chu DC, Fox KR, Chen LJ, et al. Components of late-life exercise and cognitive function: an 8-year longitudinal study. Prevention Science. 2015 May;16(4):568-77. PMID 25297968. *No relevant outcomes reported*

137. Chuang CS, Lin CL, Lin MC, et al. Decreased prevalence of dementia associated with statins: A national population-based study. European Journal of Neurology. 2015 01 Jun;22(6):912-8. PMID 2015971469. *Not cognitive decline prevention intervention*

138. Chuang YF, Breitner JC, Chiu YL, et al. Use of diuretics is associated with reduced risk of Alzheimer's disease: the Cache County Study. Neurobiology of Aging. 2014 Nov;35(11):2429-35. PMID 24910391. *Ineligible study design*

139. Ciarmiello A, Gaeta MC, Benso F, et al. FDG-PET in the evaluation of brain metabolic changes induced by cognitive stimulation in aMCI subjects. Current Radiopharmaceuticals. 2015 01 Jun;8(1):69-75. PMID 2015110096. *Inadequate follow up time*

140. Clare L, Linden DE, Woods RT, et al. Goal-oriented cognitive rehabilitation for people with early-stage Alzheimer disease: a single-blind randomized controlled trial of clinical efficacy. American Journal of Geriatric Psychiatry. 2010 Oct;18(10):928-39. PMID 20808145. *Ineligible population*

141. Claxton A, Baker LD, Hanson A, et al. Long-acting intranasal insulin detemir improves cognition for adults with mild cognitive impairment or early-stage Alzheimer's disease dementia.[Erratum appears in J Alzheimers Dis. 2015;45(4):1269-70; PMID: 25869922]. Journal of Alzheimer's Disease. 2015;44(3):897-906. PMID 25374101. *Ineligible population*

142. Claxton A, Baker LD, Hanson A, et al. Long-acting intranasal insulin detemir improves cognition for adults with mild cognitive impairment or early-stage Alzheimer's Disease dementia. Journal of Alzheimer's Disease. 2015;44(3):897-906. PMID 2015740466. *Ineligible population*

143. Claxton A, Baker LD, Wilkinson CW, et al. Sex and ApoE genotype differences in treatment response to two doses of intranasal insulin in adults with mild cognitive impairment or Alzheimer's disease. Journal of Alzheimer's Disease. 2013;35(4):789-97. PMID 23507773. *Ineligible population*

144. Collins N, Sachs-Ericsson N, Preacher KJ, et al. Smoking increases risk for cognitive decline among community-dwelling older Mexican Americans. American Journal of Geriatric Psychiatry. 2009 Nov;17(11):934-42. PMID 20104052. *Not cognitive decline prevention intervention*

145. Concha JB, Kravitz HM, Chin MH, et al. Review of type 2 diabetes management interventions for addressing emotional well-being in Latinos. Diabetes Educator. 2009 Nov-Dec;35(6):941-58. PMID 19773526. *Ineligible study design*

146. Cooper ZD, Foltin RW, Hart CL, et al. A human laboratory study investigating the effects of quetiapine on marijuana withdrawal and relapse in daily marijuana smokers. Addiction Biology. 2013 Nov;18(6):993-1002. PMID 22741619. *Inadequate follow up time*

147. Cordasco KM, Asch SM, Bell DS, et al. A low-literacy medication education tool for safety-net hospital patients. American Journal of Preventive Medicine. 2009 Dec;37(6 Suppl 1):S209-16. PMID 19896021. *No relevant outcomes reported*

148. Cornelli U. Treatment of Alzheimer's disease with a cholinesterase inhibitor combined with antioxidants. Neurodegenerative Diseases. 2010;7(1-3):193-202. PMID 20224285. *Ineligible population*

149. Corsentino EA, Collins N, Sachs-Ericsson N, et al. Religious attendance reduces cognitive decline among older women with high levels of depressive symptoms. Journals of Gerontology Series A-Biological Sciences & Medical Sciences. 2009 Dec;64(12):1283-9. PMID 19675176. *Not cognitive decline prevention intervention*

150. Cote S, Carmichael PH, Verreault R, et al. Nonsteroidal anti-inflammatory drug use and the risk of cognitive impairment and Alzheimer's disease. Alzheimer's & Dementia. 2012 May;8(3):219-26. PMID 22546354. *Not cognitive decline prevention intervention*

151. Cotroneo AM, Castagna A, Putignano S, et al. Effectiveness and safety of citicoline in mild vascular cognitive impairment: the IDEALE study. Clinical Interventions In Aging. 2013;8:131-7. PMID 23403474. *Ineligible population*

152. Craft S, Baker LD, Montine TJ, et al. Intranasal insulin therapy for Alzheimer disease and amnestic mild cognitive impairment: a pilot clinical trial. Archives of Neurology. 2012 Jan;69(1):29-38. PMID 21911655. *Ineligible population*

153. Crane PK, Gibbons LE, Arani K, et al. Midlife use of written Japanese and protection from late life dementia. Epidemiology. 2009 Sep;20(5):766-74. PMID 19593152. *Not cognitive decline prevention intervention*

154. Creavin ST, Gallacher J, Pickering J, et al. High caloric intake, poor cognition and dementia: the Caerphilly Prospective Study. European Journal of Epidemiology. 2012 Mar;27(3):197-203. PMID 22392589. *Not cognitive decline prevention intervention*

155. Crichton GE, Elias MF, Dore GA, et al. Measurement-to-measurement blood pressure variability is related to cognitive performance: the Maine Syracuse study. Hypertension. 2014 Nov;64(5):1094-101. PMID 25156168. *No relevant outcomes reported*

156. Cronberg T, Lilja G, Horn J, et al. Neurologic Function and Health-Related Quality of Life in Patients Following Targeted Temperature Management at 33degreeC vs 36degreeC After Out-of-Hospital Cardiac Arrest: A Randomized Clinical Trial. JAMA Neurology. 2015 Jun;72(6):634-41. PMID 25844993. *Ineligible population*

157. Cukierman-Yaffe T, Anderson C, Teo K, et al. Dysglycemia and Cognitive Dysfunction and Ill Health in People With High CV Risk: Results From the ONTARGET/TRANSCEND Studies. Journal of Clinical Endocrinology & Metabolism. 2015 Jul;100(7):2682-9. PMID 26020764. *Not cognitive decline prevention intervention*

158. Cukierman-Yaffe T, Gerstein HC, Williamson JD, et al. Relationship between baseline glycemic control and cognitive function in individuals with type 2 diabetes and other cardiovascular risk factors: the action to control cardiovascular risk in diabetes-memory in diabetes (ACCORD-MIND) trial. Diabetes Care. 2009 Feb;32(2):221-6. PMID 19171735. *Not cognitive decline prevention intervention*

159. Cummings J, Froelich L, Black SE, et al. Randomized, double-blind, parallel-group, 48-week study for efficacy and safety of a higher-dose rivastigmine patch (15 vs. 10 cm) in Alzheimer's disease. Dementia and Geriatric Cognitive Disorders. 2012 July;33(5):341-53. PMID 2012461797. *Ineligible population*

160. Cummings JL, Lyketsos CG, Peskind ER, et al. Effect of Dextromethorphan-Quinidine on Agitation in Patients With Alzheimer Disease Dementia: A Randomized Clinical Trial. JAMA. 2015 Sep 22-29;314(12):1242-54. PMID 26393847. *Ineligible population*

161. Dahl A, Hassing LB, Fransson E, et al. Being overweight in midlife is associated with lower cognitive ability and steeper cognitive decline in late life. Journals of Gerontology Series A-Biological Sciences & Medical Sciences. 2010 Jan;65(1):57-62. PMID 19349594. *Ineligible population*

162. Damoiseaux JS, Prater KE, Miller BL, et al. Functional connectivity tracks clinical deterioration in Alzheimer's disease. Neurobiology of Aging. 2012 April;33(4):828.e19-.e30. PMID 2012085742. *Ineligible population*

163. Dangour AD, Allen E, Elbourne D, et al. Fish consumption and cognitive function among older people in the UK: baseline data from the OPAL study. Journal of Nutrition, Health & Aging. 2009 Mar;13(3):198-202. PMID 19262951. *Not cognitive decline prevention intervention*

164. Danhauer SC, Legault C, Bandos H, et al. Positive and negative affect, depression, and cognitive processes in the Cognition in the Study of Tamoxifen and Raloxifene (Co-STAR) Trial. Aging Neuropsychology & Cognition. 2013;20(5):532-52. PMID 23237718. *No relevant outcomes reported*

165. Dannhauser TM, Cleverley M, Whitfield TJ, et al. A complex multimodal activity intervention to reduce the risk of dementia in mild cognitive impairment--ThinkingFit: pilot and feasibility study for a randomized controlled trial. BMC Psychiatry. 2014;14:129. PMID 24886353. *Inadequate follow up time*

166. Danthiir V, Burns NR, Nettelbeck T, et al. 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 Journal. 2011;10:117. PMID 22011460. *Ineligible study design*

167. Davis JL, Rhudy JL, Pruiksma KE, et al. Physiological predictors of response to exposure, relaxation, and rescripting therapy for chronic nightmares in a randomized clinical trial. Journal of Clinical Sleep Medicine. 2011 Dec 15;7(6):622-31. PMID 22171201. *Ineligible population*

168. de Andrade LP, Gobbi LT, Coelho FG, et al. Benefits of multimodal exercise intervention for postural control and frontal cognitive functions in individuals with Alzheimer's disease: a controlled trial. Journal of the American Geriatrics Society. 2013 Nov;61(11):1919-26. PMID 24219193. *Ineligible population*

169. de Bruijn RF, Bos MJ, Portegies ML, et al. The potential for prevention of dementia across two decades: the prospective, population-based Rotterdam Study. BMC Medicine. 2015;13:132. PMID 26195085. *Not cognitive decline prevention intervention*

170. de Bruijn RF, Schrijvers EM, de Groot KA, et al. The association between physical activity and dementia in an elderly population: the Rotterdam Study.[Erratum appears in Eur J Epidemiol. 2013 May;28(5):447-8]. European Journal of Epidemiology. 2013 Mar;28(3):277-83. PMID 23385659. *Ineligible study design*

171. De Bruijn RFAG, Schrijvers EMC, De Groot KA, et al. The association between physical activity and dementia in an elderly population: The Rotterdam Study. European Journal of Epidemiology. 2013 March;28(3):277-83. PMID 2013314732. *Not cognitive decline prevention intervention*

172. de Jong FJ, Masaki K, Chen H, et al. Thyroid function, the risk of dementia and neuropathologic changes: the Honolulu-Asia aging study. Neurobiology of Aging. 2009 Apr;30(4):600-6. PMID 17870208. *Not cognitive decline prevention intervention*

173. Dean AJ, Bellgrove MA, Hall T, et al. Effects of vitamin D supplementation on cognitive and emotional functioning in young adults--a randomised controlled trial. PLoS ONE [Electronic Resource]. 2011;6(11):e25966. PMID 22073146. *Inadequate follow up time*

174. Defina LF, Willis BL, Radford NB, et al. The association between midlife cardiorespiratory fitness levels and later-life dementia: a cohort study.[Summary for patients in Ann Intern Med. 2013 Feb 5;158(3):I-36; PMID: 23381057]. Annals of Internal Medicine. 2013 Feb 5;158(3):162-8. PMID 23381040. *Not cognitive decline prevention intervention*

175. DeHaven MJ, Ramos-Roman MA, Gimpel N, et al. The GoodNEWS (Genes, Nutrition, Exercise, Wellness, and Spiritual Growth) Trial: a community-based participatory research (CBPR) trial with African-American church congregations for reducing cardiovascular disease risk factors--recruitment, measurement, and randomization.[Erratum appears in Contemp Clin Trials. 2012 Nov;33(6):1321 Note: Duval, Julie [corrected to Duvahl, Julie]]. Contemporary Clinical Trials. 2011 Sep;32(5):630-40. PMID 21664298. *No relevant outcomes reported*

176. Dersu, II, Spencer HT, Grigorian PA, et al. The effect of mydriatic solutions on cognitive function. Seminars in Ophthalmology. 2015 Jan;30(1):36-9. PMID 23952181. *Inadequate follow up time*

177. Desideri G, Kwik-Uribe C, Grassi D, et al. Benefits in cognitive function, blood pressure, and insulin resistance through cocoa flavanol consumption in elderly subjects with mild cognitive impairment: the Cocoa, Cognition, and Aging (CoCoA) study. Hypertension. 2012 Sep;60(3):794-801. PMID 22892813. *Inadequate follow up time*

178. Desikan RS, Thompson WK, Holland D, et al. Heart fatty acid binding protein and Abeta-associated Alzheimer's neurodegeneration. Molecular Neurodegeneration. 2013;8:39. PMID 24088526. *Cohort study with inadequate sample size*

179. Devanand DP. Donepezil treatment of older adults with cognitive impairment and depression (DOTCODE study): clinical rationale and design. Contemporary clinical trials. 2014 01 Mar;37(2):200-8. PMID 24315979. *Ineligible population*

180. Devore EE, Grodstein F, van Rooij FJ, et al. Dietary intake of fish and omega-3 fatty acids in relation to long-term dementia risk. American Journal of Clinical Nutrition. 2009 Jul;90(1):170-6. PMID 19474131. *Not cognitive decline prevention intervention*

181. Devore EE, Grodstein F, van Rooij FJ, et al. Dietary antioxidants and long-term risk of dementia. Archives of Neurology. 2010 Jul;67(7):819-25. PMID 20625087. *Not cognitive decline prevention intervention*

182. Devore EE, Kang JH, Breteler MM, et al. Dietary intakes of berries and flavonoids in relation to cognitive decline. Annals of Neurology. 2012 Jul;72(1):135-43. PMID 22535616. *Not cognitive decline prevention intervention*

183. Di Stefano F, Epelbaum S, Coley N, et al. Prediction of Alzheimer's Disease Dementia: Data from the GuidAge Prevention Trial. Journal of Alzheimer's Disease. 2015 01 Oct;48(3):793-804. PMID 2015438468. *Ineligible study design*

184. Diamond K, Mowszowski L, Cockayne N, et al. Randomized controlled trial of a healthy brain ageing cognitive training program: effects on memory, mood, and sleep. Journal of Alzheimer's Disease. 2015;44(4):1181-91. PMID 25408218. *Ineligible population*

185. Diener HC. [No immediate dementia prevention from antihypertensive therapy]. 2009. http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/346/CN-00757346/frame.html. Accessed on 1 32. *Not available in English*

186. Diniz BS, Pinto JA, Jr., Gonzaga ML, et al. To treat or not to treat? A meta-analysis of the use of cholinesterase inhibitors in mild cognitive impairment for delaying progression to Alzheimer's disease. European Archives of Psychiatry & Clinical Neuroscience. 2009 Jun;259(4):248-56. PMID 19224111. *Ineligible study design*

187. Dodel R, Rominger A, Bartenstein P, et al. Intravenous immunoglobulin for treatment of mild-to-moderate Alzheimer's disease: a phase 2, randomised, double-blind, placebo-controlled, dose-finding trial. Lancet Neurology. 2013 Mar;12(3):233-43. PMID 23375965. *Ineligible population*

188. Doi T, Makizako H, Shimada H, et al. Effects of multicomponent exercise on spatial-temporal gait parameters among the elderly with amnestic mild cognitive impairment (aMCI): preliminary results from a randomized controlled trial (RCT). Archives of Gerontology & Geriatrics. 2013 Jan-Feb;56(1):104-8. PMID 23063111. *No relevant outcomes reported*

189. Dong ZH, Zhang CY, Pu BH. [Effects of ginkgo biloba tablet in treating mild cognitive impairment]. [Chinese]. Zhongguo Zhong xi yi jie he za zhi Zhongguo Zhongxiyi jiehe zazhi = Chinese journal of integrated traditional and Western medicine / Zhongguo Zhong xi yi jie he xue hui, Zhongguo Zhong yi yan jiu yuan zhu ban. 2012 Sep;32(9):1208-11. PMID 23185760. *Not available in English*

190. D'Onofrio G, Sancarlo D, Addante F, et al. A pilot randomized controlled trial evaluating an integrated treatment of rivastigmine transdermal patch and cognitive stimulation in patients with Alzheimer's disease. International Journal of Geriatric Psychiatry. 2015 01 Sep;30(9):965-75. PMID 2015662652. *Ineligible population*

191. Doody RS, Ferris S, Salloway S, et al. Safety and tolerability of donepezil in mild cognitive impairment: open-label extension study. American Journal of Alzheimer's Disease & Other Dementias. 2010 Mar;25(2):155-9. PMID 19949165. *Ineligible population*

192. Doody RS, Geldmacher DS, Farlow MR, et al. Efficacy and safety of donepezil 23 mg versus donepezil 10 mg for moderate-to-severe Alzheimer's disease: a subgroup analysis in patients already taking or not taking concomitant memantine. Dementia & Geriatric Cognitive Disorders. 2012;33(2-3):164-73. PMID 22572767. *Ineligible population*

193. Doody RS, Thomas RG, Farlow M, et al. Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. New England Journal of Medicine. 2014 Jan 23;370(4):311-21. PMID 24450890. *Ineligible population*

194. Dotson VM, Beydoun MA, Zonderman AB. Recurrent depressive symptoms and the incidence of dementia and mild cognitive impairment. Neurology. 2010 Jul 6;75(1):27-34. PMID 20603482. *Not cognitive decline prevention intervention*

195. Drake C, Gumenyuk V, Roth T, et al. Effects of armodafinil on simulated driving and alertness in shift work disorder. Sleep. 2014 Dec;37(12):1987-94. PMID 25325498. *No relevant outcomes reported*

196. Dretsch MN, Johnston D, Bradley RS, et al. Effects of omega-3 fatty acid supplementation on neurocognitive functioning and mood in deployed U.S. soldiers: a pilot study. Military Medicine. 2014 Apr;179(4):396-403. PMID 24690964. *Ineligible population*

197. Drks. ELITE study - Nutrition, lifestyle and individual information for the prevention of stroke, dementia and heart attack. 2014. http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/895/CN-01066895/frame.html. *Ineligible study design*

198. Drumond Marra HL, Myczkowski ML, Maia Memoria C, et al. Transcranial Magnetic Stimulation to Address Mild Cognitive Impairment in the Elderly: A Randomized Controlled Study. Behavioural Neurology. 2015;2015(287843)PMID 2015173487. *Inadequate follow up time*

199. Dunbar GC, Kuchibhatla RV, Lee G. A randomized double-blind study comparing 25 and 50 mg TC-1734 (AZD3480) with placebo, in older subjects with age-associated memory impairment. Journal of Psychopharmacology. 2011 August;25(8):1020-9. PMID 2011470672. *Ineligible population*

200. Duron E, Rigaud AS, Dubail D, et al. Effects of antihypertensive therapy on cognitive decline in Alzheimer's disease. American Journal of Hypertension. 2009 Sep;22(9):1020-4. PMID 19590498. *Ineligible population*

201. Dysken MW, Sano M, Asthana S, et al. Effect of vitamin E and memantine on functional decline in Alzheimer disease: The TEAM-AD VA cooperative randomized trial. JAMA - Journal of the American Medical Association. 2014;311(1):33-44. PMID 2014045856. *Ineligible population*

202. Dysken MW, Sano M, Asthana S, et al. Effect of vitamin E and memantine on functional decline in Alzheimer disease: the TEAM-AD VA cooperative randomized trial.[Erratum appears in JAMA. 2014 Mar 19;311(11):1161]. JAMA. 2014 Jan 1;311(1):33-44. PMID 24381967. *Ineligible population*

203. Eckroth-Bucher M, Siberski J. Preserving cognition through an integrated cognitive stimulation and training program. American Journal of Alzheimer's Disease & Other Dementias. 2009 Jun-Jul;24(3):234-45. PMID 19346501. *Ineligible population*

204. Elias MF, Goodell AL. Diet and exercise: blood pressure and cognition: to protect and serve. Hypertension. 2010 Jun;55(6):1296-8. PMID 20385968. *Inadequate follow up time*

205. Ellis KA, Bush AI, Darby D, et al. The Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging: methodology and baseline characteristics of 1112 individuals recruited for a longitudinal study of Alzheimer's disease. International Psychogeriatrics. 2009 Aug;21(4):672-87. PMID 19470201. *Ineligible study design*

206. Ellis KA, Rowe CC, Villemagne VL, et al. Addressing population aging and Alzheimer's disease through the Australian imaging biomarkers and lifestyle study: collaboration with the Alzheimer's Disease Neuroimaging Initiative. Alzheimer's & Dementia. 2010 May;6(3):291-6. PMID 20451879. *Ineligible study design*

207. Ellis KA, Szoeke C, Bush AI, et al. Rates of diagnostic transition and cognitive change at 18-month follow-up among 1,112 participants in the Australian Imaging, Biomarkers and Lifestyle Flagship Study of Ageing (AIBL). International Psychogeriatrics. 2014 Apr;26(4):543-54. PMID 24252258. *Ineligible study design*

208. Elmstahl S, Widerstrom E. Orthostatic intolerance predicts mild cognitive impairment: incidence of mild cognitive impairment and dementia from the Swedish general population cohort Good Aging in Skane. Clinical Interventions In Aging. 2014;9:1993-2002. PMID 25429211. *Not cognitive decline prevention intervention*

209. Engedal K, Davis B, Richarz U, et al. Two galantamine titration regimens in patients switched from donepezil. Acta Neurologica Scandinavica. 2012 Jul;126(1):37-44. PMID 21992111. *Ineligible population*

210. Esin E, Ergen A, Cankurtaran M, et al. Influence of antimuscarinic therapy on cognitive functions and quality of life in geriatric patients treated for overactive bladder. Aging & Mental Health. 2015;19(3):217-23. PMID 25555041. *Ineligible population*

211. Eskelinen MH, Ngandu T, Tuomilehto J, et al. Midlife coffee and tea drinking and the risk of late-life dementia: a population-based CAIDE study. Journal of Alzheimer's Disease. 2009;16(1):85-91. PMID 19158424. *Not cognitive decline prevention intervention*

212. Espeland MA, Rapp SR, Bray GA, et al. Long-term impact of behavioral weight loss intervention on cognitive function. Journals of Gerontology Series A-Biological Sciences & Medical Sciences. 2014 Sep;69(9):1101-8. PMID 24619151. *Ineligible population*

213. Espeland MA, Tindle HA, Bushnell CA, et al. Brain volumes, cognitive impairment, and conjugated equine estrogens. Journals of Gerontology Series A-Biological Sciences & Medical Sciences. 2009 Dec;64(12):1243-50. PMID 19729392. *Not cognitive decline prevention intervention*

214. Etgen T, Sander D, Chonchol M, et al. Chronic kidney disease is associated with incident cognitive impairment in the elderly: The INVADE study. Nephrology Dialysis Transplantation. 2009 October;24(10):3144-50. PMID 2009517458. *Not cognitive decline prevention intervention*

215. Etgen T, Sander D, Huntgeburth U, et al. Physical activity and incident cognitive impairment in elderly persons: the INVADE study. Archives of Internal Medicine. 2010 Jan 25;170(2):186-93. PMID 20101014. *Not cognitive decline prevention intervention*

216. Euser SM, Sattar N, Witteman JC, et al. A prospective analysis of elevated fasting glucose levels and cognitive function in older people: results from PROSPER and the Rotterdam Study. Diabetes. 2010 Jul;59(7):1601-7. PMID 20393152. *Ineligible population*

217. Fairchild JK, Scogin FR. Training to Enhance Adult Memory (TEAM): an investigation of the effectiveness of a memory training program with older adults. Aging & Mental Health. 2010 Apr;14(3):364-73. PMID 20425656. *Inadequate follow up time*

218. Fallah N, Hsu CL, Bolandzadeh N, et al. A multistate model of cognitive dynamics in relation to resistance training: the contribution of baseline function. Annals of Epidemiology. 2013 Aug;23(8):463-8. PMID 23830936. *No relevant outcomes reported*

219. Fan HG, Park A, Xu W, et al. The influence of erythropoietin on cognitive function in women following chemotherapy for breast cancer. Psycho-Oncology. 2009 Feb;18(2):156-61. PMID 18561284. *Ineligible population*

220. Fan YL, Wan JQ, Zhou ZW, et al. Neurocognitive improvement after carotid artery stenting in patients with chronic internal carotid artery occlusion: a prospective, controlled, single-center study. Vascular & Endovascular Surgery. 2014 May;48(4):305-10. PMID 24643000. *Ineligible population*

221. Farokhnia M, Shafiee Sabet M, Iranpour N, et al. Comparing the efficacy and safety of Crocus sativus L. with memantine in patients with moderate to severe Alzheimer's disease: a double-blind randomized clinical trial. Human Psychopharmacology. 2014 Jul;29(4):351-9. PMID 25163440. *Ineligible population*

222. Feart C, Samieri C, Rondeau V, et al. Adherence to a Mediterranean diet, cognitive decline, and risk of dementia.[Erratum appears in JAMA. 2009 Dec 9;302(22):2436]. JAMA. 2009 Aug 12;302(6):638-48. PMID 19671905. *Ineligible population*

223. Feldman HH, Doody RS, Kivipelto M, et al. Randomized controlled trial of atorvastatin in mild to moderate Alzheimer disease: LEADe. Neurology. 2010 March;74(12):956-64. PMID 2010189030. *Ineligible population*

224. Felix HC, Adams B, Fausett JK, et al. Calculating reach of evidence-based weight loss and memory improvement interventions among older adults attending Arkansas senior centers, 2008-2011. Preventing Chronic Disease. 2012;9:E63. PMID 22360874. *No relevant outcomes reported*

225. Feliziani FT, Polidori MC, De Rango P, et al. Cognitive performance in elderly patients undergoing carotid endarterectomy or carotid artery stenting: a twelve-month follow-up study. Cerebrovascular Diseases. 2010 Aug;30(3):244-51. PMID 20664257. *Ineligible population*

226. Feng L, Fam J, Rawtaer I, et al. Mindful awareness practice for the prevention of dementia: A randomised controlled trial [Journal: Conference Abstract]. 2014. http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/105/CN-01053105/frame.html. Accessed on 10 suppl. 1 43. *Ineligible study design*

227. Feng L, Li J, Ng TP, et al. Tea drinking and cognitive function in oldest-old Chinese. Journal of Nutrition, Health & Aging. 2012;16(9):754-8. PMID 23131816. *Ineligible population*

228. Ferris S, Lane R, Sfikas N, et al. Effects of gender on response to treatment with rivastigmine in mild cognitive impairment: A post hoc statistical modeling approach. Gender Medicine. 2009 Jul;6(2):345-55. PMID 19682661. *Ineligible study design*

229. Ferris S, Nordberg A, Soininen H, et al. Progression from mild cognitive impairment to Alzheimer's disease: effects of sex, butyrylcholinesterase genotype, and rivastigmine treatment. Pharmacogenetics and Genomics. 2009 Aug;19(8):635-46. PMID 19617863. *Ineligible study design*

230. Fiala M, Halder RC, Sagong B, et al. omega-3 Supplementation increases amyloid-beta phagocytosis and resolvin D1 in patients with minor cognitive impairment. FASEB Journal. 2015 Jul;29(7):2681-9. PMID 25805829. *Ineligible population*

231. Fields C, Drye L, Vaidya V, et al. Celecoxib or naproxen treatment does not benefit depressive symptoms in persons age 70 and older: findings from a randomized controlled trial. American Journal of Geriatric Psychiatry. 2012 Jun;20(6):505-13. PMID 21775876. *No relevant outcomes reported*

232. Finn M, McDonald S. Computerised cognitive training for older persons with mild cognitive impairment: A pilot study using a randomised controlled trial design. Brain Impairment. 2011 December;12(3):187-99. PMID 2012003537. *Inadequate follow up time*

233. Fiocco AJ, Scarcello S, Marzolini S, et al. The effects of an exercise and lifestyle intervention program on cardiovascular, metabolic factors and cognitive performance in middle-aged adults with type II diabetes: a pilot study. Canadian Journal of Diabetes. 2013 Aug;37(4):214-9. PMID 24070883. *Ineligible study design*

234. Ford AH, Flicker L, Alfonso H, et al. Vitamins B(12), B(6), and folic acid for cognition in older men.[Erratum appears in Neurology. 2011 Aug 23;77((8):804 Note: Dosage error in published abstract; MEDLINE/PubMed abstract corrected; Dosage error in article text]. Neurology. 2010 Oct 26;75(17):1540-7. PMID 20861451. *Ineligible population*

235. Forster S, Buschert VC, Buchholz HG, et al. Effects of a 6-month cognitive intervention program on brain metabolism in amnestic mild cognitive impairment and mild Alzheimer's disease. Journal of Alzheimer's Disease. 2011;25(4):695-706. PMID 21498904. *Ineligible population*

236. Forti P, Olivelli V, Rietti E, et al. Serum thyroid-stimulating hormone as a predictor of cognitive impairment in an elderly cohort. Gerontology. 2012;58(1):41-9. PMID 21430364. *Not cognitive decline prevention intervention*

237. Foubert-Samier A, Le Goff M, Helmer C, et al. Change in leisure and social activities and risk of dementia in elderly cohort. Journal of Nutrition, Health & Aging. 2014 Dec;18(10):876-82. PMID 25470802. *Not cognitive decline prevention intervention*

238. Fowler SB. Cognition training interventions for healthy older people and older people with mild cognitive impairment. Clinical Nurse Specialist. 2011 Jul-Aug;25(4):178-9. PMID 21654372. *Ineligible study design*

239. Fox C, Richardson K, Maidment ID, et al. Anticholinergic medication use and cognitive impairment in the older population: the medical research council cognitive function and ageing study. Journal of the American Geriatrics Society. 2011 Aug;59(8):1477-83. PMID 21707557. *Not cognitive decline prevention intervention*

240. Fox M, Berzuini C, Knapp LA. Cumulative estrogen exposure, number of menstrual cycles, and Alzheimer's risk in a cohort of British women. Psychoneuroendocrinology. 2013 Dec;38(12):2973-82. PMID 24064221. *Ineligible population*

241. Frolich L, Ashwood T, Nilsson J, et al. Effects of AZD3480 on cognition in patients with mild-to-moderate Alzheimer's disease: a phase IIb dose-finding study. Journal of Alzheimer's Disease. 2011;24(2):363-74. PMID 21258153. *Inadequate follow up time*

242. Gaitan A, Garolera M, Cerulla N, et al. Efficacy of an adjunctive computer-based cognitive training program in amnestic mild cognitive impairment and Alzheimer's disease: a single-blind, randomized clinical trial. International Journal of Geriatric Psychiatry. 2013 Jan;28(1):91-9. PMID 22473855. *Ineligible population*

243. Galasko DR, Peskind E, Clark CM, et al. Antioxidants for Alzheimer disease: a randomized clinical trial with cerebrospinal fluid biomarker measures. Archives of Neurology. 2012 Jul;69(7):836-41. PMID 22431837. *Ineligible population*

244. Ganio MS, Armstrong LE, Casa DJ, et al. Mild dehydration impairs cognitive performance and mood of men. British Journal of Nutrition. 2011 Nov;106(10):1535-43. PMID 21736786. *No relevant outcomes reported*

245. Gao Q, Niti M, Feng L, et al. Omega-3 polyunsaturated fatty acid supplements and cognitive decline: Singapore Longitudinal Aging Studies. Journal of Nutrition, Health & Aging. 2011 Jan;15(1):32-5. PMID 21267519. *Not cognitive decline prevention intervention*

246. Gao S, Nguyen JT, Hendrie HC, et al. Accelerated weight loss and incident dementia in an elderly African-American cohort. Journal of the American Geriatrics Society. 2011 Jan;59(1):18-25. PMID 21054328. *Not cognitive decline prevention intervention*

247. Garand L, Rinaldo DE, Alberth MM, et al. Effects of problem solving therapy on mental health outcomes in family caregivers of persons with a new diagnosis of mild cognitive impairment or early dementia: a randomized controlled trial. American Journal of Geriatric Psychiatry. 2014 Aug;22(8):771-81. PMID 24119856. *Ineligible population*

248. Gates NJ, Valenzuela M, Sachdev PS, et al. Study of Mental Activity and Regular Training (SMART) in at risk individuals: a randomised double blind, sham controlled, longitudinal trial. BMC Geriatrics. 2011;11:19. PMID 21510896. *Ineligible study design*

249. Gaudig M, Richarz U, Han J, et al. Effects of galantamine in Alzheimer's disease: double-blind withdrawal studies evaluating sustained versus interrupted treatment. Current Alzheimer Research. 2011 Nov;8(7):771-80. PMID 21707533. *Ineligible population*

250. Gavrilova SI, Fedorova IB, Gantman, et al. [Ceraxon (citicoline) in the treatment of the mild cognitive impairment syndrome]. [Russian]. Zhurnal nevrologii i psikhiatrii imeni S.S. 2011;Korsakova / Ministerstvo zdravookhraneniia i meditsinskoi promyshlennosti Rossiiskoi Federatsii, Vserossiiskoe obshchestvo nevrologov [i] Vserossiiskoe obshchestvo psikhiatrov. 111(12):16-20. PMID 22433803. *Not available in English*

251. Gavrilova SI, Kolykhalov IV, Fedorova Ya B, et al. Possibilities of preventive treatment of Alzheimer's disease: Results of the 3-year open prospective comparative study on efficacy and safety of the course therapy with cerebrolysin and cavinton in elderly patients with the syndrome of mild cognitive impairment. [Russian]. Zhurnal Nevrologii i Psihiatrii imeni S.S. 2010;Korsakova. 110(1):62-9. PMID 2010707327. *Not available in English*

252. Geda YE, Roberts RO, Knopman DS, et al. Physical exercise, aging, and mild cognitive impairment: a population-based study. Archives of Neurology. 2010 Jan;67(1):80-6. PMID 20065133. *Not cognitive decline prevention intervention*

253. Geda YE, Silber TC, Roberts RO, et al. Computer activities, physical exercise, aging, and mild cognitive impairment: a population-based study. Mayo Clinic Proceedings. 2012 May;87(5):437-42. PMID 22560523. *Not cognitive decline prevention intervention*

254. Gelber RP, Petrovitch H, Masaki KH, et al. Lifestyle and the risk of dementia in Japanese-american men. Journal of the American Geriatrics Society. 2012 Jan;60(1):118-23. PMID 22211390. *Ineligible study design*

255. Gelber RP, Ross GW, Petrovitch H, et al. Antihypertensive medication use and risk of cognitive impairment: the Honolulu-Asia Aging Study. Neurology. 2013 Sep 3;81(10):888-95. PMID 23911753. *Ineligible population*

256. Genon S, Collette F, Moulin CJ, et al. Verbal learning in Alzheimer's disease and mild cognitive impairment: fine-grained acquisition and short-delay consolidation performance and neural correlates. Neurobiology of Aging. 2013 Feb;34(2):361-73. PMID 22592018. *Ineligible population*

257. Germano da Paz O, Guillaumon AT, Lopes TM, et al. Carotid stenting versus endarterectomy cognitive outcomes. Annals of Vascular Surgery. 2014 May;28(4):893-900. PMID 24361382. *Ineligible population*

258. Gharacholou SM, Reid KJ, Arnold SV, et al. Cognitive impairment and outcomes in older adult survivors of acute myocardial infarction: findings from the translational research investigating underlying disparities in acute myocardial infarction patients' health status registry. American Heart Journal. 2011 Nov;162(5):860-9.e1. PMID 22093202. *Ineligible population*

259. Giannantoni A, Cagini R, Del Zingaro M, et al. Botulinum A toxin intravesical injections for painful bladder syndrome: impact upon pain, psychological functioning and Quality of Life. Current Drug Delivery. 2010 Dec;7(5):442-6. PMID 20950262. *Ineligible study design*

260. Gilbertson R, Prather R, Nixon SJ. Acute alcohol administration and placebo effectiveness in older moderate drinkers: influences on cognitive performance. Journal of Studies on Alcohol & Drugs. 2010 May;71(3):345-50. PMID 20409427. *Inadequate follow up time*

261. Glasser SP, Wadley V, Judd S, et al. The association of statin use and statin type and cognitive performance: analysis of the reasons for geographic and racial differences in stroke (REGARDS) study. Clinical Cardiology. 2010 May;33(5):280-8. PMID 20513066. *Ineligible study design*

262. Goh KL, Bhaskaran K, Minassian C, et al. Angiotensin receptor blockers and risk of dementia: Cohort study in UK Clinical Practice Research Datalink. British Journal of Clinical Pharmacology. 2015 01 Feb;79(2):337-50. PMID 2015433482. *Not cognitive decline prevention intervention*

263. Gold M, Alderton C, Zvartau-Hind M, et al. Rosiglitazone monotherapy in mild-to-moderate Alzheimer's disease: results from a randomized, double-blind, placebo-controlled phase III study. Dementia & Geriatric Cognitive Disorders. 2010;30(2):131-46. PMID 20733306. *Ineligible population*

264. Gottesman RF, Schneider AL, Albert M, et al. Midlife hypertension and 20-year cognitive change: the atherosclerosis risk in communities neurocognitive study. JAMA Neurology. 2014 Oct;71(10):1218-27. PMID 25090106. *Not cognitive decline prevention intervention*

265. Goveas JS, Hogan PE, Kotchen JM, et al. Depressive symptoms, antidepressant use, and future cognitive health in postmenopausal women: the Women's Health Initiative Memory Study. International Psychogeriatrics. 2012 Aug;24(8):1252-64. PMID 22301077. *Ineligible population*

266. Graessel E, Stemmer R, Eichenseer B, et al. Non-pharmacological, multicomponent group therapy in patients with degenerative dementia: a 12-month randomzied, controlled trial. BMC Medicine. 2011 01 Dec;9(129)PMID 2012024517. *Ineligible population*

267. Grande G, Vanacore N, Maggiore L, et al. Physical activity reduces the risk of dementia in mild cognitive impairment subjects: a cohort study. Journal of Alzheimer's Disease. 2014;39(4):833-9. PMID 24296815. *Not cognitive decline prevention intervention*

268. Green RC, Schneider LS, Amato DA, et al. Effect of tarenflurbil on cognitive decline and activities of daily living in patients with mild Alzheimer disease: a randomized controlled trial. JAMA. 2009 Dec 16;302(23):2557-64. PMID 20009055. *Ineligible population*

269. Greenaway MC, Duncan NL, Smith GE. The memory support system for mild cognitive impairment: randomized trial of a cognitive rehabilitation intervention. International Journal of Geriatric Psychiatry. 2013 Apr;28(4):402-9. PMID 22678947. *NIHMS495906. PMC3766962*

270. Grossheinrich N, Rau A, Pogarell O, et al. Theta burst stimulation of the prefrontal cortex: safety and impact on cognition, mood, and resting electroencephalogram. Biological Psychiatry. 2009 May 1;65(9):778-84. PMID 19070834. *Inadequate follow up time*

271. Group AI. Study design of ASPirin in Reducing Events in the Elderly (ASPREE): a randomized, controlled trial. Contemporary Clinical Trials. 2013 Nov;36(2):555-64. PMID 24113028. *Ineligible study design*

272. Grove RA, Harrington CM, Mahler A, et al. A randomized, double-blind, placebo-controlled, 16-week study of the H3 receptor antagonist, GSK239512 as a monotherapy in subjects with mild-to-moderate Alzheimer's disease. Current Alzheimer Research. 2014 Jan;11(1):47-58. PMID 24359500. *Inadequate follow up time*

273. Gu Y, Luchsinger JA, Stern Y, et al. Mediterranean diet, inflammatory and metabolic biomarkers, and risk of Alzheimer's disease. Journal of Alzheimer's Disease. 2010;22(2):483-92. PMID 20847399. *Not cognitive decline prevention intervention*

274. Gu Y, Nieves JW, Stern Y, et al. Food combination and Alzheimer disease risk: a protective diet. Archives of Neurology. 2010 Jun;67(6):699-706. PMID 20385883. *Ineligible population*

275. Guekht AB, Moessler H, Novak PH, et al. Cerebrolysin in vascular dementia: improvement of clinical outcome in a randomized, double-blind, placebo-controlled multicenter trial. Journal of Stroke & Cerebrovascular Diseases. 2011 Jul-Aug;20(4):310-8. PMID 20656516. *Ineligible population*

276. Guo M, Mi J, Jiang QM, et al. Metformin may produce antidepressant effects through improvement of cognitive function among depressed patients with diabetes mellitus. Clinical & Experimental Pharmacology & Physiology. 2014 Sep;41(9):650-6. PMID 24862430. *Ineligible population*

277. Guo RZ, Zhou WQ, Luo ZG. [Effect of modified huanglian wendan decoction in treating senile patients with mild cognitive impairment of turbid-phlegm blocking orifice syndrome]. [Chinese]. Zhongguo Zhong xi yi jie he za zhi Zhongguo Zhongxiyi jiehe zazhi = Chinese journal of integrated traditional and Western medicine / Zhongguo Zhong xi yi jie he xue hui, Zhongguo Zhong yi yan jiu yuan zhu ban. 2010 Jan;30(1):33-6. PMID 20353029. *Ineligible population*

278. Gupta VB, Wilson AC, Burnham S, et al. Follow-up plasma apolipoprotein e levels in the Australian Imaging, Biomarkers and Lifestyle Flagship Study of Ageing (AIBL) cohort. Alzheimer's Research and Therapy. 2015 20 Feb;7 (1) (no pagination)(16)PMID 2015908818. *Not cognitive decline prevention intervention*

279. Gustafson DR, Backman K, Lissner L, et al. Leptin and dementia over 32 years-The Prospective Population Study of Women. Alzheimer's & Dementia. 2012 Jul;8(4):272-7. PMID 22748937. *No relevant outcomes reported*

280. Gustavsson A, Jonsson L, Parmler J, et al. Disease progression and costs of care in Alzheimer's disease patients treated with donepezil: a longitudinal naturalistic cohort. European Journal of Health Economics. 2012 Oct;13(5):561-8. PMID 21822729. *Ineligible study design*

281. Guvenal T, Durna A, Erden O, et al. Effects of different postmenopausal hormone therapy regimens on cerebral blood flow and cognitive functions. Advances in Therapy. 2009 Aug;26(8):805-11. PMID 19672567. *No relevant outcomes reported*

282. Haag MD, Hofman A, Koudstaal PJ, et al. Duration of antihypertensive drug use and risk of dementia: A prospective cohort study. Neurology. 2009 May 19;72(20):1727-34. PMID 19228584. *Not cognitive decline prevention intervention*

283. Haag MDM, Hofman A, Koudstaal PJ, et al. Statins are associated with a reduced risk of Alzheimer disease regardless of lipophilicity. The Rotterdam Study. Journal of Neurology, Neurosurgery and Psychiatry. 2009 January;80(1):13-7. PMID 2009031438. *Not cognitive decline prevention intervention*

284. Hackney ME, Byers C, Butler G, et al. Adapted Tango Improves Mobility, Motor-Cognitive Function, and Gait but Not Cognition in Older Adults in Independent Living. Journal of the American Geriatrics Society. 2015 Oct;63(10):2105-13. PMID 26456371. *Inadequate follow up time*

285. Haenisch B, von Holt K, Wiese B, et al. Risk of dementia in elderly patients with the use of proton pump inhibitors. European Archives of Psychiatry and Clinical Neuroscience. 2015 24 Oct;265(5):419-28. PMID 2014850429. *Not cognitive decline prevention intervention*

286. Hagger-Johnson G, Sabia S, Brunner EJ, et al. Combined impact of smoking and heavy alcohol use on cognitive decline in early old age: Whitehall II prospective cohort study. British Journal of Psychiatry. 2013 Aug;203(2):120-5. PMID 23846998. *Not cognitive decline prevention intervention*

287. Haig GM, Pritchett Y, Meier A, et al. A randomized study of H3 antagonist ABT-288 in mild-to-moderate Alzheimer's dementia. Journal of Alzheimer's Disease. 2014;42(3):959-71. PMID 25024314. *Ineligible population*

288. Haimov I, Shatil E. Cognitive training improves sleep quality and cognitive function among older adults with insomnia. PLoS ONE [Electronic Resource]. 2013;8(4):e61390. PMID 23577218. *Inadequate follow up time*

289. Hajjar I, Hart M, Chen YL, et al. Effect of antihypertensive therapy on cognitive function in early executive cognitive impairment: A double-blind randomized clinical trial. Archives of Internal Medicine. 2012 12 Mar;172(5):442-4. PMID 2012161874. *Ineligible study design*

290. Hajjar I, Hart M, Mack W, et al. Aldosterone, cognitive function, and cerebral hemodynamics in hypertension and antihypertensive therapy. American Journal of Hypertension. 2015 Mar;28(3):319-25. PMID 25213687. *Not cognitive decline prevention intervention*

291. Hajjar I, Hart M, Milberg W, et al. The rationale and design of the antihypertensives and vascular, endothelial, and cognitive function (AVEC) trial in elderly hypertensives with early cognitive impairment: role of the renin angiotensin system inhibition. BMC Geriatrics. 2009;9:48. PMID 19922631. *Ineligible study design*

292. Hajjar I, Levey A. Association Between Angiotensin Receptor Blockers and Longitudinal Decline in Tau in Mild Cognitive Impairment. JAMA neurology. 2015 01 Sep;72(9):1069-70. PMID 26368351. *Not cognitive decline prevention intervention*

293. Hall CB, Lipton RB, Sliwinski M, et al. Cognitive activities delay onset of memory decline in persons who develop dementia. Neurology. 2009 Aug 4;73(5):356-61. PMID 19652139. *Cohort study with inadequate sample size*

294. Haller S, Montandon ML, Rodriguez C, et al. Acute caffeine administration effect on brain activation patterns in mild cognitive impairment. Journal of Alzheimer's Disease. 2014;41(1):101-12. PMID 24577471. *Inadequate follow up time*

295. Hampel H, Ewers M, Burger K, et al. Lithium trial in Alzheimer's disease: A randomized, single-blind, placebo-controlled, multicenter 10-week study. Journal of Clinical Psychiatry. 2009 June;70(6):922-31. PMID 2009309012. *Inadequate follow up time*

296. Hampstead BM, Sathian K, Phillips PA, et al. Mnemonic strategy training improves memory for object location associations in both healthy elderly and patients with amnestic mild cognitive impairment: a randomized, single-blind study. Neuropsychology. 2012 May;26(3):385-99. PMID 22409311. *Inadequate follow up time*

297. Hampstead BM, Stringer AY, Stilla RF, et al. Mnemonic strategy training partially restores hippocampal activity in patients with mild cognitive impairment. Hippocampus. 2012 Aug;22(8):1652-8. PMID 22368035. *Inadequate follow up time*

298. Han JW, Oh K, Yoo S, et al. Development of the ubiquitous spaced retrieval-based memory advancement and rehabilitation training program. Psychiatry Investigation. 2014 January;11(1):52-8. PMID 2014094656. *Ineligible study design*

299. Han YR, Song MS, Lim JY. The effects of a cognitive enhancement group training program for community-dwelling elders. Journal of Korean Academy of Nursing. 2010 Oct;40(5):724-35. PMID 21157174. *Not available in English*

300. Hanson AJ, Bayer JL, Baker LD, et al. Differential effects of meal challenges on cognition, metabolism, and biomarkers for apolipoprotein Ebeta 4 carriers and adults with mild cognitive impairment. Journal of Alzheimer's Disease. 2015 28 Aug;48(1):205-18. PMID 2015360283. *Inadequate follow up time*

301. Hanson AJ, Bayer-Carter JL, Green PS, et al. Effect of apolipoprotein E genotype and diet on apolipoprotein E lipidation and amyloid peptides: randomized clinical trial. JAMA Neurology. 2013 Aug;70(8):972-80. PMID 23779114. *Inadequate follow up time*

302. Harper PC, Roe CM. Thyroid medication use and subsequent development of dementia of the Alzheimer type. Journal of Geriatric Psychiatry & Neurology. 2010 Mar;23(1):63-9. PMID 19666883. *Cohort study with inadequate sample size*

303. Harrington C, Sawchak S, Chiang C, et al. Rosiglitazone does not improve cognition or global function when used as adjunctive therapy to AChE inhibitors in mild-to-moderate Alzheimer's disease: two phase 3 studies. Current Alzheimer Research. 2011 Aug;8(5):592-606. PMID 21592048. *Ineligible population*

304. Harris E, Macpherson H, Vitetta L, et al. Effects of a multivitamin, mineral and herbal supplement on cognition and blood biomarkers in older men: a randomised, placebo-controlled trial. Human Psychopharmacology. 2012 Jul;27(4):370-7. PMID 22711385. *Inadequate follow up time*

305. Hasler F, Studerus E, Lindner K, et al. Investigation of serotonin-1A receptor function in the human psychopharmacology of MDMA. Journal of Psychopharmacology. 2009 Nov;23(8):923-35. PMID 18635693. *Inadequate follow up time*

306. Hauer D, Weis F, Campolongo P, et al. Glucocorticoid-endocannabinoid interaction in cardiac surgical patients: relationship to early cognitive dysfunction and late depression. Reviews in the Neurosciences. 2012;23(5-6):681-90. PMID 23006898. *Ineligible population*

307. Helmer C, Stengel B, Metzger M, et al. Chronic kidney disease, cognitive decline, and incident dementia: The 3C Study. Neurology. 2011 06 Dec;77(23):2043-51. PMID 2011672094. *Not cognitive decline prevention intervention*

308. Helmstaedter C, Witt JA. Cognitive outcome of antiepileptic treatment with levetiracetam versus carbamazepine monotherapy: a non-interventional surveillance trial. Epilepsy & Behavior. 2010 May;18(1-2):74-80. PMID 20462801. *Ineligible study design*

309. Henderson ST, Vogel JL, Barr LJ, et al. Study of the ketogenic agent AC-1202 in mild to moderate Alzheimer's disease: A randomized, double-blind, placebo-controlled, multicenter trial. Nutrition and Metabolism. 2009;6(31)PMID 2009460801. *Ineligible population*

310. Hendrie HC, Baiyewu O, Lane KA, et al. Homocysteine levels and dementia risk in Yoruba and African Americans. International Psychogeriatrics. 2013 Nov;25(11):1859-66. PMID 23899991. *Not cognitive decline prevention intervention*

311. Heneka MT, Fink A, Doblhammer G. Effect of pioglitazone medication on the incidence of dementia. Annals of Neurology. 2015 Aug;78(2):284-94. PMID 25974006. *Not cognitive decline prevention intervention*

312. Herrschaft H, Nacu A, Likhachev S, et al. Ginkgo biloba extract EGb 761 in dementia with neuropsychiatric features: a randomised, placebo-controlled trial to confirm the efficacy and safety of a daily dose of 240 mg. Journal of Psychiatric Research. 2012 Jun;46(6):716-23. PMID 22459264. *Ineligible population*

313. Hietanen H, Pietila A, Kahonen M, et al. Ankle blood pressure and dementia: A prospective follow-up study. Blood Pressure Monitoring. 2013 February;18(1):16-20. PMID 2013023251. *Not cognitive decline prevention intervention*

314. Hill NL, Kolanowski AM, Fick D, et al. Personality as a moderator of cognitive stimulation in older adults at high risk for cognitive decline. Research in Gerontological Nursing. 2014 Jul-Aug;7(4):159-70. PMID 24635006. *Not cognitive decline prevention intervention*

315. Hinkelmann K, Wingenfeld K, Kuehl LK, et al. Stimulation of the mineralocorticoid receptor improves memory in young and elderly healthy individuals. Neurobiology of Aging. 2015 Feb;36(2):919-24. PMID 25442112. *Inadequate follow up time*

316. Holinski S, Claus B, Alaaraj N, et al. Cerebroprotective effect of piracetam in patients undergoing open heart surgery. Annals of Thoracic & Cardiovascular Surgery. 2011;17(2):137-42. PMID 21597409. *Ineligible population*

317. Holtzman DM. CSF biomarkers for secondary prevention trials: Why markers of amyloid deposition and neurodegeneration are both important. Archives of Neurology. 2012 Jun;69(6):691-2. PMID 2012-16571-001. *Ineligible study design*

318. Holzgreve H. [Hypertensive and organ damage. Dementia and cognitive impairment]. MMW Fortschritte der Medizin. 2011 Sep 22;153(38):99-100. PMID 21977804. *Not available in English*

319. Homma A, Imai Y, Tago H, et al. Long-term safety and efficacy of donepezil in patients with severe Alzheimer's disease: results from a 52-week, open-label, multicenter, extension study in Japan. Dementia & Geriatric Cognitive Disorders. 2009;27(3):232-9. PMID 19246907. *Ineligible population*

320. Hoogenhout EM, de Groot RH, van der Elst W, et al. Effects of a comprehensive educational group intervention in older women with cognitive complaints: a randomized controlled trial. Aging & Mental Health. 2012;16(2):135-44. PMID 21780962. *Inadequate follow up time*

321. Hooshmand B, Solomon A, Kareholt I, et al. Associations between serum homocysteine, holotranscobalamin, folate and cognition in the elderly: a longitudinal study. Journal of Internal Medicine. 2012 Feb;271(2):204-12. PMID 22077644. *Not cognitive decline prevention intervention*

322. Hornslien AG, Sandset EC, Bath PM, et al. Effects of candesartan in acute stroke on cognitive function and quality of life: results from the Scandinavian Candesartan Acute Stroke Trial. Stroke. 2013 Jul;44(7):2022-4. PMID 23660849. *Ineligible population*

323. Howard R, McShane R, Lindesay J, et al. Donepezil and memantine for moderate-to-severe Alzheimer's disease. New England Journal of Medicine. 2012 Mar 8;366(10):893-903. PMID 22397651. *Ineligible population*

324. Hsu CC, Wahlqvist ML, Lee MS, et al. Incidence of dementia is increased in type 2 diabetes and reduced by the use of sulfonylureas and metformin. Journal of Alzheimer's Disease. 2011;24(3):485-93. PMID 21297276. *Not cognitive decline prevention intervention*

325. Hsu CY, Huang CC, Chan WL, et al. Angiotensin-receptor blockers and risk of Alzheimer's disease in hypertension population--a nationwide cohort study. Circulation Journal. 2013;77(2):405-10. PMID 23149416. *Not cognitive decline prevention intervention*

326. Hsu CY, Huang CC, Chan WL, et al. Angiotensin-receptor blockers and risk of alzheimer's disease in hypertension population - A nationwide cohort study. Circulation Journal. 2013;77(2):405-10. PMID 2013074487. *Not cognitive decline prevention intervention*

327. Huang CQ, Dong BR, Zhang YL, et al. Association of cognitive impairment with smoking, alcohol consumption, tea consumption, and exercise among Chinese nonagenarians/centenarians. Cognitive & Behavioral Neurology. 2009 Sep;22(3):190-6. PMID 19741330. *Not cognitive decline prevention intervention*

328. Hughes TF, Becker JT, Lee CW, et al. Independent and combined effects of cognitive and physical activity on incident MCI. Alzheimer's and Dementia. 2015 November;11(11):1377-84. PMID 2015949579. *Not cognitive decline prevention intervention*

329. Hughes TF, Flatt JD, Fu B, et al. Engagement in social activities and progression from mild to severe cognitive impairment: the MYHAT study. International Psychogeriatrics. 2013 Apr;25(4):587-95. PMID 23257280. *Not cognitive decline prevention intervention*

330. Ihl R, Bachinskaya N, Korczyn AD, et al. Efficacy and safety of a once-daily formulation of Ginkgo biloba extract EGb 761 in dementia with neuropsychiatric features: a randomized controlled trial. International Journal of Geriatric Psychiatry. 2011 Nov;26(11):1186-94. PMID 21140383. *Ineligible population*

331. Ihl R, Tribanek M, Bachinskaya N, et al. Efficacy and tolerability of a once daily formulation of Ginkgo biloba extract EGb 761 in Alzheimer's disease and vascular dementia: results from a randomised controlled trial. Pharmacopsychiatry. 2012 Mar;45(2):41-6. PMID 22086747. *Ineligible population*

332. Ihle-Hansen H, Thommessen B, Fagerland MW, et al. Multifactorial vascular risk factor intervention to prevent cognitive impairment after stroke and TIA: a 12-month randomized controlled trial. International Journal of Stroke. 2014 Oct;9(7):932-8. PMID 23205666. *Ineligible population*

333. Ikeda M, Mori E, Kosaka K, et al. Long-term safety and efficacy of donepezil in patients with dementia with Lewy bodies: results from a 52-week, open-label, multicenter extension study. Dementia & Geriatric Cognitive Disorders. 2013;36(3-4):229-41. PMID 23949147. *Ineligible population*

334. Ikeda M, Mori E, Matsuo K, et al. Donepezil for dementia with Lewy bodies: A randomized, placebo-controlled, confirmatory phase III trial. Alzheimer's Research and Therapy. 2015;7(1)PMID 2015872011. *Ineligible population*

335. Ilieva I, Boland J, Farah MJ. Objective and subjective cognitive enhancing effects of mixed amphetamine salts in healthy people. Neuropharmacology. 2013 Jan;64:496-505. PMID 22884611. *Inadequate follow up time*

336. Inaba M, White L, Bell C, et al. White matter lesions on brain magnetic resonance imaging scan and 5-year cognitive decline: The honolulu-asia aging study. Journal of the American Geriatrics Society. 2011 August;59(8):1484-9. PMID 2011457234. *Cohort study with inadequate sample size*

337. Irizarry MC, Raman R, Schwarzschild MA, et al. Plasma urate and progression of mild cognitive impairment. Neurodegenerative Diseases. 2009;6(1-2):23-8. PMID 19066433. *Not cognitive decline prevention intervention*

338. Irwin C, Leveritt M, Shum D, et al. The effects of dehydration, moderate alcohol consumption, and rehydration on cognitive functions. Alcohol. 2013 May;47(3):203-13. PMID 23352231. *Inadequate follow up time*

339. Ishihara H, Oka F, Shirao S, et al. Cognitive outcome differences on the side of carotid artery stenting. Journal of Vascular Surgery. 2013 Jan;57(1):125-30. PMID 23141681. *Ineligible population*

340. Iso-Markku P, Waller K, Kujala UM, et al. Physical activity and dementia: long-term follow-up study of adult twins. Annals of Medicine. 2015 Mar;47(2):81-7. PMID 25613168. *Not cognitive decline prevention intervention*

341. Iwasa H, Yoshida Y, Kai I, et al. Leisure activities and cognitive function in elderly community-dwelling individuals in Japan: a 5-year prospective cohort study. Journal of Psychosomatic Research. 2012 Feb;72(2):159-64. PMID 22281459. *Not cognitive decline prevention intervention*

342. Jackson PA, Deary ME, Reay JL, et al. No effect of 12 weeks' supplementation with 1 g DHA-rich or EPA-rich fish oil on cognitive function or mood in healthy young adults aged 18-35 years. British Journal of Nutrition. 2012 Apr;107(8):1232-43. PMID 21864417. *Inadequate follow up time*

343. Jacobs HIL, Riphagen JM, Razat CM, et al. Transcutaneous vagus nerve stimulation boosts associative memory in older individuals. Neurobiology of Aging. 2015;36(5):1860-7. PMID 2015849982. *Inadequate follow up time*

344. Jacobs V, Woller SC, Stevens SM, et al. Percent time with a supratherapeutic INR in atrial fibrillation patients also using an antiplatelet agent is associated with long-term risk of dementia. Journal of Cardiovascular Electrophysiology. 2015 November;26(11):1180-6. PMID 2015478510. *Cohort study with inadequate sample size*

345. Janicki SC, Park N, Cheng R, et al. Estrogen receptor alpha variants affect age at onset of Alzheimer's disease in a multiethnic female cohort. Dementia & Geriatric Cognitive Disorders. 2014;38(3-4):200-13. PMID 24732579. *Not cognitive decline prevention intervention*

346. Jaremka LM, Derry HM, Bornstein R, et al. Omega-3 supplementation and loneliness-related memory problems: secondary analyses of a randomized controlled trial. Psychosomatic Medicine. 2014 Oct;76(8):650-8. PMID 25264972. *Inadequate follow up time*

347. Jean L, Simard M, Wiederkehr S, et al. Efficacy of a cognitive training programme for mild cognitive impairment: results of a randomised controlled study. Neuropsychological Rehabilitation. 2010 Jun;20(3):377-405. PMID 20029715. *Inadequate follow up time*

348. Jerneren F, Elshorbagy AK, Oulhaj A, et al. Brain atrophy in cognitively impaired elderly: the importance of long-chain omega-3 fatty acids and B vitamin status in a randomized controlled trial. American Journal of Clinical Nutrition. 2015 Jul;102(1):215-21. PMID 25877495. *Ineligible study design*

349. Jiang B, Ding C, Yao G, et al. Intervention effect of folic acid and vitamin B12 on vascular cognitive impairment complicated with hyperhomocysteinemia. Journal of Medical Biochemistry. 2014 April-June;33(2):169-74. PMID 2014475097. *Ineligible population*

350. Jiang D, Chu X, Hu L, et al. Yizhi Xingnao prescription improves the cognitive function of patients after a transient ischemic attack. Neural Regeneration Research. 2012 February;7(6):434-9. PMID 2012142010. *Ineligible population*

351. Joas E, Backman K, Gustafson D, et al. Blood pressure trajectories from midlife to late life in relation to dementia in women followed for 37 years. Hypertension. 2012 Apr;59(4):796-801. PMID 22331381. *Not cognitive decline prevention intervention*

352. Johansson L, Guo X, Hallstrom T, et al. Common psychosocial stressors in middle-aged women related to longstanding distress and increased risk of Alzheimer's disease: A 38-year longitudinal population study. BMJ Open. 2013;3 (9) (no pagination)(e003142)PMID 2013640644. *Not cognitive decline prevention intervention*

353. Johnston H, Boutin H, Allan SM. Assessing the contribution of inflammation in models of Alzheimer's disease. Biochemical Society Transactions. 2011 August;39(4):886-90. PMID 2011415298. *Ineligible study design*

354. Kamegaya T, Araki Y, Kigure H, et al. Twelve-week physical and leisure activity programme improved cognitive function in community-dwelling elderly subjects: a randomized controlled trial. Psychogeriatrics:The Official Journal of the Japanese Psychogeriatric Society. 2014 Mar;14(1):47-54. PMID 24528600. *Inadequate follow up time*

355. Kang JH, Grodstein F. Regular use of nonsteroidal anti-inflammatory drugs and cognitive function in aging women. Neurology. 2003 May 27;60(10):1591-7. PMID 12771247. *Not cognitive decline prevention intervention*

356. Karr JE, Grindstaff TR, Alexander JE. Omega-3 polyunsaturated fatty acids and cognition in a college-aged population. Experimental & Clinical Psychopharmacology. 2012 Jun;20(3):236-42. PMID 22250656. *Inadequate follow up time*

357. Kaschel R. [Ginkgo extract in people with declining mental performance]. Pharmazie in Unserer Zeit. 2009;38(5):432-9. PMID 19711319. *Not available in English*

358. Kaschel R. Specific memory effects of Ginkgo biloba extract EGb 761 in middle-aged healthy volunteers. Phytomedicine. 2011 Nov 15;18(14):1202-7. PMID 21802920. *Inadequate follow up time*

359. Katon W, Lyles CR, Parker MM, et al. Association of depression with increased risk of dementia in patients with type 2 diabetes: the Diabetes and Aging Study. Archives of General Psychiatry. 2012 Apr;69(4):410-7. PMID 22147809. *Not cognitive decline prevention intervention*

360. Kawashima R. [Prevention of dementia by social activity]. Nippon Rinsho - Japanese Journal of Clinical Medicine. 2011 Dec;69 Suppl 10(Pt 2):212-6. PMID 22755186. *Not available in English*

361. Kawashima R. Mental exercises for cognitive function: clinical evidence. Journal of Preventive Medicine & Public Health / Yebang Uihakhoe Chi. 2013 Jan;46 Suppl 1:S22-7. PMID 23412645. *Ineligible population*

362. Kay GG, Maruff P, Scholfield D, et al. Evaluation of cognitive function in healthy older subjects treated with fesoterodine. Postgraduate Medicine. 2012 May;124(3):7-15. PMID 22691894. *Inadequate follow up time*

363. Kay GG, Staskin DR, MacDiarmid S, et al. Cognitive effects of oxybutynin chloride topical gel in older healthy subjects: a 1-week, randomized, double-blind, placebo- and active-controlled study. Clinical Drug Investigation. 2012 Oct 1;32(10):707-14. PMID 22909146. *Inadequate follow up time*

364. Kean RJ, Lamport DJ, Dodd GF, et al. Chronic consumption of flavanone-rich orange juice is associated with cognitive benefits: an 8-wk, randomized, double-blind, placebo-controlled trial in healthy older adults. American Journal of Clinical Nutrition. 2015 Mar;101(3):506-14. PMID 25733635. *Inadequate follow up time*

365. Kelly J, Fulford J, Vanhatalo A, et al. Effects of short-term dietary nitrate supplementation on blood pressure, O2 uptake kinetics, and muscle and cognitive function in older adults. American Journal of Physiology - Regulatory Integrative & Comparative Physiology. 2013 Jan 15;304(2):R73-83. PMID 23174856. *Inadequate follow up time*

366. Kennedy DO, Dodd FL, Robertson BC, et al. Monoterpenoid extract of sage (Salvia lavandulaefolia) with cholinesterase inhibiting properties improves cognitive performance and mood in healthy adults. Journal of Psychopharmacology. 2011 Aug;25(8):1088-100. PMID 20937617. *Inadequate follow up time*

367. Kennedy DO, Veasey RC, Watson AW, et al. Vitamins and psychological functioning: a mobile phone assessment of the effects of a B vitamin complex, vitamin C and minerals on cognitive performance and subjective mood and energy. Human Psychopharmacology. 2011 Jun-Jul;26(4-5):338-47. PMID 21751253. *Inadequate follow up time*

368. Kennelly S, Abdullah L, Kenny RA, et al. Apolipoprotein e genotype-specific short-term cognitive benefits of treatment with the antihypertensive nilvadipine in Alzheimer's patientsa-an open-label trial. International Journal of Geriatric Psychiatry. 2012 April;27(4):415-22. PMID 2012157085. *Ineligible population*

369. Kennelly S, Abdullah L, Kenny RA, et al. Apolipoprotein E genotype-specific short-term cognitive benefits of treatment with the antihypertensive nilvadipine in Alzheimer's patients--an open-label trial. International Journal of Geriatric Psychiatry. 2012 Apr;27(4):415-22. PMID 21560164. *Ineligible population*

370. Kern S, Skoog I, Ostling S, et al. Does low-dose acetylsalicylic acid prevent cognitive decline in women with high cardiovascular risk? A 5-year follow-up of a non-demented population-based cohort of Swedish elderly women. BMJ Open. 2012;2 (5) (no pagination)(e001288)PMID 2012683493. *Not cognitive decline prevention intervention*

371. Kersten H, Molden E, Tolo IK, et al. Cognitive effects of reducing anticholinergic drug burden in a frail elderly population: a randomized controlled trial. Journals of Gerontology Series A-Biological Sciences & Medical Sciences. 2013 Mar;68(3):271-8. PMID 22982689. *Ineligible population*

372. Kesler S, Hadi Hosseini SM, Heckler C, et al. Cognitive training for improving executive function in chemotherapy-treated breast cancer survivors. Clinical Breast Cancer. 2013 Aug;13(4):299-306. PMID 23647804. *Ineligible population*

373. Kesse-Guyot E, Andreeva VA, Lassale C, et al. Mediterranean diet and cognitive function: a French study. American Journal of Clinical Nutrition. 2013 Feb;97(2):369-76. PMID 23283500. *Not cognitive decline prevention intervention*

374. Kesse-Guyot E, Andreeva VA, Touvier M, et al. Overall and abdominal adiposity in midlife and subsequent cognitive function. Journal of Nutrition, Health & Aging. 2015 Feb;19(2):183-9. PMID 25651444. *Not cognitive decline prevention intervention*

375. Kessing LV, Forman JL, Andersen PK. Does lithium protect against dementia? Bipolar Disorders. 2010 Feb;12(1):87-94. PMID 20148870. *Ineligible study design*

376. Khachaturian AS, Chapman J, Farrer L, et al. Healthy aging and preclinical dementia: the United States-Israel Longitudinal Database project. Alzheimer's & Dementia. 2010 Nov;6(6):475-81. PMID 21044777. *Ineligible study design*

377. Kim DH, Grodstein F, Rosner B, et al. Seafood types and age-related cognitive decline in the Women's Health Study. Journals of Gerontology Series A-Biological Sciences & Medical Sciences. 2013 Oct;68(10):1255-62. PMID 23554464. *Not cognitive decline prevention intervention*

378. Kim GH, Jeon S, Im K, et al. Structural brain changes after traditional and robot-assisted multi-domain cognitive training in community-dwelling healthy elderly. PLoS ONE. 2015 21 Apr;10(4)PMID 2015967293. *Inadequate follow up time*

379. Kim JM, Stewart R, Bae KY, et al. Role of BDNF val66met polymorphism on the association between physical activity and incident dementia. Neurobiology of Aging. 2011 Mar;32(3):551.e5-12. PMID 20172629. *Not cognitive decline prevention intervention*

380. Kim SJ, Lee JH, Lee DY, et al. Neurocognitive dysfunction associated with sleep quality and sleep apnea in patients with mild cognitive impairment. American Journal of Geriatric Psychiatry. 2011 Apr;19(4):374-81. PMID 20808148. *Ineligible study design*

381. Kim SY, Choi SH, Rollema H, et al. Phase II crossover trial of varenicline in mild-to-moderate Alzheimer's disease. Dementia & Geriatric Cognitive Disorders. 2014;37(3-4):232-45. PMID 24247022. *Ineligible population*

382. Kim YW, Shin JC, An YS. Changes in cerebral glucose metabolism in patients with posttraumatic cognitive impairment after memantine therapy: a preliminary study. Annals of Nuclear Medicine. 2010 Jun;24(5):363-9. PMID 20237871. *Ineligible population*

383. Kinsella GJ, Mullaly E, Rand E, et al. Early intervention for mild cognitive impairment: a randomised controlled trial. Journal of Neurology, Neurosurgery & Psychiatry. 2009 Jul;80(7):730-6. PMID 19332424. *Inadequate follow up time*

384. Kivipelto M, Solomon A, Ahtiluoto S, et al. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER): study design and progress. Alzheimer's & Dementia. 2013 Nov;9(6):657-65. PMID 23332672. *Ineligible study design*

385. Klepin HD, Geiger AM, Bandos H, et al. Cognitive factors associated with adherence to oral antiestrogen therapy: results from the cognition in the study of tamoxifen and raloxifene (Co-STAR) study. Cancer Prevention Research. 2014 Jan;7(1):161-8. PMID 24253314. *No relevant outcomes reported*

386. Klusmann V, Evers A, Schwarzer R, et al. Activity experiences shape perceived fitness trajectories: results from a 6-month randomized controlled trial in older women. Aging Neuropsychology & Cognition. 2011 May;18(3):328-39. PMID 21557117. *No relevant outcomes reported*

387. Ko HJ, Youn CH. Effects of laughter therapy on depression, cognition and sleep among the community-dwelling elderly. Geriatrics & gerontology international. 2011 Jul;11(3):267-74. PMID 21241447. *Inadequate follow up time*

388. Kocoska-Maras L, Radestad AF, Carlstrom K, et al. Cognitive function in association with sex hormones in postmenopausal women. Gynecological Endocrinology. 2013 Jan;29(1):59-62. PMID 22967437. *Inadequate follow up time*

389. Kocoska-Maras L, Zethraeus N, Radestad AF, et al. A randomized trial of the effect of testosterone and estrogen on verbal fluency, verbal memory, and spatial ability in healthy postmenopausal women. Fertility & Sterility. 2011 Jan;95(1):152-7. PMID 20667535. *Inadequate follow up time*

390. Kohler S, Baars MA, Spauwen P, et al. Temporal evolution of cognitive changes in incident hypertension: prospective cohort study across the adult age span. Hypertension. 2014 Feb;63(2):245-51. PMID 24296281. *Not cognitive decline prevention intervention*

391. Konagai C, Yanagimoto K, Hayamizu K, et al. Effects of krill oil containing n-3 polyunsaturated fatty acids in phospholipid form on human brain function: a randomized controlled trial in healthy elderly volunteers. Clinical Interventions In Aging. 2013;8:1247-57. PMID 24098072. *Inadequate follow up time*

392. Koushyar H, Najafi Z, Azhari A, et al. Comparison of the effect of fun and regular physical activity on the changes in the incidence of depression and cognitive disorders of elderly women living in nursing homes at Mashhad. [Persian]. Iranian Journal of Obstetrics, Gynecology and Infertility. 2014;17(132):1-9. PMID 2015761086. *Not available in English*

393. Krikorian R, Boespflug EL, Fleck DE, et al. Concord grape juice supplementation and neurocognitive function in human aging. Journal of Agricultural & Food Chemistry. 2012 Jun 13;60(23):5736-42. PMID 22468945. *Inadequate follow up time*

394. Krikorian R, Eliassen JC, Boespflug EL, et al. Improved cognitive-cerebral function in older adults with chromium supplementation. Nutritional Neuroscience. 2010 Jun;13(3):116-22. PMID 20423560. *Inadequate follow up time*

395. Krikorian R, Nash TA, Shidler MD, et al. Concord grape juice supplementation improves memory function in older adults with mild cognitive impairment. British Journal of Nutrition. 2010 Mar;103(5):730-4. PMID 20028599. *Inadequate follow up time*

396. Krikorian R, Shidler MD, Nash TA, et al. Blueberry supplementation improves memory in older adults. Journal of Agricultural & Food Chemistry. 2010 Apr 14;58(7):3996-4000. PMID 20047325. *Inadequate follow up time*

397. Kristensen PL, Hoi-Hansen T, Boomsma F, et al. Vascular endothelial growth factor during hypoglycemia in patients with type 1 diabetes mellitus: relation to cognitive function and renin-angiotensin system activity. Metabolism: Clinical & Experimental. 2009 Oct;58(10):1430-8. PMID 19573885. *Not cognitive decline prevention intervention*

398. Krupp LB, Christodoulou C, Melville P, et al. Multicenter randomized clinical trial of donepezil for memory impairment in multiple sclerosis. Neurology. 2011 Apr 26;76(17):1500-7. PMID 21519001. *Ineligible population*

399. Kryscio RJ, Abner EL, Schmitt FA, et al. A randomized controlled Alzheimer's disease prevention trial's evolution into an exposure trial: the PREADViSE Trial. Journal of Nutrition, Health & Aging. 2013 Jan;17(1):72-5. PMID 23299383. *Ineligible study design*

400. Kulmala J, Solomon A, Kareholt I, et al. Association between mid- to late life physical fitness and dementia: evidence from the CAIDE study. Journal of Internal Medicine. 2014 Sep;276(3):296-307. PMID 24444031. *Not cognitive decline prevention intervention*

401. Kurz A, Thone-Otto A, Cramer B, et al. CORDIAL: cognitive rehabilitation and cognitive-behavioral treatment for early dementia in Alzheimer disease: a multicenter, randomized, controlled trial. Alzheimer Disease & Associated Disorders. 2012 Jul-Sep;26(3):246-53. PMID 21986341. *Ineligible population*

402. Kwok T, Lee J, Law CB, et al. A randomized placebo controlled trial of homocysteine lowering to reduce cognitive decline in older demented people. Clinical Nutrition. 2011 Jun;30(3):297-302. PMID 21216507. *Ineligible population*

403. Kwok T, Wong A, Chan G, et al. Effectiveness of cognitive training for Chinese elderly in Hong Kong. Clinical Interventions In Aging. 2013;8:213-9. PMID 23440076. *Inadequate follow up time*

404. Kwok TC, Lam LC, Sea MM, et al. A randomized controlled trial of dietetic interventions to prevent cognitive decline in old age hostel residents. European Journal of Clinical Nutrition. 2012 Oct;66(10):1135-40. PMID 22948946. *Ineligible population*

405. Kwon JC, Kim EG, Kim JW, et al. A multicenter, open-label, 24-week follow-up study for efficacy on cognitive function of donepezil in Binswanger-type subcortical vascular dementia. American Journal of Alzheimer's Disease & Other Dementias. 2009 Aug-Sep;24(4):293-301. PMID 19383979. *Ineligible population*

406. Laforce R, Jr., Buteau JP, Paquet N, et al. The value of PET in mild cognitive impairment, typical and atypical/unclear dementias: A retrospective memory clinic study. American Journal of Alzheimer's Disease & Other Dementias. 2010 Jun;25(4):324-32. PMID 20539026. *Cohort study with inadequate sample size*

407. Laitala VS, Hjelmborg J, Koskenvuo M, et al. Shorter adult stature increases the impact of risk factors for cognitive impairment: a comparison of two Nordic twin cohorts. Twin Research & Human Genetics: the Official Journal of the International Society for Twin Studies. 2011 Dec;14(6):544-52. PMID 22506310. *Ineligible study design*

408. Laitala VS, Kaprio J, Koskenvuo M, et al. Coffee drinking in middle age is not associated with cognitive performance in old age. American Journal of Clinical Nutrition. 2009 Sep;90(3):640-6. PMID 19587088. *Not cognitive decline prevention intervention*

409. Lam JH. Can leisure activities slow dementia progression in nursing home residents? A cluster-randomized controlled trial. International psychogeriatrics / IPA. 2014 01 Apr;26(4):637-43. PMID 24411480. *Ineligible population*

410. Lam LC, Chan WM, Kwok TC, et al. Effectiveness of Tai Chi in maintenance of cognitive and functional abilities in mild cognitive impairment: a randomised controlled trial. Hong Kong Medical Journal. 2014 Jun;20(3 Suppl 3):20-3. PMID 25001031. *Ineligible population*

411. Lam LC, Chau RC, Wong BM, et al. Interim follow-up of a randomized controlled trial comparing Chinese style mind body (Tai Chi) and stretching exercises on cognitive function in subjects at risk of progressive cognitive decline. International Journal of Geriatric Psychiatry. 2011 Jul;26(7):733-40. PMID 21495078. *Inadequate follow up time*

412. Lamport DJ, Saunders C, Butler LT, et al. Fruits, vegetables, 100% juices, and cognitive function. Nutrition Reviews. 2014 Dec;72(12):774-89. PMID 25399992. *Ineligible study design*

413. Langballe EM, Ask H, Holmen J, et al. Alcohol consumption and risk of dementia up to 27 years later in a large, population-based sample: the HUNT study, Norway. European Journal of Epidemiology. 2015 Sep;30(9):1049-56. PMID 25968174. *Not cognitive decline prevention intervention*

414. Langlois F, Vu TT, Chasse K, et al. Benefits of physical exercise training on cognition and quality of life in frail older adults. Journals of Gerontology Series B-Psychological Sciences & Social Sciences. 2013 May;68(3):400-4. PMID 22929394. *Inadequate follow up time*

415. Lapid MI, Drake MT, Geske JR, et al. Hypovitaminosis D in psychogeriatric inpatients. Journal of Nutrition, Health & Aging. 2013 Mar;17(3):231-4. PMID 23459975. *Cohort study with inadequate sample size*

416. Laudisio A, Marzetti E, Pagano F, et al. Digoxin and cognitive performance in patients with heart failure: A cohort, pharmacoepidemiological survey. Drugs and Aging. 2009;26(2):103-12. PMID 2009078141. *Ineligible population*

417. Launer LJ, Hughes T, Yu B, et al. Lowering midlife levels of systolic blood pressure as a public health strategy to reduce late-life dementia: perspective from the Honolulu Heart Program/Honolulu Asia Aging Study. Hypertension. 2010 Jun;55(6):1352-9. PMID 20404223. *Not cognitive decline prevention intervention*

418. Leduc V, De Beaumont L, Theroux L, et al. HMGCR is a genetic modifier for risk, age of onset and MCI conversion to Alzheimer's disease in a three cohorts study. Molecular Psychiatry. 2015 24 Jul;20(7):867-73. PMID 2014735037. *Not cognitive decline prevention intervention*

419. Lee ATC, Richards M, Chan WC, et al. Intensity and Types of Physical Exercise in Relation to Dementia Risk Reduction in Community-Living Older Adults. Journal of the American Medical Directors Association. 2015 01 Oct;16(10):899.e1-.e7. PMID 2015442379. *Not cognitive decline prevention intervention*

420. Lee CE, Kilgour A, Lau YK. Efficacy of walking exercise in promoting cognitive-psychosocial functions in men with prostate cancer receiving androgen deprivation therapy. BMC Cancer. 2012;12:324. PMID 22846379. *Ineligible population*

421. Lee J, Pase M, Pipingas A, et al. Switching to a 10-day Mediterranean-style diet improves mood and cardiovascular function in a controlled crossover study. Nutrition. 2015 May;31(5):647-52. PMID 25837207. *Inadequate follow up time*

422. Lee JG, Lee SW, Lee BJ, et al. Adjunctive memantine terapy for cognitive impairment in chronic schizophrenia: A placebo-controlled pilot study. Psychiatry Investigation. 2012;9(2):166-73. PMID 2012388152. *Ineligible population*

423. Lee TS, Goh SJ, Quek SY, et al. A brain-computer interface based cognitive training system for healthy elderly: a randomized control pilot study for usability and preliminary efficacy. PLoS ONE [Electronic Resource]. 2013;8(11):e79419. PMID 24260218. *Inadequate follow up time*

424. Lee TS, Quek SY, Goh SJ, et al. A pilot randomized controlled trial using EEG-based brain-computer interface training for a Chinese-speaking group of healthy elderly. Clinical Interventions In Aging. 2015;10:217-27. PMID 25624754. *Inadequate follow up time*

425. Lee Y, Back JH, Kim J, et al. Systematic review of health behavioral risks and cognitive health in older adults. International Psychogeriatrics. 2010 Mar;22(2):174-87. PMID 19883522. *Ineligible study design*

426. Lee Y, Kim J, Han ES, et al. Changes in physical activity and cognitive decline in older adults living in the community. Age. 2015;37(2)PMID 2015787853. *Not cognitive decline prevention intervention*

427. Lee YK, Hou SW, Lee CC, et al. Increased risk of dementia in patients with mild traumatic brain injury: a nationwide cohort study. PLoS ONE [Electronic Resource]. 2013;8(5):e62422. PMID 23658727. *Ineligible population*

428. Legault C, Jennings JM, Katula JA, et al. Designing clinical trials for assessing the effects of cognitive training and physical activity interventions on cognitive outcomes: the Seniors Health and Activity Research Program Pilot (SHARP-P) study, a randomized controlled trial. BMC Geriatrics. 2011;11:27. PMID 21615936. *Inadequate follow up time*

429. Lenz RA, Pritchett YL, Berry SM, et al. Adaptive, Dose-finding Phase 2 Trial Evaluating the Safety and Efficacy of ABT-089 in Mild to Moderate Alzheimer Disease. Alzheimer Disease and Associated Disorders. 2015 07 Sep;29(3):192-9. PMID 2015359676. *Ineligible population*

430. Leoutsakos JM, Muthen BO, Breitner JC, et al. Effects of non-steroidal anti-inflammatory drug treatments on cognitive decline vary by phase of pre-clinical Alzheimer disease: findings from the randomized controlled Alzheimer's Disease Anti-inflammatory Prevention Trial. International Journal of Geriatric Psychiatry. 2012 Apr;27(4):364-74. PMID 21560159. *Ineligible study design*

431. Leufkens TR, Lund JS, Vermeeren A. Highway driving performance and cognitive functioning the morning after bedtime and middle-of-the-night use of gaboxadol, zopiclone and zolpidem. Journal of Sleep Research. 2009 Dec;18(4):387-96. PMID 19552733. *Inadequate follow up time*

432. Leung GT, Fung AW, Tam CW, et al. Examining the association between participation in late-life leisure activities and cognitive function in community-dwelling elderly Chinese in Hong Kong. International Psychogeriatrics. 2010 Feb;22(1):2-13. PMID 19785918. *Not cognitive decline prevention intervention*

433. Leung GT, Fung AW, Tam CW, et al. Examining the association between late-life leisure activity participation and global cognitive decline in community-dwelling elderly Chinese in Hong Kong. International Journal of Geriatric Psychiatry. 2011 Jan;26(1):39-47. PMID 21157849. *Not cognitive decline prevention intervention*

434. Levin OS, Yunishchenko NA, Dudarova MA. Efficacy of akatinol memantine in moderate cognitive impairments. Neuroscience & Behavioral Physiology. 2010 Oct;40(8):926-33. PMID 20683775. *Ineligible study design*

435. Lewis JE, McDaniel HR, Agronin ME, et al. The effect of an aloe polymannose multinutrient complex on cognitive and immune functioning in Alzheimer's disease. Journal of Alzheimer's Disease. 2013;33(2):393-406. PMID 22976077. *Ineligible population*

436. Li F, Harmer P, Liu Y, et al. Tai Ji Quan and global cognitive function in older adults with cognitive impairment: a pilot study. Archives of Gerontology & Geriatrics. 2014 May-Jun;58(3):434-9. PMID 24398166. *Inadequate follow up time*

437. Li G, Shofer JB, Rhew IC, et al. Age-varying association between statin use and incident Alzheimer's disease. Journal of the American Geriatrics Society. 2010 Jul;58(7):1311-7. PMID 20533968. *Not cognitive decline prevention intervention*

438. Li NC, Lee A, Whitmer RA, et al. Use of angiotensin receptor blockers and risk of dementia in a predominantly male population: Prospective cohort analysis. BMJ (Online). 2010 16 Jan;340(7738):141. PMID 2010062843. *Not cognitive decline prevention intervention*

439. Liang J, Li F, Wei C, et al. Rationale and design of a multicenter, phase 2 clinical trial to investigate the efficacy of traditional Chinese medicine sailuotong in vascular dementia. Journal of Stroke and Cerebrovascular Diseases. 2014;23(10):2626-34. PMID 2014873944. *Ineligible study design*

440. Liao JN, Chao TF, Liu CJ, et al. Risk and prediction of dementia in patients with atrial fibrillation - A nationwide population-based cohort study. International Journal of Cardiology. 2015 15 Sep;199:25-30. PMID 2015376315. *Ineligible population*

441. Liao KM, Ho CH, Ko SC, et al. Increased Risk of Dementia in Patients With Chronic Obstructive Pulmonary Disease. Medicine. 2015 Jun;94(23):e930. PMID 26061317. *Ineligible population*

442. Liao MT, Lin LY, Yang YH, et al. ACEI and ARB did not reduce the incidence of dementia in patients with atrial fibrillation: A nationwide cohort study. Acta Cardiologica Sinica. 2013 July;29(4):323-7. PMID 2013464598. *Ineligible population*

443. Licastro F, Porcellini E, Chiappelli M, et al. Multivariable network associated with cognitive decline and dementia. Neurobiology of Aging. 2010 February;31(2):257-69. PMID 2009623669. *Not cognitive decline prevention intervention*

444. Lieb W, Beiser AS, Vasan RS, et al. Association of plasma leptin levels with incident Alzheimer disease and MRI measures of brain aging. JAMA - Journal of the American Medical Association. 2009 16 Dec;302(23):2565-72. PMID 2009657832. *Ineligible study design*

445. Lim AS, Yu L, Kowgier M, et al. Modification of the relationship of the apolipoprotein E epsilon4 allele to the risk of Alzheimer disease and neurofibrillary tangle density by sleep. JAMA Neurology. 2013 Dec;70(12):1544-51. PMID 24145819. *Not cognitive decline prevention intervention*

446. Lin CC, Chou CH, Fan YM, et al. Increased risk of dementia among sleep-related movement disorders: A population-based longitudinal study in Taiwan. Medicine (United States). 2015;94 (51) (no pagination)(e2331)PMID 20160007822. *Not cognitive decline prevention intervention*

447. Lin CH, Chen PK, Chang YC, et al. Benzoate, a D-amino acid oxidase inhibitor, for the treatment of early-phase Alzheimer disease: a randomized, double-blind, placebo-controlled trial. Biological Psychiatry. 2014 May 1;75(9):678-85. PMID 24074637. *Ineligible population*

448. Lin CH, Sheu WHH. Hypoglycaemic episodes and risk of dementia in diabetes mellitus: 7-year follow-up study. Journal of Internal Medicine. 2013 January;273(1):102-10. PMID 2013003846. *Not cognitive decline prevention intervention*

449. Lin JN, Lin CL, Lin MC, et al. Increased Risk of Dementia in Patients With Acute Organophosphate and Carbamate Poisoning: A Nationwide Population-Based Cohort Study. Medicine. 2015 Jul;94(29):e1187. PMID 26200627. *Not cognitive decline prevention intervention*

450. Lindenmayer JP, Khan A. Galantamine augmentation of long-acting injectable risperidone for cognitive impairments in chronic schizophrenia. Schizophrenia Research. 2011 February;125(2-3):267-77. PMID 2011052376. *Ineligible population*

451. Lippa CF, Rosso A, Hepler M, et al. Levetiracetam: a practical option for seizure management in elderly patients with cognitive impairment. American Journal of Alzheimer's Disease & Other Dementias. 2010 Mar;25(2):149-54. PMID 19001351. *Inadequate follow up time*

452. Lipton RB, Hirsch J, Katz MJ, et al. Exceptional parental longevity associated with lower risk of Alzheimer's disease and memory decline. Journal of the American Geriatrics Society. 2010 Jun;58(6):1043-9. PMID 20487085. *Cohort study with inadequate sample size*

453. Littlejohns TJ, Henley WE, Lang IA, et al. Vitamin D and the risk of dementia and Alzheimer disease. Neurology. 2014 Sep 2;83(10):920-8. PMID 25098535. *Not cognitive decline prevention intervention*

454. Litvinenko IV, Vorob'ev SV, Lobzin VY, et al. Possibilities of pharmacological modulation of brain glutamatergic system in the treatment of vascular cognitive impairment. [Russian]. Zhurnal Nevrologii i Psihiatrii imeni S.S. 2013;Korsakova. 2013(9):29-35. PMID 2014590162. *Not available in English*

455. Litvinenko IV, Vorob'ev SV, Lobzin VY, et al. Possibilities of pharmacological modulation of brain glutamatergic system in the treatment of vascular cognitive impairment. Zhurnal Nevrologii i Psihiatrii imeni S.S. 2013;Korsakova. 2013(9):29-35. PMID 2013654201. *Ineligible population*

456. Liu C, Zeng CL, Zhen LR. Effects of HMG-CoA reductase inhibitors on primary hypertension patients with vascular cognitive impairment. [Chinese]. Chinese Pharmaceutical Journal. 2010 May;45(9):706-9. PMID 2010492740. *Not available in English*

457. Liu YH, Wang DX, Li LH, et al. The effects of cardiopulmonary bypass on the number of cerebral microemboli and the incidence of cognitive dysfunction after coronary artery bypass graft surgery. Anesthesia & Analgesia. 2009 Oct;109(4):1013-22. PMID 19762724. *Cohort study with inadequate sample size*

458. Liu-Ambrose T, Donaldson MG. Exercise and cognition in older adults: is there a role for resistance training programmes? British Journal of Sports Medicine. 2009 Jan;43(1):25-7. PMID 19019904. *Ineligible study design*

459. Liu-Ambrose T, Eng JJ, Boyd LA, et al. Promotion of the mind through exercise (PROMoTE): a proof-of-concept randomized controlled trial of aerobic exercise training in older adults with vascular cognitive impairment. BMC Neurology. 2010;10:14. PMID 20158920. *Ineligible study design*

460. Lobo E, Dufouil C, Marcos G, et al. Is there an association between low-to-moderate alcohol consumption and risk of cognitive decline? American Journal of Epidemiology. 2010 Sep 15;172(6):708-16. PMID 20699263. *Not cognitive decline prevention intervention*

461. Loef M, Walach H. Fruit, vegetables and prevention of cognitive decline or dementia: a systematic review of cohort studies. Journal of Nutrition, Health & Aging. 2012 Jul;16(7):626-30. PMID 22836704. *Ineligible study design*

462. Lohman MC, Rebok GW, Spira AP, et al. Depressive symptoms and memory performance among older adults: results from the ACTIVE memory training intervention. Journal of Aging & Health. 2013 Dec;25(8 Suppl):209S-29S. PMID 23006426. *Not cognitive decline prevention intervention*

463. Lopez LB, Kritz-Silverstein D, Barrett Connor E. High dietary and plasma levels of the omega-3 fatty acid docosahexaenoic acid are associated with decreased dementia risk: the Rancho Bernardo study. Journal of Nutrition, Health & Aging. 2011 Jan;15(1):25-31. PMID 21267518. *Cohort study with inadequate sample size*

464. Louis ED, Benito-Leon J, Bermejo-Pareja F, et al. Antihypertensive agents and risk of Parkinson's disease, essential tremor and dementia: a population-based prospective study (NEDICES). Neuroepidemiology. 2009;33(3):286-92. PMID 19696520. *Not cognitive decline prevention intervention*

465. Lovell MA, Abner E, Kryscio R, et al. Calcium Channel Blockers, Progression to Dementia, and Effects on Amyloid Beta Peptide Production. Oxidative Medicine and Cellular Longevity. 2015;2015 (no pagination)(787805)PMID 2015195362. *Not cognitive decline prevention intervention*

466. Lovestone S, Boada M, Dubois B, et al. A phase II trial of tideglusib in alzheimer's disease. Journal of Alzheimer's Disease. 2015;45(1):75-88. PMID 2015808408. *Ineligible population*

467. Lovheim H, Gilthorpe J, Adolfsson R, et al. Reactivated herpes simplex infection increases the risk of Alzheimer's disease. Alzheimer's and Dementia. 2015 01 Jun;11(6):593-9. PMID 2014736948. *Not cognitive decline prevention intervention*

468. Low LF, Anstey KJ, Sachdev P. Use of medications with anticholinergic properties and cognitive function in a young-old community sample. International Journal of Geriatric Psychiatry. 2009 Jun;24(6):578-84. PMID 19021151. *Not cognitive decline prevention intervention*

469. Lu PH, Edland SD, Teng E, et al. Donepezil delays progression to AD in MCI subjects with depressive symptoms. Neurology. 2009 Jun 16;72(24):2115-21. PMID 19528519. *No relevant outcomes reported*

470. Luck T, Luppa M, Angermeyer MC, et al. Impact of impairment in instrumental activities of daily living and mild cognitive impairment on time to incident dementia: results of the Leipzig Longitudinal Study of the Aged. Psychological Medicine. 2011 May;41(5):1087-97. PMID 20667169. *Ineligible study design*

471. Luck T, Luppa M, Wiese B, et al. Prediction of incident dementia: impact of impairment in instrumental activities of daily living and mild cognitive impairment-results from the German study on ageing, cognition, and dementia in primary care patients. American Journal of Geriatric Psychiatry. 2012 Nov;20(11):943-54. PMID 22706332. *Not cognitive decline prevention intervention*

472. Luck T, Riedel-Heller SG, Luppa M, et al. Apolipoprotein E epsilon 4 genotype and a physically active lifestyle in late life: analysis of gene-environment interaction for the risk of dementia and Alzheimer's disease dementia. Psychological Medicine. 2014 Apr;44(6):1319-29. PMID 23883793. *Not cognitive decline prevention intervention*

473. Luck T, Riedel-Heller SG, Luppa M, et al. Risk factors for incident mild cognitive impairment--results from the German Study on Ageing, Cognition and Dementia in Primary Care Patients (AgeCoDe). Acta Psychiatrica Scandinavica. 2010 Apr;121(4):260-72. PMID 19824992. *Not cognitive decline prevention intervention*

474. Luttenberger K, Hofner B, Graessel E. Are the effects of a non-drug multimodal activation therapy of dementia sustainable? Follow-up study 10 months after completion of a randomised controlled trial. BMC Neurology. 2012;12:151. PMID 23217188. *Ineligible population*

475. Lynga P, Persson H, Hagg-Martinell A, et al. Weight monitoring in patients with severe heart failure (WISH). A randomized controlled trial. European Journal of Heart Failure. 2012 Apr;14(4):438-44. PMID 22371525. *No relevant outcomes reported*

476. Ma F, Wu T, Miao R, et al. Conversion of mild cognitive impairment to dementia among subjects with diabetes: a population-based study of incidence and risk factors with five years of follow-up. Journal of Alzheimer's Disease. 2015;43(4):1441-9. PMID 25159674. *Not cognitive decline prevention intervention*

477. Mahdavi A, Besharat MA, Taghizadeh ME, et al. Effectiveness of multi-sensory stimulations upon restoration of cognitive performance of patients exposed vascular dementia. Der Pharmacia Lettre. 2015;7(7):19-22. PMID 2015257115. *Ineligible population*

478. Maher-Edwards G, De'Ath J, Barnett C, et al. A 24-week study to evaluate the effect of rilapladib on cognition and cerebrospinal fluid biomarkers of Alzheimer's disease. Alzheimer's and Dementia: Translational Research and Clinical Interventions. 2015 15 Oct;1(2):131-40. PMID 2015445710. *Ineligible population*

479. Maher-Edwards G, Dixon R, Hunter J, et al. SB-742457 and donepezil in Alzheimer disease: a randomized, placebo-controlled study. International Journal of Geriatric Psychiatry. 2011 May;26(5):536-44. PMID 20872778. *Ineligible population*

480. Maher-Edwards G, Watson C, Ascher J, et al. Two randomized controlled trials of SB742457 in mild-to-moderate Alzheimer's disease. Alzheimer's and Dementia: Translational Research and Clinical Interventions. 2015 14 Oct;1(1):23-36. PMID 2015441551. *Ineligible population*

481. Maher-Edwards G, Zvartau-Hind M, Hunter AJ, et al. Double-blind, controlled phase ii study of a 5-ht6 receptor antagonist, sb-742457, in alzheimer's disease. Current Alzheimer Research. 2010;7(5):374-85. PMID 2010637453. *Ineligible population*

482. Maillot P, Perrot A, Hartley A. Effects of interactive physical-activity video-game training on physical and cognitive function in older adults. Psychology & Aging. 2012 Sep;27(3):589-600. PMID 22122605. *Inadequate follow up time*

483. Maki PM, Dennerstein L, Clark M, et al. Perimenopausal use of hormone therapy is associated with enhanced memory and hippocampal function later in life. Brain Research. 2011 Mar 16;1379:232-43. PMID 21078303. *Cohort study with inadequate sample size*

484. Maki PM, Henderson VW. Hormone therapy, dementia, and cognition: the Women's Health Initiative 10 years on. Climacteric. 2012 Jun;15(3):256-62. PMID 22612612. *Ineligible study design*

485. Makino KM, Porsteinsson AP. Memantine: A treatment for Alzheimers disease with a new formulation. Aging Health. 2011 June;7(3):349-62. PMID 2011351492. *Ineligible study design*

486. Makizako H, Doi T, Shimada H, et al. Does a multicomponent exercise program improve dual-task performance in amnestic mild cognitive impairment? A randomized controlled trial. Aging-Clinical & Experimental Research. 2012 Dec;24(6):640-6. PMID 23211228. *No relevant outcomes reported*

487. Malkki H. Dementia: New study puts its FINGER on prevention of cognitive decline. Nature Reviews Neurology. 2015 11 May;11(5):248. PMID 2015865264. *Ineligible study design*

488. Mamikonyan E, Xie SX, Melvin E, et al. Rivastigmine for mild cognitive impairment in Parkinson disease: A placebo-controlled study. Movement Disorders. 2015 01 Jun;30(7):912-8. PMID 2015970313. *Ineligible population*

489. Mammarella N, Fairfield B. Where did I put my keys? - a 'we' intervention to promote memory in healthy older adults: a controlled pilot study. Gerontology. 2013;59(4):349-54. PMID 23364128. *Inadequate follow up time*

490. Man DW, Chung JC, Lee GY. Evaluation of a virtual reality-based memory training programme for Hong Kong Chinese older adults with questionable dementia: a pilot study. International Journal of Geriatric Psychiatry. 2012 May;27(5):513-20. PMID 21681818. *Ineligible population*

491. Manenti R, Brambilla M, Petesi M, et al. Enhancing verbal episodic memory in older and young subjects after non-invasive brain stimulation. Frontiers in Aging Neuroscience. 2013;5(SEP)PMID 2014170746. *Inadequate follow up time*

492. Mangialasche F, Solomon A, Kareholt I, et al. Serum levels of vitamin E forms and risk of cognitive impairment in a Finnish cohort of older adults. Experimental Gerontology. 2013 Dec;48(12):1428-35. PMID 24113154. *Cohort study with inadequate sample size*

493. Mannikko R, Komulainen P, Schwab U, et al. The Nordic diet and cognition--The DR's EXTRA Study. British Journal of Nutrition. 2015 Jul;114(2):231-9. PMID 26104270. *No relevant outcomes reported*

494. Marek GJ, Katz DA, Meier A, et al. Efficacy and safety evaluation of HSD-1 inhibitor ABT-384 in Alzheimer's disease. Alzheimer's & Dementia. 2014 Oct;10(5 Suppl):S364-73. PMID 24418055. *Ineligible population*

495. Marmeleira JF, Godinho MB, Fernandes OM. The effects of an exercise program on several abilities associated with driving performance in older adults. Accident Analysis & Prevention. 2009 Jan;41(1):90-7. PMID 19114142. *Inadequate follow up time*

496. Marshall GA, Zoller AS, Lorius N, et al. Functional activities questionnaire items that best discriminate and predict progression from clinically normal to mild cognitive impairment. Current Alzheimer Research. 2015;12(5):493-502. PMID 2015125099. *Ineligible study design*

497. Marzona I, O'Donnell M, Teo K, et al. Increased risk of cognitive and functional decline in patients with atrial fibrillation: results of the ONTARGET and TRANSCEND studies. CMAJ Canadian Medical Association Journal. 2012 Apr 3;184(6):E329-36. PMID 22371515. *No relevant outcomes reported*

498. Mastroiacovo D, Kwik-Uribe C, Grassi D, et al. Cocoa flavanol consumption improves cognitive function, blood pressure control, and metabolic profile in elderly subjects: the Cocoa, Cognition, and Aging (CoCoA) Study--a randomized controlled trial. American Journal of Clinical Nutrition. 2015 Mar;101(3):538-48. PMID 25733639. *Inadequate follow up time*

499. Matousek RH, Sherwin BB. A randomized controlled trial of add-back estrogen or placebo on cognition in men with prostate cancer receiving an antiandrogen and a gonadotropin-releasing hormone analog. Psychoneuroendocrinology. 2010 Feb;35(2):215-25. PMID 19615826. *Inadequate follow up time*

500. Mavaddat N, Roalfe A, Fletcher K, et al. Warfarin versus aspirin for prevention of cognitive decline in atrial fibrillation: randomized controlled trial (Birmingham Atrial Fibrillation Treatment of the Aged Study). Stroke. 2014 May;45(5):1381-6. PMID 24692475. *Ineligible population*

501. McGuinness B, Fuchs M, Barrett SL, et al. Platelet membrane beta-secretase activity in mild cognitive impairment and conversion to dementia: A longitudinal study. Journal of Alzheimer's Disease. 2015 24 Dec;49(4):1095-103. PMID 20160029198. *Cohort study with inadequate sample size*

502. McIntyre RS, Lophaven S, Olsen CK. A randomized, double-blind, placebo-controlled study of vortioxetine on cognitive function in depressed adults. International Journal of Neuropsychopharmacology. 2014 Oct;17(10):1557-67. PMID 24787143. *Inadequate follow up time*

503. Meador KJ, Gevins A, Leese PT, et al. Neurocognitive effects of brivaracetam, levetiracetam, and lorazepam. Epilepsia. 2011 Feb;52(2):264-72. PMID 20887370. *Inadequate follow up time*

504. Mechaeil R, Gard P, Jackson A, et al. Cognitive enhancement following acute losartan in normotensive young adults. Psychopharmacology. 2011 Sep;217(1):51-60. PMID 21484242. *Inadequate follow up time*

505. Mecocci P, Bladstrom A, Stender K. Effects of memantine on cognition in patients with moderate to severe Alzheimer's disease: post-hoc analyses of ADAS-cog and SIB total and single-item scores from six randomized, double-blind, placebo-controlled studies. International Journal of Geriatric Psychiatry. 2009 May;24(5):532-8. PMID 19274640. *Ineligible population*

506. Mehlig K, Skoog I, Waern M, et al. Physical activity, weight status, diabetes and dementia: a 34-year follow-up of the population study of women in Gothenburg. Neuroepidemiology. 2014;42(4):252-9. PMID 24923622. *Not cognitive decline prevention intervention*

507. Meinzer M, Antonenko D, Lindenberg R, et al. Electrical brain stimulation improves cognitive performance by modulating functional connectivity and task-specific activation. Journal of Neuroscience. 2012 Feb 1;32(5):1859-66. PMID 22302824. *Not cognitive decline prevention intervention*

508. Meinzer M, Lindenberg R, Antonenko D, et al. Anodal transcranial direct current stimulation temporarily reverses age-associated cognitive decline and functional brain activity changes. Journal of Neuroscience. 2013 Jul 24;33(30):12470-8. PMID 23884951. *Inadequate follow up time*

509. Meinzer M, Lindenberg R, Phan MT, et al. Transcranial direct current stimulation in mild cognitive impairment: Behavioral effects and neural mechanisms. Alzheimer's and Dementia. 2015 01 Sep;11(9):1032-40. PMID 2015397617. *Inadequate follow up time*

510. Meiron O, Lavidor M. Prefrontal oscillatory stimulation modulates access to cognitive control references in retrospective metacognitive commentary. Clinical Neurophysiology. 2014 Jan;125(1):77-82. PMID 23831184. *Inadequate follow up time*

511. Mejia-Arango S, Zuniga-Gil C. Diabetes mellitus as a risk factor for dementia in the mexican elder population

Diabetes mellitus como factor de riesgo de demencia en la poblacion adulta mayor mexicana. Revista de Neurologia. 2011;53(7):397-405. PMID 2011559427. *Not available in English*

512. Melloni M, Sedeno L, Couto B, et al. Preliminary evidence about the effects of meditation on interoceptive sensitivity and social cognition. Behavioral & Brain Functions [Electronic Resource]: BBF. 2013;9:47. PMID 24365106. *Inadequate follow up time*

513. Merchant RA, Li B, Yap KB, et al. Use of drugs with anticholinergic effects and cognitive impairment in community-living older persons. Age & Ageing. 2009 Jan;38(1):105-8. PMID 19008305. *Not cognitive decline prevention intervention*

514. Merritt P, Stangl B, Hirshman E, et al. Administration of dehydroepiandrosterone (DHEA) increases serum levels of androgens and estrogens but does not enhance short-term memory in post-menopausal women. Brain Research. 2012 Nov 5;1483:54-62. PMID 22985672. *Inadequate follow up time*

515. Miao YC, Tian JZ, Shi J, et al. Effects of Chinese medicine for tonifying the kidney and resolving phlegm and blood stasis in treating patients with amnestic mild cognitive impairment: a randomized, double-blind and parallel-controlled trial. Zhong Xi Yi Jie He Xue Bao/Journal of Chinese Integrative Medicine. 2012 Apr;10(4):390-7. PMID 22500712. *Inadequate follow up time*

516. Middleton LE, Manini TM, Simonsick EM, et al. Activity energy expenditure and incident cognitive impairment in older adults. Archives of Internal Medicine. 2011 Jul 25;171(14):1251-7. PMID 21771893. *Cohort study with inadequate sample size*

517. Miettinen PS, Jauhiainen AM, Tarkka IM, et al. Long-term response to cholinesterase inhibitor treatment is related to functional MRI response in Alzheimer's disease. Dementia and Geriatric Cognitive Disorders. 2015 14 Oct;40(5-6):243-55. PMID 2015348323. *Ineligible population*

518. Milte CM, Sinn N, Street SJ, et al. Erythrocyte polyunsaturated fatty acid status, memory, cognition and mood in older adults with mild cognitive impairment and healthy controls. Prostaglandins Leukotrienes & Essential Fatty Acids. 2011 May-Jun;84(5-6):153-61. PMID 21392955. *Not cognitive decline prevention intervention*

519. Mintzer MZ, Kleykamp BA, Griffiths RR. Dose Effects of Triazolam and Scopolamine on Metamemory. Experimental and Clinical Psychopharmacology. 2010 February;18(1):17-31. PMID 2010110883. *Inadequate follow up time*

520. Miwa K, Tanaka M, Okazaki S, et al. Increased total homocysteine levels predict the risk of incident dementia independent of cerebral small-vessel diseases and vascular risk factors. Journal of Alzheimer's Disease. 2015 09 Oct;49(2):503-13. PMID 2015551994. *Not cognitive decline prevention intervention*

521. Miyoshi I, Fujimoto Y, Yamada M, et al. Safety and pharmacokinetics of PF-04360365 following a single-dose intravenous infusion in Japanese subjects with mild-to-moderate Alzheimer's disease: a multicenter, randomized, double-blind, placebo-controlled, dose-escalation study. International Journal of Clinical Pharmacology & Therapeutics. 2013 Dec;51(12):911-23. PMID 24131736. *Ineligible population*

522. Modrego PJ, Fayed N, Errea JM, et al. Memantine versus donepezil in mild to moderate Alzheimer's disease: a randomized trial with magnetic resonance spectroscopy. European Journal of Neurology. 2010 Mar;17(3):405-12. PMID 19874395. *Ineligible population*

523. Mohs RC, Shiovitz TM, Tariot PN, et al. Atomoxetine augmentation of cholinesterase inhibitor therapy in patients with Alzheimer disease: 6-month, randomized, double-blind, placebo-controlled, parallel-trial study. American Journal of Geriatric Psychiatry. 2009 Sep;17(9):752-9. PMID 19700948. *Ineligible population*

524. Mokhova OI. [The use of reminyl (galantamine) in the treatment of probable vascular dementia]. Zhurnal Nevrologii i Psikhiatrii Imeni S.S. Korsakova. 2009;109(9):77-9. PMID 19911468. *Not available in English*

525. Molinuevo JL, Berthier ML, Rami L. Donepezil provides greater benefits in mild compared to moderate Alzheimer's disease: implications for early diagnosis and treatment. Archives of Gerontology & Geriatrics. 2011 Jan-Feb;52(1):18-22. PMID 19948364. *Ineligible population*

526. Molinuevo JL, Frolich L, Grossberg GT, et al. Responder analysis of a randomized comparison of the 13.3 mg/24 h and 9.5 mg/24 h rivastigmine patch. Alzheimer's Research and Therapy. 2015 08 Mar;7(1)PMID 2015957412. *Ineligible population*

527. Montine TJ, Sonnen JA, Montine KS, et al. Adult changes in thought study: Dementia is an individually varying convergent syndrome with prevalent clinically silent diseases that may be modified by some commonly used therapeutics. Current Alzheimer Research. 2012 July;9(6):718-23. PMID 2012391770. *Ineligible study design*

528. Moon JH, Lim S, Han JW, et al. Serum 25-hydroxyvitamin D level and the risk of mild cognitive impairment and dementia: The Korean Longitudinal Study on Health and Aging (KLoSHA). Clinical Endocrinology. 2015 01 Jul;83(1):36-42. PMID 2015796039. *Cohort study with inadequate sample size*

529. Moon SY, Na DL, Seo SW, et al. Impact of white matter changes on activities of daily living in mild to moderate dementia. European Neurology. 2011 April;65(4):223-30. PMID 2011224387. *Ineligible population*

530. Moore EM, Mander AG, Ames D, et al. Increased risk of cognitive impairment in patients with diabetes is associated with metformin. Diabetes Care. 2013 October;36(10):2981-7. PMID 2014022050. *Ineligible population*

531. Moore EM, Mander AG, Ames D, et al. Increased risk of cognitive impairment in patients with diabetes is associated with metformin.[Erratum appears in Diabetes Care. 2013 Nov;36(11):3850]. Diabetes Care. 2013 Oct;36(10):2981-7. PMID 24009301. *Ineligible population*

532. Morgan GS, Gallacher J, Bayer A, et al. Physical activity in middle-age and dementia in later life: findings from a prospective cohort of men in Caerphilly, South Wales and a meta-analysis. Journal of Alzheimer's Disease. 2012;31(3):569-80. PMID 22647258. *Not cognitive decline prevention intervention*

533. Morillas-Ruiz JM, Rubio-Perez JM, Albaladejo MD, et al. Effect of an antioxidant drink on homocysteine levels in Alzheimer's patients. Journal of the Neurological Sciences. 2010 Dec 15;299(1-2):175-8. PMID 20850133. *Ineligible population*

534. Morimoto BH, Schmechel D, Hirman J, et al. A double-blind, placebo-controlled, ascending-dose, randomized study to evaluate the safety, tolerability and effects on cognition of AL-108 after 12 weeks of intranasal administration in subjects with mild cognitive impairment. Dementia & Geriatric Cognitive Disorders. 2013;35(5-6):325-36. PMID 23594991. *Inadequate follow up time*

535. Moro V, Condoleo MT, Valbusa V, et al. Cognitive stimulation of executive functions in mild cognitive impairment: Specific efficacy and impact in memory. American Journal of Alzheimer's Disease and other Dementias. 2015 25 Mar;30(2):153-64. PMID 2015867211. *Ineligible study design*

536. Morris MC, Tangney CC, Wang Y, et al. MIND diet slows cognitive decline with aging. Alzheimer's and Dementia. 2015 01 Sep;11(9):1015-22. PMID 2015186686. *No relevant outcomes reported*

537. Morris MC, Tangney CC, Wang Y, et al. MIND diet associated with reduced incidence of Alzheimer's disease. Alzheimer's and Dementia. 2015 01 Sep;11(9):1007-14. PMID 2015807456. *Not cognitive decline prevention intervention*

538. Moss DE, Fariello RG, Sahlmann J, et al. A randomized phase I study of methanesulfonyl fluoride, an irreversible cholinesterase inhibitor, for the treatment of Alzheimer's disease. British Journal of Clinical Pharmacology. 2013 May;75(5):1231-9. PMID 2013232518. *Inadequate follow up time*

539. Mowszowski L, Hermens DF, Diamond K, et al. Cognitive training enhances pre-attentive neurophysiological responses in older adults 'at risk' of dementia. Journal of Alzheimer's Disease. 2014;41(4):1095-108. PMID 24787916. *Inadequate follow up time*

540. Mozolic JL, Long AB, Morgan AR, et al. A cognitive training intervention improves modality-specific attention in a randomized controlled trial of healthy older adults. Neurobiology of Aging. 2011 Apr;32(4):655-68. PMID 19428142. *Inadequate follow up time*

541. Mrazek MD, Franklin MS, Phillips DT, et al. Mindfulness training improves working memory capacity and GRE performance while reducing mind wandering. Psychological Science. 2013 May;24(5):776-81. PMID 23538911. *Inadequate follow up time*

542. Muller U, Rowe JB, Rittman T, et al. Effects of modafinil on non-verbal cognition, task enjoyment and creative thinking in healthy volunteers. Neuropharmacology. 2013 Jan;64:490-5. PMID 22820554. *Inadequate follow up time*

543. Muniz R, Serra CM, Reisberg B, et al. Cognitive-motor intervention in alzheimer's disease: Long-term results from the maria wolff trial. Journal of Alzheimer's Disease. 2015;45(1):295-304. PMID 2015808400. *Ineligible population*

544. Murphy GM, Jr., Sarginson JE, Ryan HS, et al. BDNF and CREB1 genetic variants interact to affect antidepressant treatment outcomes in geriatric depression. Pharmacogenetics and Genomics. 2013 Jun;23(6):301-13. PMID 23619509. *Inadequate follow up time*

545. Musicco M. Lifestyle and rate of progression of cognitive decline: Results of the SINDEM cohort study. Journal of Alzheimer's Disease. 2011;23(SUPPL. 1):S17-S8. PMID 2011121429. *Not cognitive decline prevention intervention*

546. Musicco M, Adorni F, Di Santo S, et al. Inverse occurrence of cancer and Alzheimer disease: A population-based incidence study. Neurology. 2013 23 Jul;81(4):322-8. PMID 2013498921. *Not cognitive decline prevention intervention*

547. Na HR, Kim S, Choi SH, et al. Donepezil treatment in Alzheimer's disease patients with and without cerebrovascular lesions: a preliminary report. Geriatrics & gerontology international. 2011 Jan;11(1):90-7. PMID 20825496. *Ineligible population*

548. Nagata K, Yokoyama E, Yamazaki T, et al. Effects of yokukansan on behavioral and psychological symptoms of vascular dementia: an open-label trial. Phytomedicine. 2012 Apr 15;19(6):524-8. PMID 22421528. *Ineligible population*

549. Naismith SL, Diamond K, Carter PE, et al. Enhancing memory in late-life depression: the effects of a combined psychoeducation and cognitive training program. American Journal of Geriatric Psychiatry. 2011 Mar;19(3):240-8. PMID 20808114. *Inadequate follow up time*

550. Naismith SL, Glozier N, Burke D, et al. Early intervention for cognitive decline: is there a role for multiple medical or behavioural interventions? Early intervention in psychiatry. 2009 Feb;3(1):19-27. PMID 21352171. *Ineligible study design*

551. Nakamura Y, Kitamura S, Homma A, et al. Efficacy and safety of memantine in patients with moderate-to-severe Alzheimer's disease: results of a pooled analysis of two randomized, double-blind, placebo-controlled trials in Japan. Expert Opinion on Pharmacotherapy. 2014 May;15(7):913-25. PMID 24673497. *Ineligible population*

552. Napryeyenko O, Sonnik G, Tartakovsky I. Efficacy and tolerability of Ginkgo biloba extract EGb 761 by type of dementia: analyses of a randomised controlled trial. Journal of the Neurological Sciences. 2009 Aug 15;283(1-2):224-9. PMID 19286192. *Ineligible population*

553. Naqvi R, Liberman D, Rosenberg J, et al. Preventing cognitive decline in healthy older adults. CMAJ Canadian Medical Association Journal. 2013 Jul 9;185(10):881-5. PMID 23589432. *Ineligible study design*

554. Narasimhalu K, Effendy S, Sim CH, et al. A randomized controlled trial of rivastigmine in patients with cognitive impairment no dementia because of cerebrovascular disease. Acta Neurologica Scandinavica. 2010 Apr;121(4):217-24. PMID 19951274. *Ineligible population*

555. Nardone R, Tezzon F, Holler Y, et al. Transcranial magnetic stimulation (TMS)/repetitive TMS in mild cognitive impairment and Alzheimer's disease. Acta Neurologica Scandinavica. 2014 Jun;129(6):351-66. PMID 24506061. *Ineligible study design*

556. Narendran R, Frankle WG, Mason NS, et al. Improved working memory but no effect on striatal vesicular monoamine transporter type 2 after omega-3 polyunsaturated fatty acid supplementation. PLoS ONE [Electronic Resource]. 2012;7(10):e46832. PMID 23056476. *No relevant outcomes reported*

557. Nasab NM, Bahrammi MA, Nikpour MR, et al. Efficacy of rivastigmine in comparison to ginkgo for treating Alzheimer's dementia. JPMA - Journal of the Pakistan Medical Association. 2012 Jul;62(7):677-80. PMID 23866514. *Ineligible population*

558. Nascimento CM, Teixeira CV, Gobbi LT, et al. A controlled clinical trial on the effects of exercise on neuropsychiatric disorders and instrumental activities in women with Alzheimer's disease. Revista Brasileira de Fisioterapia. 2012 Jun;16(3):197-204. PMID 22499405. *Ineligible population*

559. Nathan PJ, Watson J, Lund J, et al. The potent M1 receptor allosteric agonist GSK1034702 improves episodic memory in humans in the nicotine abstinence model of cognitive dysfunction. International Journal of Neuropsychopharmacology. 2013 May;16(4):721-31. PMID 22932339. *Inadequate follow up time*

560. Nelson C, Wengreen HJ, Munger RG, et al. Dietary folate, vitamin B-12, vitamin B-6 and incident Alzheimer's disease: the cache county memory, health and aging study. Journal of Nutrition, Health & Aging. 2009 Dec;13(10):899-905. PMID 19924351. *Not cognitive decline prevention intervention*

561. Newhouse P, Albert K, Astur R, et al. Tamoxifen improves cholinergically modulated cognitive performance in postmenopausal women. Neuropsychopharmacology. 2013 Dec;38(13):2632-43. PMID 23867982. *Inadequate follow up time*

562. Newhouse PA, Dumas J, Wilkins H, et al. Estrogen treatment impairs cognitive performance after psychosocial stress and monoamine depletion in postmenopausal women. Menopause. 2010 Jul;17(4):860-73. PMID 20616673. *Inadequate follow up time*

563. Neznamov GG, Teleshova ES. Comparative studies of Noopept and piracetam in the treatment of patients with mild cognitive disorders in organic brain diseases of vascular and traumatic origin. Neuroscience & Behavioral Physiology. 2009 Mar;39(3):311-21. PMID 19234797. *Inadequate follow up time*

564. Ng TP, Feng L, Yap KB, et al. Long-term metformin usage and cognitive function among older adults with diabetes. Journal of Alzheimer's Disease. 2014;41(1):61-8. PMID 24577463. *Cohort study with inadequate sample size*

565. Ngandu T, Lehtisalo J, Levalahti E, et al. Recruitment and baseline characteristics of participants in the finnish geriatric intervention study to prevent cognitive impairment and disability (FINGER)-A randomized controlled lifestyle trial. International Journal of Environmental Research and Public Health. 2014 10 Sep;11(9):9345-60. PMID 2014842635. *Ineligible population*

566. Nilsson A, Radeborg K, Salo I, et al. Effects of supplementation with n-3 polyunsaturated fatty acids on cognitive performance and cardiometabolic risk markers in healthy 51 to 72 years old subjects: a randomized controlled cross-over study. Nutrition Journal. 2012;11:99. PMID 23173831. *Inadequate follow up time*

567. Nishiguchi S, Yamada M, Tanigawa T, et al. A 12-Week Physical and Cognitive Exercise Program Can Improve Cognitive Function and Neural Efficiency in Community-Dwelling Older Adults: A Randomized Controlled Trial. Journal of the American Geriatrics Society. 2015 Jul;63(7):1355-63. PMID 26114906. *Inadequate follow up time*

568. Noguchi-Shinohara M, Yuki S, Dohmoto C, et al. Consumption of green tea, but not black tea or coffee, is associated with reduced risk of cognitive decline. PLoS ONE. 2014 14 May;9(5)PMID 2014356288. *Cohort study with inadequate sample size*

569. Nolan JM, Loskutova E, Howard A, et al. The impact of supplemental macular carotenoids in Alzheimer's disease: a randomized clinical trial. Journal of Alzheimer's Disease. 2015;44(4):1157-69. PMID 25408222. *Ineligible population*

570. Nordberg A, Kadir A, Andreasen N, et al. Correlations between Alzheimer's Disease Cerebrospinal Fluid Biomarkers and Cerebral Glucose Metabolism after 12 Months of Phenserine Treatment. Journal of Alzheimer's Disease. 2015 03 Aug;47(3):691-704. PMID 2015255626. *Ineligible population*

571. Norton MC, Clark CJ, Tschanz JT, et al. The design and progress of a multidomain lifestyle intervention to improve brain health in middle-aged persons to reduce later Alzheimer's disease risk: The Gray Matters randomized trial. Alzheimer's and Dementia: Translational Research and Clinical Interventions. 2015 14 Oct;1(1):53-62. PMID 2015440968. *Ineligible study design*

572. Norton MC, Dew J, Smith H, et al. Lifestyle behavior pattern is associated with different levels of risk for incident dementia and Alzheimer's disease: the Cache County study. Journal of the American Geriatrics Society. 2012 Mar;60(3):405-12. PMID 22316091. *Not cognitive decline prevention intervention*

573. Nouchi R, Taki Y, Takeuchi H, et al. Brain training game improves executive functions and processing speed in the elderly: a randomized controlled trial. PLoS ONE [Electronic Resource]. 2012;7(1):e29676. PMID 22253758. *Inadequate follow up time*

574. Nouchi R, Taki Y, Takeuchi H, et al. Four weeks of combination exercise training improved executive functions, episodic memory, and processing speed in healthy elderly people: evidence from a randomized controlled trial. Age. 2014 Apr;36(2):787-99. PMID 24065294. *Inadequate follow up time*

575. Novak V, Milberg W, Hao Y, et al. Enhancement of vasoreactivity and cognition by intranasal insulin in type 2 diabetes. Diabetes Care. 2014;37(3):751-9. PMID 24101698. *Inadequate follow up time*

576. Nozawa M, Ichimiya Y, Nozawa E, et al. Clinical effects of high oral dose of donepezil for patients with Alzheimer's disease in Japan. Psychogeriatrics:The Official Journal of the Japanese Psychogeriatric Society. 2009 Jun;9(2):50-5. PMID 19604325. *Ineligible population*

577. Nunes MA, Viel TA, Buck HS. Microdose lithium treatment stabilized cognitive impairment in patients with Alzheimer's disease. Current Alzheimer Research. 2013;10(1):104-7. PMID 2013746091. *Ineligible population*

578. O'Callaghan N, Parletta N, Milte CM, et al. Telomere shortening in elderly individuals with mild cognitive impairment may be attenuated with omega-3 fatty acid supplementation: a randomized controlled pilot study. Nutrition. 2014 Apr;30(4):489-91. PMID 24342530. *No relevant outcomes reported*

579. Oehlrich D, Berthelot DJ, Gijsen HJ. gamma-Secretase modulators as potential disease modifying anti-Alzheimer's drugs. Journal of Medicinal Chemistry. 2011 Feb 10;54(3):669-98. PMID 21141968. *Ineligible study design*

580. Oei NY, Tollenaar MS, Elzinga BM, et al. Propranolol reduces emotional distraction in working memory: a partial mediating role of propranolol-induced cortisol increases? Neurobiology of Learning & Memory. 2010 Mar;93(3):388-95. PMID 20018249. *Inadequate follow up time*

581. Ogunniyi A, Gao S, Unverzagt FW, et al. Weight loss and incident dementia in elderly Yoruba Nigerians: a 10-year follow-up study. International Psychogeriatrics. 2011 Apr;23(3):387-94. PMID 20735893. *Ineligible population*

582. Ohara T, Ninomiya T, Kubo M, et al. Apolipoprotein genotype for prediction of Alzheimer's disease in older Japanese: the Hisayama Study. Journal of the American Geriatrics Society. 2011 Jun;59(6):1074-9. PMID 21649613. *Not cognitive decline prevention intervention*

583. O'Hare AM, Walker R, Haneuse S, et al. Relationship between longitudinal measures of renal function and onset of dementia in a community cohort of older adults. Journal of the American Geriatrics Society. 2012 December;60(12):2215-22. PMID 2012730823. *Not cognitive decline prevention intervention*

584. Ohnishi T, Sakiyama Y, Okuri Y, et al. The prediction of response to galantamine treatment in patients with mild to moderate Alzheimer's disease. Current Alzheimer Research. 2014 Feb;11(2):110-8. PMID 24156269. *Ineligible population*

585. Okereke OI, Kurth T, Pollak MN, et al. Fasting plasma insulin, C-peptide and cognitive change in older men without diabetes: results from the Physicians' Health Study II. Neuroepidemiology. 2010;34(4):200-7. PMID 20197703. *Not cognitive decline prevention intervention*

586. Okereke OI, Rosner BA, Kim DH, et al. Dietary fat types and 4-year cognitive change in community-dwelling older women.[Erratum appears in Ann Neurol. 2012 Oct;72(4):627]. Annals of Neurology. 2012 Jul;72(1):124-34. PMID 22605573. *Ineligible study design*

587. Okonkwo OC, Schultz SA, Oh JM, et al. Physical activity attenuates age-related biomarker alterations in preclinical AD. Neurology. 2014 04 Nov;83(19):1753-60. PMID 25298312. *Cohort study with inadequate sample size*

588. Okonkwo OC, Xu G, Dowling NM, et al. Family history of Alzheimer disease predicts hippocampal atrophy in healthy middle-aged adults. Neurology. 2012 May 29;78(22):1769-76. PMID 22592366. *Not cognitive decline prevention intervention*

589. Olchik MR, Farina J, Steibel N, et al. Memory training (MT) in mild cognitive impairment (MCI) generates change in cognitive performance. Archives of Gerontology & Geriatrics. 2013 May-Jun;56(3):442-7. PMID 23260332. *Inadequate follow up time*

590. Olde Rikkert MG, Verhey FR, Blesa R, et al. Tolerability and safety of Souvenaid in patients with mild Alzheimer's disease: results of multi-center, 24-week, open-label extension study. Journal of Alzheimer's Disease. 2015;44(2):471-80. PMID 25322923. *Ineligible population*

591. Olde Rikkert MG, Verhey FR, Sijben JW, et al. Differences in nutritional status between very mild Alzheimer's disease patients and healthy controls. Journal of Alzheimer's Disease. 2014;41(1):261-71. PMID 24614903. *Not cognitive decline prevention intervention*

592. Olin JT, Bhatnagar V, Reyes P, et al. Safety and tolerability of rivastigmine capsule with memantine in patients with probable Alzheimer's disease: a 26-week, open-label, prospective trial (Study ENA713B US32). International Journal of Geriatric Psychiatry. 2010 Apr;25(4):419-26. PMID 19670390. *Ineligible population*

593. Onur OA, Schlaepfer TE, Kukolja J, et al. The N-Methyl-D-Aspartate Receptor Co-agonist D-Cycloserine Facilitates Declarative Learning and Hippocampal Activity in Humans. Biological Psychiatry. 2010 15 Jun;67(12):1205-11. PMID 2010302403. *Inadequate follow up time*

594. Optale G, Urgesi C, Busato V, et al. Controlling memory impairment in elderly adults using virtual reality memory training: a randomized controlled pilot study. Neurorehabilitation & Neural Repair. 2010 May;24(4):348-57. PMID 19934445. *Ineligible population*

595. Orgeta V, Leung P, Yates L, et al. Individual cognitive stimulation therapy for dementia: A clinical effectiveness and cost-effectiveness pragmatic, multicentre, randomised controlled trial. Health Technology Assessment. 2015 01 Aug;19(64):7-73. PMID 2015323100. *Ineligible population*

596. Ormstad H, Rosness TA, Bergem ALM, et al. Alcohol consumption in the elderly and risk of dementia related death - A Norwegian prospective study with a 17-year follow-up. International Journal of Neuroscience. 2016 01 Feb;126(2):135-44. PMID 2015246336. *No relevant outcomes reported*

597. Orrell M, Aguirre E, Spector A, et al. Maintenance cognitive stimulation therapy for dementia: single-blind, multicentre, pragmatic randomised controlled trial. British Journal of Psychiatry. 2014 Jun;204(6):454-61. PMID 24676963. *Ineligible population*

598. Ostrowitzki S, Deptula D, Thurfjell L, et al. Mechanism of amyloid removal in patients with Alzheimer disease treated with gantenerumab. Archives of Neurology. 2012 Feb;69(2):198-207. PMID 21987394. *Ineligible population*

599. Otilingam PG, Gatz M, Tello E, et al. Buenos habitos alimenticios para una buena salud : evaluation of a nutrition education program to improve heart health and brain health in Latinas. Journal of Aging & Health. 2015 Feb;27(1):177-92. PMID 25231884. *Inadequate follow up time*

600. Owen L, Scholey A, Finnegan Y, et al. Response variability to glucose facilitation of cognitive enhancement. British Journal of Nutrition. 2013 Nov;110(10):1873-84. PMID 23789911. *Inadequate follow up time*

601. Ozawa M, Ninomiya T, Ohara T, et al. Dietary patterns and risk of dementia in an elderly Japanese population: the Hisayama Study. American Journal of Clinical Nutrition. 2013 May;97(5):1076-82. PMID 23553168. *Not cognitive decline prevention intervention*

602. Ozawa M, Ninomiya T, Ohara T, et al. Self-reported dietary intake of potassium, calcium, and magnesium and risk of dementia in the Japanese: the Hisayama Study. Journal of the American Geriatrics Society. 2012 Aug;60(8):1515-20. PMID 22860881. *Not cognitive decline prevention intervention*

603. Ozawa M, Ohara T, Ninomiya T, et al. Milk and dairy consumption and risk of dementia in an elderly Japanese population: the Hisayama Study. Journal of the American Geriatrics Society. 2014 Jul;62(7):1224-30. PMID 24916840. *Not cognitive decline prevention intervention*

604. Packard CJ, Westendorp RG, Stott DJ, et al. Association between apolipoprotein E4 and cognitive decline in elderly adults. Journal of the American Geriatrics Society. 2007 Nov;55(11):1777-85. PMID 17979899. *Not cognitive decline prevention intervention*

605. Paganini-Hill A. Hypertension and dementia in the elderly: The leisure world cohort study. International Journal of Hypertension. 2012;2012 (no pagination)(205350)PMID 2012644430. *Not cognitive decline prevention intervention*

606. Paganini-Hill A, White SC, Atchison KA. Dentition, dental health habits, and dementia: the Leisure World Cohort Study. Journal of the American Geriatrics Society. 2012 Aug;60(8):1556-63. PMID 22860988. *Not cognitive decline prevention intervention*

607. Page KA, Williamson A, Yu N, et al. Medium-chain fatty acids improve cognitive function in intensively treated type 1 diabetic patients and support in vitro synaptic transmission during acute hypoglycemia. Diabetes. 2009 May;58(5):1237-44. PMID 19223595. *Inadequate follow up time*

608. Pai MC, Aref H, Bassil N, et al. Real-world evaluation of compliance and preference in Alzheimer's disease treatment. Clinical Interventions in Aging. 2015 03 Nov;10:1779-88. PMID 2015508490. *No relevant outcomes reported*

609. Paillard-Borg S, Fratiglioni L, Xu W, et al. An active lifestyle postpones dementia onset by more than one year in very old adults. Journal of Alzheimer's Disease. 2012;31(4):835-42. PMID 22751170. *Not cognitive decline prevention intervention*

610. Pakdaman H, Harandi AA, Hatamian H, et al. Effectiveness and safety of MLC601 in the treatment of mild to moderate Alzheimer's disease: A multicenter, randomized controlled trial. Dementia and Geriatric Cognitive Disorders Extra. 2015;5(1):96-106. PMID 2015140253. *Ineligible population*

611. Palinkas LA, Reedy KR, Shepanek M, et al. A randomized placebo-controlled clinical trial of the effectiveness of thyroxine and triiodothyronine and short-term exposure to bright light in prevention of decrements in cognitive performance and mood during prolonged Antarctic residence. Clinical Endocrinology. 2010 Apr;72(4):543-50. PMID 19650782. *Inadequate follow up time*

612. Panza F, Frisardi V, Seripa D, et al. Alcohol consumption in mild cognitive impairment and dementia: harmful or neuroprotective? International Journal of Geriatric Psychiatry. 2012 Dec;27(12):1218-38. PMID 22396249. *Ineligible study design*

613. Panza F, Solfrizzi V, Barulli MR, et al. Coffee, tea, and caffeine consumption and prevention of late-life cognitive decline and dementia: a systematic review. Journal of Nutrition, Health & Aging. 2015 Mar;19(3):313-28. PMID 25732217. *Ineligible study design*

614. Parikh NM, Morgan RO, Kunik ME, et al. Risk factors for dementia in patients over 65 with diabetes. International Journal of Geriatric Psychiatry. 2011 July;26(7):749-57. PMID 2011213017. *Not cognitive decline prevention intervention*

615. Park SH, Seo JH, Kim YH, et al. Long-term effects of transcranial direct current stimulation combined with computer-assisted cognitive training in healthy older adults. Neuroreport. 2014 Jan 22;25(2):122-6. PMID 24176927. *Inadequate follow up time*

616. Park SK, Jung IC, Lee WK, et al. A combination of green tea extract and l-theanine improves memory and attention in subjects with mild cognitive impairment: a double-blind placebo-controlled study. Journal of Medicinal Food. 2011 Apr;14(4):334-43. PMID 21303262. *Inadequate follow up time*

617. Parnetti L, Chiasserini D, Andreasson U, et al. Changes in CSF acetyl- and butyrylcholinesterase activity after long-term treatment with AChE inhibitors in Alzheimer's disease. Acta Neurologica Scandinavica. 2011 Aug;124(2):122-9. PMID 20880294. *Ineligible population*

618. Pasqualetti P, Bonomini C, Dal Forno G, et al. A randomized controlled study on effects of ibuprofen on cognitive progression of Alzheimer's disease. Aging-Clinical & Experimental Research. 2009 Apr;21(2):102-10. PMID 19448381. *Ineligible population*

619. Patat A, Parks V, Raje S, et al. Safety, tolerability, pharmacokinetics and pharmacodynamics of ascending single and multiple doses of lecozotan in healthy young and elderly subjects. British Journal of Clinical Pharmacology. 2009 Mar;67(3):299-308. PMID 19523013. *Inadequate follow up time*

620. Pathan SS, Gottesman RF, Mosley TH, et al. Association of lung function with cognitive decline and dementia: the Atherosclerosis Risk in Communities (ARIC) Study. European Journal of Neurology. 2011 Jun;18(6):888-98. PMID 21244584. *Not cognitive decline prevention intervention*

621. Peneau S, Galan P, Jeandel C, et al. Fruit and vegetable intake and cognitive function in the SU.VI.MAX 2 prospective study. American Journal of Clinical Nutrition. 2011 Nov;94(5):1295-303. PMID 21955649. *No relevant outcomes reported*

622. Peng J, Lu F, Wang Z, et al. Excessive lowering of blood pressure is not beneficial for progression of brain white matter hyperintensive and cognitive impairment in elderly hypertensive patients: 4-year follow-up study. Journal of the American Medical Directors Association. 2014 Dec;15(12):904-10. PMID 25239015. *Cohort study with inadequate sample size*

623. Peng YH, Wu BR, Su CH, et al. Adult asthma increases dementia risk: a nationwide cohort study. Journal of Epidemiology & Community Health. 2015 Feb;69(2):123-8. PMID 25271249. *Not cognitive decline prevention intervention*

624. Pengelly A, Snow J, Mills SY, et al. Short-term study on the effects of rosemary on cognitive function in an elderly population. Journal of Medicinal Food. 2012 Jan;15(1):10-7. PMID 21877951. *Inadequate follow up time*

625. Perez L, Heim L, Sherzai A, et al. Nutrition and vascular dementia. Journal of Nutrition, Health & Aging. 2012 Apr;16(4):319-24. PMID 22499449. *Ineligible study design*

626. Perkins KA, Karelitz JL, Jao NC, et al. Effects of bupropion on cognitive performance during initial tobacco abstinence. Drug & Alcohol Dependence. 2013 Nov 1;133(1):283-6. PMID 23726977. *Inadequate follow up time*

627. Persson CM, Wallin AK, Levander S, et al. Changes in cognitive domains during three years in patients with Alzheimer's disease treated with donepezil. BMC Neurology. 2009;9:7. PMID 19208247. *Ineligible population*

628. Persson N, Viitanen M, Almkvist O, et al. A principal component model of medical health: implications for cognitive deficits and decline among adults in a population-based sample. Journal of Health Psychology. 2013 Oct;18(10):1268-87. PMID 23180878. *Ineligible study design*

629. Peters O. [Alzheimer's disease: are non-steroidal anti-inflammatory drugs effective?]. Deutsche Medizinische Wochenschrift. 2012 Dec;137(50):2627. PMID 23225182. *Not available in English*

630. Peters R, Beckett N, Fagard R, et al. Increased pulse pressure linked to dementia: further results from the Hypertension in the Very Elderly Trial - HYVET. Journal of Hypertension. 2013 Sep;31(9):1868-75. PMID 23743809. *Ineligible study design*

631. Phung KTT, Waldorff FB, Buss DV, et al. A three-year follow-up on the efficacy of psychosocial interventions for patients with mild dementia and their caregivers: The multicentre, rater-blinded, randomised Danish Alzheimer Intervention Study (DAISY). BMJ Open. 2013;3(11)PMID 2013772352. *Ineligible population*

632. Pietrzak RH, Lim YY, Ames D, et al. Trajectories of memory decline in preclinical Alzheimer's disease: results from the Australian Imaging, Biomarkers and Lifestyle Flagship Study of ageing. Neurobiology of Aging. 2015 Mar;36(3):1231-8. PMID 25585532. *Not cognitive decline prevention intervention*

633. Piette F, Belmin J, Vincent H, et al. Masitinib as an adjunct therapy for mild-to-moderate Alzheimer's disease: A randomised, placebo-controlled phase 2 trial. Alzheimer's Research and Therapy. 2011;3(2)PMID 2011300018. *Ineligible population*

634. Pilatus U, Lais C, Rochmont Adu M, et al. Conversion to dementia in mild cognitive impairment is associated with decline of N-actylaspartate and creatine as revealed by magnetic resonance spectroscopy. Psychiatry Research. 2009 Jul 15;173(1):1-7. PMID 19427767. *Cohort study with inadequate sample size*

635. Pitkala KH, Poysti MM, Laakkonen ML, et al. Effects of the Finnish Alzheimer disease exercise trial (FINALEX): a randomized controlled trial. JAMA Internal Medicine. 2013 May 27;173(10):894-901. PMID 23589097. *Ineligible population*

636. Pitkala KH, Raivio MM, Laakkonen ML, et al. Exercise rehabilitation on home-dwelling patients with Alzheimer disease: A randomized, controlled trial. Baseline findings and feasibility. European Geriatric Medicine. 2011 December;2(6):338-43. PMID 2011616075. *Ineligible population*

637. Pitkala KH, Routasalo P, Kautiainen H, et al. Effects of socially stimulating group intervention on lonely, older people's cognition: a randomized, controlled trial. American Journal of Geriatric Psychiatry. 2011 Jul;19(7):654-63. PMID 21709611. *Ineligible population*

638. Plassman BL, Williams JW, Jr., Burke JR, et al. Systematic review: factors associated with risk for and possible prevention of cognitive decline in later life. Annals of Internal Medicine. 2010 Aug 3;153(3):182-93. PMID 20547887. *Ineligible study design*

639. Plastino M, Fava A, Pirritano D, et al. Effects of insulinic therapy on cognitive impairment in patients with Alzheimer disease and diabetes mellitus type-2. Journal of the Neurological Sciences. 2010 Jan 15;288(1-2):112-6. PMID 19836029. *Ineligible population*

640. Polito L, Abbondanza S, Vaccaro R, et al. Cognitive stimulation in cognitively impaired individuals and cognitively healthy individuals with a family history of dementia: Short-term results from the "allena-Mente" randomized controlled trial. International Journal of Geriatric Psychiatry. 2015 01 Jun;30(6):631-8. PMID 2015029633. *Inadequate follow up time*

641. Poly C, Massaro JM, Seshadri S, et al. The relation of dietary choline to cognitive performance and white-matter hyperintensity in the Framingham Offspring Cohort. American Journal of Clinical Nutrition. 2011 Dec;94(6):1584-91. PMID 22071706. *No relevant outcomes reported*

642. Popa MA, Reynolds SL, Small BJ. Is the effect of reported physical activity on disability mediated by cognitive performance in white and african american older adults? Journals of Gerontology Series B-Psychological Sciences & Social Sciences. 2009 Jan;64(1):4-13. PMID 19196688. *No relevant outcomes reported*

643. Postuma RB, Gagnon JF, Vendette M, et al. Idiopathic REM sleep behavior disorder in the transition to degenerative disease. Movement Disorders. 2009 Nov 15;24(15):2225-32. PMID 19768814. *Cohort study with inadequate sample size*

644. Potter AS, Ryan KK, Newhouse PA. Effects of acute ultra-low dose mecamylamine on cognition in adult attention-deficit/hyperactivity disorder (ADHD). Human Psychopharmacology. 2009 Jun;24(4):309-17. PMID 19475630. *Inadequate follow up time*

645. Power BD, Alfonso H, Flicker L, et al. Body adiposity in later life and the incidence of dementia: The health in men study. PLoS ONE. 2011;6 (3) (no pagination)(e17902)PMID 2011168273. *Not cognitive decline prevention intervention*

646. Pratt SI, Mueser KT, Bartels SJ, et al. The impact of skills training on cognitive functioning in older people with serious mental illness. American Journal of Geriatric Psychiatry. 2013 Mar;21(3):242-50. PMID 23395191. *Ineligible population*

647. Pregelj P. Safety and tolerability of rivastigmine transdermal patch formulation in newly diagnosed patients with Alzheimer's dementia in naturalistic conditions. Psychogeriatrics:The Official Journal of the Japanese Psychogeriatric Society. 2012 Sep;12(3):165-71. PMID 22994614. *Ineligible population*

648. Pressman P, Gottfried JA. Journal Club: A randomized, double-blind, placebo-controlled trial of simvastatin to treat Alzheimer disease. Neurology. 2012 24 Jul;79(4):e33-e6. PMID 2012534317. *Ineligible population*

649. Pribis P, Bailey RN, Russell AA, et al. Effects of walnut consumption on cognitive performance in young adults. British Journal of Nutrition. 2012 May;107(9):1393-401. PMID 21923981. *Inadequate follow up time*

650. Puustinen J, Nurminen J, Lopponen M, et al. Use of CNS medications and cognitive decline in the aged: a longitudinal population-based study. BMC Geriatrics. 2011;11:70. PMID 22044595. *No relevant outcomes reported*

651. Qin B, Adair LS, Plassman BL, et al. Dietary Patterns and Cognitive Decline among Chinese Older Adults. Epidemiology. 2015 25 Sep;26(5):758-68. PMID 2015328540. *Ineligible study design*

652. Qin B, Plassman BL, Edwards LJ, et al. Fish intake is associated with slower cognitive decline in Chinese older adults. Journal of Nutrition. 2014 Oct;144(10):1579-85. PMID 25080536. *Ineligible study design*

653. Qiu C, Winblad B, Fratiglioni L. Low diastolic pressure and risk of dementia in very old people: a longitudinal study. Dementia & Geriatric Cognitive Disorders. 2009;28(3):213-9. PMID 19752556. *Cohort study with inadequate sample size*

654. Quinn JF, Raman R, Thomas RG, et al. Docosahexaenoic acid supplementation and cognitive decline in Alzheimer disease: a randomized trial. JAMA. 2010 Nov 3;304(17):1903-11. PMID 21045096. *Ineligible population*

655. Raabe RD, Burr RB, Short R. One-year cognitive outcomes associated with carotid artery stent placement. Journal of Vascular & Interventional Radiology. 2010 Jul;21(7):983-8; quiz 9. PMID 20537561. *Ineligible study design*

656. Radaideh GA, Choueiry P, Ismail A, et al. Eprosartan-based hypertension therapy, systolic arterial blood pressure and cognitive function: analysis of Middle East data from the OSCAR study. Vascular Health & Risk Management. 2011;7:491-5. PMID 21915165. *Cohort study with inadequate sample size*

657. Rahe J, Petrelli A, Kaesberg S, et al. Effects of cognitive training with additional physical activity compared to pure cognitive training in healthy older adults. Clinical Interventions In Aging. 2015;10:297-310. PMID 25632227. *Cohort study with inadequate sample size*

658. Rainer M, Wuschitz A, Jagsch C, et al. Memantine in moderate to severe Alzheimer's disease: an observational post-marketing study. Journal of Neural Transmission. 2011 Aug;118(8):1255-9. PMID 21461744. *Cohort study with inadequate sample size*

659. Ramirez A, Wolfsgruber S, Lange C, et al. Elevated HbA1c is associated with increased risk of incident dementia in primary care patients. Journal of Alzheimer's Disease. 2015;44(4):1203-12. PMID 25524954. *Ineligible study design*

660. Rantanen KK, Strandberg AY, Pitkala K, et al. Cholesterol in midlife increases the risk of Alzheimer's disease during an up to 43-year follow-up. European Geriatric Medicine. 2014 01 Dec;5(6):390-3. PMID 2015641416. *Ineligible study design*

661. Ravona-Springer R, Beeri MS, Goldbourt U. Repetitive thinking as a psychological cognitive style in midlife is associated with lower risk for dementia three decades later. Dementia & Geriatric Cognitive Disorders. 2009;28(6):513-20. PMID 19996596. *Ineligible study design*

662. Ravona-Springer R, Beeri MS, Goldbourt U. Exposure to the Holocaust and World War II concentration camps during late adolescence and adulthood is not associated with increased risk for dementia at old age. Journal of Alzheimer's Disease. 2011;23(4):709-16. PMID 21157030. *Ineligible study design*

663. Ravona-Springer R, Beeri MS, Goldbourt U. Satisfaction with current status at work and lack of motivation to improve it during midlife is associated with increased risk for dementia in subjects who survived thirty-seven years later. Journal of Alzheimer's Disease. 2013;36(4):769-80. PMID 23703153. *Ineligible study design*

664. Razay G, Williams J, King E, et al. Blood pressure, dementia and Alzheimer's disease: the OPTIMA longitudinal study. Dementia & Geriatric Cognitive Disorders. 2009;28(1):70-4. PMID 19648748. *Cohort study with inadequate sample size*

665. Redick TS, Shipstead Z, Harrison TL, et al. No evidence of intelligence improvement after working memory training: a randomized, placebo-controlled study. Journal of Experimental Psychology: General. 2013 May;142(2):359-79. PMID 22708717. *Inadequate follow up time*

666. Reiner M, Niermann C, Jekauc D, et al. Long-term health benefits of physical activity--a systematic review of longitudinal studies. BMC Public Health. 2013;13:813. PMID 24010994. *Ineligible study design*

667. Reitz C, Tang MX, Miller J, et al. Plasma homocysteine and risk of mild cognitive impairment. Dementia and Geriatric Cognitive Disorders. 2009 February;27(1):11-7. PMID 2009076033. *Ineligible study design*

668. Reitz C, Tang MX, Schupf N, et al. Association of higher levels of high-density lipoprotein cholesterol in elderly individuals and lower risk of late-onset Alzheimer disease. Archives of Neurology. 2010 Dec;67(12):1491-7. PMID 21149810. *Ineligible population*

669. Relkin NR, Szabo P, Adamiak B, et al. 18-Month study of intravenous immunoglobulin for treatment of mild Alzheimer disease. Neurobiology of Aging. 2009 November;30(11):1728-36. PMID 2009480127. *Ineligible population*

670. Remington R, Bechtel C, Larsen D, et al. A Phase II Randomized Clinical Trial of a Nutritional Formulation for Cognition and Mood in Alzheimer's Disease. Journal of Alzheimer's Disease. 2015;45(2):395-405. PMID 2015856032. *Ineligible population*

671. Remington R, Chan A, Paskavitz J, et al. Efficacy of a vitamin/nutriceutical formulation for moderate-stage to later-stage Alzheimer's disease: a placebo-controlled pilot study. American Journal of Alzheimer's Disease & Other Dementias. 2009 Feb-Mar;24(1):27-33. PMID 19056706. *Ineligible population*

672. Reppermund S, Brodaty H, Crawford JD, et al. Impairment in instrumental activities of daily living with high cognitive demand is an early marker of mild cognitive impairment: the Sydney memory and ageing study. Psychological Medicine. 2013 Nov;43(11):2437-45. PMID 23308393. *Ineligible study design*

673. Ribeiro Salomon AL, Carvalho Garbi Novaes MR. Outcomes of enteral nutrition for patients with advanced dementia - A systematic review. Journal of Nutrition, Health and Aging. 2015;19(2):169-77. PMID 2014834627. *Ineligible population*

674. Ribeiro Salomon AL, Carvalho Garbi Novaes MR. Outcomes of enteral nutrition for patients with advanced dementia: a systematic review. Journal of Nutrition, Health & Aging. 2015 Feb;19(2):169-77. PMID 25651442. *Ineligible population*

675. Richard E, Gouw AA, Scheltens P, et al. Vascular care in patients with Alzheimer disease with cerebrovascular lesions slows progression of white matter lesions on MRI: The evaluation of vascular care in Alzheimer's disease (EVA) study. Stroke. 2010 March;41(3):554-6. PMID 2010142301. *Ineligible population*

676. Richard E, Kuiper R, Dijkgraaf MG, et al. Vascular care in patients with Alzheimer's disease with cerebrovascular lesions-a randomized clinical trial. Journal of the American Geriatrics Society. 2009 May;57(5):797-805. PMID 19484836. *Ineligible population*

677. Richard E, Van den Heuvel E, Moll van Charante EP, et al. Prevention of dementia by intensive vascular care (PreDIVA): a cluster-randomized trial in progress. Alzheimer Disease & Associated Disorders. 2009 Jul-Sep;23(3):198-204. PMID 19812459. *Inadequate follow up time*

678. Richardson K, Schoen M, French B, et al. Statins and cognitive function: a systematic review. Annals of Internal Medicine. 2013 Nov 19;159(10):688-97. PMID 24247674. *Ineligible study design*

679. Richarz U, Gaudig M, Rettig K, et al. Galantamine treatment in outpatients with mild Alzheimer's disease. Acta Neurologica Scandinavica. 2014 Jun;129(6):382-92. PMID 24461047. *Ineligible population*

680. Richmond LL, Morrison AB, Chein JM, et al. Working memory training and transfer in older adults. Psychology & Aging. 2011 Dec;26(4):813-22. PMID 21707176. *Inadequate follow up time*

681. Riepe M, Weinman J, Osae-Larbi J, et al. Factors Associated with Greater Adherence to and Satisfaction with Transdermal Rivastigmine in Patients with Alzheimer's Disease and Their Caregivers. Dementia and Geriatric Cognitive Disorders. 2015 22 Jul;40(1-2):107-19. PMID 2015125853. *Ineligible population*

682. Rijpma A, Meulenbroek O, Van Hees AMJ, et al. Effects of Souvenaid on plasma micronutrient levels and fatty acid profiles in mild and mild-to-moderate Alzheimer's disease. Alzheimer's Research and Therapy. 2015 24 Jul;7(1)PMID 2015224044. *Ineligible population*

683. Rinne JO, Brooks DJ, Rossor MN, et al. 11C-PiB PET assessment of change in fibrillar amyloid-beta load in patients with Alzheimer's disease treated with bapineuzumab: a phase 2, double-blind, placebo-controlled, ascending-dose study. Lancet Neurology. 2010 Apr;9(4):363-72. PMID 20189881. *Ineligible population*

684. Rist PM, Capistrant BD, Wu Q, et al. Dementia and dependence: do modifiable risk factors delay disability? Neurology. 2014 Apr 29;82(17):1543-50. PMID 24682970. *Ineligible study design*

685. Ritchie K, Ancelin ML, Amieva H, et al. The association between caffeine and cognitive decline: examining alternative causal hypotheses. International Psychogeriatrics. 2014 Apr;26(4):581-90. PMID 24423697. *Ineligible study design*

686. Ritchie K, Carriere I, Ritchie CW, et al. Designing prevention programmes to reduce incidence of dementia: prospective cohort study of modifiable risk factors. BMJ. 2010;341:c3885. PMID 20688841. *Ineligible study design*

687. Ritchie LJ. Identifying mild cognitive impairment in older adults. Dissertation Abstracts International: Section B: The Sciences and Engineering. 2010;71(6-B):3945. PMID Dissertation Abstract: 2010-99240-330. *Ineligible study design*

688. Roberts RO, Geda YE, Cerhan JR, et al. Vegetables, unsaturated fats, moderate alcohol intake, and mild cognitive impairment. Dementia & Geriatric Cognitive Disorders. 2010;29(5):413-23. PMID 20502015. *Ineligible study design*

689. Roberts RO, Geda YE, Knopman DS, et al. Cardiac disease associated with increased risk of nonamnestic cognitive impairment. JAMA Neurology. 2013 March;70(3):374-82. PMID 2013161568. *Ineligible study design*

690. Roberts RO, Roberts LA, Geda YE, et al. Relative intake of macronutrients impacts risk of mild cognitive impairment or dementia. Journal of Alzheimer's Disease. 2012;32(2):329-39. PMID 22810099. *Ineligible study design*

691. Rockwood K, Fay S, Gorman M. The ADAS-cog and clinically meaningful change in the VISTA clinical trial of galantamine for Alzheimer's disease. International Journal of Geriatric Psychiatry. 2010 Feb;25(2):191-201. PMID 19548273. *Ineligible population*

692. Rodriguez-Sanchez E, Criado-Gutierrez JM, Mora-Simon S, et al. Physical activity program for patients with dementia and their relative caregivers: randomized clinical trial in Primary Health Care (AFISDEMyF study). BMC Neurology. 2014;14:63. PMID 24684948. *Ineligible population*

693. Rojas G, Bartoloni L, Serrano C, et al. Naturalist observational study on effectiveness of drug treatment of a cohort of patients with Alzheimer type dementia. [Spanish]. Estudio observacional naturalistico sobre la efectividad del tratamiento farmacologico en una cohorte de pacientes con demencia tipo Alzheimer. Neurologia Argentina. 2010;2(1):21-8. PMID 2010675945. *Ineligible population*

694. Rondeau V, Jacqmin-Gadda H, Commenges D, et al. Aluminum and silica in drinking water and the risk of Alzheimer's disease or cognitive decline: findings from 15-year follow-up of the PAQUID cohort. American Journal of Epidemiology. 2009 Feb 15;169(4):489-96. PMID 19064650. *Ineligible study design*

695. Ronnemaa E, Zethelius B, Sundelof J, et al. Glucose metabolism and the risk of Alzheimer's disease and dementia: a population-based 12 year follow-up study in 71-year-old men. Diabetologia. 2009 Aug;52(8):1504-10. PMID 19455303. *Ineligible study design*

696. Ronnemaa E, Zethelius B, Vessby B, et al. Serum fatty-acid composition and the risk of Alzheimer's disease: a longitudinal population-based study. European Journal of Clinical Nutrition. 2012 Aug;66(8):885-90. PMID 22713770. *Ineligible study design*

697. Rosano C, Longstreth WT, Jr., Boudreau R, et al. High blood pressure accelerates gait slowing in well-functioning older adults over 18-years of follow-up. Journal of the American Geriatrics Society. 2011 Mar;59(3):390-7. PMID 21391929. *No relevant outcomes reported*

698. Rosen AC, Sugiura L, Kramer JH, et al. Cognitive training changes hippocampal function in mild cognitive impairment: a pilot study. Journal of Alzheimer's Disease. 2011;26 Suppl 3:349-57. PMID 21971474. *Inadequate follow up time*

699. Rosenberg PB, Mielke MM, Han D, et al. The association of psychotropic medication use with the cognitive, functional, and neuropsychiatric trajectory of Alzheimer's disease. International Journal of Geriatric Psychiatry. 2012 Dec;27(12):1248-57. PMID 22374884. *Cohort study with inadequate sample size*

700. Rosenbloom MH, Barclay TR, Pyle M, et al. A single-dose pilot trial of intranasal rapid-acting insulin in apolipoprotein E4 carriers with mild-moderate Alzheimer's disease. CNS Drugs. 2014 Dec;28(12):1185-9. PMID 25373630. *Ineligible population*

701. Rovner BW, Casten RJ, Leiby BE, et al. Activity loss is associated with cognitive decline in age-related macular degeneration. Alzheimer's & Dementia. 2009 Jan;5(1):12-7. PMID 19118805. *Cohort study with inadequate sample size*

702. Ruiz JR, Gil-Bea F, Bustamante-Ara N, et al. Resistance training does not have an effect on cognition or related serum biomarkers in nonagenarians: a randomized controlled trial. International Journal of Sports Medicine. 2015 Jan;36(1):54-60. PMID 25329433. *Inadequate follow up time*

703. Ryan J, Carriere I, Carcaillon L, et al. Estrogen receptor polymorphisms and incident dementia: the prospective 3C study. Alzheimer's & Dementia. 2014 Jan;10(1):27-35. PMID 23491264. *Ineligible study design*

704. Ryan J, Carriere I, Scali J, et al. Characteristics of hormone therapy, cognitive function, and dementia: the prospective 3C Study. Neurology. 2009 Nov 24;73(21):1729-37. PMID 19933973. *Ineligible population*

705. Ryberg C, Rostrup E, Paulson OB, et al. Corpus callosum atrophy as a predictor of age-related cognitive and motor impairment: a 3-year follow-up of the LADIS study cohort. Journal of the Neurological Sciences. 2011 Aug 15;307(1-2):100-5. PMID 21621224. *Ineligible study design*

706. Sabbagh M, Cummings J, Christensen D, et al. Evaluating the cognitive effects of donepezil 23 mg/d in moderate and severe Alzheimer's disease: analysis of effects of baseline features on treatment response. BMC Geriatrics. 2013;13:56. PMID 23742728. *Ineligible population*

707. Sachs-Ericsson NJ, Sawyer KA, Corsentino EA, et al. APOE epsilon4 allele carriers: Biological, psychological, and social variables associated with cognitive impairment. Aging & Mental Health. 2010 Aug;14(6):679-91. PMID 20686979. *Ineligible study design*

708. Sadhu A, Upadhyay P, Agrawal A, et al. Management of cognitive determinants in senile dementia of Alzheimer's type: therapeutic potential of a novel polyherbal drug product. Clinical Drug Investigation. 2014 Dec;34(12):857-69. PMID 25316430. *Ineligible population*

709. Sadowsky CH, Dengiz A, Meng X, et al. Switching from oral donepezil to rivastigmine transdermal patch in alzheimer's disease: 20-week extension phase results. Primary Care Companion to the Journal of Clinical Psychiatry. 2010;12(5):e1-e8. PMID 2010710976. *Ineligible population*

710. Safouris A, Tsivgoulis G, Sergentanis TN, et al. Mediterranean diet and risk of dementia. Current Alzheimer Research. 2015 01 Sep;12(8):736-44. PMID 2015398944. *Ineligible study design*

711. Sakurai H, Hanyu H, Sato T, et al. Effects of cilostazol on cognition and regional cerebral blood flow in patients with Alzheimer's disease and cerebrovascular disease: a pilot study. Geriatrics & gerontology international. 2013 Jan;13(1):90-7. PMID 22672107. *Ineligible population*

712. Salloway S, Mintzer J, Cummings JL, et al. Subgroup analysis of US and non-US patients in a global study of high-dose donepezil (23 mg) in moderate and severe Alzheimer's disease. American Journal of Alzheimer's Disease & Other Dementias. 2012 Sep;27(6):421-32. PMID 22930699. *Ineligible population*

713. Salloway S, Sperling R, Fox NC, et al. Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease. New England Journal of Medicine. 2014 Jan 23;370(4):322-33. PMID 24450891. *Ineligible population*

714. Salloway S, Sperling R, Gilman S, et al. A phase 2 multiple ascending dose trial of bapineuzumab in mild to moderate Alzheimer disease. Neurology. 2009 Dec 15;73(24):2061-70. PMID 19923550. *Ineligible population*

715. Salloway S, Sperling R, Keren R, et al. A phase 2 randomized trial of ELND005, scyllo-inositol, in mild to moderate Alzheimer disease. Neurology. 2011 Sep 27;77(13):1253-62. PMID 21917766. *Ineligible population*

716. Salvatore C, Cerasa A, Battista P, et al. Magnetic resonance imaging biomarkers for the early diagnosis of Alzheimer's disease: A machine learning approach. Frontiers in Neuroscience. 2015;9 (SEP) (no pagination)(307)PMID 2015508042. *Ineligible study design*

717. Samieri C, Grodstein F, Rosner BA, et al. Mediterranean diet and cognitive function in older age. Epidemiology. 2013 Jul;24(4):490-9. PMID 23676264. *Ineligible study design*

718. Sano M, Bell KL, Galasko D, et al. A randomized, double-blind, placebo-controlled trial of simvastatin to treat Alzheimer disease. Neurology. 2011 Aug 9;77(6):556-63. PMID 21795660. *Ineligible population*

719. Sano M, Egelko S, Donohue M, et al. Developing dementia prevention trials: baseline report of the Home-Based Assessment study. Alzheimer Disease & Associated Disorders. 2013 Oct-Dec;27(4):356-62. PMID 23151596. *Ineligible study design*

720. Sano M, Egelko S, Donohue MC, et al. Assessing clinical progression for dementia prevention trial: Results from the HBA trial [Journal: Conference Abstract]. 2014. http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/788/CN-01056788/frame.html10. *Ineligible study design*

721. Santoro A, Siviero P, Minicuci N, et al. Effects of donepezil, galantamine and rivastigmine in 938 Italian patients with Alzheimer's disease: a prospective, observational study. CNS Drugs. 2010 Feb;24(2):163-76. PMID 20088621. *Ineligible population*

722. Santos C, Costa J, Santos J, et al. Caffeine intake and dementia: systematic review and meta-analysis. Journal of Alzheimer's Disease. 2010;20 Suppl 1:S187-204. PMID 20182026. *Ineligible study design*

723. Santos-Galduroz RF, Galduroz JC, Facco RL, et al. Effects of isoflavone on the learning and memory of women in menopause: a double-blind placebo-controlled study. Brazilian Journal of Medical & Biological Research. 2010 Nov;43(11):1123-6. PMID 20945036. *Inadequate follow up time*

724. Sato N, Saijo Y, Sasagawa Y, et al. Combination of antihypertensive therapy in the elderly, multicenter investigation (CAMUI) trial: results after 1 year. Journal of Hypertension. 2013 Jun;31(6):1245-55. PMID 23492647. *No relevant outcomes reported*

725. Sato T, Hanyu H, Hirao K, et al. Efficacy of PPAR-gamma agonist pioglitazone in mild Alzheimer disease. Neurobiology of Aging. 2011 Sep;32(9):1626-33. PMID 19923038. *Ineligible population*

726. Sattler C, Erickson KI, Toro P, et al. Physical fitness as a protective factor for cognitive impairment in a prospective population-based study in Germany. Journal of Alzheimer's Disease. 2011;26(4):709-18. PMID 21694450. *Cohort study with inadequate sample size*

727. Sattler C, Toro P, Schonknecht P, et al. Cognitive activity, education and socioeconomic status as preventive factors for mild cognitive impairment and Alzheimer's disease. Psychiatry Research. 2012 Mar 30;196(1):90-5. PMID 22390831. *Cohort study with inadequate sample size*

728. Saumier D, Duong A, Haine D, et al. Domain-specific cognitive effects of tramiprosate in patients with mild to moderate Alzheimer's disease: ADAS-cog subscale results from the alphase study. Journal of Nutrition, Health and Aging. 2009;13(9):808-12. PMID 2009650262. *Ineligible population*

729. Scapagnini G, Sonya V, Nader AG, et al. Modulation of Nrf2/ARE pathway by food polyphenols: A nutritional neuroprotective strategy for cognitive and neurodegenerative disorders. Molecular Neurobiology. 2011 October;44(2):192-201. PMID 2011592755. *Ineligible study design*

730. Scarmeas N, Luchsinger JA, Brickman AM, et al. Physical activity and Alzheimer disease course. American Journal of Geriatric Psychiatry. 2011 May;19(5):471-81. PMID 20808142. *Ineligible study design*

731. Scarmeas N, Luchsinger JA, Schupf N, et al. Physical activity, diet, and risk of Alzheimer disease. JAMA. 2009 Aug 12;302(6):627-37. PMID 19671904. *Cohort study with inadequate sample size*

732. Scarmeas N, Stern Y, Mayeux R, et al. Mediterranean diet and mild cognitive impairment. Archives of Neurology. 2009 Feb;66(2):216-25. PMID 19204158. *Ineligible study design*

733. Scarpini E, Bruno G, Zappala G, et al. Cessation versus continuation of galantamine treatment after 12 months of therapy in patients with Alzheimer's disease: a randomized, double blind, placebo controlled withdrawal trial. Journal of Alzheimer's Disease. 2011;26(2):211-20. PMID 21606568. *Ineligible population*

734. Schega L, Peter B, Torpel A, et al. Effects of intermittent hypoxia on cognitive performance and quality of life in elderly adults: a pilot study. Gerontology. 2013;59(4):316-23. PMID 23652274. *Inadequate follow up time*

735. Scheltens P, Twisk JW, Blesa R, et al. Efficacy of Souvenaid in mild Alzheimer's disease: results from a randomized, controlled trial. Journal of Alzheimer's Disease. 2012;31(1):225-36. PMID 22766770. *Ineligible population*

736. Schenck CH, Boeve BF, Mahowald MW. Delayed emergence of a parkinsonian disorder or dementia in 81% of older men initially diagnosed with idiopathic rapid eye movement sleep behavior disorder: a 16-year update on a previously reported series. Sleep Medicine. 2013 Aug;14(8):744-8. PMID 23347909. *Ineligible study design*

737. Schiepers OJ, van Boxtel MP, de Groot RH, et al. Serum iron parameters, HFE C282Y genotype, and cognitive performance in older adults: results from the FACIT study. Journals of Gerontology Series A-Biological Sciences & Medical Sciences. 2010 Dec;65(12):1312-21. PMID 20813792. *Ineligible study design*

738. Schiepers OJ, van Boxtel MP, de Groot RH, et al. DNA methylation and cognitive functioning in healthy older adults. British Journal of Nutrition. 2012 Mar;107(5):744-8. PMID 21791146. *Cohort study with inadequate sample size*

739. Schifitto G, Yiannoutsos CT, Ernst T, et al. Selegiline and oxidative stress in HIV-associated cognitive impairment. Neurology. 2009 December;73(23):1975-81. PMID 2010015684. *Ineligible population*

740. Schlesinger D, Grinberg LT, Alba JG, et al. African ancestry protects against Alzheimer's disease-related neuropathology. Molecular Psychiatry. 2013 Jan;18(1):79-85. PMID 22064377. *Ineligible study design*

741. Schmidt A, Hammann F, Wolnerhanssen B, et al. Green tea extract enhances parieto-frontal connectivity during working memory processing. Psychopharmacology. 2014 Oct;231(19):3879-88. PMID 24643507. *Ineligible study design*

742. Schmitter-Edgecombe M, Dyck DG. Cognitive rehabilitation multi-family group intervention for individuals with mild cognitive impairment and their care-partners. Journal of the International Neuropsychological Society. 2014 Oct;20(9):897-908. PMID 25222630. *Inadequate follow up time*

743. Schneider AL, Lutsey PL, Alonso A, et al. Vitamin D and cognitive function and dementia risk in a biracial cohort: the ARIC Brain MRI Study. European Journal of Neurology. 2014 Sep;21(9):1211-8, e69-70. PMID 24846449. *Ineligible study design*

744. Schneider LS, Insel PS, Weiner MW, et al. Treatment with cholinesterase inhibitors and memantine of patients in the Alzheimer's Disease Neuroimaging Initiative. Archives of Neurology. 2011 Jan;68(1):58-66. PMID 21220675. *Inadequate follow up time*

745. Schneider P, Buerger K, Teipel S, et al. Antihypertensive therapy is associated with reduced rate of conversion to Alzheimer's disease in midregional proatrial natriuretic peptide stratified subjects with mild cognitive impairment. Biological Psychiatry. 2011 Jul 15;70(2):145-51. PMID 21457948. *Cohort study with inadequate sample size*

746. Scholey A, Ossoukhova A, Owen L, et al. Effects of American ginseng (Panax quinquefolius) on neurocognitive function: an acute, randomised, double-blind, placebo-controlled, crossover study. Psychopharmacology. 2010 Oct;212(3):345-56. PMID 20676609. *Inadequate follow up time*

747. Schott JM, Reiniger L, Thom M, et al. Brain biopsy in dementia: clinical indications and diagnostic approach. Acta Neuropathologica. 2010 Sep;120(3):327-41. PMID 20640903. *Cohort study with inadequate sample size*

748. Schrijvers EM, Witteman JC, Sijbrands EJ, et al. Insulin metabolism and the risk of Alzheimer disease: the Rotterdam Study. Neurology. 2010 Nov 30;75(22):1982-7. PMID 21115952. *Ineligible population*

749. Schulz V. Ginkgo biloba extract for the prevention of dementia? Placebo-controlled 6-year prevention study without proof of efficacy. 2009. http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/812/CN-00756812/frame.html. Accessed on 1 30. *Not available in English*

750. Schwam E, Xu Y. Cognition and function in Alzheimer's disease: identifying the transitions from moderate to severe disease. Dementia & Geriatric Cognitive Disorders. 2010;29(4):309-16. PMID 20395684. *Ineligible study design*

751. Scogin F, Fairchild JK, Yon A, et al. Cognitive bibliotherapy and memory training for older adults with depressive symptoms. Aging & Mental Health. 2014 Jul;18(5):554-60. PMID 24073847. *Inadequate follow up time*

752. Segal SK, Cotman CW, Cahill LF. Exercise-induced noradrenergic activation enhances memory consolidation in both normal aging and patients with amnestic mild cognitive impairment. Journal of Alzheimer's Disease. 2012;32(4):1011-8. PMID 22914593. *Inadequate follow up time*

753. Selnes OA, Grega MA, Bailey MM, et al. Do management strategies for coronary artery disease influence 6-year cognitive outcomes? Annals of Thoracic Surgery. 2009 Aug;88(2):445-54. PMID 19632391. *Ineligible population*

754. Shah RC, Kamphuis PJ, Leurgans S, et al. The S-Connect study: Results from a randomized, controlled trial of Souvenaid in mild-to-moderate Alzheimer's disease. Alzheimer's Research and Therapy. 2013 26 Nov;5(6)PMID 2014019819. *Ineligible population*

755. Shao H, Breitner JC, Whitmer RA, et al. Hormone therapy and Alzheimer disease dementia: new findings from the Cache County Study. Neurology. 2012 Oct 30;79(18):1846-52. PMID 23100399. *Ineligible study design*

756. Shatil E. Does combined cognitive training and physical activity training enhance cognitive abilities more than either alone? A four-condition randomized controlled trial among healthy older adults. Frontiers in Aging Neuroscience. 2013;5(MAR)PMID 2013561527. *Inadequate follow up time*

757. Shatil E, Mikulecka J, Bellotti F, et al. Novel television-based cognitive training improves working memory and executive function. PLoS ONE [Electronic Resource]. 2014;9(7):e101472. PMID 24992187. *Inadequate follow up time*

758. Sherwin BB, Chertkow H, Schipper H, et al. A randomized controlled trial of estrogen treatment in men with mild cognitive impairment. Neurobiology of Aging. 2011 Oct;32(10):1808-17. PMID 20004499. *Inadequate follow up time*

759. Sherwin BB, Grigorova M. Differential effects of estrogen and micronized progesterone or medroxyprogesterone acetate on cognition in postmenopausal women. Fertility & Sterility. 2011 Aug;96(2):399-403. PMID 21703613. *Inadequate follow up time*

760. Shimizu S, Kanetaka H, Hirose D, et al. Differential effects of acetylcholinesterase inhibitors on clinical responses and cerebral blood flow changes in patients with Alzheimer's disease: A 12-month, randomized, and open-label trial. Dementia and Geriatric Cognitive Disorders Extra. 2015;5(1):135-46. PMID 2015140257. *Ineligible population*

761. Shin KY, Lee JY, Won BY, et al. BT-11 is effective for enhancing cognitive functions in the elderly humans. Neuroscience Letters. 2009 Nov 13;465(2):157-9. PMID 19699261. *Inadequate follow up time*

762. Shinto L, Quinn J, Montine T, et al. A randomized placebo-controlled pilot trial of omega-3 fatty acids and alpha lipoic acid in Alzheimer's disease. Journal of Alzheimer's Disease. 2014;38(1):111-20. PMID 24077434. *Ineligible population*

763. Silverman DH, Geist CL, Kenna HA, et al. Differences in regional brain metabolism associated with specific formulations of hormone therapy in postmenopausal women at risk for AD. Psychoneuroendocrinology. 2011 May;36(4):502-13. PMID 20810219. *Inadequate follow up time*

764. Sittironnarit G, Ames D, Bush AI, et al. Effects of anticholinergic drugs on cognitive function in older Australians: results from the AIBL study. Dementia & Geriatric Cognitive Disorders. 2011;31(3):173-8. PMID 21389718. *Ineligible population*

765. Siuda J, Gorzkowska A, Patalong-Ogiewa M, et al. From mild cognitive impairment to Alzheimer's disease - influence of homocysteine, vitamin B12 and folate on cognition over time: results from one-year follow-up. Neurologia i Neurochirurgia Polska. 2009 Jul-Aug;43(4):321-9. PMID 19742390. *Ineligible study design*

766. Small BJ, Dixon RA, McArdle JJ, et al. Do changes in lifestyle engagement moderate cognitive decline in normal aging? Evidence from the Victoria Longitudinal Study. Neuropsychology. 2012 Mar;26(2):144-55. PMID 22149165. *Ineligible study design*

767. Smith GE, Housen P, Yaffe K, et al. A cognitive training program based on principles of brain plasticity: results from the Improvement in Memory with Plasticity-based Adaptive Cognitive Training (IMPACT) study. Journal of the American Geriatrics Society. 2009 Apr;57(4):594-603. PMID 19220558. *Inadequate follow up time*

768. Smith PJ, Blumenthal JA, Babyak MA, et al. Effects of the dietary approaches to stop hypertension diet, exercise, and caloric restriction on neurocognition in overweight adults with high blood pressure. Hypertension. 2010 Jun;55(6):1331-8. PMID 20305128. *Inadequate follow up time*

769. Smyth A, Dehghan M, O'Donnell M, et al. Healthy eating and reduced risk of cognitive decline: A cohort from 40 countries. Neurology. 2015 Jun 2;84(22):2258-65. PMID 25948720. *Ineligible study design*

770. Sofi F, Abbate R, Gensini GF, et al. Accruing evidence on benefits of adherence to the Mediterranean diet on health: an updated systematic review and meta-analysis. American Journal of Clinical Nutrition. 2010 Nov;92(5):1189-96. PMID 20810976. *Ineligible study design*

771. Solfrizzi V, Scafato E, Frisardi V, et al. Angiotensin-converting enzyme inhibitors and incidence of mild cognitive impairment. The Italian Longitudinal Study on Aging. Age. 2013 Apr;35(2):441-53. PMID 22203459. *Ineligible study design*

772. Solomon A, Kareholt I, Ngandu T, et al. Serum total cholesterol, statins and cognition in non-demented elderly. Neurobiology of Aging. 2009 Jun;30(6):1006-9. PMID 18022292. *Ineligible study design*

773. Solomon A, Kivipelto M, Wolozin B, et al. Midlife serum cholesterol and increased risk of Alzheimer's and vascular dementia three decades later. Dementia & Geriatric Cognitive Disorders. 2009;28(1):75-80. PMID 19648749. *Ineligible study design*

774. Solomon A, Sippola R, Soininen H, et al. Lipid-lowering treatment is related to decreased risk of dementia: a population-based study (FINRISK). Neurodegenerative Diseases. 2010;7(1-3):180-2. PMID 20224281. *Ineligible study design*

775. Song Y, Nie H, Xu Y, et al. Association of statin use with risk of dementia: a meta-analysis of prospective cohort studies. Geriatrics & gerontology international. 2013 Oct;13(4):817-24. PMID 23461525. *Ineligible study design*

776. Sonnen JA, Larson EB, Walker RL, et al. Nonsteroidal anti-inflammatory drugs are associated with increased neuritic plaques. Neurology. 2010 Sep 28;75(13):1203-10. PMID 20811000. *Ineligible population*

777. Sorman DE, Sundstrom A, Ronnlund M, et al. Leisure activity in old age and risk of dementia: a 15-year prospective study. Journals of Gerontology Series B-Psychological Sciences & Social Sciences. 2014 Jul;69(4):493-501. PMID 23766435. *Ineligible study design*

778. Soto ME, Secher M, Gillette-Guyonnet S, et al. Weight loss and rapid cognitive decline in community-dwelling patients with Alzheimer's disease. Journal of Alzheimer's Disease. 2012;28(3):647-54. PMID 22045479. *Ineligible study design*

779. Soto ME, van Kan GA, Nourhashemi F, et al. Angiotensin-converting enzyme inhibitors and Alzheimer's disease progression in older adults: results from the Reseau sur la Maladie d'Alzheimer Francais cohort. Journal of the American Geriatrics Society. 2013 Sep;61(9):1482-8. PMID 24000874. *Ineligible population*

780. Spalletta G, Caltagirone C, Girardi P, et al. The role of persistent and incident major depression on rate of cognitive deterioration in newly diagnosed Alzheimer's disease patients. Psychiatry Research. 2012 30 Jul;198(2):263-8. PMID 2012633360. *Ineligible study design*

781. Spalletta G, Caltagirone C, Padovani A, et al. Cognitive and affective changes in mild to moderate Alzheimer's disease patients undergoing switch of cholinesterase inhibitors: a 6-month observational study. PLoS ONE [Electronic Resource]. 2014;9(2):e89216. PMID 24586603. *Cohort study with inadequate sample size*

782. Sparks DL, Kryscio RJ, Connor DJ, et al. Cholesterol and cognitive performance in normal controls and the influence of elective statin use after conversion to mild cognitive impairment: results in a clinical trial cohort. Neurodegenerative Diseases. 2010;7(1-3):183-6. PMID 20224282. *Ineligible study design*

783. Sperling R, Johnson K. To sleep, perchance to delay dementia. Archives of Neurology. 2012 Jan;69(1):118-20. PMID 22232352. *Ineligible study design*

784. Sperling RA, Rentz DM, Johnson KA, et al. The A4 study: Stopping AD before symptoms begin? Science Translational Medicine. 2014 19 Mar;6(228)PMID 2014282892. *Ineligible study design*

785. St John JA, Henderson VW, Hodis HN, et al. Associations between urine excretion of isoflavonoids and cognition in postmenopausal women in the Women's Isoflavone Soy Health clinical trial. Journal of the American Geriatrics Society. 2014 Apr;62(4):629-35. PMID 24617349. *Ineligible study design*

786. Steenland K, Zhao L, Goldstein FC, et al. Statins and cognitive decline in older adults with normal cognition or mild cognitive impairment. Journal of the American Geriatrics Society. 2013 September;61(9):1449-55. PMID 2013584156. *Ineligible study design*

787. Stein EM, Loos S, Schneider A, et al. The effectiveness of regular physical activity and exercise in the prevention and treatment of cognitive impairment and early Alzheimer's disease. [German]. Regelmasige korperliche aktivitat als nichtpharmakologischer praventionsund behandlungsansatz im fruhstadium der Alzheimer-demenz. Neurologie und Rehabilitation. 2010;16(5):247-50. PMID 2011007309. *Ineligible study design*

788. Stein MS, Scherer SC, Ladd KS, et al. A randomized controlled trial of high-dose vitamin D2 followed by intranasal insulin in Alzheimer's disease. Journal of Alzheimer's Disease. 2011;26(3):477-84. PMID 21694461. *Ineligible population*

789. Stephan BCM, Tzourio C, Auriacombe S, et al. Usefulness of data from magnetic resonance imaging to improve prediction of dementia: Population based cohort study. BMJ (Online). 2015 22 Jun;350 (no pagination)(h2863)PMID 2015303074. *Ineligible study design*

790. Stewart R, Xue QL, Masaki K, et al. Change in blood pressure and incident dementia: a 32-year prospective study. Hypertension. 2009 Aug;54(2):233-40. PMID 19564551. *Ineligible study design*

791. Stough C, Downey L, Silber B, et al. The effects of 90-day supplementation with the omega-3 essential fatty acid docosahexaenoic acid (DHA) on cognitive function and visual acuity in a healthy aging population. Neurobiology of Aging. 2012 Apr;33(4):824.e1-3. PMID 21531481. *Inadequate follow up time*

792. Strand BH, Langballe EM, Hjellvik V, et al. Midlife vascular risk factors and their association with dementia deaths: results from a Norwegian prospective study followed up for 35 years. Journal of the Neurological Sciences. 2013 Jan 15;324(1-2):124-30. PMID 23146611. *Cohort study with inadequate sample size*

793. Strobel G. Alzheimer's prevention initiative. Journal of Alzheimer's Disease. 2010;21(3):1025-35. PMID 20844340. *Ineligible study design*

794. Stuart K, Summers MJ, Valenzuela MJ, et al. BDNF and COMT polymorphisms have a limited association with episodic memory performance or engagement in complex cognitive activity in healthy older adults. Neurobiology of learning and memory. 2014 01 Apr;110:1-7. PMID 24468545. *Ineligible study design*

795. Styliadis C, Kartsidis P, Paraskevopoulos E, et al. Neuroplastic effects of combined computerized physical and cognitive training in elderly individuals at risk for dementia: an eLORETA controlled study on resting states. Neural Plasticity. 2015;2015:172192. PMID 25945260. *Inadequate follow up time*

796. Sun L, Zhang XQ, Tang Z, et al. Cognitive function changes in patients with vascular dementia before and after symptom onset and analysis of its cognitive predictor. [Chinese]. Chinese Journal of Cerebrovascular Diseases. 2012 March;9(3):132-5. PMID 2012220434. *Ineligible study design*

797. Sundelof J, Kilander L, Helmersson J, et al. Systemic tocopherols and F2-isoprostanes and the risk of Alzheimer's disease and dementia: a prospective population-based study. Journal of Alzheimer's Disease. 2009;18(1):71-8. PMID 19542632. *Ineligible study design*

798. Suzuki H, Kuraoka M, Yasunaga M, et al. Cognitive intervention through a training program for picture book reading in community-dwelling older adults: a randomized controlled trial. BMC Geriatrics. 2014;14:122. PMID 25416537. *Inadequate follow up time*

799. Sweetlove M. Phase III CONCERT trial of latrepirdine: Negative results. Pharmaceutical Medicine. 2012;26(2):113-5. PMID 2012165417. *Ineligible population*

800. Tadini L, El-Nazer R, Brunoni AR, et al. Cognitive, mood, and electroencephalographic effects of noninvasive cortical stimulation with weak electrical currents. Journal of ECT. 2011 Jun;27(2):134-40. PMID 20938352. *Inadequate follow up time*

801. Tam CW, Lam LC. Clinical remission of late-onset depression in elderly Chinese: a short-term outcome study. East Asian Archives of Psychiatry. 2013 Sep;23(3):126-32. PMID 24088406. *Ineligible study design*

802. Tanasugarn L, Natearpha P, Kongsakon R, et al. Physical effects and cognitive function after exercising "Rue-si-dad-ton" (exercise using the posture of the hermit doing body contortion): a randomized controlled pilot trial. Journal of the Medical Association of Thailand. 2015 Mar;98(3):306-13. PMID 25920302. *Inadequate follow up time*

803. Tangwongchai S, Thavichachart N, Senanarong V, et al. Galantamine for the treatment of BPSD in Thai patients with possible Alzheimer's disease with or without cerebrovascular disease. American Journal of Alzheimer's Disease and other Dementias. 2009 December-January;23(6):593-601. PMID 2009009394. *Ineligible population*

804. Tariot P, Salloway S, Yardley J, et al. Long-term safety and tolerability of donepezil 23 mg in patients with moderate to severe Alzheimer's disease. BMC Research Notes. 2012;5:283. PMID 22681723. *Ineligible population*

805. Tariot PN, Schneider LS, Cummings J, et al. Chronic divalproex sodium to attenuate agitation and clinical progression of Alzheimer disease. Archives of General Psychiatry. 2011 Aug;68(8):853-61. PMID 21810649. *Ineligible population*

806. Tasci I, Naharci MI, Bozoglu E, et al. Cognitive and functional influences of vildagliptin, a DPP-4 inhibitor, added to ongoing metformin therapy in elderly with type 2 diabetes. Endocrine, Metabolic & Immune Disorders Drug Targets. 2013 Sep;13(3):256-63. PMID 23848558. *Ineligible study design*

807. Teixeira CV, Gobbi LT, Corazza DI, et al. Non-pharmacological interventions on cognitive functions in older people with mild cognitive impairment (MCI). Archives of Gerontology & Geriatrics. 2012 Jan-Feb;54(1):175-80. PMID 21397960. *Ineligible study design*

808. Thiel C, Vogt L, Tesky VA, et al. Cognitive intervention response is related to habitual physical activity in older adults. Aging-Clinical & Experimental Research. 2012 Feb;24(1):47-55. PMID 21406956. *Inadequate follow up time*

809. Thivierge S, Jean L, Simard M. A randomized cross-over controlled study on cognitive rehabilitation of instrumental activities of daily living in Alzheimer disease. American Journal of Geriatric Psychiatry. 2014 Nov;22(11):1188-99. PMID 23871120. *Ineligible population*

810. Tierney MC, Ryan J, Ancelin ML, et al. Lifelong estrogen exposure and memory in older postmenopausal women. Journal of Alzheimer's Disease. 2013;34(3):601-8. PMID 23246919. *Ineligible study design*

811. Tolppanen AM, Solomon A, Kulmala J, et al. Leisure-time physical activity from mid- to late life, body mass index, and risk of dementia. Alzheimer's & Dementia. 2015 Apr;11(4):434-43.e6. PMID 24721528. *Ineligible study design*

812. Tranah GJ, Blackwell T, Stone KL, et al. Circadian activity rhythms and risk of incident dementia and mild cognitive impairment in older women. Annals of Neurology. 2011 Nov;70(5):722-32. PMID 22162057. *Ineligible study design*

813. Tsai PF, Chang JY, Beck C, et al. A pilot cluster-randomized trial of a 20-week tai chi program in elders with cognitive impairment and osteoarthritic knee: Effects on pain and other health outcomes. Journal of Pain and Symptom Management. 2013 April;45(4):660-9. PMID 2013213752. *Inadequate follow up time*

814. Tsantali E, Economidis D. Implications of a longitudinal cognitive intervention program in mild Alzheimer's disease. Archives of Psychiatric Nursing. 2014 Apr;28(2):128-34. PMID 24673788. *Ineligible population*

815. Tseng CH, Huang WS, Muo CH, et al. Increased risk of dementia among chronic osteomyelitis patients. European Journal of Clinical Microbiology & Infectious Diseases. 2015 Jan;34(1):153-9. PMID 25098680. *Not cognitive decline prevention intervention*

816. Tsivgoulis G, Judd S, Letter AJ, et al. Adherence to a Mediterranean diet and risk of incident cognitive impairment. Neurology. 2013 Apr 30;80(18):1684-92. PMID 23628929. *Not cognitive decline prevention intervention*

817. Tzimopoulou S, Cunningham VJ, Nichols TE, et al. A multi-center randomized proof-of-concept clinical trial applying [18F]FDG-PET for evaluation of metabolic therapy with rosiglitazone XR in mild to moderate Alzheimer's disease. Journal of Alzheimer's Disease. 2010;22(4):1241-56. PMID 2011081259. *Ineligible study design*

818. Tzourio C, Anderson C, Chapman N, et al. Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. Archives of Internal Medicine. 2003 May 12;163(9):1069-75. PMID 12742805. *Ineligible population*

819. Ukawa S, Yuasa M, Ikeno T, et al. Randomised controlled pilot study in Japan comparing a home visit program using a Functioning Improvement Tool with a home visit with conversation alone. Australasian Journal on Ageing. 2012 September;31(3):187-9. PMID 22950591. *Inadequate follow up time*

820. Vaillant GE, Okereke OI, Mukamal K, et al. Antecedents of intact cognition and dementia at age 90 years: a prospective study. International Journal of Geriatric Psychiatry. 2014 Dec;29(12):1278-85. PMID 24733646. *Cohort study with inadequate sample size*

821. Valen-Sendstad A, Engedal K, Stray-Pedersen B, et al. Effects of hormone therapy on depressive symptoms and cognitive functions in women with Alzheimer disease: a 12 month randomized, double-blind, placebo-controlled study of low-dose estradiol and norethisterone. American Journal of Geriatric Psychiatry. 2010 Jan;18(1):11-20. PMID 20094015. *Ineligible population*

822. van de Rest O, Berendsen AA, Haveman-Nies A, et al. Dietary patterns, cognitive decline, and dementia: a systematic review. Advances in Nutrition. 2015 Mar;6(2):154-68. PMID 25770254. *Ineligible study design*

823. van de Rest O, van der Zwaluw NL, de Groot LC. Literature review on the role of dietary protein and amino acids in cognitive functioning and cognitive decline. Amino Acids. 2013 Nov;45(5):1035-45. PMID 23990160. *Ineligible study design*

824. van der Schaft J, Koek HL, Dijkstra E, et al. The association between vitamin D and cognition: a systematic review. Ageing Research Reviews. 2013 Sep;12(4):1013-23. PMID 23727408. *Ineligible study design*

825. van Himbergen TM, Beiser AS, Ai M, et al. Biomarkers for insulin resistance and inflammation and the risk for all-cause dementia and alzheimer disease: results from the Framingham Heart Study. Archives of Neurology. 2012 May;69(5):594-600. PMID 22213409. *No relevant outcomes reported*

826. van Paasschen J, Clare L, Yuen KS, et al. Cognitive rehabilitation changes memory-related brain activity in people with Alzheimer disease. Neurorehabilitation & Neural Repair. 2013 Jun;27(5):448-59. PMID 23369983. *Ineligible population*

827. van Uffelen JG, Chinapaw MJ, Hopman-Rock M, et al. Feasibility and effectiveness of a walking program for community-dwelling older adults with mild cognitive impairment. Journal of Aging & Physical Activity. 2009 Oct;17(4):398-415. PMID 19940321. *Not cognitive decline prevention intervention*

828. Vandewoude MFJ. Management of patients with mild cognitive impairment and mild to moderate dementia. Acta Clinica Belgica. 2009 March/April;64(2):92-9. PMID 2009191218. *Ineligible population*

829. Vaughan C, Goldstein FC, Tenover JL. Exogenous testosterone alone or with finasteride does not improve measurements of cognition in healthy older men with low serum testosterone. Journal of Andrology. 2007 Nov-Dec;28(6):875-82. PMID 17609296. *Not cognitive decline prevention intervention*

830. Vaughan L, Espeland MA, Snively B, et al. The rationale, design, and baseline characteristics of the Women's Health Initiative Memory Study of Younger Women (WHIMS-Y). Brain Research. 2013 Jun 13;1514:3-11. PMID 23578696. *Ineligible study design*

831. Vedin I, Cederholm T, Freund-Levi Y, et al. Effects of DHA-rich n-3 fatty acid supplementation on gene expression in blood mononuclear leukocytes: the OmegAD study. PLoS ONE [Electronic Resource]. 2012;7(4):e35425. PMID 22545106. *Ineligible population*

832. Vedin I, Cederholm T, Freund-Levi Y, et al. Reduced prostaglandin F2 alpha release from blood mononuclear leukocytes after oral supplementation of omega3 fatty acids: the OmegAD study. Journal of Lipid Research. 2010 May;51(5):1179-85. PMID 19965584. *Ineligible population*

833. Vellas B, Black R, Thal LJ, et al. Long-term follow-up of patients immunized with AN1792: Reduced functional decline in antibody responders. Current Alzheimer Research. 2009 April;6(2):144-51. PMID 2009182642. *Ineligible population*

834. Venturelli M, Scarsini R, Schena F. Six-month walking program changes cognitive and ADL performance in patients with Alzheimer. American Journal of Alzheimer's Disease & Other Dementias. 2011 Aug;26(5):381-8. PMID 21852281. *Ineligible population*

835. Vercambre MN, Berr C, Ritchie K, et al. Caffeine and cognitive decline in elderly women at high vascular risk. Journal of Alzheimer's Disease. 2013;35(2):413-21. PMID 23422357. *Not cognitive decline prevention intervention*

836. Vercambre MN, Grodstein F, Kang JH. Dietary fat intake in relation to cognitive change in high-risk women with cardiovascular disease or vascular factors. European Journal of Clinical Nutrition. 2010 Oct;64(10):1134-40. PMID 20648044. *Not cognitive decline prevention intervention*

837. Verdelho A, Madureira S, Ferro JM, et al. Physical activity prevents progression for cognitive impairment and vascular dementia: results from the LADIS (Leukoaraiosis and Disability) study. Stroke. 2012 Dec;43(12):3331-5. PMID 23117721. *Not cognitive decline prevention intervention*

838. Vigen CL, Mack WJ, Keefe RS, et al. Cognitive effects of atypical antipsychotic medications in patients with Alzheimer's disease: outcomes from CATIE-AD. American Journal of Psychiatry. 2011 Aug;168(8):831-9. PMID 21572163. *Ineligible population*

839. Viola S, Viola P, Buongarzone MP, et al. New brain reperfusion rehabilitation therapy improves cognitive impairment in mild alzheimer's disease: A prospective, controlled, open-label 12-month study with nirs correlates. Aging Clinical and Experimental Research. 2014;26(4):417-25. PMID 2015687983. *Ineligible population*

840. Virta JJ, Heikkila K, Perola M, et al. Midlife cardiovascular risk factors and late cognitive impairment. European Journal of Epidemiology. 2013 May;28(5):405-16. PMID 23532744. *No relevant outcomes reported*

841. Viswanathan A. High-dose B vitamin supplementation as a disease-modifying therapy in alzheimer disease. Archives of Neurology. 2009 April;66(4):520-2. PMID 2009196917. *Ineligible population*

842. Viswanathan A, Raj S, Greenberg SM, et al. Plasma Abeta, homocysteine, and cognition: the Vitamin Intervention for Stroke Prevention (VISP) trial. Neurology. 2009 Jan 20;72(3):268-72. PMID 19153374. *Ineligible population*

843. Voigt-Radloff S, Hull M. [Daily functioning in dementia: pharmacological and non-pharmacological interventions demonstrate small effects on heterogeneous scales]. Psychiatrische Praxis. 2011 Jul;38(5):221-31. PMID 21425035. *Ineligible population*

844. Voss MW, Erickson KI, Prakash RS, et al. Neurobiological markers of exercise-related brain plasticity in older adults. Brain, Behavior, & Immunity. 2013 Feb;28:90-9. PMID 23123199. *No relevant outcomes reported*

845. Vranic A, Spanic AM, Carretti B, et al. The efficacy of a multifactorial memory training in older adults living in residential care settings. International Psychogeriatrics. 2013 Nov;25(11):1885-97. PMID 23899952. *Ineligible population*

846. Wade AG, Farmer M, Harari G, et al. Add-on prolonged-release melatonin for cognitive function and sleep in mild to moderate Alzheimer's disease: a 6-month, randomized, placebo-controlled, multicenter trial. Clinical Interventions In Aging. 2014;9:947-61. PMID 24971004. *Ineligible population*

847. Wagner G, Icks A, Abholz HH, et al. Antihypertensive treatment and risk of dementia: a retrospective database study.[Erratum appears in Int J Clin Pharmacol Ther. 2012 Nov;50(11):850]. International Journal of Clinical Pharmacology & Therapeutics. 2012 Mar;50(3):195-201. PMID 22373832. *Ineligible study design*

848. Wagner S, Paulsen S, Bleichner F, et al. Cognitive training in rehabilitation: a program to treat mild cognitive impairment. [German]. Gedachtnismanagementtraining in der Rehabilitation (KTR): Programm zur Behandlung leichter kognitiver Beeintrachtigungen. Zeitschrift fur Gerontologie und Geriatrie : Organ der Deutschen Gesellschaft fur Gerontologie und Geriatrie. 2009 Dec;42(6):479-87. PMID 19543680. *Not available in English*

849. Wagner S, Paulsen S, Bleichner F, et al. [Cognitive training in rehabilitation: a program to treat mild cognitive impairment]. Zeitschrift fur Gerontologie und Geriatrie. 2009 Dec;42(6):479-87. PMID 19543680. *Ineligible population*

850. Waldorff FB, Buss DV, Eckermann A, et al. Efficacy of psychosocial intervention in patients with mild Alzheimer's disease: The multicentre, rater blinded, randomised Danish Alzheimer Intervention Study (DAISY). BMJ (Online). 2012 18 Aug;345(7870)PMID 2012491882. *Ineligible population*

851. Wallin AK, Wattmo C, Minthon L. Galantamine treatment in Alzheimer's disease: Response and long-term outcome in a routine clinical setting. Neuropsychiatric Disease and Treatment. 2011;7(1):565-76. PMID 2011624724. *Ineligible population*

852. Wallin K, Solomon A, Kareholt I, et al. Midlife rheumatoid arthritis increases the risk of cognitive impairment two decades later: a population-based study. Journal of Alzheimer's Disease. 2012;31(3):669-76. PMID 22647255. *Not cognitive decline prevention intervention*

853. Wang HK, Lin SH, Sung PS, et al. Population based study on patients with traumatic brain injury suggests increased risk of dementia. Journal of Neurology, Neurosurgery & Psychiatry. 2012 Nov;83(11):1080-5. PMID 22842203. *Ineligible population*

854. Wang HX, Karp A, Herlitz A, et al. Personality and lifestyle in relation to dementia incidence. Neurology. 2009 Jan 20;72(3):253-9. PMID 19153372. *No relevant outcomes reported*

855. Wang HX, Wahlberg M, Karp A, et al. Psychosocial stress at work is associated with increased dementia risk in late life. Alzheimer's & Dementia. 2012;8(2):114-20. PMID 22404853. *No relevant outcomes reported*

856. Wang JR, Hsieh S. Neurofeedback training improves attention and working memory performance. Clinical Neurophysiology. 2013 Dec;124(12):2406-20. PMID 23827814. *Inadequate follow up time*

857. Wang LP, Zhang XY, Liu N, et al. Comparison of integrated traditional Chinese and western medicine therapy on vascular cognitive impairment with no dementia. Genetics and Molecular Research. 2015 11 May;14(2):4896-902. PMID 2015041645. *Ineligible population*

858. Wang LQ, Chien WT. Randomised controlled trial of a family-led mutual support programme for people with dementia. Journal of Clinical Nursing. 2011 August;20(15-16):2362-6. PMID 21752121. *Ineligible population*

859. Wang LY, Larson EB, Sonnen JA, et al. Blood pressure and brain injury in older adults: Findings from a community-based autopsy study. Journal of the American Geriatrics Society. 2009 November;57(11):1975-81. PMID 2009560327. *Cohort study with inadequate sample size*

860. Wang S, Jacobs D, Andrews H, et al. Cardiovascular risk and memory in non-demented elderly women. Neurobiology of Aging. 2010 Jul;31(7):1250-3. PMID 18805604. *Not cognitive decline prevention intervention*

861. Wang S, Luo X, Barnes D, et al. Physical activity and risk of cognitive impairment among oldest-old women. American Journal of Geriatric Psychiatry. 2014 Nov;22(11):1149-57. PMID 23831179. *Not cognitive decline prevention intervention*

862. Wang T, Huang Q, Reiman EM, et al. Effects of memantine on clinical ratings, fluorodeoxyglucose positron emission tomography measurements, and cerebrospinal fluid assays in patients with moderate to severe Alzheimer dementia: a 24-week, randomized, clinical trial. Journal of Clinical Psychopharmacology. 2013 Oct;33(5):636-42. PMID 23948786. *Ineligible population*

863. Wang X, Hjorth E, Vedin I, et al. Effects of n-3 FA supplementation on the release of proresolving lipid mediators by blood mononuclear cells: The omegAD study. Journal of Lipid Research. 2015 01 Mar;56(3):674-81. PMID 2015856468. *Ineligible population*

864. Watfa G, Rossignol P, Kearney-Schwartz A, et al. Use of calcium channel blockers is associated with better cognitive performance in older hypertensive patients with subjective memory complaints. Journal of Hypertension. 2010 December;28(12):2485-93. PMID 2012369475. *Ineligible study design*

865. Watson GS, Baker LD, Cholerton BA, et al. Effects of insulin and octreotide on memory and growth hormone in Alzheimer's disease. Journal of Alzheimer's Disease. 2009;18(3):595-602. PMID 19625744. *Ineligible population*

866. Wattmo C, Londos E, Minthon L. Solitary living in Alzheimer's disease over 3 years: association between cognitive and functional impairment and community-based services. Clinical Interventions In Aging. 2014;9:1951-62. PMID 25484578. *Ineligible population*

867. Wattmo C, Wallin AK, Londos E, et al. Long-term outcome and prediction models of activities of daily living in Alzheimer disease with cholinesterase inhibitor treatment. Alzheimer Disease & Associated Disorders. 2011 Jan-Mar;25(1):63-72. PMID 20847636. *Ineligible population*

868. Wattmo C, Wallin AK, Minthon L. Functional response to cholinesterase inhibitor therapy in a naturalistic Alzheimer's disease cohort. BMC Neurology. 2012;12:134. PMID 23126532. *Ineligible population*

869. Wei XH, Ji LL. Effect of handball training on cognitive ability in elderly with mild cognitive impairment. Neuroscience Letters. 2014 Apr 30;566:98-101. PMID 24582900. *Ineligible population*

870. Weiner MW, Sadowsky C, Saxton J, et al. Magnetic resonance imaging and neuropsychological results from a trial of memantine in Alzheimer's disease. Alzheimer's & Dementia. 2011 Jul;7(4):425-35. PMID 21646051. *Ineligible population*

871. Weinstein G, Beiser AS, Choi SH, et al. Serum brain-derived neurotrophic factor and the risk for dementia: the Framingham Heart Study. JAMA Neurology. 2014 Jan;71(1):55-61. PMID 24276217. *Not cognitive decline prevention intervention*

872. Weintraub D, Rosenberg PB, Drye LT, et al. Sertraline for the treatment of depression in Alzheimer disease: week-24 outcomes. American Journal of Geriatric Psychiatry. 2010 Apr;18(4):332-40. PMID 20220589. *Ineligible population*

873. Weintraub D, Somogyi M, Meng X. Rivastigmine in alzheimer's disease and Parkinson's disease dementia: An ADAS-Cog factor analysis. American Journal of Alzheimer's Disease and other Dementias. 2011 September;26(6):443-9. PMID 2012001003. *Ineligible population*

874. Welmer AK, Rizzuto D, Qiu C, et al. Walking speed, processing speed, and dementia: a population-based longitudinal study. Journals of Gerontology Series A-Biological Sciences & Medical Sciences. 2014 Dec;69(12):1503-10. PMID 24706441. *Not cognitive decline prevention intervention*

875. Wenger NS, Roth CP, Shekelle PG, et al. A practice-based intervention to improve primary care for falls, urinary incontinence, and dementia. Journal of the American Geriatrics Society. 2009 Mar;57(3):547-55. PMID 19175441. *No relevant outcomes reported*

876. Werner NS, Duschek S, Schandry R. D-camphor-crataegus berry extract combination increases blood pressure and cognitive functioning in the elderly - a randomized, placebo controlled double blind study. Phytomedicine. 2009 Dec;16(12):1077-82. PMID 19560327. *Inadequate follow up time*

877. Westwoo W, Beiser A, DeCarli C, et al. Insulin-like growth factor-1 and risk of Alzheimer dementia and brain atrophy. Neurology. 2014 06 May;82(18):1613-9. PMID 2014392068. *Not cognitive decline prevention intervention*

878. Weyerer S, Schaufele M, Wiese B, et al. Current alcohol consumption and its relationship to incident dementia: results from a 3-year follow-up study among primary care attenders aged 75 years and older. Age & Ageing. 2011 Jul;40(4):456-63. PMID 21367764. *Not cognitive decline prevention intervention*

879. Whalley LJ, Duthie SJ, Collins AR, et al. Homocysteine, antioxidant micronutrients and late onset dementia. European Journal of Nutrition. 2014 Feb;53(1):277-85. PMID 23625136. *Not cognitive decline prevention intervention*

880. Whalley LJ, Sharma S, Fox HC, et al. Anticholinergic drugs in late life: adverse effects on cognition but not on progress to dementia. Journal of Alzheimer's Disease. 2012;30(2):253-61. PMID 22426015. *Cohort study with inadequate sample size*

881. Wharton W, Baker LD, Gleason CE, et al. Short-term hormone therapy with transdermal estradiol improves cognition for postmenopausal women with Alzheimer's disease: results of a randomized controlled trial. Journal of Alzheimer's Disease. 2011;26(3):495-505. PMID 21694454. *Ineligible population*

882. Wharton W, Gleason CE, Dowling NM, et al. The KEEPS-Cognitive and Affective Study: baseline associations between vascular risk factors and cognition. Journal of Alzheimer's Disease. 2014;40(2):331-41. PMID 24430001. *Not cognitive decline prevention intervention*

883. White RS, Lipton RB, Hall CB, et al. Nonmelanoma skin cancer is associated with reduced Alzheimer disease risk. Neurology. 2013 May 21;80(21):1966-72. PMID 23677746. *Not cognitive decline prevention intervention*

884. White WB, Marfatia R, Schmidt J, et al. INtensive versus standard ambulatory blood pressure lowering to prevent functional DeclINe in the ElderlY (INFINITY). American Heart Journal. 2013 Mar;165(3):258-65.e1. PMID 23453090. *Ineligible population*

885. Whitehair DC, Sherzai A, Emond J, et al. Influence of apolipoprotein E varepsilon4 on rates of cognitive and functional decline in mild cognitive impairment. Alzheimer's & Dementia. 2010 Sep;6(5):412-9. PMID 20813342. *Ineligible study design*

886. Whitmer RA, Quesenberry CP, Zhou J, et al. Timing of hormone therapy and dementia: the critical window theory revisited. Annals of Neurology. 2011 Jan;69(1):163-9. PMID 21280086. *No relevant outcomes reported*

887. Wightman EL, Reay JL, Haskell CF, et al. Effects of resveratrol alone or in combination with piperine on cerebral blood flow parameters and cognitive performance in human subjects: a randomised, double-blind, placebo-controlled, cross-over investigation. British Journal of Nutrition. 2014 Jul;112(2):203-13. PMID 24804871. *Inadequate follow up time*

888. Wilkinson D, Fox NC, Barkhof F, et al. Memantine and brain atrophy in Alzheimer's disease: a 1-year randomized controlled trial. Journal of Alzheimer's Disease. 2012;29(2):459-69. PMID 22269160. *Ineligible population*

889. Wilkinson D, Roman G, Salloway S, et al. The long-term efficacy and tolerability of donepezil in patients with vascular dementia. International Journal of Geriatric Psychiatry. 2010 Mar;25(3):305-13. PMID 19623601. *Ineligible population*

890. Wilkinson D, Schindler R, Schwam E, et al. Effectiveness of donepezil in reducing clinical worsening in patients with mild-to-moderate alzheimer's disease. Dementia & Geriatric Cognitive Disorders. 2009;28(3):244-51. PMID 19786776. *Ineligible population*

891. Wilkinson D, Windfeld K, Colding-Jorgensen E. Safety and efficacy of idalopirdine, a 5-HT6 receptor antagonist, in patients with moderate Alzheimer's disease (LADDER): a randomised, double-blind, placebo-controlled phase 2 trial. Lancet Neurology. 2014 Nov;13(11):1092-9. PMID 25297016. *Ineligible population*

892. Williams PT. Lower risk of Alzheimer's disease mortality with exercise, statin, and fruit intake. Journal of Alzheimer's Disease. 2015;44(4):1121-9. PMID 25408208. *Ineligible population*

893. Wilson RS, Barnes LL, Aggarwal NT, et al. Cognitive activity and the cognitive morbidity of Alzheimer disease. Neurology. 2010 Sep 14;75(11):990-6. PMID 20811001. *Ineligible population*

894. Winblad B, Black SE, Homma A, et al. Donepezil treatment in severe Alzheimer's disease: a pooled analysis of three clinical trials. Current Medical Research & Opinion. 2009 Nov;25(11):2577-87. PMID 19735164. *Ineligible population*

895. Winblad B, Gauthier S, Astrom D, et al. Memantine benefits functional abilities in moderate to severe Alzheimer's disease. Journal of Nutrition, Health & Aging. 2010 Nov;14(9):770-4. PMID 21085908. *Ineligible population*

896. Winblad B, Giacobini E, Frolich L, et al. Phenserine efficacy in Alzheimer's disease. Journal of Alzheimer's Disease. 2010;22(4):1201-8. PMID 20930279. *Ineligible population*

897. Winchester J, Dick MB, Gillen D, et al. Walking stabilizes cognitive functioning in Alzheimer's disease (AD) across one year. Archives of Gerontology & Geriatrics. 2013 Jan-Feb;56(1):96-103. PMID 22959822. *Ineligible population*

898. Wingenfeld K, Kuffel A, Uhlmann C, et al. Effects of noradrenergic stimulation on memory in patients with major depressive disorder. Stress. 2013 Mar;16(2):191-201. PMID 22746337. *Inadequate follow up time*

899. Winslow BT, Onysko MK, Stob CM, et al. Treatment of Alzheimer disease. American Family Physician. 2011 June;83(12):1403-12. PMID 2011343700. *Ineligible population*

900. Wolkenstein L, Plewnia C. Amelioration of cognitive control in depression by transcranial direct current stimulation. Biological Psychiatry. 2013 Apr 1;73(7):646-51. PMID 23219367. *No relevant outcomes reported*

901. Wong RH, Howe PR, Bryan J, et al. Chronic effects of a wild green oat extract supplementation on cognitive performance in older adults: a randomised, double-blind, placebo-controlled, crossover trial. Nutrients. 2012 May;4(5):331-42. PMID 22690320. *Inadequate follow up time*

902. Wright RM, Roumani YF, Boudreau R, et al. Effect of central nervous system medication use on decline in cognition in community-dwelling older adults: findings from the Health, Aging And Body Composition Study. Journal of the American Geriatrics Society. 2009 Feb;57(2):243-50. PMID 19207141. *Ineligible study design*

903. Wroolie TE, Kenna HA, Williams KE, et al. Differences in verbal memory performance in postmenopausal women receiving hormone therapy: 17beta-estradiol versus conjugated equine estrogens. American Journal of Geriatric Psychiatry. 2011 Sep;19(9):792-802. PMID 21873835. *Ineligible study design*

904. Wroolie TE, Kenna HA, Williams KE, et al. Cognitive effects of memantine in postmenopausal women at risk of dementia: a pilot study. Acta Neurologica Scandinavica. 2009 Mar;119(3):172-9. PMID 18705678. *Ineligible study design*

905. Wu MS, Lan TH, Chen CM, et al. Socio-demographic and health-related factors associated with cognitive impairment in the elderly in Taiwan. BMC Public Health. 2011;11:22. PMID 21223555. *Ineligible study design*

906. Wucherer D, Eichler T, Kilimann I, et al. Antidementia drug treatment in people screened positive for dementia in primary care. Journal of Alzheimer's Disease. 2015;44(3):1015-21. PMID 25391382. *Ineligible population*

907. Xiu LL, Wahlqvist ML, Lee MS, et al. Cognitive impairment and limited dietary diversity or physical inactivity are conjoint precursors of incident diabetes more so in elderly women than men. Asia Pacific Journal of Clinical Nutrition. 2013;22(4):635-45. PMID 24231025. *Ineligible study design*

908. Xu WL, von Strauss E, Qiu CX, et al. Uncontrolled diabetes increases the risk of Alzheimer's disease: a population-based cohort study. Diabetologia. 2009 Jun;52(6):1031-9. PMID 19280172. *Ineligible study design*

909. Xu ZQ, Liang XM, Juan W, et al. Treatment with Huperzine A improves cognition in vascular dementia patients. Cell Biochemistry & Biophysics. 2012 Jan;62(1):55-8. PMID 21833673. *Ineligible population*

910. Yaffe K, Falvey CM, Hamilton N, et al. Association between hypoglycemia and dementia in a biracial cohort of older adults with diabetes mellitus. JAMA Internal Medicine. 2013 22 Jul;173(14):1300-6. PMID 2013468296. *Ineligible study design*

911. Yakoot M, Salem A, Helmy S. Effect of Memo, a natural formula combination, on Mini-Mental State Examination scores in patients with mild cognitive impairment. Clinical Interventions In Aging. 2013;8:975-81. PMID 23950642. *Inadequate follow up time*

912. Yamada S, Akishita M, Fukai S, et al. Effects of dehydroepiandrosterone supplementation on cognitive function and activities of daily living in older women with mild to moderate cognitive impairment. Geriatrics & gerontology international. 2010 Oct;10(4):280-7. PMID 20497239. *Ineligible population*

913. Yamamoto T, Kondo K, Hirai H, et al. Association between self-reported dental health status and onset of dementia: A 4-year prospective cohort study of older Japanese adults from the Aichi Gerontological Evaluation Study (AGES) Project. Psychosomatic Medicine. 2012 April;74(3):241-8. PMID 2012211620. *Ineligible study design*

914. Yamashita T, Ogasawara K, Kuroda H, et al. Combination of preoperative cerebral blood flow and 123I-iomazenil SPECT imaging predicts postoperative cognitive improvement in patients undergoing uncomplicated endarterectomy for unilateral carotid stenosis. Clinical Nuclear Medicine. 2012 Feb;37(2):128-33. PMID 22228333. *Ineligible population*

915. Yancheva S, Ihl R, Nikolova G, et al. Ginkgo biloba extract EGb 761, donepezil or both combined in the treatment of Alzheimer's disease with neuropsychiatric features: A randomised, double-blind, exploratory trial. Aging and Mental Health. 2009 March;13(2):183-90. PMID 2009516891. *Ineligible population*

916. Yancheva S, Ihl R, Nikolova G, et al. Ginkgo biloba extract EGb 761(R), donepezil or both combined in the treatment of Alzheimer's disease with neuropsychiatric features: a randomised, double-blind, exploratory trial. Aging & Mental Health. 2009 Mar;13(2):183-90. PMID 19347685. *Ineligible population*

917. Yang BF, Zeng XH, Liu Y, et al. Effect of acupuncture treatment on vascular cognitive impairment without dementia: study protocol for a randomized controlled trial. Trials [Electronic Resource]. 2014;15:442. PMID 25391431. *Ineligible study design*

918. Yang CM, Shen YC, Weng SF, et al. Increased Risk of Dementia in Patients With Erectile Dysfunction: A Population-Based, Propensity Score-Matched, Longitudinal Follow-Up Study. Medicine. 2015 Jun;94(24):e990. PMID 26091478. *Ineligible study design*

919. Yang YH, Chen CH, Chou MC, et al. Concentration of donepezil to the cognitive response in Alzheimer disease. Journal of Clinical Psychopharmacology. 2013 Jun;33(3):351-5. PMID 23609381. *Ineligible population*

920. Yang YH, Teng HW, Lai YT, et al. Statins reduces the risk of dementia in patients with late-onset depression: A retrospective cohort study. PLoS ONE. 2015 18 Sep;10 (9) (no pagination)(e0137914)PMID 2015503958. *Ineligible study design*

921. Yang Z, Zhou X, Zhang Q. Effectiveness and safety of memantine treatment for Alzheimer's disease. Journal of Alzheimer's Disease. 2013;36(3):445-58. PMID 2013505142. *Ineligible population*

922. Yannakoulia M, Kontogianni M, Scarmeas N. Cognitive health and Mediterranean diet: just diet or lifestyle pattern? Ageing Research Reviews. 2015 Mar;20:74-8. PMID 25461244. *Ineligible study design*

923. Yasar S, Lin FM, Fried LP, et al. Diuretic use is associated with better learning and memory in older adults in the Ginkgo Evaluation of Memory Study. Alzheimer's & Dementia. 2012 May;8(3):188-95. PMID 22465175. *Not cognitive decline prevention intervention*

924. Yasar S, Xia J, Yao W, et al. Antihypertensive drugs decrease risk of Alzheimer disease: Ginkgo Evaluation of Memory Study. Neurology. 2013 Sep 3;81(10):896-903. PMID 23911756. *Not cognitive decline prevention intervention*

925. Ye R, Hu Y, Yao A, et al. Impact of renin - angiotensin system-targeting antihypertensive drugs on treatment of Alzheimer's disease: A meta-analysis. International Journal of Clinical Practice. 2015 01 Jun;69(6):674-81. PMID 2015077237. *Ineligible study design*

926. Yeh YC, Liu CL, Peng LN, et al. Potential benefits of reducing medication-related anticholinergic burden for demented older adults: a prospective cohort study. Geriatrics & gerontology international. 2013 Jul;13(3):694-700. PMID 23216534. *Ineligible population*

927. Yeung CM, St John PD, Menec V, et al. Is bilingualism associated with a lower risk of dementia in community-living older adults? Cross-sectional and prospective analyses. Alzheimer Disease & Associated Disorders. 2014 Oct-Dec;28(4):326-32. PMID 24614266. *Not cognitive decline prevention intervention*

928. Young H, Benton D, Carter N. The effect of chicken extract on mood, cognition and heart rate variability. Nutrients. 2015;7(2):887-904. PMID 25642970. *Inadequate follow up time*

929. Yu F, Bronas UG, Konety S, et al. Effects of aerobic exercise on cognition and hippocampal volume in Alzheimer's disease: study protocol of a randomized controlled trial (The FIT-AD trial). Trials [Electronic Resource]. 2014;15:394. PMID 25304364. *Ineligible population*

930. Yu F, Nelson NW, Savik K, et al. Affecting Cognition and Quality of Life via Aerobic Exercise in Alzheimer's Disease. Western Journal of Nursing Research. 2013 January;35(1):24-38. PMID 21911546. *Ineligible population*

931. Yu F, Ryan LH, Schaie KW, et al. Factors associated with cognition in adults: the Seattle Longitudinal Study. Research in Nursing & Health. 2009 Oct;32(5):540-50. PMID 19606423. *No relevant outcomes reported*

932. Yu F, Savik K, Wyman JF, et al. Maintaining physical fitness and function in Alzheimer's disease: a pilot study. American Journal of Alzheimer's Disease & Other Dementias. 2011 Aug;26(5):406-12. PMID 21750046. *Ineligible population*

933. Yu F, Thomas W, Nelson NW, et al. Impact of 6-month aerobic exercise on Alzheimer's symptoms. Journal of Applied Gerontology. 2015 04 Jun;34(4):484-500. PMID 2015097557. *Ineligible population*

934. Yu L, Lin SM, Zhou RQ, et al. Chinese herbal medicine for patients with mild to moderate Alzheimer disease based on syndrome differentiation: A randomized controlled trial. Journal of Chinese Integrative Medicine. 2012 July;10(7):766-76. PMID 2012439210. *Ineligible population*

935. Yu L, Shulman JM, Chibnik L, et al. The CETP I405V polymorphism is associated with an increased risk of Alzheimer's disease. Aging Cell. 2012 Apr;11(2):228-33. PMID 22122979. *Ineligible study design*

936. Yu WK, Chen YT, Wang SJ, et al. Cataract surgery is associated with a reduced risk of dementia: A nationwide population-based cohort study. European Journal of Neurology. 2015 01 Oct;22(10):1370-e80. PMID 2014941288. *Ineligible study design*

937. Zanchetti A, Liu L, Mancia G, et al. Blood pressure and LDL-cholesterol targets for prevention of recurrent strokes and cognitive decline in the hypertensive patient: Design of the European Society of Hypertension-Chinese Hypertension League Stroke in Hypertension Optimal Treatment randomized trial. Journal of Hypertension. 2014 September;32(9):1888-97. PMID 2014544821. *Ineligible population*

938. Zaninotto AL, Bueno OF, Pradella-Hallinan M, et al. Acute cognitive effects of donepezil in young, healthy volunteers. Human Psychopharmacology. 2009 Aug;24(6):453-64. PMID 19637397. *Inadequate follow up time*

939. Zeidan F, Johnson SK, Diamond BJ, et al. Mindfulness meditation improves cognition: evidence of brief mental training. Consciousness & Cognition. 2010 Jun;19(2):597-605. PMID 20363650. *Inadequate follow up time*

940. Zelinski EM, Spina LM, Yaffe K, et al. Improvement in memory with plasticity-based adaptive cognitive training: results of the 3-month follow-up. Journal of the American Geriatrics Society. 2011 Feb;59(2):258-65. PMID 21314646. *Inadequate follow up time*

941. Zhang N, Wei C, Du H, et al. The Effect of Memantine on Cognitive Function and Behavioral and Psychological Symptoms in Mild-to-Moderate Alzheimer's Disease Patients. Dementia and Geriatric Cognitive Disorders. 2015 22 Jul;40(1-2):85-93. PMID 2015126070. *Ineligible population*

942. Zhang X, Ni X, Chen P. Study about the effects of different fitness sports on cognitive function and emotion of the aged. Cell Biochemistry & Biophysics. 2014 Dec;70(3):1591-6. PMID 24997050. *Cohort study with inadequate sample size*

943. Zhao MX, Dong ZH, Yu ZH, et al. Effects of Ginkgo biloba extract in improving episodic memory of patients with mild cognitive impairment: A randomized controlled trial. Journal of Chinese Integrative Medicine. 2012 June;10(6):628-34. PMID 2012376956. *Not available in English*

944. Zhao Q, Lee JH, Pang D, et al. Estrogen receptor-Beta variants are associated with increased risk of Alzheimer's disease in women with down syndrome. Dementia & Geriatric Cognitive Disorders. 2011;32(4):241-9. PMID 22156442. *Cohort study with inadequate sample size*

945. Zhao X, Zhou R, Fu L. Working memory updating function training influenced brain activity. PLoS ONE [Electronic Resource]. 2013;8(8):e71063. PMID 24015182. *No relevant outcomes reported*

946. Zhao Y, Navia BA, Marra CM, et al. Memantine for AIDS dementia complex: open-label report of ACTG 301. HIV Clinical Trials. 2010 Jan-Feb;11(1):59-67. PMID 20400412. *Inadequate follow up time*

947. Zheng Z, Zhu X, Yin S, et al. Combined cognitive-psychological-physical intervention induces reorganization of intrinsic functional brain architecture in older adults. Neural Plasticity. 2015;2015:713104. PMID 25810927. *Inadequate follow up time*

948. Zhong Y, Miao Y, Jia WP, et al. Hyperinsulinemia, insulin resistance and cognitive decline in older cohort. Biomedical & Environmental Sciences. 2012 Feb;25(1):8-14. PMID 22424621. *Cohort study with inadequate sample size*

949. Zhong Y, Zheng X, Miao Y, et al. Effect of CYP2D6 10 and APOE polymorphisms on the efficacy of donepezil in patients with Alzheimer's disease. American Journal of the Medical Sciences. 2013 Mar;345(3):222-6. PMID 22986607. *Ineligible population*

950. Zhuang JP, Fang R, Feng X, et al. The impact of human-computer interaction-based comprehensive training on the cognitive functions of cognitive impairment elderly individuals in a nursing home. Journal of Alzheimer's Disease. 2013;36(2):245-51. PMID 23587747. *Ineligible population*

951. Zieschang T, Schwenk M, Oster P, et al. Sustainability of motor training effects in older people with dementia. Journal of Alzheimer's Disease. 2013;34(1):191-202. PMID 23202438. *Ineligible population*

952. Zimmermann N, Netto TM, Amodeo MT, et al. Working memory training and poetry-based stimulation programs: are there differences in cognitive outcome in healthy older adults? Neurorehabilitation. 2014;35(1):159-70. PMID 24990015. *Inadequate follow up time*

953. Zlatic CO, Mao Y, Ryan TM, et al. FluphenazineHCl and Epigallocatechin Gallate Modulate the Rate of Formation and Structural Properties of Apolipoprotein C-II Amyloid Fibrils. Biochemistry. 2015 Jun 23;54(24):3831-8. PMID 26021642. *Ineligible study design*

Appendix E. Prospective Cohort Studies

The Health and Medicine Division (HMD) committee of the National Academies of Sciences, Engineering, and Medicine (NASEM) provided a list of longitudinal studies that may provide evidence on interventions to prevent age-related cognitive decline, MCI, and clinical Alzheimer's-type dementia. We used Google search engine to locate, where available, the longitudinal study's website, and where not available, academic sites or curated databases that provided a description of the study. (Some longitudinal studies are hosted or conducted primarily in countries where English is not the first language; descriptions for those studies were drawn from the associated publications in the table.) Study descriptions were used to confirm the prospective cohort study design, usually interested in determining incidence or risk factors, and that treatment was not assigned.

For each study, we iteratively searched PubMed using the study name and a key word (such as "cognitive impairment" and "dementia") derived from the search algorithms in Appendix A to identify related publications. These example articles were compared to the general search results to try to identify gaps in the literature. No gaps were found. Articles that were examples of the type of publication derived from the prospective cohort study but excluded from this review are provided in the table below. The studies were excluded because treatment was not assigned and appropriate techniques to address selection bias were not employed in order to provide information on causal relationships.

Next, for each study we again iteratively searched PubMed using the study name and key words that identify an analytic method that may be applied to a prospective cohort study to simulate an experimental design by "assigning" exposure to the intervention, for example, "instrumental variable" (IV) or "Mendelian randomization." No publications were identified using this method.

As can be seen in the cohort study descriptions, many of these prospective cohort studies have been generating data for decades. The derivative publications can number in the hundreds, possibly greater than 1000 articles per cohort study. Given the potentially large number of publications, which, based on our searches, did not rise to inclusion criteria due to study design (treatment was not assigned or appropriate techniques to address selection bias were not employed in order to provide information on causal relationships), we did not provide full bibliographies for each cohort study.

Appendix Table E1. Prospective cohort studies searched for relevant literature

Committee-suggested Cohort Studies Country	Cohort Study Description	Example of excluded publication derived from cohort study
3C (Three Cities Study) France	The Three-City Study (3C Study) is a population-based longitudinal study aiming to examine the relation between vascular diseases and dementia in adults 65 years and older. http://www.three-city-study.com/the-three-city-study.php	Ancelin ML,et al. Steroid and nonsteroidal anti-inflammatory drugs, cognitive decline, and dementia. Neurobiology of Aging, 2011, doi:10.1016/j.neurobiolaging.2011.09.038.
Adult Changes in	ACT is made up of 3 cohorts. Current total enrollment is 4,960. Between 1994 and	Gray SL, et al. Antioxidant vitamin supplement use

Committee-suggested Cohort Studies Country	Cohort Study Description	Example of excluded publication derived from cohort study
Thought Study (ACT) US	1996, the study enrolled 2,581 participants. The purpose of this cohort study is to prospectively examine the incidence of AD and dementia, as well as risk factors for those conditions. https://www.maelstrom-research.org/mica/study/act	and risk of dementia or Alzheimer's disease in older adults. J Am Geriatr Soc. 2008 Feb;56(2):291-5.
Age, Gene/Environment Susceptibility – Reykjavik Study (AGES-RS) Iceland	The AGES will phenotype the surviving 12,000 members of the Reykjavik Study cohort (now 67 years and older) for quantitative traits related to diseases and conditions of old age, and collect genetic and other biologic specimens. http://www.hjartarannsokn.is/index.aspx?GroupId=346	Sigurdur Sigurdsson, et.al. Brain tissue volumes in the general population of the elderly: The AGES-Reykjavik Study, NeuroImage, Volume 59, Issue 4, 15 February 2012, Pages 3862-3870, ISSN 1053-8119, http://dx.doi.org/10.1016/j.neuroimage.2011.11.024.
Atherosclerosis Risk in Communities (ARIC) US	The Atherosclerosis Risk in Communities Study (ARIC), sponsored by the National Heart, Lung, and Blood Institute (NHLBI) is a prospective epidemiologic study conducted in four U.S. The Cohort Component of the ARIC study began in 1987, and each of the four ARIC field centers randomly selected and recruited a cohort sample of approximately 4,000 individuals aged 45-64 from a defined population in their community. A total of 15,792 participants received an extensive examination, including medical, social, and demographic data. https://www2.cscc.unc.edu/aric/desc	Lutsey PL, et. al. 2016. Obstructive Sleep Apnea and 15-Year Cognitive Decline: The Atherosclerosis Risk in Communities (ARIC) Study. Sleep. 39(2):309-16.PubMed
Austrian Study of Stroke Prevention (ASPS) Austria	Community-based cohort study on vascular risk factors and brain structure and function in older adults. 2000 participants, 1000 with imaging, healthy population, aged 45 – 85 years old (non-English website)	Enzinger C, et al. Risk factors for progression of brain atrophy: 6-year follow up of the ASPS. Neurology, 2005
Baltimore Longitudinal Study of Aging (BLSA) US	The BLSA is a longitudinal study, with over 1300 participants currently and over 3100 since study inception. The aim of the study is to understand what is aging. Researchers measure physical and cognitive changes associated with aging in real time among a dedicated group of BLSA participants who come in for testing at regular intervals over the course of their lives. https://www.blsa.nih.gov/	Beydoun MA, et al. Statins and serum cholesterol's associations with incident dementia and mild cognitive impairment. Journal of epidemiology and community health. 2011;65(11):949-957. doi:10.1136/jech.2009.100826.
Cache County Study on Memory Health and Aging US	The study is designed to examine genetic and environmental factors associated with risk for Alzheimer's disease and other forms of dementia. Started in 1995, the study enrolled 5,092 permanent residents of the county (90%), including approximately 800 individuals aged 85 years and older. The CCMS is a longitudinal investigation of aging and Alzheimer's disease (AD) based in an exceptionally long-lived population residing in northern Utah. The elderly of Cache County have a longer life expectancy, higher educational attainment, and lower incidence of chronic disease (which can complicate the diagnosis of dementias) than other similar populations. http://www.usu.edu/epicenter/htm/studies/memorystudy	Peters M, et al. Neuropsychiatric symptoms as risk factors for progression from CIND to dementia: The Cache County Study. The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry. 2013;21(11):10.1016/j.jagp.2013.01.049. doi:10.1016/j.jagp.2013.01.049.
Cardiovascular Health Study	The Cardiovascular Health Study (CHS) is an NHLBI-funded observational study of risk factors for cardiovascular disease in adults 65 years or older. Starting in 1989,	Incidence of mild cognitive impairment in the Pittsburgh Cardiovascular Health Study–Cognition

Committee-suggested Cohort Studies Country	Cohort Study Description	Example of excluded publication derived from cohort study
(CHS) US	and continuing through 1999, participants underwent annual extensive clinical examinations. Measurements included traditional risk factors such as blood pressure and lipids as well as measures of subclinical disease, including echocardiography of the heart, carotid ultrasound, and cranial magnetic-resonance imaging (MRI). At six month intervals between clinic visits, and once clinic visits ended, participants were contacted by phone to ascertain hospitalizations and health status. The main outcomes are coronary heart disease (CHD), angina, heart failure (HF), stroke, transient ischemic attack (TIA), claudication, and mortality. Participants continue to be followed for these events. https://chs-nhlbi.org/	Study Oscar L. et. al. October 9, 2012, 79:15 1599-1606; published ahead of print September 26, 2012, doi:10.1212/WNL.0b013e31826e25f0: 1526-632X
Chicago Health and Aging Project (CHAP) US	CHAP is a longitudinal population study of common chronic health problems of older persons, especially of risk factors for incident Alzheimer's disease, in a biracial neighborhood of the south side of Chicago. http://www.alzrisk.org/cohort.aspx?cohortID=15&rfid=2	Morris MC, et al. Dietary intake of antioxidant nutrients and the risk of incident Alzheimer disease in a biracial community study. JAMA. 2002 Jun 26;287(24):3230-7.
Coronary Artery Risk Development in Young Adults Study (CARDIA) US	The Coronary Artery Risk Development in Young Adults (CARDIA) Study is a study examining the development and determinants of clinical and subclinical cardiovascular disease and their risk factors. It began in 1985-6 with a group of 5115 black and white men and women aged 18-30 years. The participants were selected so that there would be approximately the same number of people in subgroups of race, gender, education (high school or less and more than high school) and age (18-24 and 25-30) in each of 4 centers: Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA. http://www.cardia.dopm.uab.edu/	No relevant studies immediately found
Framingham Heart Study (note: Framingham cohorts include the Original, Offspring and Gen 3 cohorts) US	The objective of the Framingham Heart Study was to identify the common factors or characteristics that contribute to CVD by following its development over a long period of time in a large group of participants who had not yet developed overt symptoms of CVD or suffered a heart attack or stroke. The researchers recruited 5,209 men and women between the ages of 30 and 62 from the town of Framingham, Massachusetts. Since 1948, the subjects have continued to return to the study every two years for a detailed medical history, physical examination, and laboratory tests. In 1971, the Study enrolled a second generation - 5,124 of the original participants' adult children and their spouses - to participate in similar examinations. In 1994, the need to establish a new study reflecting a more diverse community of Framingham was recognized, and the first Omni cohort of the Framingham Heart Study was enrolled. In April 2002 the Study entered a new phase, the enrollment of a third generation of participants, the grandchildren of the Original Cohort. In 2003, a second group of Omni participants was enrolled. https://www.framinghamheartstudy.org/	Karakis I, et al. Association of Serum Vitamin D with the Risk of Incident Dementia and Subclinical Indices of Brain Aging: The Framingham Heart Study. J Alzheimers Dis. 2016. Epub 2016/02/19. doi: 10.3233/jad-150991. (PubMed ID Number: 26890771).
Health and Retirement Study (HRS)	The University of Michigan Health and Retirement Study (HRS) is a longitudinal panel study that surveys a representative sample of approximately 20,000 people in America over the age of 50 every two years. http://hrsonline.isr.umich.edu/	Saczynski JS, et al. Antidepressant Use and Cognitive Decline: The Health and Retirement Study. The American journal of medicine. 2015;128(7):739-746.

Committee-suggested Cohort Studies Country	Cohort Study Description	Example of excluded publication derived from cohort study
US		doi:10.1016/j.amjmed.2015.01.007.
Health, Aging and Body Composition Study (Health ABC) US	The HEALTH ABC Study will characterize the extent of change in body composition in older men and women, identify clinical conditions accelerating these changes, and examine the health impact of these changes on strength, endurance, disability, and weight-related diseases of old age. The study population consists of 3,075 persons age 70-79 at baseline with about equal numbers of men and women. Thirty-three percent of the men are African-Americans as are 46% of the women. All persons in the study were selected to be free of disability in activities of daily living and free of functional limitation (defined as any difficulty walking a quarter of a mile or any difficulty walking up 10 steps without resting) at baseline. https://www.nia.nih.gov/research/intramural-research-program/dynamics-health-aging-and-body-composition-health-abc	No relevant studies immediately found
Honolulu-Asia Aging Study (HAAS) US	The Honolulu-Asia Aging Study (HAAS) is a longitudinal epidemiologic investigation of rates, risk factors, and neuropathologic abnormalities associated with cognitive decline and dementia in aged Japanese-American men. http://www.alzrisk.org/cohort.aspx?cohortID=3&rfid=5	Taaffe, Dennis R., et al. "Physical activity, physical function, and incident dementia in elderly men: the Honolulu–Asia Aging Study." The Journals of Gerontology Series A: Biological Sciences and Medical Sciences 63.5 (2008): 529-535.
Kame Project (a cohort study of Japanese Americans in King County, Washington) US	A large population-based prospective study of Japanese Americans in King County, Washington, who were followed from 1992 to 2001, as part of the Ni-Hon-Sea Project, a cross-cultural study of prevalence and incidence rates of Alzheimer's disease and vascular dementia among Japanese populations living in Hiroshima, Japan; Oahu, Hawaii; and the metropolitan area of Seattle, Washington. http://www.alzrisk.org/cohort.aspx?cohortID=55&rfid=6	Dai Q, et al. Fruit and Vegetable Juices and Alzheimer's Disease: The Kame Project. The American journal of medicine. 2006;119(9):751-759. doi:10.1016/j.amjmed.2006.03.045.
Kungsholmen Project Sweden	The Kungsholmen Project is a longitudinal population-based study on ageing and dementia, carried out by the Stockholm Gerontology Research Center in collaboration with Aging Research Center (ARC), Karolinska Institutet. The project, which started in 1987, has gathered a 12-year long database and offers information on aging from a multidisciplinary perspective. http://www.kungsholmenproject.se/	Qiu C, et. al. Decline in blood pressure over time and risk of dementia: a longitudinal study from the Kungsholmen project. Stroke 2004;35:1810-5.
Leisure World Cohort Study (note: the Leisure World is now extended as the 90+ Study) US	The Leisure World Cohort Study was established to study the effect of modifiable lifestyle practices on longevity and successful aging when all residents of a California retirement community (Leisure World Laguna Hills) were mailed a postal health survey in 1981. New residents who moved into the community after this date were mailed the survey in 1982, 1983, and 1985. Of the 22,910 residents, 13,978 (61%) completed the questionnaire. The population and cohort are mostly Caucasian, well educated, upper-middle class, and elderly. https://www.mind.uci.edu/research/90plus-study/	Paganini-Hill, Annlia. "Hypertension and Dementia in the Elderly: The Leisure World Cohort Study." International journal of hypertension 2012 (2011).
Lothian Birth Cohorts	The Lothian Birth Cohorts of 1921 and 1936 are follow-up studies of the Scottish Mental Surveys of 1932 and 1947. The surveys had, respectively, tested the	No relevant studies immediately found

Committee-suggested Cohort Studies Country	Cohort Study Description	Example of excluded publication derived from cohort study
UK	intelligence of almost every child born in 1921 or 1936 and attending school in Scotland in the month of June in those years. Therefore, tracing, recruiting and re-testing people who had taken part in the Surveys offered a rare opportunity to examine the distribution and causes of cognitive ageing across most of the human life course. The studies described here were initially set up to study determinants of non-pathological cognitive ageing; i.e. the ageing of cognitive functions largely in the normal range, and not principally dementia or other pathological cognitive disordershttp://www.lothianbirthcohort.ed.ac.uk/	
Mayo Clinic Study of Aging (MCSA) US	The MCSA is a population-based study that was designed to study incident mild cognitive impairment and dementia. The sampling frame included all persons aged 70–89 years who were residents of Olmsted County, Minnesota, as of October 1, 2004 (age- and sex-stratified random sample). The medical records of potential participants were formally reviewed prior to contact to exclude those with diagnoses of dementia, those in hospice care, or those considered to have conditions deemed imminently fatal. (Mayo Clinic does not appear to have a searchable site for this study.)	Vassilaki, Maria, et al. "Multimorbidity and risk of mild cognitive impairment." Journal of the American Geriatrics Society 63.9 (2015): 1783-1790.
MEMENTO France	This cohort aims at studying the evolution of a variety of potentially early signs (cognitive complaints, deficit in some domain of cognition, psycho-behavioural disturbances, changes in imaging or biological markers) of Alzheimer's disease and related dementia and to estimate the prognostic value of different markers (neuro-psychological, vascular, psychopathological, socio-educational, genetic, biological, neuro-imaging) on the progression to clinical dementia or severe cognitive deterioration stages, and then to death. http://www.memento-cohort.org/memento_web/Portals/0/Chercheurs/MEMENTO_Formulaire_AccesDonnees.pdf	No relevant studies immediately found
Minority Aging Research Study (MARS) US	The Minority Aging Research Study (MARS) began in 2004 and is a study of risk factors for cognitive decline in older Blacks. Participants are recruited from community-based organizations, churches, and senior-subsidized housing facilities; the catchment area is within that of MAP. Study participation requires agreeing to detailed annual clinical evaluations and cognitive testing. Between 2004 and 2007, >350 older persons enrolled in the study. https://www.rush.edu/services-treatments/alzheimers-disease-center/minority-aging-research-study	No relevant studies immediately found
Monongahela Valley Independent Elders Survey (MoVIES) US	The MoVIES project investigated various aspects of normal and abnormal aging. It also studied the incidence, risk factors, and outcome in late-life dementia, including Alzheimer's disease, in a prospective community-based epidemiologic study for 15 years. The study cohort was drawn from a rural, largely blue-collar community in the mid-Monongahela Valley of Southwestern Pennsylvania. The original cohort of 1681 individuals aged 65+ years was assembled between 1987 and 1989 and was followed until 2002 with multi-stage clinical "Waves" of cognitive and risk factor screening. Screening waves were interspersed with multi-stage clinical evaluations to detect the	No relevant studies immediately found

Committee-suggested Cohort Studies Country	Cohort Study Description	Example of excluded publication derived from cohort study
	presence of Alzheimer's and other dementias. http://www.wpic.pitt.edu/research/dementia_epidemiology/Movies/MoviesHomePage.htm	
Monongahela-Youghiogheny Healthy Aging Team (MYHAT) US	The MYHAT project seeks to describe the distribution of Cognitive Impairment, No Dementia (CIND) and Mild Cognitive Impairment (MCI) and related entities, their associated features, their outcomes over time, and the predictors of these outcomes. An age-stratified random community sample of approximately 2,100 was recruited and screened using cognitive, functional, and other health-related measures to identify the non-demented who are cognitively impaired. Among them, we identified subgroups meeting operational criteria for MCI of amnestic and other varieties. http://www.wpic.pitt.edu/research/dementia_epidemiology/MYHAT/MYHATHomePage.htm	Hughes TF,et al. Independent and combined effects of cognitive and physical activity on incident MCI. Alzheimers and Dement. 2015 Nov; 11(11): 1377-84. doi: 10.1016/j.jalz.2014.11.007. (PMC4536189) Ganguli M, et al. Rates and risk factors for progression to incident dementia vary by age in population cohort. Neurology, 84(1):72-80. (PMC4336092)
Multi-Ethnic Study of Atherosclerosis (MESA) US	The MESA study examines the characteristics of subclinical cardiovascular disease (disease detected non-invasively before it has produced clinical signs and symptoms) and the risk factors that predict progression to clinically overt cardiovascular disease or progression of the subclinical disease. From July 2000 to January 2012, MESA is a prospective population-based sample of 6,814 asymptomatic men and women aged 45-84. Approximately 38 percent of the recruited participants are white, 28 percent African-American, 22 percent Hispanic, and 12 percent Asian, predominantly of Chinese descent. https://www.mesa-nhlbi.org/	No relevant studies immediately found
Northern Manhattan Study (NOMAS) US	NOMAS)is a study of the population of Washington Heights in Northern Manhattan. The ongoing study, which began in 1990, is based in the Neurological Institute of Columbia Presbyterian Hospital, located in Washington Heights. NOMAS has enrolled over 4,400 people from the surrounding community. NOMAS is the first study of its kind to focus on stroke risk factors in whites, blacks, and Hispanics living in the same community. It is helping to fill gaps in our knowledge of stroke epidemiology in minority populations. http://columbianomas.org/	No relevant studies immediately found
Nurses' Health Study US	The Nurses' Health Studies are among the largest prospective investigations into the risk factors for major chronic diseases in women. Starting with the original Nurses' Health Study in 1976, the studies are now in their third generation with Nurses' Health Study 3 (which is still enrolling male and female nurses) and count more than 275,000 participants. http://www.nurseshealthstudy.org/	Devore, Elizabeth E., et al. "Dietary intakes of berries and flavonoids in relation to cognitive decline." Annals of neurology 72.1 (2012): 135-143. Okereke, Olivia I., et al. "Plasma C-peptide levels and rates of cognitive decline in older, community-dwelling women without diabetes." Psychoneuroendocrinology 33.4 (2008): 455-461.
Reasons for Geographic and Racial Differences in Stroke	REGARDS is an observational study of risk factors for stroke in adults 45 years or older. 30,239 participants were recruited between January 2003 and October 2007. They completed a telephone interview followed by an in-home physical exam. Measurements included traditional risk factors such as blood pressure and cholesterol levels, and an echocardiogram of the heart. At six month intervals, participants are	Zhu, Wenfei, et al. "Association Between Objectively Measured Physical Activity and Cognitive Function in Older Adults—The Reasons for Geographic and Racial Differences in Stroke Study." Journal of the American Geriatrics Society 63.12 (2015): 2447-

Committee-suggested Cohort Studies Country	Cohort Study Description	Example of excluded publication derived from cohort study
(REGARDS) US	contacted by phone to ask about stroke symptoms, hospitalizations and general health status. The study is ongoing and will follow participants for many years. http://www.regardsstudy.org/	2454.
Religious Orders Study US	The Religious Orders Study is a collaborative study with Rush and other U.S. medical centers. It involves more than 1,100 older religious clergy (nuns, priests and brothers) who have agreed to medical and psychological evaluation each year and brain donation after death. Researchers are using information from the study to discover what changes in the brain are responsible for memory and movement problems. https://www.rush.edu/services-treatments/alzheimers-disease-center/religious-orders-study	Yu, Lei, et al. "The CETP I405V polymorphism is associated with an increased risk of Alzheimer's disease." Aging cell 11.2 (2012): 228-233.
Rochester Epidemiology Project (Olmsted County Study) US	The REP includes the medical records of all persons who have ever lived in Olmsted County, Minnesota between January 1, 1966 and the present, and who have given permission for their medical information to be used for research.[6] Those persons comprise more than 500,000 unique individuals and more than 6 million person years of follow-up through 2010. http://www.mayo.edu/research/centers-programs/rochester-epidemiology-project/overview	Savica, Rodolfo, et al. "Incidence of dementia with Lewy bodies and Parkinson disease dementia." JAMA neurology 70.11 (2013): 1396-1402.
Rotterdam Study Netherlands	The Rotterdam Elderly Study is a prospective cohort study in the Ommoord district in the city of Rotterdam, the Netherlands. Recruitment started in January 1990. The main objectives of the Rotterdam Study were to investigate the risk factors of cardiovascular, neurological, ophthalmological and endocrine diseases in the elderly. Up to 2008, approximately 15,000 subjects aged 45 years or over have been recruited. http://www.epib.nl/research/ergo.htm	Ruitenberg A, et al. "Cerebral hypoperfusion and clinical onset of dementia: the Rotterdam Study." Annals of neurology 57.6 (2005): 789-794. Engelhart, Marianne J., et al. "Inflammatory proteins in plasma and the risk of dementia: the Rotterdam study." Archives of neurology 61.5 (2004): 668-672.
Rush Memory and Aging Project (MAP) US	The Rush MAP is a companion study that is more diverse in life experience make-up than ROS. Participants are older community-dwelling persons who are recruited and followed with nearly identical annual evaluations to ROS and all agree to donate brain, spinal cord, nerve and muscle to Rush investigator's at the time of death. More than 1,350 participants have enrolled and are seen annually and have had up to 13 clinical evaluations. https://www.rush.edu/services-treatments/alzheimers-disease-center/radc-research/memory-and-aging-project-rush	Buchman, A. S., et al. "Total daily physical activity and the risk of AD and cognitive decline in older adults." Neurology 78.17 (2012): 1323-1329.
The Sacramento Area Latino Study on Aging (SALSA) US	The Sacramento Area Latino Study on Aging (SALSA Study) project tracked the incidence of physical and cognitive impairment as well as dementia and cardiovascular diseases in elderly Latinos in the Sacramento, California, region. http://www.icpsr.umich.edu/icpsrweb/NACDA/studies/29323	Haan, Mary N., et al. "Homocysteine, B vitamins, and the incidence of dementia and cognitive impairment: results from the Sacramento Area Latino Study on Aging." The American journal of clinical nutrition 85.2 (2007): 511-517.
Singapore Longitudinal Ageing Study (SLAS)	Between September 2003 and December 2005, a whole population of older adults aged 55 years and above who were Singaporean residents in contiguous precincts in the South East region of Singapore were identified from a door–to–door census and invited to participate in the Singapore Longitudinal Ageing Study (SLAS). (No identifiable website)	Ng, Tze Pin, et al. "Metabolic Syndrome and the Risk of Mild Cognitive Impairment and Progression to Dementia: Follow-up of the Singapore Longitudinal Ageing Study Cohort." JAMA neurology 73.4 (2016): 456-463.

Committee-suggested Cohort Studies Country	Cohort Study Description	Example of excluded publication derived from cohort study
Singapore		
Study of Osteoporotic Fractures (SOF) US	The multi-center Study of Osteoporotic Fractures (SOF) has 20 years of prospective data about osteoporosis that has served as the basis for many findings about osteoporosis and aging in women ≥ age 65. In addition to adjudication of fractures, SOF has tracked cases of incident breast cancer, and total and cause-specific mortalityhttp://sof.ucsf.edu/interface/	Slinin, Yelena, et al. "Cystatin C and cognitive impairment 10 years later in older women." The Journals of Gerontology Series A: Biological Sciences and Medical Sciences 70.6 (2015): 771-778.
The Sydney Memory and Ageing Study (Sydney MAS) Australia	The Sydney Memory and Ageing Study (Sydney MAS) began in 2005 to examine the clinical characteristics and prevalence of mild cognitive impairment (MCI) and related syndromes, and to determine the rate of change in cognitive function over time. It is one of the largest longitudinal studies of this kind in Australia. At the baseline assessment from 2005 to 2007, 1037 non-demented individuals aged 70-90 were recruited from two areas of Sydney, following a random approach to 8914 individuals on the electoral roll. They underwent detailed neuropsychological and medical assessments and donated a blood sample for clinical chemistry, proteomics and genomics. https://cheba.unsw.edu.au/project/sydney-memory-and-ageing-study	Heffernan, Megan, et al. "Alcohol Consumption and Incident Dementia: Evidence from the Sydney Memory and Ageing Study." Journal of Alzheimer's Disease Preprint (2016): 1-10. Sachdev, Perminder S., et al. "Risk profiles for mild cognitive impairment vary by age and sex: the Sydney Memory and Ageing Study." The American Journal of Geriatric Psychiatry 20.10 (2012): 854-865.
UK Health and Lifestyle Study UK	The Health Survey for England (HSE) is an important annual survey looking at changes in the health and lifestyles of people all over the country. Around 8,000 adults and 2,000 children take part in the survey each year. Information is collected through an interview, and if participants agree, a visit from a specially trained nurse. The surveys, which have been carried out since 1991, provide regular information that cannot be obtained from other sources. https://www.ucl.ac.uk/hssrg/studies/hse	No relevant studies immediately found
Washington-Heights Inwood Columbia Aging Project (WHICAP) US	The Washington Heights-Hamilton Heights-Inwood Community Aging Project (WHICAP) is a community-based longitudinal study of aging and dementia among elderly, urban-dwelling residents. The project began enrolling patients in 1989 and has followed more than 5,900 residents over 65 years of age. The WHICAP study has enabled researchers to capture detailed information about the onset of dementia and how symptoms develop over time. http://www.alzrisk.org/cohort.aspx?cohortID=16&rfid=3	Helzner, Elizabeth P., et al. "Contribution of vascular risk factors to the progression in Alzheimer disease." Archives of neurology 66.3 (2009): 343-348.
Whitehall II Prospective Cohort Study UK	Whitehall II is a longitudinal, prospective cohort study of 10,308 women and men, all of whom were employed in the London offices of the British Civil Service at the time they were recruited to the study in 1985. The initial data collection included a clinical examination and self-report questionnaire. Research continues to explore the pathways and mechanisms through which social position influences health. The research group aims to build a causal model leading from social position through psychosocial and behavioural pathways to pathophysiological changes, sub-clinical markers of disease, functional change, and clinical disease. https://www.ucl.ac.uk/whitehallII	Singh-Manoux, Archana, et al. "Interleukin-6 and C-reactive protein as predictors of cognitive decline in late midlife." Neurology 83.6 (2014): 486-493. Akbaraly, Tasnime N., et al. "Metabolic Syndrome Over 10 Years and Cognitive Functioning in Late Midlife The Whitehall II study." Diabetes care 33.1 (2010): 84-89.

Appendix F. Cognitive Training Interventions

Appendix Table F1. Characteristics of eligible studies: ACTIVE trial publications

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]**
Rebok 2014[1] RCT US High	2832	Older adults aged 65 to 94 years with good functional and cognitive status and a MMSE score greater than 22 Age, Mean (SD) 74 (6) 76% Female 73% White 88.6% High School Graduate MMSE, Mean (SD) 27.2 (2.0)	Verbal episodic memory training or reasoning training or speed of processing training -10 small group sessions, 60-75 minutes each over 5 to 6 weeks	No contact control group (study duration)	10 years	Memory [Memory Composite] Executive, Attention, Processing Speed [Reasoning Composite] Executive, Attention, Processing Speed [Speed of Processing Composite]
Rebok 2013[2] RCT US High	629	Older adults aged 65 to 94 years with good functional and cognitive status and a MMSE score greater than 22 Age, Mean (SD) 73.5 (6.0) 77% Female 76% White Years Education, Mean (SD) 13.7 (2.7) MMSE, Mean (SD) 27.3 (2)	Verbal episodic memory training -10 small group sessions, 60-75 minutes each over 5 to 6 weeks	No contact control group (study duration)	1 year 2 years 3 years 5 years	Memory [Memory Composite]

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]**
Jones, 2013[3] RCT US High	1659	Older adults aged 65 to 94 years with good functional and cognitive status and a MMSE score greater than 22 Age, Mean (SD) 74 (6) 77% Female 73% White Education, Mean (SD) 13.5 (3) MMSE, Mean (SD) 27 (2)	Verbal episodic memory training or reasoning training or speed of processing training -10 small group sessions, 60-75 minutes each over 5 to 6 weeks	No contact control group (study duration)	5 years	Memory [Memory Composite] Executive, Attention, Processing Speed [Reasoning Composite] Executive, Attention, Processing Speed [Speed of Processing Composite]
Sisco 2013[4] RCT US High	1912	Older adults aged 65 to 94 years with good functional and cognitive status and a MMSE score greater than 22 Age, Mean (SD) 72.9 (5.4) 76% Female 72% White Years Education, Mean (SD) 13.2 (2.6) MMSE, Mean (SD) 27.3 (2)	Verbal episodic memory training or reasoning training or speed of processing training -10 small group sessions, 60-75 minutes each over 5 to 6 weeks	No contact control group (study duration)	1 year 2 years 3 years 5 years	Memory [Rivermead Paragraph Recall Test, Verbatim Recall] Memory [Rivermead Paragraph Recall Test, Paraphrase Recall] Memory [HVLT, Total Recall] Memory [AVLT, Total Recall]
Valdes 2012[5] RCT US High	195	Older adults from ACTIVE trial with psychometrically-defined MCI	Speed of processing training -10 small group sessions, 60-75 minutes each over	No contact control group (study duration)	10 years	Executive, Attention, Processing Speed [UFOV Performance]

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]**
		Age, Mean (SD) 78 (6) 67% Female 60% White Education Level, Mean (SD) 12 (2.5) Baseline Cognition NR	5 to 6 weeks			
Unverzagt 2012[6] RCT US High		Older adults aged 65 to 94 years with good functional and cognitive status and a MMSE score greater than 22 Age, Mean (SD) 74 (6) 76% Female 73% White 88.6% High School Graduate MMSE, Mean (SD) 27.2 (2.0)	Verbal episodic memory training or reasoning training or speed of processing training -10 small group sessions, 60-75 minutes each over 5 to 6 weeks	No contact control group (study duration)	5 years	Diagnosis [Dementia
Wolinsky, 2010[7] RCT US High	1534	Older adults aged 65 to 94 years with good functional and cognitive status and a MMSE score greater than 22 Age, Mean 73 78% Female 73% White Education Level,	Verbal episodic memory training or reasoning training or speed of processing training -10 small group sessions, 60-75 minutes each over 5 to 6 weeks	No contact control group (study duration)	5 years	Executive, Attention, Processing Speed [Internal locus of control] Executive, Attention, Processing Speed [Chance locus of control] Executive, Attention, Processing Speed [Powerful others locus of control]

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]
		Mean 13 Baseline Cognition NR				
Wolinsky, 2010b[8] RCT US High	1804	Older adults aged 65 to 94 years with good functional and cognitive status and a MMSE score greater than 22 Age, Mean (SD) 74 (6) 76% Female 73% White 88.6% High School Graduate MMSE, Mean (SD) 27.2 (2.0)	Verbal episodic memory training or reasoning training or speed of processing training -10 small group sessions, 60-75 minutes each over 5 to 6 weeks	No contact control group (study duration)	2 years 3 years 5 years	Memory [Memory Composite] Executive, Attention, Processing Speed [Reasoning Composite] Executive, Attention, Processing Speed [Speed of Processing Composite]
Unverzagt 2007[9] RCT US High	2832	Older adults aged 65 to 94 years with good functional and cognitive status and a MMSE score greater than 22 Age, Mean (SD) 74 (6) 76% Female 73% White 88.6% High School Graduate MMSE, Mean (SD) 27.2 (2.0)	Verbal episodic memory training or reasoning training or speed of processing training -10 small group sessions, 60-75 minutes each over 5 to 6 weeks	No contact control group (study duration)	2 years	Memory [Memory Composite] Executive, Attention, Processing Speed [Reasoning Composite] Executive, Attention, Processing Speed [Speed of Processing Composite]
Willis 2006[10] US	2832	Older adults aged 65 to 94 years with	Verbal episodic memory training or reasoning	No contact control group (study duration)	5 years	Memory [Memory Composite] Executive, Attention, Processing Speed

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]**
RCT High		good functional and cognitive status and a MMSE score greater than 22 Age, Mean (SD) 74 (6) 76% Female 73% White 88.6% High School Graduate MMSE, Mean (SD) 27.2 (2.0)	training or speed of processing training -10 small group sessions, 60-75 minutes each over 5 to 6 weeks			[Reasoning Composite] Executive, Attention, Processing Speed [Speed of Processing Composite]
Ball 2002[11] RCT US Medium	2832	Older adults aged 65 to 94 years with good functional and cognitive status and a MMSE score greater than 22 Age, Mean (SD) 74 (6) 76% Female 73% White 88.6% High School Graduate MMSE, Mean (SD) 27.2 (2.0)	Verbal episodic memory training or reasoning training or speed of processing training -10 small group sessions, 60-75 minutes each over 5 to 6 weeks	No contact control group (study duration)	2 years	Memory [Memory Composite] Executive, Attention, Processing Speed [Reasoning Composite] Executive, Attention, Processing Speed [Speed of Processing Composite]

ACTIVE=Advanced Cognitive Training for Independent and Vital Elderly; AVLT=Auditory Verbal Learning Test; HVLT=Hopkins Verbal Learning Test; MCI=Mild Cognitive Impairment; MMSE=Mini Mental Status Exam; RCT=Randomized Controlled Trial; RoB=Risk of Bias; SD=Standard Deviation

Appendix Table F2. Summary risk of bias assessments: ACTIVE trial

Study	Overall Risk of Bias Assessment	Rationale
Rebok 2014[1]	High	Potential attrition bias with attrition rate of 57%.
Rebok 2013[2]	High	Potential attrition and reporting bias.
Jones 2013[3]	High	Attrition rate is greater than 21% with insufficient analysis to address potential for bias.
Sisco 2013[4]	High	Attrition rate is 33% with insufficient analysis to address potential for bias.
Valdes 2012[5]	High	Potential attrition and reporting bias.
Unverzagt 2012[6]	High	Attrition rate is 33% with insufficient analysis to address potential for bias.
Wolinsky 2010[7]	High	Potential attrition bias with attrition rate of 55%.
Wolinsky 2010b[8]	High	Attrition rate is 36% with insufficient analysis to address potential for bias.
Unverzagt 2007[9]	High	Attrition rate is greater than 21% with insufficient analysis to address potential for bias.
Willis 2006[10]	High	Attrition rate is 33% with insufficient analysis to address potential for bias.
Ball 2002[11]	Medium	Potential attrition and detection bias.

Appendix Table F3. Strength of evidence assessments: ACTIVE Trial

Outcome	# Trials (n)	Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
2-Year Outcomes									
Memory	1 (2,832)	Improvement with memory training intervention (ES=0.17). No significant differences with reasoning speed of processing training.	Medium	Indirect	Precise	Unknown	Undetected	NA	Moderate
Reasoning	1 (2,832)	Improvement with reasoning training (ES=0.257). No significant differences with memory or speed of processing training.	Medium	Indirect	Precise	Unknown	Undetected	NA	Moderate
Speed of Processing	1 (2,832)	Improvement with speed of processing training (ES=0.87). No significant differences with reasoning or memory training.	Medium	Indirect	Precise	Unknown	Undetected	NA	Moderate
5- and 10-Year Outcomes									
Diagnosis	1 (2,832)	No statistically significant differences between intervention arms (aggregate) and control (5-Years).	High	Direct	Precise	Unknown	Undetected	NA	Insufficient
Memory	1 (2,832)	<u>5-Years</u> Improvement with memory training (ES=0.23). No significant differences with reasoning speed of processing training. <u>10 Years</u> No statistically significant differences between intervention arms and control.	High	Indirect	Precise	Unknown	Undetected	NA	Low
Reasoning	1 (2,832)	Improvement with reasoning training (5-Years: ES=0.26; 10-Years: ES=0.23). No significant differences with memory or speed of processing training.	High	Indirect	Precise	Unknown	Undetected	NA	Low
Speed of Processing	1 (2,832)	<u>5-Years</u> Improvement with reasoning training (ES=0.15) and speed of processing training	High	Indirect	Precise	Unknown	Undetected	NA	Low

Outcome	# Trials (n)	Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
		(ES=0.076). No significant differences with memory training. <u>10 Years</u> Improvement with speed of processing training (ES=0.66). No significant differences with reasoning or memory training.							

ES=Effect Size

Appendix Table F4. Characteristics of eligible studies: other cognitive training trials in adults with normal cognition

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]**
Stine-Morrow 2014[12] RCT US Medium	461	Adults without dementia or neurological impairment Age, Mean (SD) 23 (7.6) 75% Female Race NR Education Level, Mean (SD) 15.4 (2.6) MoCA, Mean (SD) 26 (3)	Odyssey of the Mind engagement program –16 weekly meetings for 1.5 hours Home-based reasoning training -10 weekly lessons supplemented with 6 packs of crossword and Sudoku puzzles	Waitlist control	8 months	Visuospatial [Visuospatial Composite] Executive, Attention, Processing Speed [Processing Speed Composite] Memory [Episodic Memory Composite]
Carretti 2013[13] RCT Italy Medium	40	Healthy older adults active in cultural and social activities in their neighborhood Age, Mean (SD) 70 (3.6) Sex NR Race NR Education, Mean (SD) 8.56 (4.3) Baseline Cognition NR	Six individual training sessions over 2 weeks (sessions 2-4 were training, sessions 1, 5, and 6 were for baseline, posttest, and 6 month follow-up, respectively)	Paper-and-pencil questionnaires	6 months	Memory [Categorization Working Memory Span Test (CWMS)] Memory [Working Memory Updating Word Span Test (Updating)]
Miller 2013[14] RCT US Medium	84	Adults with no signs of dementia and a MMSE score of 24 or more Age, Mean (SD) 81.8 (6) 67% Female 96% White Years Education, Mean (SD) 16 (2.2) MMSE, Mean (SD)	Computer brain fitness program -5 days a week for 20-25 minutes/day for 8 weeks followed by 4 months of doing as many sessions as they preferred	Wait-list control -2 months wait period prior to access to intervention for 4 months	6 months	Memory [Delayed Memory Composite] Memory [Immediate Memory Composite] Language [Language Composite]

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]
		28 (1.6)				
Wolinsky 2013[15] RCT US Low	681	Adults without a diagnosis of cognitive impairment Age, Mean 57.2 68.6% Female 94.2% White 71.9% College Graduate Baseline Cognition NR	On-site visual speed of processing training with and without 2 hour boosters after 11 months - Five weekly, 2 hour training sessions At home visual speed of processing training -10 hours	On-site computerized crossword game – Five weekly, 2 hour training session	1 year	Executive, Attention, Processing Speed [UFOV] Executive, Attention, Processing Speed [TMT-A] Executive, Attention, Processing Speed [TMT-B] Executive, Attention, Processing Speed [SDMT] Executive, Attention, Processing Speed [Stroop Word] Executive, Attention, Processing Speed [Stroop color] Executive, Attention, Processing Speed [Stroop Color-Word] Executive, Attention, Processing Speed [COWAT] Executive, Attention, Processing Speed [DVT, Time] Executive, Attention, Processing Speed [DVT, Errors]
Cheng 2012[16] RCT China High	270	Older adults with no evidence of significant cognitive impairment Age, Mean (SD) 70 (3.5) 48% Female Race NR Education, Mean (SD) 9.6 (3.9) Baseline Cognition NR	Multidomain training or reasoning training group cognitive training sessions –Twice a week for 12 weeks	Wait list control	6 months 12 months	Multidomain Neuropsychological Performance [RBANS total score] Memory [RBANS Immediate memory] Visuospatial [RBANS Visuospatial/Constructional] Language [RBANS Language] Executive, Attention, Processing Speed [RBANS Attention] Memory [RBANS Delayed Memory] Memory [Visual Reasoning Test] Executive, Attention, Processing Speed [Stroop Color interference score] Executive, Attention, Processing Speed

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]
						[Stroop Word interference score] Executive, Attention, Processing Speed [Stroop Number of naming errors] Executive, Attention, Processing Speed [Trails A complete time] Executive, Attention, Processing Speed [Trails B complete time] Executive, Attention, Processing Speed [Trails A approximate error number] Brief Cognitive Test Performance [MMSE]
Mortimer 2012[17] RCT China High	75	Adults age 60-79 with an education-adjusted Chinese MMSE score greater than 26 Age, Mean (SD) 67.8 (5.8) 67% Female Race NR Years of Education, Mean (SD) 11.7 (3.4) Mattis Dementia Scale Score, Mean (SD) 137.6 (7.6)	Social interaction –Meeting at community center for 1 hr, 3 times/week	Inactive control with 4 check-in calls over 40 weeks	40 weeks	Executive, Attention, Processing Speed [WAIS digit span (forward)[Executive, Attention, Processing Speed [WAIS digit span (backward)] Visuospatial [Bell cancellation test] Visuospatial Memory [Rey Figure (copying)] Visuospatial Memory [Rey Figure (recall)] Executive, Attention, Processing Speed [Stroop Test (word)] Executive, Attention, Processing Speed [Stroop Test (color)] Executive, Attention, Processing Speed [Stroop Test (color-word)] Memory [Auditory Verbal Learning Test, Immediate Recall] Memory [Auditory Verbal Learning Test, Delayed Recall] Memory [Auditory Verbal Learning Test (delayed recognition] Language [Category Verbal Fluency, Animals] Executive, Attention, Processing Speed [WAIS Similarities] Executive, Attention, Processing Speed [Trails A Time (seconds)] Executive, Attention, Processing Speed [Trails B Time (seconds)]

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]
						Visuospatial [Clock drawing test] Language [Boston Naming Test (correct names)] Multidomain Neuropsychological Performance [Mattis Dementing Rating Scale (total score)] Executive, Attention, Processing Speed [Mattis Attention Score] Executive, Attention, Processing Speed [Mattis Initiation Score] Visuospatial Mattis Construction Score] Executive, Attention, Processing Speed Mattis Conceptualization Score] Memory [Mattis Memory Score] Biomarker [Whole brain volume (% of total intracranial volume)]
Szelag 2012[18] RCT Poland High	30	Healthy adults between 65 and 75 years old Age, Mean (SD) 69 (2) 57% Female Race NR Years Education, Mean (SD) 13 (3) MMSE, Range 27-30	Temporal information processing training -32 hour-long sessions for 8 weeks	Non-temporal training using computer games or no intervention over 8 weeks	18 months	Memory [Spatial Span] Memory [Delayed Matching to Sample] Memory [Pattern Recognition Memory Test] Executive, Attention, Processing Speed [Attention Measure]
Evers 2011[19] RCT Germany High	161	Women age 70 and over with no more than 4 errors on the MMSE Age, Mean (SD) 73.6 (4.2) 100% Female Race NR Years of Education, Mean (SD) 12 (2.6)	Computer course (writing, playing, calculating, surfing the Internet, emailing, drawing, image editing, and video taping)	Inactive control (live their habitual life)	6 months	Memory [RMBT, Immediate] Memory [RBMT, Delayed Recall] Memory [FCSRT, Short Delay] Memory [FCSRT, Long Delay] Langue [Semantic Verbal Fluency] Executive, Attention, Processing Speed Executive, Attention, Processing Speed [Stroop Test] Executive, Attention, Processing Speed [Trail Making Tests B/A]

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]**
		MMSE, Mean (SD) 28.78 (0.96)				
Borella 2010[20] RCT Italy High	40	Healthy adults with not pathologies causing possible cognitive impairments Age, Mean (SD) 69 (3) Sex NR Race NR Education, Mean (SD) 9.3 (3.7) Baseline Cognition NR	Working memory training -3 60- minute sessions over 2 weeks	Memory questionnaires -3 60-minute sessions over 2 weeks	8 months	Memory [CWMS] Visuospatial [Dot Matrix] Executive, Attention Processing Speed Executive, Attention Processing Speed [Forward Span] [Executive, Attention Processing Speed Backward Span] [Executive, Attention Processing Speed Stroop Color Incongruent, RTs] Executive, Attention Processing Speed [Stroop Color Control II, RTs] Executive, Attention Processing Speed [Stroop Color Index, RTs] Executive, Attention Processing Speed [Stroop Color Incongruent, Errors] Executive, Attention Processing Speed [Stroop Color Control II, Errors] [Executive, Attention Processing Speed Stroop Color Index, Errors] Executive, Attention Processing Speed [Pattern Comparison]
Klusmann, 2010[21] RCT Germany Medium	168	Women older than 70 without cognitive impairment Age, Mean (SD) 74 (4) 100% Female Race NR Years Education, Mean (SD) 12 (2.6)	Computer courses focusing on creative tasks and coordinative and memory tasks -75 intervention units of 90 minutes over 6 months	Living habitual life over 6 months	6 months	Memory [RBMT, Immediate Memory [RBMT, Delayed Recall] Memory [FCSRT, Short Delay] Memory [FCSRT, Long Delay] Executive, Attention, Processing Speed [TMT-A/B] Executive, Attention, Processing Speed [Stroop]

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]
		MMSE, Mean (SD) 28.8 (0.97)				
McDougall 2010[22] RCT US High	265	Non-demented older adults Age, Mean 75 79% Female 71% White Education, Mean (SD) 13.6 (3.8) Baseline Cognition MMSE, Mean 26	Small group memory training -2 times/week for a month, 12 hours total with 4, 2-hour booster sessions over 3 months following training	Health promotion training focusing on 18 topics -2 times/week for a month, 12 hours total with 4, 2-hour booster sessions over 3 months following training	6 months 14 months 26 months	Brief Cognitive Test Performance [MMSE] Memory [Rivermead Behavioral Memory Performance Test] Memory [BVMT, Delayed Recall] Memory [HVLT, Delayed Recall]
Park 2009[23] RCT South Korea High	129	Adults age 65 and over without clinically significant diseases Age, Mean (SD) 78.3 (6,22) 93% Female Race NR Years Education, Mean (SD) 4.62 (4.33) MMSE, Mean (SD) 22.14 (4.61)	Cognitive training program -12, 60-minute sessions followed by an observational period	Delayed cognitive training program -8 weeks of observation followed by cognitive training program	24 weeks	Brief Cognitive Test Performance [MMSE-KC]
Slegers 2009[24] RCT Netherlands High	191	Healthy older adults with no prior computer experience Age NR Sex NR Race NR Education NR MMSE, Mean (SD) 28 (1.4)	Small group practice with personal computer following by at home practice with a personal computer with at home assignments -4 hour training sessions over 2 weeks followed by home practice over 12 months	No training/no intervention	12 months	Memory [Visual Verbal Learning Test] Motor [Motor Choice Reaction Time] Executive, Attention, Processing Speed [Letter-Digit Substitution Test] Executive, Attention, Processing Speed [Stroop Color Word Test] Brief Cognitive Test Performance [Cognitive Failures Questionnaire]
Buiza 2008[25]	238	Adults age 65 and over	Structured and	No training (regular	1 year	Memory [Immediate Memory, WMS-R]

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]**
RCT Spain High		without cognitive impairment Age, Mean (SD) 74 (8) 73% Female Race NR Education NR Baseline Cognition NR	unstructured cognitive training with and without information on well-being – Weekly sessions with 180 sessions over 2 years	daily activities)	2 years	Memory [Recent Logical Execution Memory, AVLT] Memory [Short Term Memory] Memory [Working Memory] Executive, Attention, Processing Speed [VICOS] Motor [VICOC] Executive, Attention, Processing Speed [PFLE] Executive, Attention, Processing Speed [ABSTRAC] Executive, Attention, Processing Speed [Praxia]
Yesavage 2008[26] RCT US High	168	Community-dwelling adults aged 55-90 with a MMSE score between 24 and 30 Age, Mean (SD) 65 (8) 52% Female Race NR Education, Mean (SD) 16.3 (2.3) MMSE, Mean (SD) 28.6 (1.2)	Daily dose of 5 mg of Donepezil for 6 weeks, then increased to 10mg daily for 46 weeks; 2 weeks of cognitive training at weeks 13-14	Placebo and 2 weeks of cognitive training at weeks 13-14	1 year	Memory [Word list recall] Memory [Name-face recall] Memory [Logical Memory I score] Memory [Logical Memory II score] Executive, Attention, Processing Speed [Symbol Digit Span]

AVLT=Auditory Verbal Learning Test; BVMT= ; CWMS= Categorization Working Memory Span Test; DVT=Digit Vigilance Test; FCSRT= ; HVLT=Hopkins Verbal Learning Test; MCI=Mild Cognitive Impairment; MMSE=Mini Mental Status Exam; NR=not reported; PFLE= ; RBAN=Repeat Battery for the Assessment of Neuropsychological Status; RBMT= ; RCT=Randomized Controlled Trial; RoB=Risk of Bias; RT=Reaction Time; SD=Standard Deviation; SDMT=Symbol Digit Modalities Test; TMT=Trail Making Trial; VICOC= ; WAIS=Wechsler Adult Intelligence Scale; WMS=Wechsler Memory Scale

Appendix Table F5. Summary risk of bias assessments: other cognitive training trials in adults with normal cognition

Study	Overall Risk of Bias Assessment	Rationale
Stine-Morrow 2014[12]	Medium	Process for randomization is unclear with potential attrition bias.
Carretti 2013[13]	Medium	Process for randomization is unclear with potential performance bias.
Miller 2013[14]	Medium	Process for randomization is unclear with potential attrition bias.
Wolinsky 2013[15]	Low	No suspected biases
Cheng 2012[16]	High	Potential attrition bias with attrition rate of 40%.
Mortimer 2012[17]	High	Potential selection bias due to process for randomization
Szelag 2012[18]	High	Potential selection and attrition bias.
Evers 2011[19]	High	Potential selection, attrition, and performance bias.
Borella 2010[20]	High	Process for randomization is unclear and potential detection bias.
Klusmann 2010[21]	Medium	Process for randomization is unclear with potential attrition bias.
McDougall 2010[22]	High	Potential attrition and reporting bias.
Park 2009[23]	High	Process for randomization is unclear with potential attrition and reporting bias.
Slegers 2009[24]	High	Potential reporting bias and selection bias due to process for selecting participants.
Buiza 2008[25]	High	Potential attrition, detection, and reporting bias.
Yesavage 2008[26]	High	Potential attrition bias with attrition rate of 29%.

Appendix Table F6. Characteristics of eligible studies: other cognitive training trials in adults with MCI

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]**
Lam 2015[27] RCT China High	277	Chinese older adults with MCI (presence of subjective cognitive complaints, and objective impairments in cognitive function) Age, Mean (SD) 75.4 (6.5) 78.2% Female Race NR Education Level, Mean (SD) 3.9 (3.6) ADAS-cog, Mean (SD) 11.5 (3.3)	Cognitive and mind-body exercises -1 hour sessions 3 times/week	Cognitively demanding activities (e.g., reading and discussing news, board games) –At least 3 sessions/weeks	8 months 12 months	Diagnosis [CDR-SOB] Multidomain Neuropsychological Performance [ADAS-Cog (Chinese version)] Memory [Delayed recall] Brief Cognitive Test Performance [MMSE] Language [CVFT]
Vidovich 2015[28] RCT US Low (52 weeks) High (104 Weeks)	150	Adults age 65 years and older with MCI Age, Mean (SD) 75 (6) 54% Female 80% With High School Education Baseline Cognition NR	Cognitive activity training strategy program (attention, memory, and executive processes) -10, 90-minute sessions/week over 5 weeks; Booster telephone call at 6 months	Education about healthy aging -10, 90-minute sessions/week over 5 weeks; Booster telephone call at 6 months	52 weeks 104 weeks	Brief Cognitive Test Performance [CAMCOG-R score] Memory [CVLT-II Total Recall] Memory [CVLT-II Short Delay Free Recall] Memory [CVLT-II Long Delay Free Recall] Executive, Attention, Processing Speed [Digit Span Forward Span] Executive, Attention, Processing Speed [Digit Span Backward Span] Executive, Attention, Processing Speed [Digit Span Total Score] Executive, Attention, Processing Speed [TMT A time (sec)] Executive, Attention, Processing Speed [TMT B time (sec)] Executive, Attention, Processing Speed [Symbol Search (items completed)] Language, Executive, Attention, Processing Speed [COWAT Total Score]

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]**
Fiatarone Singh 2014[29] RCT Australia High	51	Adults age 55 and older with a MCI diagnosis consistent with Petersen criteria Age NR Sex NR Education NR MMSE, Mean (SD) 27 (1)	Cognitive training (computer-based exercises targeting memory, executive function, attention, and processing speed) -100 minutes 2 days/week for 6 months	Sham cognitive training and sham exercise	6 months 18 months	Multidomain Neuropsychological Performance [ADAS COG] Multidomain Neuropsychological Performance [Global Cognition Domain Composite] Executive, Attention, Processing Speed [WAIS III-Similarities] Executive, Attention, Processing Speed [WAIS III-Matrices] Language [Category Fluency (Animal Naming)] Language, Executive, Attention, Processing Speed [COWAT] Executive, Attention, Processing Speed [Executive Function Domain Composite] Memory [List learning Memory Sum from ADAS-COG] Memory [BVRT] Memory [Logical Memory, Immediate] Memory [Logical Memory, Delayed] Memory [Memory Domain Composite] Executive, Attention, Processing Speed [SDMT]
Kwok 2013[30] RCT China Medium	223	Chinese adults aged 65 and over with subjective memory complaints Age, Mean (SD) 75 (6) 85% Female Race NR 70% Below or at primary level education MMSE. Mean (SD) 25.6 (2.6)	Cognitive therapy delivered by an occupation therapist 1 time/week, 1.5 hours each session for 12 weeks	Health-related educational lectures for 12 weeks, delivered by occupational therapist	12 months	Executive, Attention, Processing Speed [Attention Composite] Executive, Attention, Processing Speed [Initiation/Perseveration] Executive, Attention, Processing Speed [Conceptualization] Memory [Memory Composite]

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]**
Rojas 2013[31] RCT Argentina High	46	Adults with MCI based on Petersen's criteria Age, Mean (SD) 74 (10.7) 43% Female Race NR Education Level, Mean (SD) 10.54 (3.8) MMSE. Mean (SD) 27.3 (2)	Group cognitive stimulation training sessions and cognitive training –120 minutes/week over 6 months	Routine treatment with monthly consultations with doctor over 6 months	1 year	Brief Cognitive Test Performance [MMSE] Diagnosis [CDR] Memory [Signoret's Memory Battery] Language [Boston Naming Test] Language [Verbal Fluency] Language [Vocabulary, WAIS] Executive, Attention, Processing Speed [Similarities and Matrix Reasoning] Visuospatial [Block Design] Executive, Attention, Processing Speed [TMT A] Executive, Attention, Processing Speed [TMT B] Executive, Attention, Processing Speed [Digit Span Forward] Executive, Attention, Processing Speed [Digit Span Backwards]
Buschert 2012[32] Forster 2011[33] RCT Germany Medium	24	Participants with aMCI based on Petersen's criteria Age, Mean (SD) 73 (6.6) 55% Male Race NR Years Education, Mean (SD) 12.8 (5) MMSE, Mean (SD) 26.3 (2)	Group-based formal mnemonic memory training and informal cognitive and social engagement activities -120 minutes/week for 6 months	Exercises of isolated, sustained attention – Monthly sessions for 8 months followed by cross-over to intervention	15 months 28 months	Diagnosis [Conversion to Alzheimer's Disorder] Brief Cognitive Test Performance [MMSE] Multidomain Neuropsychological Performance [ADAS-cog] Memory [RBANS-Memory] RBANS [Story Recall] Executive, Attention, Processing Speed [TMT-A/B] Biomarker [FDG-PET Reuptake]
Herrera 2012[34] RCT France Medium	22	Adults with a MCI based on Petersen's criteria Age, Mean (SD) 77 (1.71) 50% Female Race NR 14% With More than	Computer-based memory and attention training -24, 1-hour sessions over 12 weeks	Cognitive activities (e.g., organizing lists, reading comprehension -24, 1-hour sessions over 12 weeks	6 months	Memory [Doors recognition subtest, Set A] Memory [Doors recognition subtest, Set B] Memory [DMS48 Test] Executive, Attention, Processing Speed [Digit Span Forward] Executive, Attention, Processing Speed [Digit Span Backward]

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]**
		Secondary School MMSE. Mean (SD) 27.4 (0.5)				Memory [BEM-144 Word List Recall] Memory [16-Item Free and Cued Reminding Test] Memory [MMSE-Recall of 3 Words] Memory [Recall of Rey's Complex Figure]
Moro 2012[35] RCT Italy High		Adults with a MCI Age, Mean (SD) 71 (8) Sex NR Race NR Education, Mean (SD) 10 (3.5) Baseline Cognition NR	Individual cognitive training sessions- 3 sessions/week for one month. 1 session/week (at home with support of caregiver) for the subsequent 5 months.	No intervention for 6 months (crossover design)	6 months 12 months	Executive, Attention, Processing Speed [Attentional matrices] Executive, Attention, Processing Speed [Trial-making test (A)] Executive, Attention, Processing Speed [Bourdon test (mean)] Executive, Attention, Processing Speed [Verbal span] Memory [AVLT (immediate recall)] Memory [AVLT (delayed recall)] Memory [Omissions] Memory [False recognitions] Memory [Listening Span Test] Memory [Story Recall] Language [Verbal fluency (category)] Executive, Attention, Processing Speed [Tower of London] Executive, Attention, Processing Speed [Analogies] Executive, Attention, Processing Speed [Stroop] Executive, Attention, Processing Speed [Trail Making B-A]
Rapp 2002[36] RCT US Medium	19	Older adults meeting criteria for MCI based on Petersen's criteria Age, Mean (SD) 74 (6.8) 58% Female 95% White 37% With Some College	Memory training and education –Six weekly, 2 hour group meetings with homework assignments	No memory education or training (no intervention)	6 months	Memory [Word List, Immediate] Memory [Word List Delayed] Memory [Shopping List Immediate] Memory [Shopping List Delayed] Memory [Names and Faces Immediate] Memory [Names and Faces Delayed] Memory [Paragraph: Immediate] Memory [Paragraph: Delayed]

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]
		MMSE. Mean (SD) 27.6 (1.7)				

ADAS=Cog-Alzheimer's Disease Assessment Scale-Cognitive; AVLT=Auditory Verbal Learning Test; BEM=; BVRT=Benton Visual Retention Test; CDR=Change in Dementia Rating; COWAT=Controlled Oral Word Association Test; CVFT= ; CVLT=California Verbal Learning Test; DSM=Diagnostic Statistical Manual of Mental Disorders; FDG-PET=; MCI=Mild Cognitive Impairment; MMSE=Mini Mental Status Exam; NR=not reported ; RBANS=Repeat Battery for the Assessment of Neuropsychological Status; RCT=Randomized Controlled Trial; RoB=Risk of Bias; SD=Standard Deviation; TMT=Trail Making Trial; WAIS=Wechsler Adult Intelligence Scale

Appendix TableF7. Summary risk of bias assessments: other cognitive training trials in adults with MCI

Study	Overall Risk of Bias Assessment	Rationale
Lam 2015[27]	High	Potential selection bias with attrition greater than 21%
Vidovich 2015[28]	Low (52 Weeks) High (104 weeks)	Attrition rate greater than 21% at 104 weeks with no analysis to address potential bias.
Fiatarone Singh 2014[29]	High	Potential reporting bias.
Kwok 2013[30]	Medium	Potential selection, attrition, and performance bias.
Rojas 2013[31]	High	Potential selection bias with an attrition rate of 35%.
Buschert 2012[32] Forster 2011[33]	Medium	Process for randomization is unclear.
Herrera 2012[34]	Medium	Process for randomization is unclear with potential detection bias.
Moro 2012[35]	High	Potential selection, detection, and performance bias.
Rapp 2002[36]	Medium	Process for randomization unclear.

References for Appendix F

1. Rebok GW, Ball K, Guey LT, et al. Ten-year effects of the advanced cognitive training for independent and vital elderly cognitive training trial on cognition and everyday functioning in older adults. Journal of the American Geriatrics Society. 2014 Jan;62(1):16-24. doi: http://dx.doi.org/10.1111/jgs.12607. PMID: 24417410.

2. Rebok GW, Langbaum JB, Jones RN, et al. Memory training in the ACTIVE study: how much is needed and who benefits? Journal of Aging & Health. 2013 Dec;25(8 Suppl):21S-42S. doi: http://dx.doi.org/10.1177/0898264312461937. PMID: 23103452.

3. Jones RN, Marsiske M, Ball K, et al. The ACTIVE cognitive training interventions and trajectories of performance among older adults. Journal of Aging & Health. 2013 Dec;25(8 Suppl):186S-208S. doi: http://dx.doi.org/10.1177/0898264312461938. PMID: 23103453.

4. Sisco SM, Marsiske M, Gross AL, et al. The influence of cognitive training on older adults' recall for short stories. Journal of Aging & Health. 2013 Dec;25(8 Suppl):230S-48S. doi: http://dx.doi.org/10.1177/0898264313501386. PMID: 24385636.

5. Valdes EG, O'Connor ML, Edwards JD. The effects of cognitive speed of processing training among older adults with psychometrically- defined mild cognitive impairment. Current Alzheimer Research. 2012 Nov;9(9):999-1009. PMID: 22594383.

6. Unverzagt FW, Guey LT, Jones RN, et al. ACTIVE cognitive training and rates of incident dementia. J Int Neuropsychol Soc. 2012 Jul;18(4):669-77. doi: 10.1017/s1355617711001470. PMID: 22400989.

7. Wolinsky FD, Mahncke H, Vander Weg MW, et al. Speed of processing training protects self-rated health in older adults: enduring effects observed in the multi-site ACTIVE randomized controlled trial. International Psychogeriatrics. 2010 May;22(3):470-8. doi: http://dx.doi.org/10.1017/S1041610209991281. PMID: 20003628.

8. Wolinsky FD, Vander Weg MW, Martin R, et al. Does cognitive training improve internal locus of control among older adults? Journals of Gerontology Series B-Psychological Sciences & Social Sciences. 2010 Sep;65(5):591-8. doi: http://dx.doi.org/10.1093/geronb/gbp117. PMID: 20008028.

9. Unverzagt FW, Kasten L, Johnson KE, et al. Effect of memory impairment on training outcomes in ACTIVE. Journal of the International Neuropsychological Society. 2007 Nov;13(6):953-60. PMID: 17942013.

10. Willis SL, Tennstedt SL, Marsiske M, et al. Long-term effects of cognitive training on everyday functional outcomes in older adults. JAMA. 2006 Dec 20;296(23):2805-14. PMID: 17179457.

11. Ball K, Berch DB, Helmers KF, et al. Effects of cognitive training interventions with older adults: a randomized controlled trial. JAMA. 2002 Nov 13;288(18):2271-81. PMID: 12425704.

12. Stine-Morrow EA, Payne BR, Roberts BW, et al. Training versus engagement as paths to cognitive enrichment with aging. Psychology & Aging. 2014 Dec;29(4):891-906. doi: http://dx.doi.org/10.1037/a0038244. PMID: 25402337.

13. Carretti B, Borella E, Zavagnin M, et al. Gains in language comprehension relating to working memory training in healthy older adults. Int J Geriatr Psychiatry. 2013 May;28(5):539-46. doi: 10.1002/gps.3859. PMID: 22821686.

14. Miller KJ, Dye RV, Kim J, et al. Effect of a computerized brain exercise program on cognitive performance in older adults. American Journal of Geriatric Psychiatry. 2013 Jul;21(7):655-63. doi: http://dx.doi.org/10.1016/j.jagp.2013.01.077. PMID: 23602310.

15. Wolinsky FD, Vander Weg MW, Howren MB, et al. A randomized controlled trial of cognitive training using a visual speed of processing intervention in middle aged and older adults. PLoS ONE [Electronic Resource]. 2013;8(5):e61624. doi: http://dx.doi.org/10.1371/journal.pone.0061624. PMID: 23650501.

16. Cheng Y, Wu W, Feng W, et al. The effects of multi-domain versus single-domain cognitive training in non-demented older people: a randomized controlled trial. BMC Med. 2012;10:30. doi: 10.1186/1741-7015-10-30. PMID: 22453114.

17. Mortimer JA, Ding D, Borenstein AR, et al. Changes in brain volume and cognition in a randomized trial of exercise and social interaction in a community-based sample of non-demented Chinese elders. J Alzheimers Dis. 2012;30(4):757-66. doi: 10.3233/JAD-2012-120079. PMID: 22451320.

18. Szelag E, Skolimowska J. Cognitive function in elderly can be ameliorated by training in temporal information processing. Restorative Neurology & Neuroscience. 2012;30(5):419-34. doi: http://dx.doi.org/10.3233/RNN-2012-120240. PMID: 22751354.

19. Evers A, Klusmann V, Schwarzer R, et al. Improving cognition by adherence to physical or mental exercise: a moderated mediation analysis. Aging Ment Health. 2011 May;15(4):446-55. doi: 10.1080/13607863.2010.543657. PMID: 21500011.

20. Borella E, Carretti B, Riboldi F, et al. Working memory training in older adults: evidence of transfer and maintenance effects. Psychol Aging. 2010 Dec;25(4):767-78. doi: 10.1037/a0020683. PMID: 20973604.

21. Klusmann V, Evers A, Schwarzer R, et al. Complex mental and physical activity in older women and cognitive performance: a 6-month randomized controlled trial. J Gerontol A Biol Sci Med Sci. 2010 Jun;65(6):680-8. doi: 10.1093/gerona/glq053. PMID: 20418350.

22. McDougall GJ, Jr., Becker H, Pituch K, et al. Differential benefits of memory training for minority older adults in the SeniorWISE study. Gerontologist. 2010 Oct;50(5):632-45. doi: http://dx.doi.org/10.1093/geront/gnq017. PMID: 20203096.

23. Park MH, Kwon DY, Seo WK, et al. The effects of cognitive training on community-dwelling elderly Koreans. Journal of Psychiatric & Mental Health Nursing. 2009 Dec;16(10):904-9. doi: http://dx.doi.org/10.1111/j.1365-2850.2009.01467.x. PMID: 19930364.

24. Slegers K, van Boxtel M, Jolles J. Effects of computer training and internet usage on cognitive abilities in older adults: a randomized controlled study. Aging-Clinical & Experimental Research. 2009 Feb;21(1):43-54. PMID: 19225269.

25. Buiza C, Etxeberria I, Galdona N, et al. A randomized, two-year study of the efficacy of cognitive intervention on elderly people: the Donostia Longitudinal Study. Int J Geriatr Psychiatry. 2008 Jan;23(1):85-94. doi: 10.1002/gps.1846. PMID: 17530622.

26. Yesavage JA, Friedman L, Ashford JW, et al. Acetylcholinesterase inhibitor in combination with cognitive training in older adults. J Gerontol B Psychol Sci Soc Sci. 2008 Sep;63(5):P288-94. PMID: 18818443.

27. Lam LC, Chan WC, Leung T, et al. Would older adults with mild cognitive impairment adhere to and benefit from a structured lifestyle activity intervention to enhance cognition?: a cluster randomized controlled trial. PLoS One. 2015 31 Mar;10(3):e0118173. doi: 10.1371/journal.pone.0118173. PMID: 25826620.

28. Vidovich MR, Lautenschlager NT, Flicker L, et al. The PACE study: A randomized clinical trial of cognitive activity strategy training for older people with mild cognitive impairment. American Journal of Geriatric Psychiatry. 2015 01 Apr;23(4):360-72. doi: http://dx.doi.org/10.1016/j.jagp.2014.04.002. PMID: 2014736543.

29. Fiatarone Singh MA, Gates N, Saigal N, et al. The Study of Mental and Resistance Training (SMART) study-resistance training and/or cognitive training in mild cognitive impairment: a randomized, double-blind, double-sham controlled trial. J Am Med Dir Assoc. 2014 Dec;15(12):873-80. doi: 10.1016/j.jamda.2014.09.010. PMID: 25444575.

30. Kwok TC, Bai X, Li JC, et al. Effectiveness of cognitive training in Chinese older people with subjective cognitive complaints: a randomized placebo-controlled trial. International Journal of Geriatric Psychiatry. 2013 Feb;28(2):208-15. doi: http://dx.doi.org/10.1002/gps.3812. PMID: 22528470.

31. Rojas GJ, Villar V, Iturry M, et al. Efficacy of a cognitive intervention program in patients with mild cognitive impairment. International Psychogeriatrics. 2013 May;25(5):825-31. doi: http://dx.doi.org/10.1017/S1041610213000045. PMID: 23414646.

32. Buschert VC, Giegling I, Teipel SJ, et al. Long-term observation of a multicomponent cognitive intervention in mild cognitive impairment. Journal of Clinical Psychiatry. 2012 Dec;73(12):e1492-8. doi: http://dx.doi.org/10.4088/JCP.11m07270. PMID: 23290333.

33. Forster S, Buschert VC, Teipel SJ, et al. Effects of a 6-month cognitive intervention on brain metabolism in patients with amnestic MCI and mild Alzheimer's disease. Journal of Alzheimer's Disease. 2011;26 Suppl 3:337-48. doi: http://dx.doi.org/10.3233/JAD-2011-0025. PMID: 21971473.

34. Herrera C, Chambon C, Michel BF, et al. Positive effects of computer-based cognitive training in adults with mild cognitive impairment. Neuropsychologia. 2012 Jul;50(8):1871-81. doi: http://dx.doi.org/10.1016/j.neuropsychologia.2012.04.012. PMID: 22525705.

35. Moro V, Condoleo MT, Sala F, et al. Cognitive stimulation in a-MCI: an experimental study. American Journal of Alzheimer's Disease & Other Dementias. 2012 Mar;27(2):121-30. doi: http://dx.doi.org/10.1177/1533317512441386. PMID: 22495340.

36. Rapp S, Brenes G, Marsh AP. Memory enhancement training for older adults with mild cognitive impairment: a preliminary study. Aging & Mental Health. 2002 Feb;6(1):5-11. PMID: 11827617

Appendix G. Physical Activity Interventions

Appendix Table G1. Characteristics of eligible studies: physical activity interventions vs. inactive controls in adults with normal cognition

Study **Design** **Country** **RoB**	**N=**	**Population** **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]**
Multicomponent Physical Activity						
Bun 2015[1] Observational Japan High	1268	Cognitively normal, community-dwelling volunteers aged 65 Age, Mean (SD) 72.8 (5.1) 42% Female Race NR Years Education, Mean (SD) 10.55 (2.6) Baseline Cognition NR	Stretching, massaging, ball exercise, and easy dancing - 60 minute sessions 6 times/month for 2 years	No Intervention or Nutritional supplementation (n-3 polyunsaturated fatty acid, Ginkgo biloba, leaf dry extracts, and 84 mg of lycopene) for 3 years	3 years 7 years	Incident Dementia and AD [DSM-III-R criteria and NINCDS-ADRDA criteria]
Sink 2015[2] RCT USA Medium	1635	Sedentary adults without a diagnosis of dementia or significant cognitive impairment aged 70 to 89 57% aged 70 to 79 43% aged 80 to 89 67% Female 76% White 67% With a College Education 3MSE, Mean (SD): 91.7 (5.4)	Individual physical activity training intervention focused on walking, strength, flexibility, and balance -2 center-based visits/week and 3-4 home-based activities/week for 2 years	Group health education workshops - 1 workshop/week for 26 weeks, at least once a month after for 2 years	NP battery: 2 years Computer battery: 18 or 30 months depending on enrollment	Incident Dementia [Panel of Clinical Experts] Incident MCI [Panel of Clinical Experts] Incident MCI or Dementia [Panel of Clinical Experts] Multidomain Neuropsychological Performance [Composite] Executive, Attention, Processing Speed [Digit Symbol Coding (WAIS-III)] Executive, Attention, Processing Speed [n-back Task, 1-back] Executive, Attention, Processing Speed [n-back Task, 2-back] Executive, Attention, Processing Speed [Eriksen Flanker Task, Congruent]

						Executive, Attention, Processing Speed [Eriksen Flanker Task, Incongruent] Executive, Attention, Processing Speed [Eriksen Flanker Task, Composite] Executive, Attention, Processing Speed [Task Switching Exercise, No] Executive, Attention, Processing Speed [Task Switching Exercise, Yes] Memory [Hopkins Verbal Learning Test, Immediate Word Recall] Memory [Hopkins Verbal Learning Test, Delayed Word Recall] Memory [Hopkins Verbal Learning Test, Composite]
Napoli 2014[3] RCT US Medium	53	Obese, sedentary adults age 65 and older with a stable weight and a minimum MMSE score of 24 Age, Mean (SD) 70 (4) 63% Female 85% White Years of Education, Mean (SD) 16.3 (3.7) 3MS, Mean (SD) 95.7 (0.8)	Aerobic exercise, resistance training, and balance exercises -90 minutes sessions 3 times/week at an exercise facility for 1 year	Information about healthy diet (not allowed to participate in any exercise program)	1 year	Brief Cognitive Test Performance [3MS] Executive, Attention, Processing Speed [Trail Making Test Part A] Executive, Attention, Processing Speed [Trail Making Test Part B] Memory [Word List Fluency]
Klusmann 2010[4] Evers 2011[5] RCT Germany High	167	Women age 70 and over with no more than 4 errors on the MMSE Age, Mean (SD) 73.6 (4.2) 100% Female Race NR Years of Education, Mean (SD) 12 (2.6) MMSE, Mean (SD) 28.78 (0.96)	Aerobic, endurance, strength and flexibility training, and balance and coordination training -90 minute sessions for 6 months	Inactive control (live their habitual life)	6 months	Memory [RMBT, Immediate] Memory [RBMT, Delayed Recall] Memory [FCSRT, Short Delay] Memory [FCSRT, Long Delay] Langue [Semantic Verbal Fluency] Executive, Attention, Processing Speed [Stroop Test] Executive, Attention, Processing Speed [Trail Making Tests B/A]
Rosano 2010[6] RCT	30	Sedentary older adults	Aerobic, strength, balance, and flexibility exercises -150	Successful aging sessions –Weekly	2 years	Brief cognitive test performance [MMSE] Executive, Attention, Processing Speed [Digit

US High		Age, Mean (SD) 81.1 (3.36) 40% Female Race NR 43% Completed High School or Equivalent MMSE, Mean (SD) 27.7 (2)	minutes per week for 1 year	sessions for 26 weeks followed by monthly sessions for duration of study		Symbol Substitution Test] Biomarker [MRI]
Taylor-Pillae 2010[7] RCT US Medium-6 mo High-12 mo	95	Sedentary adults aged 60 years or older without severe cognitive impairment Age, Mean (SD) 69.0 (5.8) 70% Female 85% White Years of Education, Mean (SD) 16.1 (2.1)	Western Exercise: Endurance, resistance/strength, and flexibility exercises- 60 minutes classes 2.times/week and home based exercise 3 times/week for 6 months, 1 class-based session/week and 3 home-based exercise sessions for the remaining 6 months	Healthy aging classes on topics including health eating, elder law, and foot and eye care -90 minute classes 1 time/week for 6 months	6 months 12 months	Language [Animal Naming] Executive, Attention, Processing Speed [Digit Span Test, Forward] Executive, Attention, Processing Speed [Digit Span Test, Backwards]
Williamson 2009[8] (early results Sink 2015)[2] RCT US Medium	102	Sedentary adults aged 70-89 years with a MMSE score of 21 or more. Age, Mean (SD) 77.4 (4.3) 70.6% Female 81% White 77% with more than a high school education MMSE, Mean (SD) 90.3 (6.4)	Aerobic (walking), strength, balance, and flexibility exercises - 60 minute center-based sessions 3 times/week for 2 months -60 minute center-based sessions 2 times/per week and home-based exercise (endurance, strengthening, flexibility) at least 3 times/week for 4 months	Successful aging health education – Weekly small group sessions for 26 weeks -Monthly small group sessions for 26 weeks	12 months	Brief Cognitive Test Performance [3MSE] Executive, Attention, Processing Speed [Modified Stroop] Memory [Digit Symbol Substitution Test] Memory [RAVLT]
Resistance Training						
van de Rest 2014[9] RCT Netherlands Medium	62	Frail and pre-frail adults age 65 and over Age, Mean (SD) 79 (8) 61% Female Race NR 44% With Higher Education MMSE, Mean	Resistance-type exercise program and placebo -2 sessions/week with personal supervision for 24 weeks	Usual Care and placebo for 24 weeks	24 weeks	Memory [Word Learning Test, Immediate Recall-75 Words] Memory [Word Learning Test, Delayed Recall-15 Words] Memory [Word Learning Test, Decay] Memory [Word Learning Test, Recognition, 30 Words] Executive, Attention, Processing Speed [Digit Span Forward (WAIS-R)] Executive, Attention, Processing Speed [Digit

		(Range) 28 (26-30)				Span Backwards (WAIS-R)] Executive, Attention, Processing Speed [Trail Making Test Part A] Executive, Attention, Processing Speed [Trail Making Test Part B/A] Executive, Attention, Processing Speed [Stroop Color-Word Test 1] Executive, Attention, Processing Speed [Stroop Color-Word Test 2] Executive, Attention, Processing Speed [Stroop Interference] Language [Word Fluency-Animals] Language, Executive, Attention, Processing Speed [Word Fluency-Letter P] Executive, Attention, Processing Speed [Finger Precuing, Reaction Time Uncued] Executive, Attention, Processing Speed [Finger Precuing, Reaction Time Cued] Memory [Attention and Working Memory Composite] Executive, Attention, Processing Speed [Information Processing Speed Composite] Executive, Attention, Processing Speed [Executive Functioning Composite]
Hotting, 2012 RCT Germany High	66	Healthy, sedentary men and women aged 40-56 years Age, Mean (SD) 47.8 (4.35) 82% Female Race NR Education NR Baseline Cognition NR	Stretching and coordination training exercises -60 minute sessions 2 times/week for 6 months	Sedentary control (no exercise intervention for 6 months)	6 months	Executive, Attention, Processing Speed [d2 Test] Memory [Auditory Verbal Learning Test (German)] Executive, Attention, Processing Speed [Zahlenverbindungstest (German)] Executive, Attention, Processing Speed [Stroop Task] Visuospatial [Leistungsprufystem, Subtests 8 and 9]
Cassilhas 2007[10] RCT Brazil Medium	43	Sedentary males age 65-75 with a minimum MMSE score of 24 Age, Mean (SD) 68.2 (0.77) 100% Male Race NR Education NR Baseline Cognition	High intensity resistance training -60 minute sessions, 3 times/week for 24 weeks	Warm-up and stretching at center once a week for 24 weeks	24 weeks	Executive, Attention, Processing Speed [Digit Span, Forward] Executive, Attention, Processing Speed [Digit Span, Backward] Executive, Attention, Processing Speed [Corsi Block-Tapping, Forward] Executive, Attention, Processing Speed [Corsi Block-Tapping, Backward] Executive, Attention, Processing Speed [Corsi Block-Tapping, Similarities]

		NR				Executive, Attention, Processing Speed [Toulouse-Pieron, Cancellations Numbers] Executive, Attention, Processing Speed [Toulouse-Pieron, Errors] Memory [Rey Osterrieth Figure, Copy] Memory [Rey Osterrieth Figure, Immediate Recall]
Cassilhas 2007[10] RCT Brazil Medium	42	Sedentary males age 65-75 with a minimum MMSE score of 24 Age, Mean (SD) 68.2 (0.77) 100% Male Race NR Education NR Baseline Cognition NR	Moderate intensity resistance training -60 minute sessions, 3 times/week for 24 weeks	Warm-up and stretching at center once a week for 24 weeks	24 weeks	Executive, Attention, Processing Speed [Digit Span, Forward] Executive, Attention, Processing Speed [Digit Span, Backward] Executive, Attention, Processing Speed [Corsi Block-Tapping, Forward] Executive, Attention, Processing Speed [Corsi Block-Tapping, Backward] Executive, Attention, Processing Speed [Corsi Block-Tapping, Similarities] Executive, Attention, Processing Speed [Toulouse-Pieron, Cancellations Numbers] Executive, Attention, Processing Speed [Toulouse-Pieron, Errors] Memory [Rey Osterrieth Figure, Copy] Memory [Rey Osterrieth Figure, Immediate Recall]
Aerobic Training						

Antunes 2015[11] RCT Brazil Medium	46	Healthy, sedentary men with minimum MMSE score of 24 Age, Mean(SD): 66.94 (4.65) Race NR Education NR Baseline Cognition NR	Aerobic physical fitness regime with supplementary stretching and joint flexibility exercises -60 minute sessions 3 times/week for 6 months	Maintain regular everyday activities. Instructed to not start a physical exercise program for study duration	6 months	Executive, Attention, Processing Speed [Picture Arrangement (WAIS-III)] Executive, Attention, Processing Speed [Corsi Block-tapping, Forward] Executive, Attention, Processing Speed [Corsi Block-tapping, Backward] Memory [Verbal Paired Associates, Trial 1, Easy Pair] Memory [Verbal Paired Associates, Trial 1, Hard Pair] Memory [Verbal Paired Associates, Trial 2, Easy Pair] Memory [Verbal Paired Associates, Trial 2, Hard Pair] Memory [Verbal Paired Associates, Trial 3, Easy Pair] Memory [Verbal Paired Associates, Trial 3, Hard Pair] Memory [Verbal Paired Associates, Recall Test, Easy Pair] Memory [Verbal Paired Associates, Recall Test, Hard Pair] Memory [Free Word Recall. Total Words Recalled (Non-Semantic)] Memory [Free Word Recall, Total Words Recalled (Semantic)] Memory [Free Word Recall, Intrusions] Memory [Free Word Recall, Repetitions] Memory [Free Word Recall, Preservations]
Satoh 2014[12] RCT Japan High	79	Physically and psychologically healthy residents age 65 and older Age, Mean (SD) 72.9 (4.6) 64% Female Race NR Years Education, Mean (SD) 10.4 (1.8) MMSE, Mean (SD) 27.6 (2.2)	Physical exercise -40, 60-minute exercise sessions over 1 year	Inactive control group (no intervention)	1 year	Brief Cognitive Test Performance [MMSE] Executive, Attention, Processing Speed [Raven's Coloured Progressive Matrices] Executive, Attention, Processing Speed [Trail Making Test A] Executive, Attention, Processing Speed [Trail Making Test B] Executive, Attention, Processing Speed [Word Fluency] Memory [Logical Memory-I] Memory [Logical Memory-II]

Mortimer 2012[13] RCT China High	75	Adults age 60-79 with an education-adjusted Chinese MMSE score greater than 26 Age, Mean (SD) 67.8 (5.8) 67% Female Race NR Years of Education, Mean (SD) 11.7 (3.4) Mattis Dementia Scale Score, Mean (SD) 137.6 (7.6)	Walking-50 minute group sessions 3 times/week for 40 weeks	Inactive control with 4 check-in calls over 40 weeks	40 weeks	Executive, Attention, Processing Speed [WAIS digit span (forward)[Executive, Attention, Processing Speed [WAIS digit span (backward)] Visuospatial [Bell cancellation test] Visuospatial , Memory [Rey Figure (copying)] Visuospatial , Memory [Rey Figure (recall)] Executive, Attention, Processing Speed [Stroop Test (word)] Executive, Attention, Processing Speed [Stroop Test (color)] Executive, Attention, Processing Speed [Stroop Test (color-word)] Memory [Auditory Verbal Learning Test, Immediate Recall] Memory [Auditory Verbal Learning Test, Delayed Recall] Memory [Auditory Verbal Learning Test (delayed recognition] Language [Category Verbal Fluency, Animals] Executive, Attention, Processing Speed [WAIS Similarities] Executive, Attention, Processing Speed [Trails A Time (seconds)] Executive, Attention, Processing Speed [Trails B Time (seconds)] Visuospatial [Clock drawing test] Language [Boston Naming Test (correct names)] Multidomain Neuropsychological Performance [Mattis Dementing Rating Scale (total score)] Executive, Attention, Processing Speed [Mattis Attention Score] Executive, Attention, Processing Speed [Mattis Initiation Score] Visuospatial Mattis Construction Score] Executive, Attention, Processing Speed Mattis Conceptualization Score] Memory [Mattis Memory Score] Biomarker [Whole brain volume (% of total intracranial volume)]
Hotting 2012 RCT Germany High	67	Healthy, sedentary men and women aged 40-56 years Age, Mean (SD)	Indoor cycling on stationary bikes -60 minute sessions 2 times/week for 6 months	Sedentary control (no exercise intervention for 6 months)	6 months	Executive, Attention, Processing Speed [d2 Test] Memory [Auditory Verbal Learning Test (German)]

		47.8 (4.35) 82% Female Race NR Education NR Baseline Cognition NR				Executive, Attention, Processing Speed [Zahlenverbindungstest (German)] Executive, Attention, Processing Speed [Stroop Task] Visuospatial [Leistungsprufystem, Subtests 8 and 9]
Muscari 2010 RCT Italy Medium	120	Healthy adults age 64-75 with a minimum MMSE of 24 Age, Mean (SD) 69.2 (2.7) 52% Male Race NR Years of Education, Mean (Range) 6.5 (5-13) MMSE, Mean (Range) 27.0 [25.9-28.0]	Group endurance exercise training (cycle ergometer, treadmill and free-body activity) -60 minute sessions 3 times/week for 1 year	Educational materials that provided suggestions to improve lifestyle. Suggestions included individualized self-administered programs to increase physical activity	12 months	Brief Cognitive Test Performance [MMSE]
Lautenschlager 2008 RCT Australia Low	170	Adults reporting difficulty with memory and a MMSE score of at least 24 Age, Mean (SD): 68.7 (8.6) 51% Female Race NR Years of Education, Mean (SD) 12.4 (3.3) ADAS-Cog, Mean (SD) 7.0 (1.8)	Home-based physical activity program with behavioral intervention –At minimum 50 minutes sessions 3 times/week of moderately intense exercise for 24 weeks and a social cognitive theory-based behavioral package (workshop, manual, newsletters, and telephone calls)	Educational material about memory loss, stress management, healthful diet, alcohol consumption, and smoking. No materials on physical activity.	18 months	Multidomain Neuropsychological Performance [ADAS-Cog] Diagnosis [Clinical Dementia Rating, Sum of Boxes] Executive, Attention, Processing Speed [Digit Symbol Coding (WAIS-III)] Memory [Word List, Immediate Recall (CERAD)] Memory [Word List, Delayed Recall (CERAD)] Language [Verbal Fluency (Delis-Kaplin Executive Function Battery)]
Tai Chi						
Mortimer 2012 RCT China High	74	Adults age 60-79 with an education-adjusted Chinese MMSE score greater than 26 Age, Mean (SD) 67.8 (5.8) 67% Female	Tai Chi -50 minute group sessions 3 times/week for 40 weeks	Inactive control with 4 check-in calls over 40 weeks	40 weeks	Executive, Attention, Processing Speed [WAIS digit span (forward)[Executive, Attention, Processing Speed [WAIS digit span (backward)] Visuospatial [Bell cancellation test] Visuospatial , Memory [Rey Figure (copying)] Visuospatial , Memory [Rey Figure (recall)] Executive, Attention, Processing Speed

		Race NR Years of Education, Mean (SD) 11.7 (3.4) Mattis Dementia Scale Score, Mean (SD) 137.6 (7.6)				[Stroop Test (word)] Executive, Attention, Processing Speed [Stroop Test (color)] Executive, Attention, Processing Speed [Stroop Test (color-word)] Memory [Auditory Verbal Learning Test (immed. recall)[Memory [Auditory Verbal Learning Test (delayed recall)] Memory [Auditory Verbal Learning Test (delayed recognition] Language [Category Verbal Fluency (animals)] Executive, Attention, Processing Speed [WAIS Similarities] Executive, Attention, Processing Speed [Trails A Time (seconds)] Executive, Attention, Processing Speed [Trails B Time (seconds)] Visuospatial [Clock drawing test] Language [Boston Naming Test (correct names)] Multidomain Neuropsychological Performance [Mattis Dementing Rating Scale (total score)] Executive, Attention, Processing Speed [Mattis Attention Score] Executive, Attention, Processing Speed [Mattis Initiation Score] Visuospatial Mattis Construction Score] Executive, Attention, Processing Speed Mattis Conceptualization Score] Memory [Mattis Memory Score] Biomarker [Whole brain volume (% of total intracranial volume)]
Nguyen 2012[14] RCT Germany High	96	Adults age 60-75 with a minimum MMSE score of 25 Age, Mean (SD) 68.98 (5.1) 50% Female Race NR 28.1% With more than 12 years of education Baseline Cognition NR	Tai Chi Exercise -60 minute sessions 2 times/ week for 6 months	Routine daily activities (instructed not to start exercise program) for study duration	6 months	Executive, Attention, Processing Speed [Trail Making Test A] Executive, Attention, Processing Speed [Trail Making Test B]

Taylor-Pillae 2010[7] RCT US Medium-6 mo High-12 mo	93	Sedentary adults aged 60 years or older without severe cognitive impairment Age, Mean (SD) 69.0 (5.8) 70% Female 85% White Years of Education, Mean (SD) 16.1 (2.1)	Tai Chi -45 minutes classes 2.times/week and home based exercise 3 times/week for 6 months, 1 class-based session/week and 3 home-based exercise sessions for the remaining 6 months	Healthy aging classes on topics including health eating, elder law, and foot and eye care -90 minute classes 1 time/week for 6 months	6 months 12 months	Language [Animal Naming] Executive, Attention, Processing Speed [Digit Span Test, Forward] Executive, Attention, Processing Speed [Digit Span Test, Backwards]

3MS=; 3MSE=Modified Mini Mental Status Examination; AD=Alzheimer's disease; ADAS=Cog-Alzheimer's Disease Assessment Scale-Cognitive; CERAD=Consortium to Establish a Registry for Alzheimer's Disease; DSM=Diagnostic Statistical Manual of Mental Disorders; FCSRT=; MCI=Mild Cognitive Impairment; MMSE=Mini Mental Status Exam; MRI=Magnetic Resonance Imaging; NINCDS-ADRDA=National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease; NR=not reported; RAVLT=Rey's Auditory Verbal Learning Test; RBMT=; RCT=Randomized Controlled Trial; RMBT=; RoB=Risk of Bias; SD=Standard Deviation; SOE=Strength of Evidence TMT=Trail Making Trial; WAIS=Wechsler Adult Intelligence Scale

Appendix Table G2. Characteristics of eligible studies: physical activity interventions vs. active controls in adults with normal cognition

Study Design Country RoB	N=	Population 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]
Eggenberge 2015[15] RCT Switzerland Medium	46	Seniors older than 70 years with an MMSE score greater than 22 Age, Mean (SD) 78.9 (5.4) 52% Female Race NR Years of Education, Mean (SD) 13.2 (1.9) MMSE, Mean (SD) 28.2 (1.4)	Virtual reality video game dancing with cognitive training -60 minute group sessions 2 times/week for 6 months	Treadmill walking with verbal memory exercise -60 minute group sessions 2 times/week for 6 months	6 months	Executive, Attention, Processing Speed [WAIS-R, Trail Making Test Part A] Executive, Attention, Processing Speed [WAIS-R, Trail Making Test Part B] Executive, Attention, Processing Speed [Executive Control Task] Memory [Paired-Associates Learning] Memory [WMS-R, Story Recall] Executive, Attention, Processing Speed [WMS-R, Digit Forward] Executive, Attention, Processing Speed [Age Concentration Test A] Executive, Attention, Processing Speed [Age Concentration Test B] Executive, Attention, Processing Speed [WAIS-R, Digit Symbol Substitution]
Ferreira 2015[16] RCT Brazil High	102	Adults age 60 to 79 years with no MCI or diagnosis of dementia Age, Mean (SD) 67.1 (5.2) 87% Female Race NR MMSE, Mean (SD) 28.5 (1.5)	Supervised walking -40-50 minute sessions 3 times/ week for 6 months	Social interaction group without physical exercise or respiratory training (breathing exercises) -40-50 minute sessions 3 times/ week for 6 months	6 months	Brief Cognitive Test Performance [MMSE] Executive, Attention, Processing Speed [Wechsler Adult Intelligence Scale, subscales Digit Span, Vocabulary, Information, and Symbol Search] Memory [Wechsler Memory Scale, subscales Logic Memory I and II] Executive, Attention, Processing Speed [Corsi block-tapping test] Executive, Attention, Processing Speed [Wisconsin Card Sorting Test]
Napoli 2014[3] RCT US Medium	53	Obese, sedentary adults age 65 and older with a stable weight and a minimum MMSE score of 24 Age, Mean (SD)	Aerobic exercise, resistance training, and balance exercises -90 minutes sessions 3 times/week at an exercise facility for 1 year	Diet and aerobic exercise, resistance training, and balance exercises -90 minutes sessions 3 times/week at an exercise facility for 1	1 year	Brief Cognitive Test Performance [3MS] Executive, Attention, Processing Speed [Trail Making Test Part A] Executive, Attention, Processing Speed [Trail Making Test Part B] Memory [Word List Fluency]

Study Design Country RoB	N=	Population 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]
		70 (4) 63% Female 85% White Years of Education, Mean (SD) 16.3 (3.7) 3MS, Mean (SD) 95.7 (0.8)		year and energy deficit of 500-750 kcal/day to achieve 10% weight loss over 6 months followed by 6 months of weight maintenance		
Mortimer 2012[13] RCT China High	74	Adults age 60-79 with an education-adjusted Chinese MMSE score greater than 26 Age, Mean (SD) 67.8 (5.8) 67% Female Race NR Years of Education, Mean (SD) 11.7 (3.4) Mattis Dementia Scale Score, Mean (SD) 137.6 (7.6)	Walking-50 minute group sessions 3 times/week for 40 weeks	Social interaction – Meeting at community center for 1 hr 3 times/week	40 weeks	Executive, Attention, Processing Speed [WAIS digit span (forward)[Executive, Attention, Processing Speed [WAIS digit span (backward)] Visuospatial [Bell cancellation test] Visuospatial , Memory [Rey Figure (copying)] Visuospatial , Memory [Rey Figure (recall)] Executive, Attention, Processing Speed [Stroop Test (word)] Executive, Attention, Processing Speed [Stroop Test (color)] Executive, Attention, Processing Speed [Stroop Test (color-word)] Memory [Auditory Verbal Learning Test, Immediate Recall] Memory [Auditory Verbal Learning Test, Delayed Recall] Memory [Auditory Verbal Learning Test (delayed recognition] Language [Category Verbal Fluency, Animals] Executive, Attention, Processing Speed [WAIS Similarities] Executive, Attention, Processing Speed [Trails A Time (seconds)] Executive, Attention, Processing Speed [Trails B Time (seconds)] Visuospatial [Clock drawing test] Language [Boston Naming Test (correct

Study Design Country RoB	N=	Population 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]
						names)] Multidomain Neuropsychological Performance [Mattis Dementing Rating Scale (total score)] Executive, Attention, Processing Speed [Mattis Attention Score] Executive, Attention, Processing Speed [Mattis Initiation Score] Visuospatial Mattis Construction Score] Executive, Attention, Processing Speed Mattis Conceptualization Score] Memory [Mattis Memory Score] Biomarker [Whole brain volume (% of total intracranial volume)]
Mortimer 2012[13] RCT China High	73	Adults age 60-79 with an education-adjusted Chinese MMSE score greater than 26 Age, Mean (SD) 67.8 (5.8) 67% Female Race NR Years of Education, Mean (SD) 11.7 (3.4) Mattis Dementia Scale Score, Mean (SD) 137.6 (7.6)	Tai Chi -50 minute group sessions 3 times/week for 40 weeks	Social interaction – Meeting at community center for 1 hr 3 times/week	40 weeks	Executive, Attention, Processing Speed [WAIS digit span (forward)[Executive, Attention, Processing Speed [WAIS digit span (backward)] Visuospatial [Bell cancellation test] Visuospatial , Memory [Rey Figure (copying)] Visuospatial , Memory [Rey Figure (recall)] Executive, Attention, Processing Speed [Stroop Test (word)] Executive, Attention, Processing Speed [Stroop Test (color)] Executive, Attention, Processing Speed [Stroop Test (color-word)] Memory [Auditory Verbal Learning Test, Immediate Recall] Memory [Auditory Verbal Learning Test, Delayed Recall] Memory [Auditory Verbal Learning Test (delayed recognition] Language [Category Verbal Fluency, Animals] Executive, Attention, Processing Speed [WAIS Similarities] Executive, Attention, Processing Speed [Trails

Study Design Country RoB	N=	Population 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]
						A Time (seconds)] Executive, Attention, Processing Speed [Trails B Time (seconds)] Visuospatial [Clock drawing test] Language [Boston Naming Test (correct names)] Multidomain Neuropsychological Performance [Mattis Dementing Rating Scale (total score)] Executive, Attention, Processing Speed [Mattis Attention Score] Executive, Attention, Processing Speed [Mattis Initiation Score] Visuospatial Mattis Construction Score] Executive, Attention, Processing Speed Mattis Conceptualization Score] Memory [Mattis Memory Score] Biomarker [Whole brain volume (% of total intracranial volume)]
Mortimer 2012[13] RCT China High	74	Adults age 60-79 with an education-adjusted Chinese MMSE score greater than 26 Age, Mean (SD) 67.8 (5.8) 67% Female Race NR Years of Education, Mean (SD) 11.7 (3.4) Mattis Dementia Scale Score, Mean (SD) 137.6 (7.6)	Tai Chi -50 minute group sessions 3 times/week for 40 weeks	Walking-50 minute group sessions 3 times/week for 40 weeks	40 weeks	Executive, Attention, Processing Speed [WAIS digit span (forward)[Executive, Attention, Processing Speed [WAIS digit span (backward)] Visuospatial [Bell cancellation test] Visuospatial , Memory [Rey Figure (copying)] Visuospatial , Memory [Rey Figure (recall)] Executive, Attention, Processing Speed [Stroop Test (word)] Executive, Attention, Processing Speed [Stroop Test (color)] Executive, Attention, Processing Speed [Stroop Test (color-word)] Memory [Auditory Verbal Learning Test, Immediate Recall] Memory [Auditory Verbal Learning Test, Delayed Recall] Memory [Auditory Verbal Learning Test

Study Design Country RoB	N=	Population 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]
						(delayed recognition] Language [Category Verbal Fluency, Animals] Executive, Attention, Processing Speed [WAIS Similarities] Executive, Attention, Processing Speed [Trails A Time (seconds)] Executive, Attention, Processing Speed [Trails B Time (seconds)] Visuospatial [Clock drawing test] Language [Boston Naming Test (correct names)] Multidomain Neuropsychological Performance [Mattis Dementing Rating Scale (total score)] Executive, Attention, Processing Speed [Mattis Attention Score] Executive, Attention, Processing Speed [Mattis Initiation Score] Visuospatial Mattis Construction Score] Executive, Attention, Processing Speed Mattis Conceptualization Score] Memory [Mattis Memory Score] Biomarker [Whole brain volume (% of total intracranial volume)]
Hotting, 2011[17] RCT Germany High	97	Healthy, sedentary men and women aged 40-56 years Age, Mean (SD) 47.8 (4.35) 82% Female Race NR Education NR Baseline Cognition NR	Stretching and coordination training exercises -60 minute sessions 2 times/week for 6 months	Indoor cycling on stationary bikes -60 minute sessions 2 times/week for 6 months	6 months	Executive, Attention, Processing Speed [d2 Test] Memory [Auditory Verbal Learning Test (German)] Executive, Attention, Processing Speed [Zahlenverbindungstest (German)] Executive, Attention, Processing Speed [Stroop Task] Visuospatial [Leistungsprufystem, Subtests 8 and 9]

Study Design Country RoB	N=	Population 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]
Baker 2010[18,19] RCT US Medium	28	Individuals with abnormal glucose tolerance and normal cognitive status Age, Mean (SD) 68.5 (6.8) 64% Female Race NR	Aerobic exercise (using a treadmill, stationary bicycle, or elliptical machine) -45-60 minutes sessions 4 times/week for 6 months	Stretching -45-60 minutes sessions 4 times/week for 6 months	6 months	Executive, Attention, Processing Speed [Trail Making Test B] Executive, Attention, Processing Speed [Task Switching] Executive, Attention, Processing Speed [Stroop Color-Word Interference] Executive, Attention, Processing Speed [Self-ordered Pointing Test] Executive, Attention, Processing Speed [Verbal Fluency] Memory [Story Recall] Memory [List Learning]
Taylor-Pillae 2010[7] RCT US Medium-6 mo High-12 mo	76	Sedentary adults aged 60 years or older without severe cognitive impairment Age, Mean (SD) 69.0 (5.8) 70% Female 85% White Years of Education, Mean (SD) 16.1 (2.1)	Western Exercise: Endurance, resistance/strength, and flexibility exercises- 60 minutes classes 2.times/week and home based exercise 3 times/week for 6 months, 1 class-based session/week and 3 home-based exercise sessions for the remaining 6 months	Tai Chi -45 minutes classes 2.times/week and home based exercise 3 times/week for 6 months, 1 class-based session/week and 3 home-based exercise sessions for the remaining 6 months	6 months 12 months	Language [Animal Naming] Executive, Attention, Processing Speed [Digit Span Test, Forward] Executive, Attention, Processing Speed [Digit Span Test, Backwards]
Cassilhas 2007[10] RCT Brazil Medium	39	Sedentary males age 65-75 with a minimum MMSE score of 24 Age, Mean (SD) 68.2 (0.77) 100% Male Race NR Education NR Baseline Cognition NR	High intensity resistance training -60 minute sessions, 3 times/week for 24 weeks	Moderate intensity resistance training -60 minute sessions, 3 times/week for 24 weeks	24 weeks	Executive, Attention, Processing Speed [Digit Span, Forward] Executive, Attention, Processing Speed [Digit Span, Backward] Executive, Attention, Processing Speed [Corsi Block-Tapping, Forward] Executive, Attention, Processing Speed [Corsi Block-Tapping, Backward] Executive, Attention, Processing Speed [Corsi Block-Tapping, Similarities] Executive, Attention, Processing Speed [Toulouse-Pieron, Cancellations Numbers]

Study Design Country RoB	N=	Population 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]
						Executive, Attention, Processing Speed [Toulouse-Pieron, Errors] Memory [Rey Osterrieth Figure, Copy] Memory [Rey Osterrieth Figure, Immediate Recall]

3MS=; MMSE=Mini Mental Status; NR=not reported; RCT=Randomized Controlled Trial; SD=Standard Deviation; SOE=Strength of Evidence; WAIS=Wechsler Adult Intelligence Scale; WMS=Wechsler Memory Scale

Appendix Table G3. Summary risk of bias assessments: physical activity interventions in adults with normal cognition

Study	Overall Risk of Bias Assessment	Rationale
Antunes 2015[11]	Medium	Process for randomization is unclear/poorly described.
Bun 2015[1]	High	No randomization (participants self-selected into study arms) and attrition greater than 21%.
Eggenberger 2015[15]	Medium	Attrition rate is 20% with potential performance bias.
Ferreira 2015[16]	High	High attrition rate with suspected reporting bias.
Sink 2015[2]	Medium	Attrition 10%; potential differences in timing of certain outcomes measurements.
Napoli 2014[3]	Medium	Process for randomization is unclear and 13% attrition rate.
Satoh 2014[12]	High	Semi-randomly assigned groups and 33% attrition rate.
van de Rest 2014[20, 21]	Medium	Attrition is 15% with potential reporting bias.
Mortimer 2012[13]	High	Suspected selection bias due to modifications post-randomization.
Nguyen 2012[14]	High	Randomization not well described with 24% attrition rate.
Hotting, 2011[17]	High	Suspected selection bias due to selection procedure for control group.
Baker 2010[18, 19]	Medium	Attrition is 18% with potential reporting bias
Klusmann 2010[4] Evers 2011[5]	High	Attrition is over 25% with no analysis to address potential bias.
Muscari 2010[22]	Medium	Randomization not well described with 11% attrition rate.
Rosano 2010[6]	High	Participants self-selected for inclusion for additional follow-up based on willingness to participate. High attrition rate from original study population.
Taylor-Pillae 2010[7]	High-12 mo outcomes Medium-6 mo outcomes	Randomization not well described with 21% attrition at 12 months.
Williamson 2009[8]	Medium	Potential performance and reporting bias.
Lautenschlager 2008[23]	Low	No suspected biases.
Cassilhas 2007[10]	Medium	Randomization not well described with potential reporting bias.

Appendix Table G4. Strength of evidence assessments: physical activity interventions versus inactive control in adults with normal cognition

Outcome	# Trials (n)	Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
Multicomponent Physical Activity									
Dementia	1 (1635)	OR: 0.96 [0.57 to 1.63]	Medium	Direct	Imprecise	Unknown	Undetected	NA	Insufficient
MCI	1 (1635)	OR: 1.14 [0.79 to 1.62]	Medium	Direct	Imprecise	Unknown	Undetected	NA	Insufficient
Brief cognitive test performance	2 (155)	1 of 2 tests shows statistically significant improvement with intervention, but effect size not clinically meaningful: Napoli 2014 Difference in change from baseline (3MS): 3.0 [1.5 to 4.5] Williamson 2009 Difference in adjusted mean change from baseline (3MS): -0.86 [-3.16 to 1.44]	Medium	Indirect	Precise	Consistent	Undetected	NA	Low
Multidomain neuropsychological performance	1 (1635)	One test shows no statistically significant improvement with	Medium	Indirect	Precise	Unknown consistency	Undetected	NA	Low

Outcome	# Trials (n)	Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
		intervention. <u>Sink 2015</u> Difference in mean global composite z score: 0.029 [-0.038 to 0.095]							
Executive./Attention/ Processing Speed	4 (1885)	1 of 13 tests show statistically significant improvement with Intervention	Medium	Indirect	Imprecise	Consistent	Undetected	NA	Low
Memory	3 (1836)	1 of 6 tests show statistically significant improvement with Intervention	Medium	Indirect	Imprecise	Consistent	Undetected	NA	Low
Biomarkers	NR								Insufficient
Adverse Effects	NR								Insufficient
Resistance Training									
Dementia	NR								Insufficient
MCI	NR								Insufficient
Brief cognitive test performance	NR								Insufficient
Multidomain neuropsychological performance	NR								Insufficient
Executive Function	2 (120)	8 of 25 tests show	Medium	Indirect	Imprecise	Inconsistent	Undetected	NA	Insufficient

Outcome	# Trials (n)	Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
		statistically significant improvement with Intervention							
Memory	2 (120)	3 of 10 tests show statistically significant improvement with Intervention	Medium	Indirect	Imprecise	Inconsistent	Undetected	NA	Insufficient
Biomarkers	NR								
Adverse Effects	NR								
Aerobic Training									
Dementia	Limited data	1 of 1 test shows statistically significant improvement with intervention							Insufficient
MCI	NR								Insufficient
Brief cognitive test performance/ Multidomain neuropsychological performance	2 (290)	2 of 2 tests show statistically significant improvement with intervention data	Medium	Indirect	Precise	Consistent	Undetected	NA	Low
Executive Function	2 (216)	2 of 4 tests show statistically significant improvement with Intervention data	Medium	Indirect	Imprecise	Inconsistent	Undetected	NA	Insufficient

Outcome	# Trials (n)	Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
Memory	2 (216)	6 of 15 tests show statistically significant improvement with Intervention	Medium	Indirect	Imprecise	Inconsistent	Undetected	NA	Insufficient
Biomarkers	NR								Insufficient
Adverse Effects	NR								Insufficient
Tai Chi									
Dementia	NR								Insufficient
MCI	NR								Insufficient
Brief cognitive test performance	NR								Insufficient
Multidomain neuropsychological performance	NR								Insufficient
Executive Function	Limited data								Insufficient
Memory	NR								Insufficient
Biomarkers	NR								
Adverse Effects	NR								Insufficient

MCI=mild cognitive impairment; NR=not reported; SOE=strength of evidence

Appendix G Table 6. Characteristics of eligible studies: physical activity interventions vs. inactive controls in adults with MCI

Study Design Country RoB	N=	Population 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]
Multicomponent Physical Activity						
Suzuki 2013[24] Suzuki 2012[25] RCT Japan Medium	100	Older adults with MCI and aMCI determined Peterson's criteria Age, Mean 75,7 (7.0) 22% Female Race NR Education Level, Mean (SD) 10.95 (2.55) MMSE, Mean (SD) 26.6 (2.1)	Aerobic exercises, muscle strength training, and postural balance retraining -90 minutes, 2 times/week for 6 months	Health education/health promotion classes - 2 classes over 6 months	6 months	Brief Cognitive Test Performance [MMSE] Multidomain Neuropsychological Performance [ADAS-Cog] Memory [WMS-LM I] Memory [WMS-LM II] Adverse Events [Falls and hospitalization for illness] Biomarker [MTA-ERC] Biomarker [WBS]
Suzuki 2012[25] (subset of Suzuki 2013[24]) RCT Japan Medium	50	Older adults with aMCI determined by education-adjusted WMS-LM II score Age, Mean 75 46% Female Race NR Education Level, Mean (SD) 10.95 (2.55) MMSE, Mean (SD) 26.7 (1.7)	Aerobic exercises, muscle strength training, and postural balance retraining -90 minutes, 2 times/week for 1 years	Health education/health promotion classes - 3 classes over 1 year	6 months 12 months	Brief Cognitive Test Performance [MMSE] Memory [WMS-LM I] Memory [WMS-LM II] Executive, Attention, Processing Speed [DSC, WAIS-III] Executive, Attention, Processing Speed [SCWT-I]: NS Executive, Attention, Processing Speed [SCWT-II]: NS Language, Executive, Attention, Processing Speed [LVFT] Language [CVFT]
Resistance Training						

Fiatarone Singh 2014[26] RCT Australia High	49	Adults age 55 and older with a MCI diagnosis consistent with Petersen criteria Age NR Sex NR Education NR MMSE, Mean (SD) 27 (1)	Resistance Training -100 minutes 2 days/week for 6 months	Sham cognitive training and sham exercise	6 months 18 months	Multidomain Neuropsychological Performance [ADAS COG] Multidomain Neuropsychological Performance [Global Cognition Domain Composite] Executive, Attention, Processing Speed [WAIS III-Similarities] Executive, Attention, Processing Speed [WAIS III-Matrices] Language [Category Fluency (Animal Naming)] Language, Executive, Attention, Processing Speed [COWAT] Executive, Attention, Processing Speed [Executive Function Domain Composite] Memory [List learning Memory Sum from ADAS-COG] Memory [BVRT] Memory [Logical Memory, Immediate] Memory [Logical Memory, Delayed] Memory [Memory Domain Composite] Executive, Attention, Processing Speed [SDMT]
Aerobic Training						
Hildreth 2015[27] RCT US Medium	53	Sedentary, obese adults age 55 and over with MCI Age, Mean (SD) 65 (7) 45% Female 74% White Years of Education, Mean (SD) 16 (2) MMSE, Mean (SD) 28.6 (1.2)	Endurance exercise training – Treadmill walking for 60 minutes 3 times/week for 6 months	Maintaining current level of physical activity and placebo for study duration	6 months	Multidomain Neuropsychological Performance [ADAS-Cog] Memory[Composite]: NS Executive, Attention, Processing Speed [WMS-R (Visual Reproduction II)] Executive, Attention, Processing Speed [Composite]: NS Executive, Attention, Processing Speed [Trail Making Test B] Executive, Attention, Processing Speed [WAIS-R (Digit Symbol Test)] Executive, Attention, Processing Speed [Stroop Color-Word Interference test] Executive, Attention, Processing Speed [WAIS-III (Digits Backward) Visuospatial, Executive, Attention, Processing Speed [WAIS-R (Picture Completion)] Memory [WMS-R (Logical Memory II)]

						Memory [Rey Auditory Verbal Learning Test] Language [Composite] Language: [Boston Naming Test] Language: [Category Fluency] Visuospatial [Composite] Visuospatial [WAIS-R (Block Design)] Visuospatial [Clock Drawing Test]
Lautenschlager 2008[23] RCT Australia Low	100	Adults reporting difficulty with memory and a MMSE score of at least 24 Age, Mean (SD): 68.7 (8.6) 51% Female Race NR Years of Education, Mean (SD) 12.4 (3.3) ADAS-Cog, Mean (SD) 7.0 (1.8)	Home-based physical activity program with behavioral intervention –At minimum 50 minutes sessions 3 times/week of moderately intense exercise for 24 weeks and a social cognitive theory-based behavioral package (workshop, manual, newsletters, and telephone calls)	Educational material about memory loss, stress management, healthful diet, alcohol consumption, and smoking. No materials on physical activity.	18 months	Multidomain Neuropsychological Performance [ADAS-Cog] Diagnosis [Clinical Dementia Rating, Sum of Boxes] Executive, Attention, Processing Speed [Digit Symbol Coding (WAIS-III)] Memory [Word List, Immediate Recall (CERAD)] Memory [Word List, Delayed Recall (CERAD)] Language [Verbal Fluency (Delis-Kaplin Executive Function Battery)]

ADAS=Cog-Alzheimer's Disease Assessment Scale-Cognitive; BVRT=Benton Visual Retention Test; CERAD=Consortium to Establish a Registry for Alzheimer's Disease; COWAT=Controlled Oral Word Association Test; DSC=; MCI= mild cognitive impairment; MMSE=Mini Mental Status Exam; MTA-ERC=; NR=not reported; NS=Not significant; RCT=Randomized Controlled Trial; RoB=Risk of Bias; SCWT=; SD=; SDMT=Symbol Digit Modalities Test; SOE=Strength of Evidence; WAIS=Wechsler Adult Intelligence Scale; WBS=; WMS=Wechsler Memory Scale

Appendix Table G7. Characteristics of eligible studies: physical activity interventions vs. active controls in adults with MCI

Study **Design** **Country** **RoB**	**N=**	**Population** **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]**
Multicomponent Physical Activity vs. Active Control						
Lam 2015[28] RCT China High	278	Older adults with MCI (determined by subjective and objective impairments in cognitive function) and without dementia Age, Mean (SD) 75.4 (6.5) 78.2% Female Race NR Education Level (Years), Mean (SD) 3.9 (3.6) Catonese MMSE. Mean (SD) 25.6 (2.3)	One stretching and toning, one mind body exercise, and one aerobic session -60 minutes per session for 1 year	Social activities -At least 3, 1-hr sessions/week	12 months	Diagnosis [Clinical Dementia Rating Scale, Sum of Boxes] Multidomain Neuropsychological Performance [ADAS-Cog (Chinese version] Brief Cognitive Test Performance [MMSE] Memory [Delayed recall] Language [CVFT]

Lam 2015[28] RCT China High	292	Older adults with MCI (determined by subjective and objective impairments in cognitive function) and without dementia Age, Mean (SD) 75.4 (6.5) 78.2% Female Race NR Education Level (Years), Mean (SD) 3.9 (3.6) Catonese MMSE. Mean (SD) 25.6 (2.3)	One stretching and toning, one mind body exercise, and one aerobic session -60 minutes per session for 1 year	Cognitively demanding activities -At least 3, 1-hr sessions/week	12 months	Diagnosis [Clinical Dementia Rating Scale, Sum of Boxes] Multidomain Neuropsychological Performance [ADAS-Cog (Chinese version] Brief Cognitive Test Performance [MMSE] Memory [Delayed recall] Language [CVFT]
Lam 2015[28] RCT China High	239	Older adults with MCI (determined by subjective and objective impairments in cognitive function) and without dementia Age, Mean (SD) 75.4 (6.5) 78.2% Female Race NR Education Level (Years), Mean (SD) 3.9 (3.6) Catonese MMSE. Mean (SD) 25.6 (2.3)	One stretching and toning, one mind body exercise, and one aerobic session -60 minutes per session for 1 year	Combination of cognitive and mind body exercises –At least 3, 1-hr sessions/week	12 months	Diagnosis [Clinical Dementia Rating Scale, Sum of Boxes] Multidomain Neuropsychological Performance [ADAS-Cog (Chinese version] Brief Cognitive Test Performance [MMSE] Memory [Delayed recall] Language [CVFT]
Law 2014[29] RCT Australia Medium	83	Adults age 60 and older with MCI Age, Mean (SD) 73.8 (7.1) 60.2% Females Race NR 33% with	Functional task exercise group (FcTSim programme: 5-10 min warm-up of light stretching, 30-min core FcTSim	Active control - cognitive training group (30 min of computer-based cognitive training and 30 min of cognitive strategy	6 months	Multidomain Neuropsychological Performance [Chinese version - Neurobehavioral Cognitive Status Exam] Memory [Chinese Version, CVVLT, Immediate] Memory [Chinese Version, CVVLT, Delayed]

		Secondary or Tertiary Education MMSE, Mean (SD) 24.17 (3.29)	and 5-10 min cooldown) -13 sessions in 10 weeks	training) -6 sessions over 10 weeks		Language [Chinese Category Verbal Fluency Test (CVFT)] Executive, Attention, Processing Speed [Chinese Version of Trails A] Executive, Attention, Processing Speed [Chinese Version of Trails B]
Resistance Training vs. Active Control						
ten Brinke 2015[30] High	56	Women with probable MCI (minimum MMSE score of 24 and reported difficulty with memory) Age, Mean (SD) 75.1 (3.7) 100% Female Race NR 28% with a University Degree MMSE, Mean (SD) 26.46 (2)	Resistance Training-2 times/week for 60 minutes for 6 months Walking -2 times/week for 60 minutes for 6 months	Balance and Tone: Stretching exercises, range of motion exercises, balance exercises, functional and relaxation techniques -2 times/week for 60 minutes for 6 months	26 weeks	Memory [Rey Auditory Verbal Learning Test, Total acquisition] Memory [Rey Auditory Verbal Learning Test, Recall after interference] Memory [Rey Auditory Verbal Learning Test, Loss after interference] Memory [Rey Auditory Verbal Learning Test, Long delay free recall] Biomarker [MRI]
ten Brinke 2015[30] High	58	Women with probable MCI (minimum MMSE score of 24 and reported difficulty with memory) Age, Mean (SD) 75.1 (3.7) 100% Female Race NR 28% with a University Degree MMSE, Mean (SD) 26.46 (2)	Resistance Training-2 times/week for 60 minutes for 6 months	Walking -2 times/week for 60 minutes for 6 months	26 weeks	Memory [Rey Auditory Verbal Learning Test, Total acquisition] Memory [Rey Auditory Verbal Learning Test, Recall after interference] Memory [Rey Auditory Verbal Learning Test, Loss after interference] Memory [Rey Auditory Verbal Learning Test, Long delay free recall] Biomarker [MRI]

Fiatarone Singh 2014[26] RCT Australia High	46	Adults age 55 and older with a MCI diagnosis consistent with Petersen criteria Age NR Sex NR Education NR MMSE, Mean (SD) 27 (1)	Resistance Training -100 minutes 2 days/week for 6 months	Cognitive training (computer-based exercises targeting memory, executive function, attention, and processing speed) -100 minutes 2 days/week for 6 months	6 months 18 months	Multidomain Neuropsychological Performance [ADAS COG] Multidomain Neuropsychological Performance [Global Cognition Domain Composite] Executive, Attention, Processing Speed [WAIS III-Similarities] Executive, Attention, Processing Speed [WAIS III-Matrices] Language [Category Fluency (Animal Naming)] Language, Executive, Attention, Processing Speed [COWAT] Executive, Attention, Processing Speed [Executive Function Domain Composite] Memory [List learning Memory Sum from ADAS-COG] Memory [BVRT] Memory [Logical Memory, Immediate] Memory [Logical Memory, Delayed] Memory [Memory Domain Composite] Executive, Attention, Processing Speed [SDMT]
Fiatarone Singh 2014[26] RCT Australia High	49	Adults age 55 and older with a MCI diagnosis consistent with Petersen criteria Age NR Sex NR Education NR MMSE, Mean (SD) 27 (1)	Resistance Training -100 minutes 2 days/week for 6 months	Cognitive training (computer-based exercises targeting memory, executive function, attention, and processing speed) and Resistance Training -100 minutes 2 days/week for 6 months	6 months 18 months	Multidomain Neuropsychological Performance [ADAS COG] Multidomain Neuropsychological Performance [Global Cognition Domain Composite] Executive, Attention, Processing Speed [WAIS III-Similarities] Executive, Attention, Processing Speed [WAIS III-Matrices] Language [Category Fluency (Animal Naming)] Language, Executive, Attention, Processing Speed [COWAT] Executive, Attention, Processing Speed [Executive Function Domain Composite] Memory [List learning Memory Sum from ADAS-COG] Memory [BVRT] Memory [Logical Memory, Immediate] Memory [Logical Memory, Delayed] Memory [Memory Domain Composite] Executive, Attention, Processing Speed

						[SDMT]
Nagamatsu 2013[31] RCT Canada Medium High (Spatial Memory Outcome)	56	Women with probable MCI (minimum MMSE score of 24 and reported difficulty with memory) Age, Mean (SD) 74.9 (3.5) 100% Female Race NR 22% with a University Degree MMSE, Mean (SD) 27.2 (1.6)	Resistance Training-2 times/week for 60 minutes for 6 months	Balance and Tone: Stretching exercises, range of motion exercises, balance exercises, functional and relaxation techniques -2 times/week for 60 minutes for 6 months	26 weeks	Memory [Rey Auditory Verbal Learning Test, Total acquisition] Memory [Rey Auditory Verbal Learning Test, Recall after interference] Memory [Rey Auditory Verbal Learning Test, Loss after interference] Memory [Rey Auditory Verbal Learning Test, Long delay free recall] Adverse Events [Shortness of Breath and Falls]
Aerobic Training vs. Active Control						
ten Brinke 2015[30] High	58	Women with probable MCI (minimum MMSE score of 24 and reported difficulty with memory) Age, Mean (SD) 75.1 (3.7) 100% Female Race NR 28% with a University Degree MMSE, Mean (SD) 26.46 (2)	Walking -2 times/week for 60 minutes for 6 months	Balance and Tone: Stretching exercises, range of motion exercises, balance exercises, functional and relaxation techniques -2 times/week for 60 minutes for 6 months	26 weeks	Memory [Rey Auditory Verbal Learning Test, Total acquisition] Memory [Rey Auditory Verbal Learning Test, Recall after interference] Memory [Rey Auditory Verbal Learning Test, Loss after interference] Memory [Rey Auditory Verbal Learning Test, Long delay free recall] Biomarker [MRI]
Nagamatsu 2013[31] RCT Canada Medium	58	Women with probable MCI (minimum MMSE score of 24 and reported difficulty	Walking -2 times/week for 60 minutes for 6 months	Balance and Tone: Stretching exercises, range of motion exercises, balance exercises,	26 weeks	Memory [Rey Auditory Verbal Learning Test, Total acquisition] Memory [Rey Auditory Verbal Learning Test, Recall after interference] Memory [Rey Auditory Verbal Learning

High (Spatial Memory Outcome)		with memory) Age, Mean (SD) 74.9 (3.5) 100% Female Race NR 22% with a University Degree MMSE, Mean (SD) 27.2 (1.6))		functional and relaxation techniques -2 times/week for 60 minutes for 6 months		Test, Loss after interference] Memory [Rey Auditory Verbal Learning Test, Long delay free recall] Adverse Events [Shortness of Breath and Falls]
Baker 2010[18, 19] RCT US High	33	Sedentary adults with amnestic MCI (single or multiple domain) based on Petersen criteria Age, Mean (Range) 70 (55-85) 52% Female Race NR Education NR MMSE, Mean (SD) 27.5 (1.9)	High-intensity aerobic exercise -4 times/week for 45-60 minutes over 6 months	Supervised stretching -4 times/week for 45-60 minutes over 6 months	6 months	Executive, Attention, Processing Speed [Trail Making Test] Executive, Attention, Processing Sped [Stroop Color and Word Test] Executive, Attention, Processing Speed [Task Switching] Language [Verbal Fluency] Memory [Symbol Digit Modalities] Memory [Story Recall] Memory [List Learning] Memory [Delayed-Match-To-Sample]
Tai Chi vs. Active Control						
Lam 2012[32] RCT China High	389	Adults age 65 and older with a CDR of 0.5 or aMCI with subjective cognitive complaints Age, Mean (SD) 78 (6.4) 74% Female Race NR Education Level, Mean (SD) 3.4 (3.8) MMSE, Mean (SD) 24.5 (3.0)	Training on 24-forms of simplified Tai Chi (in person for 4-6 weeks, then via home video) -30 minutes 3 times/week for 1 year	Muscle stretching and toning exercise developed by physiotherapists (in person for 4-6 weeks, then via home video) -30 minutes 3 times/week for 1 year	1 year	Incident Dementia [DSM-IV criteria] Multidomain Neuropsychological Performance [ADAS-cog]

ADAS=Cog-Alzheimer's Disease Assessment Scale-Cognitive; BVRT=Benton Visual Retention Test; CDR= Change in Dementia Rating; CERAD=Consortium to Establish a Registry for Alzheimer's Disease; COWAT=Controlled Oral Word Association Test; CVFT=; CVVLT=; DSC=; DSM= Diagnostic Statistical Manual of Mental Disorders; MCI=

mild cognitive impairment; MMSE=Mini Mental Status Exam; MRI= Magnetic Resonance Imaging; NR=not reported; NS=Not significant; RCT=Randomized Controlled Trial; RoB=Risk of Bias; SD=Standard Deviation; SDMT=Symbol Digit Modalities Test; SOE=Strength of Evidence; WAIS=Wechsler Adult Intelligence Scale

Appendix Table G8. Summary risk of bias assessments: physical activity interventions in adults with MCI

Study	Overall Risk of Bias Assessment	Rationale
Hildreth 2015[27]	Medium	Attrition rate is 15% with differential attrition rates in study arms. No analysis to address potential attrition bias.
Fiatarone Singh 2014[26]	High	Suspected reporting bias. Results for intervention arms are combined in the analysis,
ten Brinke 2015[30]	High	Attrition rates is over 21% with no analysis to address potential attrition bias.
Law 2014[29]	Medium	Randomization not fully described and potential detection bias.
Nagamatsu 2013[31]	Medium Spatial Memory: High	Unaccounted differences in sample size for outcome measures. Spatial memory outcome is rated high due to high rate of attrition for outcome measure.
Suzuki 2013[24]	Medium	Attrition and suspected performance bias.
Lam 2012[32]	High	Attrition rate is over 30% with no analysis to address potential attrition bias.
Suzuki 2012[25]	Medium	Randomization not adequately described.
Baker 2010[19]	High	Suspected reporting bias based on reporting of study results.
Lautenschlager 2008[23]	Low	No suspected biases.

Appendix Table G9. Strength of evidence assessments: physical activity interventions versus inactive control in adults with MCI

Outcome	# Trials (n)	Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
Multicomponent Physical Activity									
Dementia	NR								
MCI	NR								
Brief cognitive test performance	2 (150)	1 of 3 tests show a statistically significant difference with the intervention	Medium	Indirect	Imprecise	Consistent	Undetected	NA	Insufficient
Multidomain neuropsychological performance	NR								
Executive/Attention/ Processing Speed	NR								
Memory	2 (150)	1 of 5 tests show a statistically significant difference with the intervention	Medium	Indirect	Imprecise	Consistent	Undetected	NA	Insufficient
Biomarkers	NR								
Adverse Effects	NR								
Aerobic Training									
Dementia	NR								
MCI	NR								
Brief cognitive test performance	NR								
Multidomain neuropsychological performance	2 (153)	1 of 2 tests shows a statistically significant difference with the intervention Hildreth 2015[27] ADAS-Cog, Mean Difference from Baseline [95% CI] I: –1.6 [–4.9, 1.6] C: –0.3, [–3.5, 3.0] Lautenschlager 2008[23] ADAS-Cog, Mean Difference from Baseline [95% CI] I: −0.38 [−1.39 to 0.63] C: 0.45 [−0.46 to 1.36]	Medium	Indirect	Imprecise	Inconsistent	Undetected	NA	Insufficient
Executive/Attention/ Processing Speed	2 (153)	8 of 8 tests do not show a statistically significant difference with the intervention	Medium	Indirect	Imprecise	Consistent	Undetected	NA	Insufficient
Memory	2 (153)	5 of 5 tests do not show a	Medium	Indirect	Imprecise	Consistent	Undetected	NA	Insufficient

Outcome	# Trials (n)	Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
		statistically significant difference with the intervention							
Biomarkers	NR	NA	NA	NA	NA	NA	NA	NA	NA
Adverse Effects	2 (153)	3 of 4 reports of adverse effects do not show a statistically significant difference with the intervention.	Medium	Indirect	Imprecise	Consistent	Undetected	NA	Insufficient

MCI=mild cognitive impairment; NR=not reported; SOE=strength of evidence

References for Appendix G

1. Bun S, Ikejima C, Kida J, et al. A combination of supplements may reduce the risk of Alzheimer's disease in elderly Japanese with normal cognition. J Alzheimers Dis. 2015;45(1):15-25. doi: 10.3233/JAD-142232. PMID: 25524956.

2. Sink KM, Espeland MA, Castro CM, et al. Effect of a 24-Month Physical Activity Intervention vs Health Education on Cognitive Outcomes in Sedentary Older Adults: The LIFE Randomized Trial. JAMA. 2015 Aug 25;314(8):781-90. doi: 10.1001/jama.2015.9617. PMID: 26305648.

3. Napoli N, Shah K, Waters DL, et al. Effect of weight loss, exercise, or both on cognition and quality of life in obese older adults. Am J Clin Nutr. 2014 Jul;100(1):189-98. doi: 10.3945/ajcn.113.082883. PMID: 24787497.

4. Klusmann V, Evers A, Schwarzer R, et al. Complex mental and physical activity in older women and cognitive performance: a 6-month randomized controlled trial. J Gerontol A Biol Sci Med Sci. 2010 Jun;65(6):680-8. doi: 10.1093/gerona/glq053. PMID: 20418350.

5. Evers A, Klusmann V, Schwarzer R, et al. Improving cognition by adherence to physical or mental exercise: a moderated mediation analysis. Aging Ment Health. 2011 May;15(4):446-55. doi: 10.1080/13607863.2010.543657. PMID: 21500011.

6. Rosano C, Venkatraman VK, Guralnik J, et al. Psychomotor speed and functional brain MRI 2 years after completing a physical activity treatment. J Gerontol A Biol Sci Med Sci. 2010 Jun;65(6):639-47. doi: 10.1093/gerona/glq038. PMID: 20348185.

7. Taylor-Piliae RE, Newell KA, Cherin R, et al. Effects of Tai Chi and Western exercise on physical and cognitive functioning in healthy community-dwelling older adults. J Aging Phys Act. 2010 Jul;18(3):261-79. PMID: 20651414.

8. Williamson JD, Espeland M, Kritchevsky SB, et al. Changes in cognitive function in a randomized trial of physical activity: results of the lifestyle interventions and independence for elders pilot study. J Gerontol A Biol Sci Med Sci. 2009 Jun;64(6):688-94. doi: 10.1093/gerona/glp014. PMID: 19244157.

9. van de Rest O, van der Zwaluw NL, Tieland M, et al. Effect of resistance-type exercise training with or without protein supplementation on cognitive functioning in frail and pre-frail elderly: secondary analysis of a randomized, double-blind, placebo-controlled trial. Mech Ageing Dev. 2014 Mar-Apr;136-137:85-93. doi: 10.1016/j.mad.2013.12.005. PMID: 24374288.

10. Cassilhas RC, Viana VA, Grassmann V, et al. The impact of resistance exercise on the cognitive function of the elderly. Med Sci Sports Exerc. 2007 Aug;39(8):1401-7. doi: 10.1249/mss.0b013e318060111f. PMID: 17762374.

11. Antunes HK, De Mello MT, Santos-Galduroz RF, et al. Effects of a physical fitness program on memory and blood viscosity in sedentary elderly men. Braz J Med Biol Res. 2015 Sep;48(9):805-12. doi: 10.1590/1414-431X20154529. PMID: 26222648.

12. Satoh M, Ogawa J, Tokita T, et al. The effects of physical exercise with music on cognitive function of elderly people: Mihama-Kiho project. PLoS One. 2014;9(4):e95230. doi: 10.1371/journal.pone.0095230. PMID: 24769624.

13. Mortimer JA, Ding D, Borenstein AR, et al. Changes in brain volume and cognition in a randomized trial of exercise and social interaction in a community-based sample of non-demented Chinese elders. J Alzheimers Dis. 2012;30(4):757-66. doi: 10.3233/JAD-2012-120079. PMID: 22451320.

14. Nguyen MH, Kruse A. A randomized controlled trial of Tai chi for balance, sleep quality and cognitive performance in elderly Vietnamese. Clin Interv Aging. 2012;7:185-90. doi: 10.2147/CIA.S32600. PMID: 22807627.

15. Eggenberger P, Schumacher V, Angst M, et al. Does multicomponent physical exercise with simultaneous cognitive training boost cognitive performance in older adults? A 6-month randomized controlled trial with a 1-year follow-up. Clin Interv Aging. 2015 17 Aug;10:1335-49. doi: 10.2147/CIA.S87732. PMID: 26316729.

16. Ferreira L, Tanaka K, Santos-Galduroz RF, et al. Respiratory training as strategy to prevent cognitive decline in aging: a randomized controlled

trial. Clin Interv Aging. 2015 20 Mar;10:593-603. doi: 10.2147/CIA.S79560. PMID: 25848235.

17. Hotting K, Reich B, Holzschneider K, et al. Differential cognitive effects of cycling versus stretching/coordination training in middle-aged adults. Health Psychol. 2012 Mar;31(2):145-55. doi: 10.1037/a0025371. PMID: 21895371.

18. Baker LD, Frank LL, Foster-Schubert K, et al. Aerobic exercise improves cognition for older adults with glucose intolerance, a risk factor for Alzheimer's disease. J Alzheimers Dis. 2010;22(2):569-79. doi: 10.3233/JAD-2010-100768. PMID: 20847403.

19. Baker LD, Frank LL, Foster-Schubert K, et al. Effects of aerobic exercise on mild cognitive impairment: a controlled trial. Arch Neurol. 2010 Jan;67(1):71-9. doi: 10.1001/archneurol.2009.307. PMID: 20065132.

20. van der Zwaluw NL, Dhonukshe-Rutten RA, van Wijngaarden JP, et al. Results of 2-year vitamin B treatment on cognitive performance: secondary data from an RCT. Neurology. 2014 Dec 2;83(23):2158-66. doi: 10.1212/WNL.0000000000001050. PMID: 25391305.

21. van der Zwaluw NL, van de Rest O, Tieland M, et al. The impact of protein supplementation on cognitive performance in frail elderly. Eur J Nutr. 2014 Apr;53(3):803-12. doi: 10.1007/s00394-013-0584-9. PMID: 24045855.

22. Muscari A, Giannoni C, Pierpaoli L, et al. Chronic endurance exercise training prevents aging-related cognitive decline in healthy older adults: a randomized controlled trial. Int J Geriatr Psychiatry. 2010 Oct;25(10):1055-64. doi: 10.1002/gps.2462. PMID: 20033904.

23. Lautenschlager NT, Cox KL, Flicker L, et al. Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. JAMA. 2008 Sep 3;300(9):1027-37. doi: 10.1001/jama.300.9.1027. PMID: 18768414.

24. Suzuki T, Shimada H, Makizako H, et al. A randomized controlled trial of multicomponent exercise in older adults with mild cognitive impairment. PLoS One. 2013;8(4):e61483. doi: 10.1371/journal.pone.0061483. PMID: 23585901.

25. Suzuki T, Shimada H, Makizako H, et al. Effects of multicomponent exercise on cognitive function in older adults with amnestic mild cognitive impairment: a randomized controlled trial. BMC Neurol. 2012;12:128. doi: 10.1186/1471-2377-12-128. PMID: 23113898.

26. Fiatarone Singh MA, Gates N, Saigal N, et al. The Study of Mental and Resistance Training (SMART) study-resistance training and/or cognitive training in mild cognitive impairment: a randomized, double-blind, double-sham controlled trial. J Am Med Dir Assoc. 2014 Dec;15(12):873-80. doi: 10.1016/j.jamda.2014.09.010. PMID: 25444575.

27. Hildreth KL, Van Pelt RE, Moreau KL, et al. Effects of pioglitazone or exercise in older adults with mild cognitive impairment and insulin resistance: a pilot study. Dement Geriatr Cogn Dis Extra. 2015 Jan-Apr;5(1):51-63. doi: 10.1159/000371509. PMID: 25852732.

28. Lam LC, Chan WC, Leung T, et al. Would older adults with mild cognitive impairment adhere to and benefit from a structured lifestyle activity intervention to enhance cognition?: a cluster randomized controlled trial. PLoS One. 2015 31 Mar;10(3):e0118173. doi: 10.1371/journal.pone.0118173. PMID: 25826620.

29. Law LL, Barnett F, Yau MK, et al. Effects of functional tasks exercise on older adults with cognitive impairment at risk of Alzheimer's disease: a randomised controlled trial. Age Ageing. 2014 Nov;43(6):813-20. doi: 10.1093/ageing/afu055. PMID: 24850540.

30. ten Brinke LF, Bolandzadeh N, Nagamatsu LS, et al. Aerobic exercise increases hippocampal volume in older women with probable mild cognitive impairment: a 6-month randomised controlled trial. Br J Sports Med. 2015 Feb;49(4):248-54. doi: 10.1136/bjsports-2013-093184. PMID: 24711660.

31. Nagamatsu LS, Chan A, Davis JC, et al. Physical activity improves verbal and spatial memory in older adults with probable mild cognitive impairment: a 6-month randomized controlled trial. J Aging Res. 2013;2013(861893):861893. doi: 10.1155/2013/861893. PMID: 23509628.

32. Lam LC, Chau RC, Wong BM, et al. A 1-year randomized controlled trial comparing mind body exercise (Tai Chi) with stretching and toning exercise on cognitive function in older Chinese adults at risk of cognitive decline. J Am Med Dir Assoc. 2012 Jul;13(6):568 e15-20. doi: 10.1016/j.jamda.2012.03.008. PMID: 22579072.

Appendix H. Nutraceutical Interventions

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

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						
Cukierman-Yaffe, 2014[1] (Substudy of ORIGIN trial) RCT Multinational Medium (High for outcomes at t5 for MMSE and t6 for DSS)	15077	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] Screening [MMSE] Executive/attention/processing speed [DSS - WAIS]

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]**
Witte, 2014[2] 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	Biomarkers [MRI: gray matter changes and white matter integrity] Executive/attention/processing speed [executive function composite = phonemic fluency, semantic fluency, TMT A, TMT B, Stroop parts 1 & 2] [attention composite = z digit span forward] [sensorimotor speed composite = TMT A, Stroop parts A & B, Digit Span Forward] Memory [memory composite = AVLT learning, AVLT delayed recall, AVLT recognition, digit span backward]
Stonehouse, 2013[3] 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 = Stroop test, choice reaction time, and digit vigilance] [reaction time attention] [processing speed = finding As task] [reaction time episodic memory] [reaction time working memory] Memory [composite episodic memory = immediate and delayed word recall, delayed word recognition, and delayed picture recognition] [composite working memory = n-back, Corsi blocks, and a letter-number sequencing task]
Geleijnse, 2012[4] 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 50% secondary	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	Placebo daily for 40 months	40 months	Screening [MMSE] [risk of cognitive decline based on MMSE score]

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]
		educ 16% higher vocational educ 12% college Mean MMSE (SD): 28.3 (1.6)	into combined group analysis of all EPA-DHA vs placebo and all ALA versus placebo)			
Andreeva, 2011 [5] 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	Screening [F-TICS-m total score] Memory [F-TICS-m memory subscore] [F-TICS-m recall subscore]
Dangour, 2010 [6] 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	Omega 3 (EPA 200 mg + DHA 500 mg) daily for 2 years	Olive oil capsules for 2 years	2 years	Multidomain composite [composite: CVLT sum of words, CVLT delayed recall, prospective memory tests 1, 2, 3, story recall-delayed, verbal fluency, letter cancellation, location memory, location memory-delayed, symbol-letter substitution, digit span forward & backward, simple reaction time, choice reaction time] Executive/attention/processing speed [executive composite: digit span backward, verbal fluency] [processing composite: letter cancellation, simple reaction time, choice reaction time, symbol-letter substitution] [letter search/cancellation - # correct, % of

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]
		18% A level, college 23% other Median MMSE (IQR): 29 (28, 30)				total attempts] [symbol letter modality - # correct] [reaction time - simple] [reaction time - choice] [digit span forward] [digit span backward] Memory [memory composite: sum of words recalled, CVLT delayed recall, location memory, location memory-delayed, story recall, story recall-delayed] [global delay composite: CVLT delayed recall, location memory delayed recall, story recall delayed] [CVLT - words correct in 1st 3 trials] [CVLT - words recalled at delayed recall] [story recall - immediate] [story recall - delayed] [spatial memory - # of correct images - immediate] [spatial memory - # correct images - delayed] Language [verbal fluency - # animals named]
Yurko-Mauro, 2010[7] 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	Screening [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]

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]
Van de Rest, 2008[8] 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: TMT A, TMT B, word fluency-animals, word fluency-letters] [attention: digit span forward] [sensorimotor speed: TMT A, Stroop part 1, Stroop part 2] [TMT A] [TMT B] [Stroop part 1] [Stroop part 2] [Stroop part 3 – (part 1 + part 2/2)] Memory [memory composite: 15 word learning-immediate, word learning-delayed, word learning recognition, digit span backward] Language [word fluency-animals] [word fluency-letter]
Ginkgo biloba efficacy						
Lewis, 2014[9] 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	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	Screening [MMSE] Executive/attention/processing speed [Stroop color and word test] [TMT A] [TMT B] [digit symbol subtest, WAIS-III] Memory [HVLT-R] Language [COWA]

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]
		criteria				
Vellas, 2012[10] 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, 2009[11] DeKosky, 2008[12] RCT USA Low	3069 (normal cog & MCI) 2587 normal cog	Community-dwelling participants aged 72 to 96 years; 15% baseline MCI Mean age (SD):	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	Diagnosis: incident dementia & AD (5 categories) [All dementia] [AD without vascular dementia] [AD with vascular dementia] [total AD [vascular dementia without AD] Multidomain composite [global composite:

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]
		79.1 (3.3) years 46% female 95% white Education mean (SD): 14.4 (3) years Mean 3MSE (SD): 93.4 (4.7)			Other cognitive outcomes at year 4	3MSE and ADAS-Cog (using TICS when 3MSE not possible)] Executive/attention/processing speed [executive composite: TMT B & Stroop color word test] [attention and psychomotor speed composite: WAIS-R digit span and TMT A] [TMT B] [Stroop color/word Test] [TMT A] [WAIS-R digit span] Memory [memory composite: CVLT & recall conditions - Modified Rey Osterrieth figure test] [CVLT] [recall conditions - Modified Rey Osterrieth figure test] Visuospatial [visuospatial composite: copy condition of the Rey Osterrieth figure test & M-WAIS-R Block Design] [copy condition of the Rey Osterrieth figure test] [modified WAIS-R block design] Language [language composite: 30-item Boston Naming Test & semantic verbal fluency] [30-item Boston Naming Test] [semantic verbal fluency]
Dodge, 2008[13] 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 CDR = 0.5] Memory [CERAD word list delayed recall]
Multi-nutraceutical						

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]
supplement efficacy						
Lewis, 2014[9] 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.	Placebo (cellulose, lactose, and beet powder) for 6 months	6 months	Screening [MMSE] Executive/attention/processing speed [Stroop color and word test] [TMT A] [TMT B] [DSS, WAIS-III] Memory [HVLT-R] Language [COWA]
Resveratrol efficacy						
Witte, 2014[14] 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	Resveratrol (200 mg/d) for 6 months	Placebo for 6 months	6 months	Biomarkers [MRI: volume, microstructure, and functional connectivity of the hippocampus] Memory [AVLT retention] [AVLT delayed recall] [AVLT recognition] [AVLT learning ability] [AVLT 5th learning trial]

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]
		Mean MMSE (SD): 29 (1)				
Red clover & black cohosh efficacy						
Maki, 2009 [15] RCT USA High	66 (originally randomized 89)	Midlife women with ≥35 hot flashes weekly Mean age (SD): 53 (4.25) years 100% female 44% white 53% African Amer Education not reported Baseline cognition not reported	Red clover (120 mg) or black cohosh (128 mg) daily for 1 year	Matching placebo daily for 1 year	1 year	Memory [CVLT] [logical memory subtest of WMS-R] [Benton Visual Retention Test] Executive/attention/processing speed [digit span forward] [digit span backward] [brief test of attention - modified] [finding As test] Language [letter fluency] Visuospatial [modified card rotations test]
Plant sterols/ plant stanols efficacy						
Schiepers, 2009[16] 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: Stroop 1, Stroop 2, concept shifting test A, concept shifting test B] [complex speed composite: Stroop 3, complex shifting test] [letter digit substitution] Memory [composite: Visual Verbal Word Learning Task total free recall, delayed recall, recognition]
Omega 3 comparative effectiveness						

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]
Andreeva, 2011[5] 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	Screening [F-TICS-m] Memory [F-TICS-m subscore] [F-TICS-m recall subscore]
Chew, 2015[17] 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	Screening [TICS total score] Composite [composite including all cognitive tests plus delayed recall of WMS-III recall paragraph] Executive/attention/processing speed [backwards counting] [verbal fluency – animal, letter & alternating – also Language] Memory [Wechsler logical memory I & II] [TICS word list recall] Language [verbal fluency – animal] [verbal fluency – letter] [verbal fluency – category]
Lutein/ Zeaxanthin						
Chew, 2015[17] RCT USA High	3501	Adults at risk for developing age-related macular degeneration Mean age (SD): 72.7 (± 7.7) years	Lutein (10mg)/ zeaxanthin (2mg) daily 5 years	No Lutein/zeaxanthin (other groups) for 5 years	Yearly for 5 years	Screening [TICS total score] Composite [composite including all cognitive tests plus delayed recall of WMS-III recall paragraph] Executive/attention/processing speed [backwards counting] [verbal fluency –

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]
		57.5% female 97% white 29% ≤ high school 49% ≥ some college 22% postgraduate Mean TICS (SD): 33 (3.4)				animal, letter & alternating – also Language] Memory [Wechsler logical memory I & II] [TICS word list recall] Language [verbal fluency – animal] [verbal fluency – letter] [verbal fluency – category]
Multi-nutraceutical supplement						
Bun, 2015[18] 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]

Cognitive test abbreviations: 3MSE=Modified Mini Mental Status Examination; ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive Subscale; AVLT=Auditory Verbal Learning Test; CVLT=California Verbal Learning Test; CANTAB=Cambridge Nueropsychological Test Automated Battery Paired Associated Learning Test; CANTAB PAL=Cambridge Nueropsychological Test Automated Battery Paired Associated Learning Test; CDR=Change in Dementia Rating; CERAD= Consortium to Establish a Registry for Alzheimer's Disease; COWA= Controlled Oral Word Association; F-TICS=French version, Telephone Interview Cognitive Status; HVLT-R=Hopkins Verbal Learning Test-Revised; MMSE=Mini-Mental State Examination; SWM=Spatial Working Memory; PRM=Pattern Recognition Memory; RT=reaction time; TICS=Telephone Interview Cognitive Status; TICS-m=Telephone Interview Cognitive Status-Modified; TMT=Trails Making Test (A & B); VRM=Verbal Recognition Memory; WAIS=Wechsler Adult Intelligence Scale; WMS= Wechsler Memory Scale

Omega 3 fatty acids: ALA=alpha-linolenic acid; DHA=docosahexaenoic acid; EPA=eicosapentaenoic acid; Lc-n3-FA=long-chain omega-3 fatty acids

Other abbreviations: AD=Alzheimer’s disease; DSM= Diagnostic and Statistical Manual of Mental Disorders (DSM); NINCDS-ADRDA=National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer’s Disease and Related Disorders Association; SD=Standard Deviation; RCT=Randomized Controlled Trial

Appendix Table H2. Summary risk of bias assessments: nutraceuticals interventions in adults with normal cognition

Study	Overall Risk of Bias Assessment	Rationale
Omega 3 fatty acids efficacy		
Cukierman-Yaffe, 2014[1]	Medium	Attrition >20% at some time points; sensitivity analysis conducted
Witte, 2014[2]	Medium	Unclear randomization procedures; attrition >10% without analysis to account for possible bias
Stonehouse, 2013[3]	High	Attrition >20% without analysis to conduct for possible bias
Geleijnse, 2012[4]	Medium	Unclear randomization procedures; attrition
Andreeva, 2011[5]	Medium	Subset of RCT followup using participants with a history of cardiovascular disease. Original RCT baseline measures on subset – no differences between groups.
Dangour, 2010[6]	Medium	Attrition >10% without analysis to correct for potential bias
Yurko-Mauro, 2010[7]	Medium	Attrition >10% without appropriate analysis; possible detection bias (unclear whether assessor was independent)
Van de Rest, 2008[8]	Low	
Ginkgo biloba efficacy		
Lewis, 2014[9]	High	Attrition >25% without analysis
Vellas, 2012[10]	Medium	Attrition >30% (analysis conducted)
Snitz, 2009[11] DeKosky, 2008[12]	Medium	High attrition, but analysis conducted to correct for potential bias
Dodge, 2008[13]	Medium	Attrition >10% without analysis; possible detection bias (unclear outcome assessment blinding/independence)
Multi-nutraceutical efficacy		
Lewis, 2014[9]	High	Attrition >25% without appropriate analysis
Resveratrol efficacy		
Witte, 2014[14]	Medium	Unclear randomization procedures; unclear whether outcome assessor was blinded and independent
Red clover & black cohosh efficacy		
Maki, 2009[15]	High	Attrition >25% from original randomization without analysis to correct for potential bias
Plant sterols or plant stanols		
Schieper[16]s 2009	Medium	Unclear randomization procedures; unclear whether outcome assessor was blind to treatment
Comparative effectiveness		
Andreeva, 2011[5] (Omega 3)	Medium	Subset of RCT followup using participants with a history of cardiovascular disease. Original RCT baseline measures on subset – no differences between groups.
Chew, 2015[17] (Omega 3 & Lutein/Zeaxanthin)	High	Unclear randomization procedures; high attrition; reporting bias due to discrepancies in number randomized in 2 study papers
Bun, 2015[18] (Multi-nutraceutical supplement)	High	Participants not randomized; high attrition

Appendix Table H3. Strength of evidence assessments: nutraceutical interventions in adults with normal cognition

Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
Omega 3 fatty acids versus inactive control									
Dementia	1 (12,536)	0 of 1 tests show statistically significant improvement with intervention Cukierman-Yaffe 2014 Hazard ratio for incident cognitive impairment (composite of either incident dementia diagnosis of follow-up MMSE <24): 0.93 [0.86 to 1.0]	High	Direct	Precise	Unknown	Undetected	N/A	Low (due to study limitation of composite outcome with component of unequal importance, one of which is not clinical diagnosis and may be achieved due to chance)
MCI		NR							Insufficient
Biomarkers	Single trial <500 participants	Limited Data							Insufficient
Brief cognitive test performance (6 months to 6 years)	4 (16,431)	0 of 9 tests show statistically significant improvement with intervention (no differences between groups) Cukierman-Yaffe, 2014[1] Rate of change from baseline MMSE: 0.0013	Medium	Indirect	Imprecise	Consistent	Undetected	NA	Low

Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
		[-0.0165, 0.0191] Geleijnse, 2012[4] *EPA-DHA* Difference in change from baseline MMSE: 0.05 [-0.07, 0.17] Risk of moderate/ severe cognitive decline (decrease of ≥3 MMSE pts or incidence of cognitive decline or dementia): OR 1.03 [0.84, 1.26] Risk of severe cognitive decline (decrease of ≥5 MMSE pts or incidence of cognitive decline or dementia): OR 0.99 [0.73, 1.34] *ALA* Difference in change from baseline MMSE: 0.14 [-0.04, 0.32] Risk of moderate /severe cognitive decline: OR 0.90 [0.74, 1.10]							

Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
		Risk of severe cognitive decline: OR 0.88 [0.65, 1.19] Andreeva, 2011[5] No statistically significant effects of group assignment on cognitive function. Difference in mean F-TICS-m scores are not reported. Yurko-Mauro, 2010[7] Difference in change from baseline MMSE treatment vs. placebo: 0 [-0.30, 0.30]							
Multidomain neuropsychological performance (2 years)	1 (744)	0 of 1 test shows statistically significant improvement with intervention (no differences between groups) Dangour, 2010[6] Difference in change from baseline (measure of global cognitive function) treatment vs placebo: -0.01 [-0.05, 0.04]	Medium	Indirect	Imprecise	Unknown	Undetected	NA	Low
Executive/ Attention/ Processing Speed	5 (5079)	2 of 31 favor I	Medium	Indirect	Imprecise	Consistent (2 I>C from n=548 over 6 months;	Undetected	NA	Low

Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
(6 months to 2 years)						29 NS from 5079 over 6 years)			
Memory (6 months to 4 years)	5 (3428)	3 of 25 favor I	Medium	Indirect	Imprecise	Consistent (3 I>C from 1 study of n=483; 22 from all)	Undetected	NA	Low
Ginkgo biloba versus inactive control									
Dementia (5-6 years)	2 (5407)	0 of 5 tests show statistically significant differences between intervention and control groups. Vellas, 2012[10] Incidence of probable AD by year of study (hazard not proportional by time) 1 year: HR 0.72 [0.32-1.61] 2 years: HR 1.66 [0.81-3.40] 3 years: HR 1.11 [0.51-2.43] 4 years: HR 0.57 [0.19-1.69] ≥5 years: HR 0.49 [0.25-0.96] DeKosky, 2008[12] Incidence of dementia: All dementia: HR 1.05 [0.84-1.30] AD without vascular	Medium	Direct	Imprecise	Consistent	Undetected	NA	Low

Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
		dementia: HR 1.13 [0.86-1.48] AD with vascular dementia: HR 1.12 [0.72-1.74] Total AD: HR 0.13 [0.90-1.42] Vascular dementia without AD: HR 0.36 [0.13-1.00]							
MCI	Single trial <500 participants	Limited Data							Insufficient (limited data)
Brief cognitive test performance	NR								Insufficient (no data)
Multidomain neuropsychological performance (6 years)	1 (3069) (includes 482 MCI; 15.7% total)	0 of 1 (no statistically significant differences between groups) Snitz, 2009[11] Results of linear mixed models: Treatment effect (overall difference in z scores ginkgo vs. placebo): mean (95% CI): 0.015 [-0.018, 0.047] Treatment x time interaction: annual difference in rates of change between ginkgo and placebo: mean (95% CI): -0.002 [-0.009,	Medium	Indirect	Imprecise	Unknown	Undetected	NA	Low

Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
		0.005]							
Executive/ Attention/ Processing Speed (6 years)	1 (3069) (includes 482 MCI; 15.7% total)	0 of 5 (no differences)	Medium	Indirect	Imprecise	Consistent	Undetected	NA	Low
Memory (3.5 to 6 years)	2 (3187)	0 of 4 (no differences)	Medium	Indirect	Imprecise	Consistent	Undetected	NA	Low
Omega 3 versus Vitamin B									
Dementia	NR								Insufficient (no data)
MCI	NR								Insufficient (no data)
Biomarkers	NR								Insufficient (no data)
Screening Tests	1 (885)	0 of 1 test show statistically significant differences	Medium	Indirect	Imprecise	Unknown	Undetected	NA	Low
Multidomain Composites	NR								Insufficient (no data)
Executive/ Attention/ Processing Speed	NR								Insufficient (no data)
Memory	1 (885)	0 of 2 tests show statistically significant differences	Medium	Indirect	Imprecise	Unknown	Undetected	NA	Low
Omega 3 versus Omega 3 + Vit B									
Dementia	NR								Insufficient (no data)
MCI	NR								Insufficient (no data)
Biomarkers	NR								Insufficient (no data)
Screening Tools	1 (877)	0 of 1 test show statistically	Medium	Indirect	Imprecise	Unknown	Undetected		Low

Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
		significant differences							
Multidomain Composites	NR								Insufficient (no data)
Executive/ Attention/ Processing Speed	NR								Insufficient (no data)
Memory (4 years)	1 (877)	0 of 2 tests show statistically significant differences	Medium	Indirect	Imprecise	Unknown	Undetected	NA	Low

AD=Alzheimer's disease; ALA=alpha-linolenic acid; DHA=docosahexaenoic acid; EPA=eicosapentaenoic acid; HR=; MCI=Mild Cognitive Impairment; MMSE= Mini Mental Status Exam; NR=; SOE=Strength of Evidence; F-TICS=French version, Telephone Interview Cognitive Status

Appendix Table H4. Characteristics of eligible studies: Intervention type in Adults with MCI

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						
Lee, 2013[19] RCT Malaysia Medium	36	Low SES people aged 60+ with MCI Mean age (SD): 65 (4) years 77% female Race not reported Mean education (SD): 5.9 (3) years Mean MMSE (95% CI): 26.7 (25.7-27.5)	Omega 3 fatty acids (DHA 430 mg and EPA 150 mg) daily for 1 year	Placebo capsules daily for 1 year	1 year	Screening [MMSE] Executive/attention/processing speed [executive function attention composite: clock drawing test, digit span forward, WAIS-R] [digit symbol substitution test, WAIS III] [digit span forward & backward, WAIS-R] Memory [memory composite: visual reproduction I, visual reproduction II, RAVLT - immediate recall, RAVLT - delayed recall, digit span backward] [visual reproduction I. WMS-R] [visual reproduction II, WMS-R] [RAVLT - immediate recall] [RAVLT - delayed recall] Visuospatial [visuospatial skills composite: block design, matrix reasoning] [clock drawing test] [matrix reasoning] [block design]
Ginkgo biloba efficacy						
Gavrilova, 2014[20] RCT Russia Low	160	People with MCI who scored at least 6 on the 12-item Neuropsychiatric Inventory (NPI) Mean age (SD): 64 (7) 62% female Race not reported Mean education (SD): 9.7 (0.9) years Mean MMSE (SD): 25.7 (1.4)	Ginkgo biloba (EGb 761) 240 mg daily for 6 months	Placebo tablet for 6 months	6 months	Executive/attention/processing speed [TMT A] [TMT B]

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]
DeKosky, 2008[12] RCT USA Medium	3069 (total) 482 MCI	For full sample: 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	Diagnosis: incident dementia & AD (5 categories) [All dementia] [AD without vascular dementia] [AD with vascular dementia] [total AD] [vascular dementia without AD]
Omega 3 fatty acids comparative effectiveness						
Sinn, 2011[21] RCT Australia High	50	People aged 65+ with MCI Mean age (SD): 74 (5) years 33% female Race not reported Average education: slightly under year 12 Mean MMSE (SD): 27 (2.5)	Omega 3 supplementation Diet rich in EPA (1.67 g EPA + 0.16 g DHA daily) or DHA (1.55 DHA + 0.40 g EPA daily) or n-6 PUFA linoleic acid (PUFA linoleic acid 2.2 g) daily for 6 months	Other groups (a diet rich in EPA, or DHA, or 6-6 PUFA linoleic acid)	6 months	Executive/attention/processing speed [digits forward & backward] [letter-number sequencing] [TMT A] [TMT B] [Stroop color-word test] Memory [RAVLT] Language [verbal fluency]

AD=Alzheimer's disease; DHA=docosahexaenoic acid; EPA=eicosapentaenoic acid; MCI=Mild Cognitive Impairment; MMSE= Mini Mental Status Exam; PUFA=; RAVLT=Rey's Auditory Verbal Learning Test; RCT=Randomized Controlled Trial; SD=Standard Deviation; TMT=Trails Making Test (A & B); WAIS=Wechsler Adult Intelligence Scale; WMS= Wechsler Memory Scale

Appendix Table H5. Summary risk of bias assessments: nutraceuticals in adults with MCI

Study	Overall Risk of Bias Assessment	Rationale
Omega 3 fatty acids efficacy		
Lee 2013[19]	Low/Medium	Possible detection bias (unclear outcomes assessment)
Ginkgo biloba		
Gavrilova, 2014[20]	Low	
DeKosky, 2008[12]	Low	
Omega 3 fatty acids comparative effectiveness		
Sinn, 2012[21]	High	Randomization not well described; attrition > 25% without appropriate analysis to account for possible bias

References for Appendix H

1. Cukierman-Yaffe T, Bosch J, Diaz R, Dyal L, Hancu N, Hildebrandt P, et al. Effects of basal insulin glargine and omega-3 fatty acid on cognitive decline and probable cognitive impairment in people with dysglycaemia: a substudy of the ORIGIN trial. Lancet Diabetes Endocrinol. 2014 Jul;2(7):562-72. PubMed PMID: 24898834. Pubmed Central PMCID: A eligible. English.

2. Witte AV, Kerti L, Hermannstadter HM, Fiebach JB, Schreiber SJ, Schuchardt JP, et al. Long-chain omega-3 fatty acids improve brain function and structure in older adults. Cereb Cortex. 2014 Nov;24(11):3059-68. PubMed PMID: 23796946. Pubmed Central PMCID: A eligible. English.

3. Stonehouse W, Conlon CA, Podd J, Hill SR, Minihane AM, Haskell C, et al. DHA supplementation improved both memory and reaction time in healthy young adults: a randomized controlled trial. Am J Clin Nutr. 2013 May;97(5):1134-43. PubMed PMID: 23515006. Pubmed Central PMCID: A eligible. English.

4. Geleijnse JM, Giltay EJ, Kromhout D. Effects of n-3 fatty acids on cognitive decline: a randomized, double-blind, placebo-controlled trial in stable myocardial infarction patients. Alzheimer's & Dementia. 2012 Jul;8(4):278-87. PubMed PMID: 21967845. Pubmed Central PMCID: A eligible. English.

5. Andreeva VA, Kesse-Guyot E, Barberger-Gateau P, Fezeu L, Hercberg S, Galan P. Cognitive function after supplementation with B vitamins and long-chain omega-3 fatty acids: ancillary findings from the SU.FOL.OM3 randomized trial. Am J Clin Nutr. 2011 Jul;94(1):278-86. PubMed PMID: 21593490. English.

6. Dangour AD, Allen E, Elbourne D, Fasey N, Fletcher AE, Hardy P, et al. Effect of 2-y n-3 long-chain polyunsaturated fatty acid supplementation on cognitive function in older people: a randomized, double-blind, controlled trial. Am J Clin Nutr. 2010 Jun;91(6):1725-32. PubMed PMID: 20410089. Pubmed Central PMCID: A eligible. English.

7. Yurko-Mauro K, McCarthy D, Rom D, Nelson EB, Ryan AS, Blackwell A, et al. Beneficial effects of docosahexaenoic acid on cognition in age-related cognitive decline. Alzheimer's & Dementia. 2010 Nov;6(6):456-64. PubMed PMID: 20434961. Pubmed Central PMCID: A eligible. English.

8. van de Rest O, Geleijnse JM, Kok FJ, van Staveren WA, Dullemeijer C, Olderikkert MG, et al. Effect of fish oil on cognitive performance in older subjects: a randomized, controlled trial. Neurology. 2008 Aug 5;71(6):430-8. PubMed PMID: 18678826. Pubmed Central PMCID: A eligible. English.

9. Lewis JE, Melillo AB, Tiozzo E, Chen L, Leonard S, Howell M, et al. A double-blind, randomized clinical trial of dietary supplementation on cognitive and immune functioning in healthy older adults.[Erratum appears in BMC Complement Altern Med. 2014;14:332]. BMC Altern Med. 2014;14:43. PubMed PMID: 24495355. Pubmed Central PMCID: A eligible. English.

10. Vellas B, Coley N, Ousset PJ, Berrut G, Dartigues JF, Dubois B, et al. Long-term use of standardised Ginkgo biloba extract for the prevention of Alzheimer's disease (GuidAge): a randomised placebo-controlled trial. Lancet neurol. 2012 Oct;11(10):851-9. PubMed PMID: 22959217. Pubmed Central PMCID: A eligible. English.

11. Snitz BE, O'Meara ES, Carlson MC, Arnold AM, Ives DG, Rapp SR, et al. Ginkgo biloba for preventing cognitive decline in older adults: a randomized trial. Jama. 2009 Dec 23;302(24):2663-70. PubMed PMID: 20040554. Pubmed Central PMCID: A eligible. English.

12. DeKosky ST, Williamson JD, Fitzpatrick AL, Kronmal RA, Ives DG, Saxton JA, et al. Ginkgo biloba for prevention of dementia: a randomized controlled trial.[Erratum appears in JAMA. 2008 Dec 17;300(23):2730]. Jama. 2008 Nov 19;300(19):2253-62. PubMed PMID: 19017911. Pubmed Central PMCID: A eligible. English.

13. Dodge HH, Zitzelberger T, Oken BS, Howieson D, Kaye J. A randomized placebo-controlled trial of Ginkgo biloba for the prevention of cognitive decline. Neurology. 2008 May 6;70(19 Pt 2):1809-17. PubMed PMID: 18305231. Pubmed Central PMCID: A eligible. English.

14. Witte AV, Kerti L, Margulies DS, Floel A. Effects of resveratrol on memory performance, hippocampal functional connectivity, and glucose metabolism in healthy older adults. J Neurosci. 2014 Jun 4;34(23):7862-70. PubMed PMID: 24899709. Pubmed Central PMCID: A eligible. English.

15. Maki PM, Rubin LH, Fornelli D, Drogos L, Banuvar S, Shulman LP, et al. Effects of botanicals and combined hormone therapy on cognition in postmenopausal women. Menopause. 2009 Nov-Dec;16(6):1167-77. PubMed PMID: 19590458. Pubmed Central PMCID: A eligible. English.

16. Schiepers OJ, de Groot RH, van Boxtel MP, Jolles J, de Jong A, Lutjohann D, et al. Consuming functional foods enriched with plant sterol or stanol esters for 85 weeks does not affect neurocognitive functioning or mood in statin-treated hypercholesterolemic individuals. J Nutr. 2009 Jul;139(7):1368-73. PubMed PMID: 19458031. Pubmed Central PMCID: A eligible. English.

17. Chew EY, Clemons TE, Agron E, Launer LJ, Grodstein F, Bernstein PS, et al. Effect of Omega-3 Fatty Acids, Lutein/Zeaxanthin, or Other Nutrient Supplementation on Cognitive Function: The AREDS2 Randomized Clinical Trial. Jama. 2015 Aug 25;314(8):791-801. PubMed PMID: 26305649. Pubmed Central PMCID: A eligible. English.

18. Bun S, Ikejima C, Kida J, Yoshimura A, Lebowitz AJ, Kakuma T, et al. A combination of supplements may reduce the risk of alzheimer's disease in elderly japanese with normal cognition. J Alzheimers Dis. 2015;45(1):15-25. PubMed PMID: 2015808390. English.

19. Lee LK, Shahar S, Chin AV, Yusoff NA. Docosahexaenoic acid-concentrated fish oil supplementation in subjects with mild cognitive impairment (MCI): a 12-month randomised, double-blind, placebo-controlled trial. Psychopharmacology (Berl). 2013 Feb;225(3):605-12. PubMed PMID: 22932777. Pubmed Central PMCID: A eligible. English.

20. Gavrilova SI, Preuss UW, Wong JW, Hoerr R, Kaschel R, Bachinskaya N, et al. Efficacy and safety of Ginkgo biloba extract EGb 761 in mild cognitive impairment with neuropsychiatric symptoms: a randomized, placebo-controlled, double-blind, multi-center trial. Int J Geriatr Psychiatry. 2014 Oct;29(10):1087-95. PubMed PMID: 24633934. Pubmed Central PMCID: Eligible. English.

21. Sinn N, Milte CM, Street SJ, Buckley JD, Coates AM, Petkov J, et al. Effects of n-3 fatty acids, EPA v. DHA, on depressive symptoms, quality of life, memory and executive function in older adults with mild cognitive impairment: a 6-month randomised controlled trial. Br J Nutr. 2012 Jun;107(11):1682-93. PubMed PMID: 21929835. Pubmed Central PMCID: A eligible. English.

Appendix I. Diet Interventions

Appendix Table I1. Characteristics of eligible studies: nutrition/lifestyle interventions in adults with normal cognition

Study **Design** **Country** **RoB**	**N=**	**Population** **Inclusion** **Age (mean)** **Sex** **Race** **Education** **Baseline Cog**	**Intervention** **Mode** **Components** **Frequency** **Duration**	**Comparison** **Mode** **Components** **Frequency** **Duration**	**Outcome timing**	**Outcome** **Domain [Instrument]**
Caloric restriction diet interventions						
Martin 2007[1] RCT USA High	48	Overweight adults aged 25 to 50 with a BMI ≤25 and <30 Mean age: 38 56% Female 63% White Education: NR Baseline cog: NR	1) calorie restriction (25% calorie restriction based on baseline energy requirements); food provided at a center weeks 1-12, and 22-24, diets self-selected in weeks 13-22 2) calorie restriction + structured exercise (12.5% calorie restriction + 12.5% increase in energy expenditure via structured exercise) 3) very low-calorie diet (890 kcal/d liquid formula diet until 15% of body weight is lost, followed by weight maintenance)	Weight maintenance diet	6 months	Executive/attention/processing speed [Conners' CPT-II] Memory [RAVLT] Memory [ACT] Memory [BVRT]
Energy restriction diet interventions						
Napoli 2014[2] RCT Italy Medium	107	Obese (BMI ≥30), sedentary adults with stable body weight aged ≥65 Mean age: 70 Sex: 63% Female Race: 85% White Mean education: 16	1) Diet: calorie restriction; counseling; goal setting; 10% weight loss with maintenance 2) Exercise: counseled on weight maintenance; multicomponent exercise 3 times/week	Information control: general nutrition information; instructed not to make changes to daily routine	1 year	Global Function [3MS] Executive/attention/processing speed [Trail Making Test A] Executive/attention/processing speed [Trail Making Test B] Language [Word List Fluency]

		years Baseline cognition:	3) Diet + Exercise: both interventions			
Brinkworth 2009[3] RCT Australia High	118	Adults aged 24 to 64 years with abdominal obesity and at least 1 additional metabolic syndrome risk factor Mean age: 50 Sex: NR Race: NR Education: NR Mean 3MS (SE): 96.3 (0.8) control 96 (0.6) diet only 95.6 (0.8) diet-exercise	Energy-restricted, planned, isocaloric, very low carbohydrate, high fat (LC) diet	High-carbohydrate, low-fat diet with individual counseling for first 8 weeks.	1 year	Executive/attention/processing speed [Digit Span Backward] Executive/attention/processing speed [Inspection Time]
Mediterranean Diet interventions						
Valls-Pedret 2015[4] PREDIMED RCT Spain High	447	Adults aged 55 to 80 with no cardiovascular disease, but high vascular risk Mean age: 67 51% Women Mean education: 7 years Baseline global cog: NR	1) Mediterranean Diet high consumption plant-based foods, fish and seafood; low consumption of dairy, meat, processed grains; regular moderate alcohol (red wine with meals preferred) plus extra-virgin olive oil 2) Mediterranean Diet + mixed nuts	Information control (leaflet about low-fat diets)	5 years	Global Function [MMSE] Memory [RAVLT, total learning and delayed recall] Executive/attention/processing speed [Digit Span Forward] Executive/attention/processing speed [Digit Span Backward] Executive/attention/processing speed [Color Trail Test Part 1] Executive/attention/processing speed [Color Trail Test Part 2] Memory [Verbal Paired Associates] Language [Verbal Fluency]
Martinez-Lapiscina 2013(a)[5] PREDIMED RCT Spain High	1055	Adults aged 55 to 80 with no cardiovascular disease, but high vascular risk Mean age: 67 55% Female Race: NR Education: >8 years: 29% Baseline global cog: NR	1) Mediterranean Diet high consumption plant-based foods, fish and seafood; low consumption of dairy, meat, processed grains; regular moderate alcohol (red wine with meals preferred) plus extra-virgin olive oil 2) Mediterranean Diet + mixed nuts	Information control (leaflet about low-fat diets)	6.5 years	Diagnosis [Incidence of MCI] Global Function [MMSE] Visuospatial [Clock Drawing Test]

Martinez-Lapiscina 2013(b)[6] PREDIMED (subgroup) RCT Spain High	285	Adults aged 55 to 80 with no cardiovascular disease, but high vascular risk Mean age: 67 55% Female Race: NR Mean education: 9 years Baseline global cog: NR	1) Mediterranean Diet high consumption plant-based foods, fish and seafood; low consumption of dairy, meat, processed grains; regular moderate alcohol (red wine with meals preferred) plus extra-virgin olive oil 2) Mediterranean Diet + mixed nuts	Information control (leaflet about low-fat diets)	6.5 years	Diagnosis [Incidence of MCI] Global Function [MMSE] Executive/attention/processing speed [Trail Making Test A] Executive/attention/processing speed [Trail Making Test B] Executive/attention/processing speed [Digit Span Forward] Executive/attention/processing speed [Digit Span Backward] Memory [RAVLT, immediate and delay] Memory [Verbal Paired Associates] Memory [Rey-Osterrich Complex Figure, immediate and delayed] Language [Similarities] Language [Semantic Verbal Fluency Test-Animals] Language [Phonemic Verbal Fluency Test] Language [Boston Naming Test] Visuospatial [Clock Drawing Test] Visuospatial [Rey-Osterrich Complex Figure, copy]
Protein supplement interventions						
van der Zwaluw 2014[7, 8] RCT Netherlands Medium	65	Elderly adults aged ≥65 and an elevated plasma Hcy level (12-50 µmol/L) Mean age: 80 55% Female Education: Low: 9% (protein) and 0% (placebo) Middle: 59% (protein) and 55% (placebo) High: 32% (protein) and 45% (placebo) Mean MMSE (IQR): 29 (26-30) protein 28 (26-30) placebo	Protein drink (15mg of protein) twice daily	Placebo drink	24 weeks	Global Function [MMSE] Memory [Word Learning Test] Executive/attention/processing speed [Digit Span Forward] Executive/attention/processing speed [Digit Span Backward] Executive/attention/processing speed [Trail Making Test A] Executive/attention/processing speed [Trail Making Test B] Executive/attention/processing speed [Stroop Color Word Test] Executive/attention/processing speed [Symbol Digit Modalities] Executive/attention/processing speed [Reaction Time test] Language [Letter Fluency]

Cognitive test abbreviations: 3MSE=Modified Mini Mental Status Examination; ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive Subscale; CVLT=California

Verbal Learning Test; CDR=Change in Dementia Rating; COWA= Controlled Oral Word Association; MMSE=Mini-Mental State Examination; TMT=Trails Making Test (A & B); WAIS=Wechsler Adult Intelligence Scale; WMS= Wechsler Memory Scale

Other abbreviations: AD=Alzheimer's disease; DSM=Diagnostic and Statistical Manual of Mental Disorders (DSM); NINCDS-ADRDA=National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association; SD=Standard Deviation; RCT=Randomized Controlled Trial

Appendix Table I2. Summary risk of bias assessments: diet interventions in adults with normal cognition

Study	Overall Risk of Bias Assessment	Rationale
Caloric restriction diet		
Martin 2007[1]	High	Method of randomization unclear. High reporting bias due to unclear results
Energy restriction diet		
Napoli 2014[2]	Medium	Method of randomization unclear. 13% attrition with no sensitivity analysis.
Brinkworth 2009[3]	High	Method of randomization unclear. Attrition 44%
Mediterranean Diet		
Valls-Pedret 2015[4]	High	Attrition 25% with no sensitivity analysis
Martinez-Lapiscina 2013(a)[5]	High	Attrition 51%
Martinez-Lapiscina 2013(b)[6]	High	Poor randomization
Protein supplement		
van der Zwaluw[7, 8]	Low	Did not report if outcome assessor was blinded or independent

References for Appendix I

1. Martin CK, Anton SD, Han H, et al. Examination of cognitive function during six months of calorie restriction: results of a randomized controlled trial. Rejuvenation Res. 2007 Jun;10(2):179-90. doi: 10.1089/rej.2006.0502. PMID: 17518698.

2. Napoli N, Shah K, Waters DL, et al. Effect of weight loss, exercise, or both on cognition and quality of life in obese older adults. Am J Clin Nutr. 2014 Jul;100(1):189-98. doi: 10.3945/ajcn.113.082883. PMID: 24787497.

3. Brinkworth GD, Buckley JD, Noakes M, et al. Long-term effects of a very low-carbohydrate diet and a low-fat diet on mood and cognitive function. Arch Intern Med. 2009 Nov 9;169(20):1873-80. doi: 10.1001/archinternmed.2009.329. PMID: 19901139.

4. Valls-Pedret C, Sala-Vila A, Serra-Mir M, et al. Mediterranean Diet and Age-Related Cognitive Decline: A Randomized Clinical Trial. JAMA Intern Med. 2015 Jul;175(7):1094-103. doi: 10.1001/jamainternmed.2015.1668. PMID: 25961184.

5. Martinez-Lapiscina EH, Clavero P, Toledo E, et al. Mediterranean diet improves cognition: the PREDIMED-NAVARRA randomised trial. J Neurol Neurosurg Psychiatry. 2013 Dec;84(12):1318-25. doi: 10.1136/jnnp-2012-304792. PMID: 23670794.

6. Martinez-Lapiscina EH, Clavero P, Toledo E, et al. Virgin olive oil supplementation and long-term cognition: the PREDIMED-NAVARRA randomized, trial. J Nutr Health Aging. 2013;17(6):544-52. doi: 10.1007/s12603-013-0027-6. PMID: 23732551.

7. van der Zwaluw NL, Dhonukshe-Rutten RA, van Wijngaarden JP, et al. Results of 2-year vitamin B treatment on cognitive performance: secondary data from an RCT. Neurology. 2014 Dec 2;83(23):2158-66. doi: 10.1212/WNL.0000000000001050. PMID: 25391305.

8. van der Zwaluw NL, van de Rest O, Tieland M, et al. The impact of protein supplementation on cognitive performance in frail elderly. Eur J Nutr. 2014 Apr;53(3):803-12. doi: 10.1007/s00394-013-0584-9. PMID: 24045855.

Appendix J. Multimodal Interventions

Appendix Table J1. Characteristics of eligible studies: multimodal interventions vs. inactive controls in adults with normal cognition

Study Design Country RoB	N=	Population 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]
Physical Activity and Diet						
Napoli 2014 [1] RCT US Medium	55	Obese, sedentary adults age 65 and older with a stable weight and a minimum MMSE score of 24 Age, Mean (SD) 70 (4) 63% Female 85% White Years of Education, Mean (SD) 16.3 (3.7) 3MS, Mean (SD) 95.7 (0.8)	Diet and aerobic exercise, resistance training, and balance exercises -90 minutes sessions 3 times/week at an exercise facility for 1 year and energy deficit of 500-750 kcal/day to achieve 10% weight loss over 6 months followed by 6 months of weight maintenance	Information about healthy diet (not allowed to participate in any exercise program)	1 year	Brief Cognitive Test Performance [3MS] Executive, Attention, Processing Speed [Trail Making Test Part A] Executive, Attention, Processing Speed [Trail Making Test Part B] Language [Word List Fluency]
Martin 2007[2] RCT US Medium	24	Overweight adults aged 25 to 50 years Age, Mean (SD) 37.5 (1.9) 56% Female 62.5% White Education NR Baseline Cognition NR	Individual-based calorie restriction (12.5% reduction) and structured exercise (12.5% increase in energy expenditure) for 6 months	Weight maintenance for 6 months	6 months	Memory [RAVLT, Trail I-V] Memory [RAVLT, Trail B] Memory [RAVLT, Trail VI] Memory [RAVLT, Delayed Recall] Memory [RAVLT, Recognition] Memory [Auditory Consonant Trigram (ACT), 9 sec] Memory [Auditory Consonant Trigram (ACT), 18 sec] Memory [Auditory Consonant Trigram (ACT), 36 sec] Memory [Benton Visual Retention Test (BVRT), Correct Deviation] Memory [Benton Visual Retention Test

Study Design Country RoB	N=	Population 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]
						(BVRT), Error Deviation] Executive, Attention, Processing Speed [CPT-II, Beta (response style)] Executive, Attention, Processing-Speed [CPT-II, Omissions] Executive, Attention, Processing-Speed [CPT-II, Detectability] Executive, Attention, Processing-Speed [CPT-II, Reaction time] Executive, Attention, Processing-Speed [CPT-II, RT Std. Error] Executive, Attention, Processing-Speed [CPT-II, Commissions] Executive, Attention, Processing-Speed [CPT-II, Perseverations] Executive, Attention, Processing-Speed [CPT-II, RT Block Changes]
Physical Activity and Cognitive Training						
Hars 2014[3] RCT Switzerland Medium	134	Community dwelling adults age 65 and older with an increased risk of falling, balance impairment, or frailty. Age, Mean (SD) 75.5 (7) 96% Female Race NR 18% With High School Education MMSE, Mean (SD) 26.1 (2.9)	Structured music-based multitask exercise classes (walking while following changes to rhythmic patterns in piano music and handling objects) -60 minute sessions, 1 session/per week for 25 weeks	Maintain usual lifestyle habits for 6 months (delayed intervention)	6 months	Brief Cognitive Test Performance [MMSE] Visuospatial [Clock-Drawing Test] Executive, Attention, Processing Speed [Frontal assessment battery (FAB)] Executive, Attention, Processing Speed [Sensitivity to Inference Sub-test, Frontal assessment battery (FAB)]

Study **Design** **Country** **RoB**	**N=**	**Population** **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]**
Tesky 2011[4] RCT Germany High	307	Adults age 65 and older with no previous diagnosis of dementia and MCI Age, Mean (SD) 71 (6) 73% Female Race NR Years Education, Mean (SD) 10.4 (1.8) ADAS-cog, Mean (SD) 7.15 (2.7)	Group cognitive stimulating leisure activities (8 weekly sessions and 2 booster sessions after 16 weeks post-intervention) with nutritional education and physical activity (courses on gymnastics, walking, yoga)	Usual care for Booklet on training topics (received at the end of the study)	32 weeks	Brief Cognitive Test Performance [MMSE] Multidomain Neuropsychological Performance [ADAS-Cog] Executive, Attention, Processing Speed [TMT A] Executive, Attention, Processing Speed [TMT B] Diagnosis [Clinical Dementia Rating]
Carlson 2008[5] RCT High US	149	Cognitively intact older adults with a MMSE of 24 or higher Age, Mean (SD) 69 (6) 90% Female 95% African American Years Education, Mean (SD) 11.5 (3) MMSE, Mean (SD) 25.1 (3)	Experience Corps Program-Cognitive activity (reading to children and library service), physical activity, and social engagement for 15 hrs/week over a school year	Wait-list control	8 months	Executive, Attention, Processing Speed [TMT A] Executive, Attention, Processing Speed [TMT B] Visuospatial, Memory [Rey-Osterrieth Complex Figure Test, Copy Score] Visuospatial, Memory [Rey-Osterrieth Complex Figure Test, Delayed Recall] Memory [Word List Memory, Immediate Recall] Memory [Word List Memory, Delayed Recall]
Physical Activity, Diet, and Cognitive Training						
Ngandu 2015[6] RCT	1260	Individuals age 60–77 years with a	Individual and group nutritional intervention,	General health advice	2 years	Multidomain Neuropsychological Performance [Neuropsychological test battery (NTB) Total

Study Design Country RoB	N=	Population 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]
Finland Low		CAIDE (Cardiovascular Risk Factors, Aging and Dementia) Dementia Risk Score of at least 6 points and cognition at mean level or slightly lower than expected for age. Age, Mean (SD) 69.5 (4.6) Race NR Years Education, Mean (SD) 10.0 (3.4) MMSE, Mean (SD) 26.7 (2)	individualized aerobic (1-3 times/week) and strength training (2-5 times/week) programs, group and individual cognitive training, and management of metabolic and vascular risk factors (via lifestyle changes) for 2 years.			Score] Executive, Attention, Processing Speed [NTB, Executive Functioning] Executive, Attention, Processing Speed [NTB, Processing Speed] Memory [NTB, Memory] Memory [NTB, Abbreviated Memory]
Physical Activity and Protein Supplementation						
van de Rest 2014[7] RCT Netherlands Medium	58	Frail and pre-frail adults age 65 and over Age, Mean (SD) 77.8 (8.5) 62% Female 34% with Higher Education Race NR MMSE, Mean (Range) 28.5 (21-30))	Resistance-type exercise program and protein supplementation -2 sessions/week with personal supervision for 24 weeks	Usual Care (no exercise) and protein supplementation for 24 weeks	24 weeks	Memory [Word Learning Test, Immediate Recall-75 Words] Memory [Word Learning Test, Delayed Recall-15 Words] Memory [Word Learning Test, Decay] Memory [Word Learning Test, Recognition, 30 Words] Executive, Attention, Processing Speed [Digit Span Forward (WAIS-R)] Executive, Attention, Processing Speed [Digit Span Backwards (WAIS-R)] Executive, Attention, Processing Speed [Trail Making Test Part A] Executive, Attention, Processing Speed [Trail Making Test Part B/A]

Study Design Country RoB	N=	Population 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]
						Executive, Attention, Processing Speed [Stroop Color-Word Test 1] Executive, Attention, Processing Speed [Stroop Color-Word Test 2] Executive, Attention, Processing Speed [Stroop Interference] Language [Word Fluency-Animals] Language, Executive, Attention, Processing Speed [Word Fluency-Letter P] Executive, Attention, Processing Speed [Finger Precuing, Reaction Time Uncued] Executive, Attention, Processing Speed [Finger Precuing, Reaction Time Cued] Memory [Attention and Working Memory Composite] Executive, Attention, Processing Speed [Information Processing Speed Composite] Executive, Attention, Processing Speed [Executive Functioning Composite]
Goal Setting						

Study Design Country RoB	**N=**	**Population 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]**
Clare 2015[8] RCT UK Medium	46	Individuals aged 50 and over, living and functioning independently in the community Age, Mean (SD) 68.21 (7.92) 86.7% Female Race NR Year of Education, Mean (SD) 13.33 (2.93) Baseline Cognition NR	Goal Setting: Structured goal-setting process using Bangor Goal Setting Interview during 90 minute session. Participant set 5 goals for the coming year relating to physical activity, cognitive activity, physical health, diet, or social engagement. OR Goal Setting and Mentoring: Goal setting with five, bimonthly follow-up mentoring calls from researchers to review progress, discuss obstacles, and reinforce success.	Information: 90-minute session with interview where information was provided about activities and health.	1 year	Brief Cognitive Test Performance [Montreal Cognitive Assessment (MoCA)] Memory [CVLT, Immediate Recall] Memory [CVLT, Delayed Recall] Executive, Attention, Processing Speed [Trail-Making Test] Language [Verbal Fluency, Delis-Kaplan Executive Function System]
Occupational Therapy						
Clark 2012[9] RCT US High	460	Individuals aged 60 years or older with no overt signs of dementia or psychosis. 52% Age 75 or older 37.4% White 16.7% with 4 or more years of college Baseline Cognition NR	Lifestyle-based occupational therapy intervention –Weekly 2 hour small group sessions for 6 months and 10 individual 1 hour sessions	No treatment	6 months	Memory [CERAD, Immediate Recall] Memory [CERAD, Delayed Recall] Memory [CERAD, Recognition] Executive, Attention, Processing Speed [Reaction Time, Visual Search Task] Executive, Attention, Processing Speed [Digit Symbol Substitution]
Care						

Study Design Country RoB	N=	Population 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]
Management						
Lee 2014[10] RCT South Korea High	1,115	Community-dwelling adults aged 60 and over Age. Mean (SD) 77.1 (2.5) 78.6% Female Race NR 21.9 % Middle school or higher MMSE, Mean (SD) 24.1 (1.7)	Telephonic or in-person care management including providing educational materials, counseling regarding health behavior, and recommendations for physical activity -Monthly or bi-monthly for 18 months	Standard care (no care management)	18 months	Brief Cognitive Test Performance [MMSE]
Cognitive Training and acetylcholinesterase inhibitor						
Yesavage 2008[11] RCT US High	168	Community-dwelling adults aged 55-90 with a MMSE score between 24 and 30 Age, Mean (SD) 65 (8) 52% Female Race NR Education, Mean (SD) 16.3 (2.3) MMSE, Mean (SD) 28.6 (1.2)	Daily dose of 5 mg of Donepezil for 6 weeks, then increased to 10mg daily for 46 weeks; 2 weeks of cognitive training at weeks 13-14	Placebo and 2 weeks of cognitive training at weeks 13-14	1 year	Memory [Word list recall] Memory [Name-face recall] Memory [Logical Memory I score] Memory [Logical Memory II score] Executive, Attention, Processing Speed [Symbol Digit Span]

3MSE=Modified Mini Mental Status Examination; ACT=Auditory Consonant Trigram; BVRT=Benton Visual Retention Test; CAIDE=; CERAD=Consortium to Establish a Registry for Alzheimer's Disease; CPT=; MMSE=Mini-Mental State Examination; CVLT=California Verbal Learning Test; FAB=Frontal assessment battery; NR=not reported; NTB=Neuropsychological test battery; RAVLT=Rey's Auditory Verbal Learning Test; RCT=Randomized Controlled Trial; SD=Standard Deviation; TMT=Trails Making Test (A & B); WAIS=Wechsler Adult Intelligence Scale

Appendix Table J2. Characteristics of eligible studies: multimodal interventions vs. active controls in adults with normal cognition

Study Design Country RoB	N=	Population 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]
Physical Activity and Diet vs. Diet						
Napoli 2014 [1] RCT US Medium	647	Obese, sedentary adults age 65 and older with a stable weight and a minimum MMSE score of 24 Age, Mean (SD) 70 (4) 63% Female 85% White Years of Education, Mean (SD) 16.3 (3.7) 3MS, Mean (SD) 95.7 (0.8)	Diet and aerobic exercise, resistance training, and balance exercises -90 minutes sessions 3 times/week at an exercise facility for 1 year and energy deficit of 500-750 kcal/day to achieve 10% weight loss over 6 months followed by 6 months of weight maintenance	Diet - Energy deficit of 500-750 kcal/day to achieve 10% weight loss over 6 months followed by 6 months of weight maintenance	1 year	Brief Cognitive Test Performance [3MS] Executive, Attention, Processing Speed [Trail Making Test Part A] Executive, Attention, Processing Speed [Trail Making Test Part B] Language [Word List Fluency]
Martin 2007[2] RCT US Medium	24	Overweight adults aged 25 to 50 years Age, Mean (SD) 37.5 (1.9) 56% Female 62.5% White Education NR Baseline Cognition NR	Individual-based calorie restriction (12.5% reduction) and structured exercise (12.5% increase in energy expenditure) for 6 months	Calorie restriction (25% restriction) for 6 months	6 months	Memory [RAVLT, Trail I-V] Memory [RAVLT, Trail B] Memory [RAVLT, Trail VI] Memory [RAVLT, Delayed Recall] Memory [RAVLT, Recognition] Memory [Auditory Consonant Trigram (ACT), 9 sec] Memory [Auditory Consonant Trigram (ACT), 18 sec] Memory [Auditory Consonant Trigram (ACT), 36 sec] Memory [Benton Visual Retention Test (BVRT), Correct Deviation] Memory [Benton Visual Retention Test (BVRT), Error Deviation] Executive, Attention, Processing-Speed [CPT-

Study Design Country RoB	N=	Population 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]
						II, Beta (response style)] Executive, Attention, Processing-Speed [CPT-II, Omissions] Executive, Attention, Processing-Speed [CPT-II, Detectability] Executive, Attention, Processing-Speed [CPT-II, Reaction time] Executive, Attention, Processing-Speed [CPT-II, RT Std. Error] Executive, Attention, Processing-Speed [CPT-II, Commissions] Executive, Attention, Processing-Speed [CPT-II, Perseverations] Executive, Attention, Processing-Speed [CPT-II, RT Block Changes]
Martin 2007[2] RCT US Medium	24	Overweight adults aged 25 to 50 years Age, Mean (SD) 37.5 (1.9) 56% Female 62.5% White Education NR Baseline Cognition NR	Individual-based calorie restriction (12.5% reduction) and structured exercise (12.5% increase in energy expenditure) for 6 months	Low-calorie diet (890 kcal/d liquid formula diet until 15% of body weight is lost, followed by weight maintenance) for 6 months	6 months	Memory [RAVLT, Trail I-V] Memory [RAVLT, Trail B] Memory [RAVLT, Trail VI] Memory [RAVLT, Delayed Recall] Memory [RAVLT, Recognition] Memory [Auditory Consonant Trigram (ACT), 9 sec] Memory [Auditory Consonant Trigram (ACT), 18 sec] Memory [Auditory Consonant Trigram (ACT), 36 sec] Memory [Benton Visual Retention Test (BVRT), Correct Deviation] Memory [Benton Visual Retention Test (BVRT), Error Deviation] Executive, Attention, Processing-Speed [CPT-II, Beta (response style)] Executive, Attention, Processing-Speed [CPT-II, Omissions] Executive, Attention, Processing-Speed [CPT-II, Detectability]

Study Design Country RoB	N=	Population 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]
						Executive, Attention, Processing-Speed [CPT-II, Reaction time] Executive, Attention, Processing-Speed [CPT-II, RT Std. Error] Executive, Attention, Processing-Speed [CPT-II, Commissions] Executive, Attention, Processing-Speed [CPT-II, Perseverations] Executive, Attention, Processing-Speed [CPT-II, RT Block Changes]
Physical Activity and Diet vs. Physical Activity						
Napoli 2014 [1] RCT US Medium	54	Obese, sedentary adults age 65 and older with a stable weight and a minimum MMSE score of 24 Age, Mean (SD) 70 (4) 63% Female 85% White Years of Education, Mean (SD) 16.3 (3.7) 3MS, Mean (SD) 95.7 (0.8)	Diet and aerobic exercise, resistance training, and balance exercises -90 minutes sessions 3 times/week at an exercise facility for 1 year and energy deficit of 500-750 kcal/day to achieve 10% weight loss over 6 months followed by 6 months of weight maintenance	Aerobic exercise, resistance training, and balance exercises -90 minutes sessions 3 times/week at an exercise facility for 1 year	1 year	Brief Cognitive Test Performance [3MS] Executive, Attention, Processing Speed [Trail Making Test Part A] Executive, Attention, Processing Speed [Trail Making Test Part B] Language [Word List Fluency]
Physical Activity and Cognitive Training vs. Physical Activity and						

Study Design Country RoB	N=	Population 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]
Cognitive Training						
Eggenberger 2015[12] RCT Switzerland Medium	89	Seniors older than 70 years with an MMSE score greater than 22 Age, Mean (SD) 78.9 (5.4) 52% Female Race NR Years of Education, Mean (SD) 13.2 (1.9) MMSE, Mean (SD) 28.2 (1.4)	Virtual reality video game dancing with cognitive training -60 minute group sessions 2 times/week for 6 months	Treadmill walking with verbal memory exercise -60 minute group sessions 2 times/week for 6 months	6 months	Executive, Attention, Processing Speed [WAIS-R, Trail Making Test Part A] Executive, Attention, Processing Speed [WAIS-R, Trail Making Test Part B] Executive, Attention, Processing Speed [Executive Control Task] Memory [Paired-Associates Learning] Memory [WMS-R, Story Recall] Executive, Attention, Processing Speed [WMS-R, Digit Forward] Executive, Attention, Processing Speed [Age Concentration Test A] Executive, Attention, Processing Speed [Age Concentration Test B] Executive, Attention, Processing Speed [WAIS-R, Digit Symbol Substitution]

Study Design Country RoB	N=	Population 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]
Physical Activity and Cognitive Training vs. Physical Activity						
McDaniel 2014[13] RCT US High	96	Adults age 55 to 75 without dementia or MCI Age, Mean (SD) 65 (8) 67% Female 88% White Years Education, Mean (SD) 16 (2) MMSE, Mean (SD) 29 (1)	Treadmill walking or exercise bicycle program (45-50 minute sessions 3 times/week) for 6 months and cognitive training 3 days/week for 8 weeks	Low-intensity home exercise program focusing on flexibility for 6 months and in-person health education for 8 weeks	6 months	Executive, Attention, Processing Speed [Stroop Part 1] Executive, Attention, Processing Speed [Stroop Part 2] Memory [Logical Memory Immediate] Memory [Logical Memory Delayed (Wechsler)] Memory [Virtual Week (5-min break)] Memory [Memory for Health Information Part 1] Memory [Memory for Health Information Part 2] Executive, Attention, Processing Speed [Digit Symbol task] Executive, Attention, Processing Speed [Trail making A and B]
McDaniel 2014[13] RCT US High	96	Adults age 55 to 75 without dementia or MCI Age, Mean (SD) 65 (8) 67% Female 88% White Years Education, Mean (SD) 16 (2) MMSE, Mean (SD) 29 (1)	Treadmill walking or exercise bicycle program (45-50 minute sessions 3 times/week) for 6 months and cognitive training 3 days/week for 8 weeks	Treadmill walking or exercise bicycle program -45-50 minute sessions 3 times/week for 6 months	6 months	Executive, Attention, Processing Speed [Stroop Part 1] Executive, Attention, Processing Speed [Stroop Part 2] Memory [Logical Memory Immediate] Memory [Logical Memory Delayed (Wechsler)] Memory [Virtual Week (5-min break)] Memory [Memory for Health Information Part 1] Memory [Memory for Health Information Part 2] Executive, Attention, Processing Speed [Digit Symbol task] Executive, Attention, Processing Speed [Trail making A and B]

Study Design Country RoB	N=	Population 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]
McDaniel 2014[13] RCT US High	96	Adults age 55 to 75 without dementia or MCI Age, Mean (SD) 65 (8) 67% Female 88% White Years Education, Mean (SD) 16 (2) MMSE, Mean (SD) 29 (1)	Treadmill walking or exercise bicycle program (45-50 minute sessions 3 times/week) for 6 months and cognitive training 3 days/week for 8 weeks	Low-intensity home exercise program focusing on flexibility for 6 months and cognitive training 3 days/week for 8 weeks	6 months	Executive, Attention, Processing Speed [Stroop Part 1] Executive, Attention, Processing Speed [Stroop Part 2] Memory [Logical Memory Immediate] Memory [Logical Memory Delayed (Wechsler)] Memory [Virtual Week (5-min break)] Memory [Memory for Health Information Part 1] Memory [Memory for Health Information Part 2] Executive, Attention, Processing Speed [Digit Symbol task] Executive, Attention, Processing Speed [Trail making A and B]

3MS=Modified Mini Mental Status; ACT=Auditory Consonant Trigram; BVRT=Benton Visual Retention Test; CPT=; MMSE=Mini-Mental State Examination; NR=not reported; RAVLT=Rey's Auditory Verbal Learning Test; RCT=Randomized Controlled Trial; SD=Standard Deviation; TMT=Trails Making Test (A & B); WAIS=Wechsler Adult Intelligence Scale; WMS= Wechsler Memory Scale

Appendix Table J3. Summary risk of bias assessments: multimodal interventions in adults with normal cognition

Study	Overall Risk of Bias Assessment	Rationale
Clare 2015[8]	Medium	Potential performance and detection bias.
Eggenberger 2015[12]	Medium	Attrition rate is 20% with potential performance bias.
Ngandu 2015[6]	Low	No significant risk of bias detected.
Hars 2014[3]	Medium	Process for randomization is unclear and attrition rate is 16%.
Lee 2014[10]	High	High potential for bias due to over 50% attrition.
McDaniel 2014[13]	High	Process for randomization is unclear with suspected reporting bias.
Napoli 2014[1]	Medium	Process for randomization is unclear and 13% attrition rate.
van de Rest 2014[7]	Medium	Attrition is 15% with potential reporting bias.
Clark 2012[9]	High	Attrition rate is greater than 21% with no analysis to address potential bias.
Tesky 2011[4]	High	Attrition rate is greater than 21% with no analysis to address potential bias.
Calrson 2008[5]	High	Attrition rate is greater than 21% with no analysis to address potential bias.
Yesavage 2008[11]	High	Attrition rate is greater than 21% with no analysis to address potential bias.
Martin 2007[2]	Medium	Process for attrition is unclear with potential detection bias.

Appendix Table J4. Strength of evidence assessments: multimodal interventions versus inactive control in adults with normal cognition

Comparison	Outcome	# Trials (n)	Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	Evidence Rating
Physical activity and diet vs. inactive control	Dementia	NR								
	MCI	NR								
	Brief Cognitive Test Performance									
	Multidomain Neuropsychological Performance	NR								
	Executive Function	2 (79)	1 of 10 tests shows a statistically significant difference with intervention.	Medium	Indirect	Imprecise	Inconsistent	Undetected	NA	Insufficient
	Memory	NR								
	Biomarkers	NR								
	Adverse Effects	NR								
Physical activity, diet, ad cognitive training vs. inactive control	Dementia	NR								
	MCI	NR								
	Brief Cognitive Test Performance	NR								
	Multidomain Neuropsychological Performance	1 (1260)	1 of 1 test show a statistically significant difference with intervention. Ngandu 2015[6] NTB,	Low	Indirect	Precise	Unknown	Undetected	NA	Low

Comparison	Outcome	# Trials (n)	Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	Evidence Rating
			Difference between groups per year [95% CI] 0.022 [0.002, 0.042]							
	Executive Function	1 (1260)	2 of 2 tests show a statistically significant difference with intervention. Ngandu 2015[6] NTB Executive Functioning, Difference between groups per year [95% CI] 0.027 [0.001, 0.052] NTB Processing Speed, Difference groups per year [95% CI] 0.030 [0.003, 0.057]	Low	Indirect	Precise	Unknown	Undetected	NA	Low
	Memory	1 (1260)	1 of 2 tests shows a statistically significant	Low	Indirect	Imprecise	Inconsistent	Undetected	NA	Insufficient

Comparison	Outcome	# Trials (n)	Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	Evidence Rating
			difference with intervention. <u>Ngandu 2015</u> NTB Memory, Difference between groups per year [95% CI] 0.015 [-0.017, 0.048] NTB Abbreviated Memory, Difference between groups per year [95% CI] 0.038 [0.002, 0.073]							
	Biomarkers	NR								
	Adverse Effects	NR								

MCI=mild cognitive impairment; NR=not reported; NTB=Neuropsychological test battery

Appendix Table J5. Strength of evidence assessments: multimodal interventions versus active comparison in adults with normal cognition

Comparison	Outcome	# Trials (n)	Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	Evidence Rating
Physical activity and diet vs. diet	Dementia	NR								
	MCI	NR								
	Brief Cognitive Test Performance									
	Multidomain Neuropsychological Performance	NR								
	Executive Function	2 (90)	18 of 18 tests show no statistically significant difference with intervention.	Medium	Indirect	Imprecise	Consistent	Undetected	NA	Insufficient
	Memory	NR								
	Biomarkers	NR								
	Adverse Effects	NR								

MCI=mild cognitive impairment; NR=not reported;

Appendix Table J6. Characteristics of eligible studies: multimodal interventions vs. inactive controls in adults with MCI

Study Design Country RoB	N=	Population 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]
Fiatarone Singh 2014[14] RCT Australia High	51	Adults age 55 and older with a MCI diagnosis consistent with Petersen criteria Age NR Sex NR Education NR MMSE, Mean (SD) 27 (1)	Cognitive training (computer-based exercises targeting memory, executive function, attention, and processing speed) and Resistance Training -100 minutes 2 days/week for 6 months	Sham cognitive training and sham exercise	6 months 18 months	Multidomain Neuropsychological Performance [ADAS COG] Multidomain Neuropsychological Performance [Global Cognition Domain Composite] Executive, Attention, Processing Speed [WAIS III-Similarities] Executive, Attention, Processing Speed [WAIS III-Matrices] Language [Category Fluency (Animal Naming)] Language, Executive, Attention, Processing Speed [COWAT] Executive, Attention, Processing Speed [Executive Function Domain Composite] Memory [List learning Memory Sum from ADAS-COG] Memory [BVRT] Memory [Logical Memory, Immediate] Memory [Logical Memory, Delayed] Memory [Memory Domain Composite] Executive, Attention, Processing Speed [SDMT]
Johari 2014[15] RCT Malaysia High	35	Individuals with MCI based on Petersen criteria Age, Mean (SD) 65.7 (3.8) 54.3% Female 83% Malay 94% with Formal Education MMSE, Mean (SD) 27 (3)	Nutrition and lifestyle education (7 guidelines) – Monthly sessions for 12 months	No education, supplementation with placebo capsule containing 1000 mg corn oil (taken 3 times a day for 12 months)	12 months	Brief Cognitive Test Performance [MMSE] Executive, Attention, Processing Speed [Digit span forward] Executive, Attention, Processing Speed [Digit span backward] Executive, Attention, Processing Speed [Digit symbol] Visuospatial [Block design] Executive, Attention, Processing Speed [Matrix reasoning] Memory [Visual reproduction I] Memory [Visual reproduction II (delayed)] Memory [RAVLT]

Study Design Country RoB	N=	Population 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]
						Visuospatial [Clock Drawing Test]

ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive Subscale; BVRT=Benton Visual Retention Test; COWAT=Controlled Oral Word Association Test; MCI=Mild Cognitive Impairment; MMSE= Mini Mental Status Exam; NR=not reported; RAVLT=Rey's Auditory Verbal Learning Test; SD=Standard Deviation; SDMT=Symbol Digit Modalities Test; WAIS=Wechsler Adult Intelligence Scale

Appendix Table J7. Characteristics of eligible studies: multimodal interventions vs. active controls in adults with MCI

Study Design Country RoB	N=	Population 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]
Lam 2015[16] RCT China High	263	Chinese older adults with MCI (presence of subjective cognitive complaints, and objective impairments in cognitive function) Age, Mean (SD) 75.4 (6.5) 78.2% Female Race NR Education Level, Mean (SD) 3.9 (3.6) ADAS-cog, Mean (SD) 11.5 (3.3)	Cognitive and mind-body exercises -1 hour sessions 3 times/week	Social activities (e.g., tea gathering, film watching) –At least 1 hour sessions 3 times/week	8 months 12 months	Diagnosis [CDR-SOB] Multidomain Neuropsychological Performance [ADAS-Cog (Chinese version)] Memory [Delayed recall] Brief Cognitive Test Performance [MMSE] Language [CVFT]
Lam 2015[16] RCT China High	277	Chinese older adults with MCI (presence of subjective cognitive complaints, and objective impairments in cognitive function) Age, Mean (SD) 75.4 (6.5) 78.2% Female Race NR Education Level, Mean (SD) 3.9 (3.6) ADAS-cog, Mean (SD) 11.5 (3.3)	Cognitive and mind-body exercises -1 hour sessions 3 times/week	Cognitively demanding activities (e.g., reading and discussing news, board games) –At least 3 sessions/weeks	8 months 12 months	Diagnosis [CDR-SOB] Multidomain Neuropsychological Performance [ADAS-Cog (Chinese version)] Memory [Delayed recall] Brief Cognitive Test Performance [MMSE] Language [CVFT]

Study **Design** **Country** **RoB**	**N=**	**Population** **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]**
Lam 2015[16] RCT China High	279	Chinese older adults with MCI (presence of subjective cognitive complaints, and objective impairments in cognitive function) Age, Mean (SD) 75.4 (6.5) 78.2% Female Race NR Education Level, Mean (SD) 3.9 (3.6) ADAS-cog, Mean (SD) 11.5 (3.3)	Cognitive and mind-body exercises -1 hour sessions 3 times/week	Stretching and toning, mind body exercise (e.g., Tai Chi), and aerobic exercise -1 session/week of each type, 60 minutes/session	8 months 12 months	Diagnosis [CDR-SOB] Multidomain Neuropsychological Performance [ADAS-Cog (Chinese version)] Memory [Delayed recall] Brief Cognitive Test Performance [MMSE] Language [CVFT]
Fiatarone Singh 2014[14] RCT Australia High	51	Adults age 55 and older with a MCI diagnosis consistent with Petersen criteria Age NR Sex NR Education NR MMSE, Mean (SD) 27 (1)	Cognitive training (computer-based exercises targeting memory, executive function, attention, and processing speed) and Resistance Training -100 minutes 2 days/week for 6 months	Cognitive training (computer-based exercises targeting memory, executive function, attention, and processing speed) -100 minutes 2 days/week for 6 months	6 months 18 months	Multidomain Neuropsychological Performance [ADAS COG] Multidomain Neuropsychological Performance [Global Cognition Domain Composite] Executive, Attention, Processing Speed [WAIS III-Similarities] Executive, Attention, Processing Speed [WAIS III-Matrices] Language [Category Fluency (Animal Naming)] Language, Executive, Attention, Processing Speed [COWAT] Executive, Attention, Processing Speed [Executive Function Domain Composite] Memory [List learning Memory Sum from ADAS-COG] Memory [BVRT] Memory [Logical Memory, Immediate] Memory [Logical Memory, Delayed] Memory [Memory Domain Composite]

Study Design Country RoB	N=	Population 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]
						Executive, Attention, Processing Speed [SDMT]
Fiatarone Singh 2014[14] RCT Australia High	49	Adults age 55 and older with a MCI diagnosis consistent with Petersen criteria Age NR Sex NR Education NR MMSE, Mean (SD) 27 (1)	Cognitive training (computer-based exercises targeting memory, executive function, attention, and processing speed) and Resistance Training -100 minutes 2 days/week for 6 months	Resistance Training - 100 minutes 2 days/week for 6 months	6 months 18 months	Multidomain Neuropsychological Performance [ADAS COG] Multidomain Neuropsychological Performance [Global Cognition Domain Composite] Executive, Attention, Processing Speed [WAIS III-Similarities] Executive, Attention, Processing Speed [WAIS III-Matrices] Language [Category Fluency (Animal Naming)] Language, Executive, Attention, Processing Speed [COWAT] Executive, Attention, Processing Speed [Executive Function Domain Composite] Memory [List learning Memory Sum from ADAS-COG] Memory [BVRT] Memory [Logical Memory, Immediate] Memory [Logical Memory, Delayed] Memory [Memory Domain Composite] Executive, Attention, Processing Speed [SDMT]

ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive Subscale; CDR=Change in Dementia Rating; COWAT=Controlled Oral Word Association Test; CVFT=; MCI=Mild Cognitive Impairment; MMSE= Mini Mental Status Exam; NR=not reported; RCT=Randomized Controlled Trial; SD=Standard Deviation; SDMT=Symbol Digit Modalities Test; WAIS=Wechsler Adult Intelligence Scale

Appendix Table J8. Summary Risk of Bias Assessments: Multimodal interventions in adults with MCI

Study	Overall Risk of Bias Assessment	Rationale
Lam 2015[16]	High	Attrition rate is higher than 21% with no analysis to address potential bias.
Fiatarone Singh 2014[14]	High	Suspected reporting bias. Results for intervention arms are combined in the analysis,
Johari 2014[15]	High	Process for randomization not described, potential detection bias, and potential performance bias due to concurrent intervention.

References for Appendix J

1. Napoli N, Shah K, Waters DL, et al. Effect of weight loss, exercise, or both on cognition and quality of life in obese older adults. Am J Clin Nutr. 2014 Jul;100(1):189-98. doi: 10.3945/ajcn.113.082883. PMID: 24787497.

2. Martin CK, Anton SD, Han H, et al. Examination of cognitive function during six months of calorie restriction: results of a randomized controlled trial. Rejuvenation Res. 2007 Jun;10(2):179-90. doi: 10.1089/rej.2006.0502. PMID: 17518698.

3. Hars M, Herrmann FR, Gold G, et al. Effect of music-based multitask training on cognition and mood in older adults. Age Ageing. 2014 Mar;43(2):196-200. doi: 10.1093/ageing/aft163. PMID: 24212920.

4. Tesky VA, Thiel C, Banzer W, et al. Effects of a Group Program to Increase Cognitive Performance Through Cognitively Stimulating Leisure Activities in Healthy Older Subjects. GeroPsych. 2011 01 Jun;24(2):83-92. doi: 10.1024/1662-9647/a000035. PMID: 2011313185.

5. Carlson MC, Saczynski JS, Rebok GW, et al. Exploring the effects of an "everyday" activity program on executive function and memory in older adults: Experience Corps. Gerontologist. 2008 Dec;48(6):793-801. PMID: 19139252.

6. Ngandu T, Lehtisalo J, Solomon A, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. Lancet. 2015 Jun 6;385(9984):2255-63. doi: 10.1016/S0140-6736(15)60461-5. PMID: 25771249.

7. van de Rest O, van der Zwaluw NL, Tieland M, et al. Effect of resistance-type exercise training with or without protein supplementation on cognitive functioning in frail and pre-frail elderly: secondary analysis of a randomized, double-blind, placebo-controlled trial. Mech Ageing Dev. 2014 Mar-Apr;136-137:85-93. doi: 10.1016/j.mad.2013.12.005. PMID: 24374288.

8. Clare L, Nelis SM, Jones IR, et al. The Agewell trial: a pilot randomised controlled trial of a behaviour change intervention to promote healthy ageing and reduce risk of dementia in later life. BMC Psychiatry. 2015;15:25. doi: 10.1186/s12888-015-0402-4. PMID: 25880911.

9. Clark F, Jackson J, Carlson M, et al. Effectiveness of a lifestyle intervention in promoting the well-being of independently living older people: results of the Well Elderly 2 Randomised Controlled Trial. J Epidemiol Community Health. 2012 Sep;66(9):782-90. doi: 10.1136/jech.2009.099754. PMID: 21636614.

10. Lee KS, Lee Y, Back JH, et al. Effects of a multidomain lifestyle modification on cognitive function in older adults: an eighteen-month community-based cluster randomized controlled trial. Psychother Psychosom. 2014;83(5):270-8. doi: 10.1159/000360820. PMID: 25116574.

11. Yesavage JA, Friedman L, Ashford JW, et al. Acetylcholinesterase inhibitor in combination with cognitive training in older adults. J Gerontol B Psychol Sci Soc Sci. 2008 Sep;63(5):P288-94. PMID: 18818443.

12. Eggenberger P, Schumacher V, Angst M, et al. Does multicomponent physical exercise with simultaneous cognitive training boost cognitive performance in older adults? A 6-month randomized controlled trial with a 1-year follow-up. Clin Interv Aging. 2015 17 Aug;10:1335-49. doi: 10.2147/CIA.S87732. PMID: 26316729.

13. McDaniel MA, Binder EF, Bugg JM, et al. Effects of cognitive training with and without aerobic exercise on cognitively demanding everyday activities. Psychol Aging. 2014 Sep;29(3):717-30. doi: 10.1037/a0037363. PMID: 25244489.

14. Fiatarone Singh MA, Gates N, Saigal N, et al. The Study of Mental and Resistance Training (SMART) study-resistance training and/or cognitive training in mild cognitive impairment: a randomized, double-blind, double-sham controlled trial. J Am Med Dir Assoc. 2014 Dec;15(12):873-80. doi: 10.1016/j.jamda.2014.09.010. PMID: 25444575.

15. Johari SM, Shahar S, Ng TP, et al. A Preliminary Randomized Controlled Trial of Multifaceted Educational Intervention for Mild Cognitive Impairment Among Elderly Malays in Kuala Lumpur. International Journal of Gerontology. 2014 Jun;8(2):74-80. doi: 10.1016/j.ijge.2013.07.002. PMID: WOS:000339088200006.

16. Lam LC, Chan WC, Leung T, et al. Would older adults with mild cognitive impairment adhere to and benefit from a structured lifestyle activity intervention to enhance cognition?: a cluster randomized controlled trial. PLoS One. 2015 31 Mar;10(3):e0118173. doi: 10.1371/journal.pone.0118173. PMID: 25826620.

Appendix K. Hormone Interventions

Appendix Table K1. Characteristics of eligible studies: hormone interventions vs. inactive controls in adults with normal cognition

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]
Hormone replacement therapies (HRT)						
HRT-Estrogen						
Rasgon 2014 [1] RCT USA High	64	Postmenopausal women aged 49-69 years at risk of developing dementia Mean age (SD): 58 (5) years Race: NR Mean education (SD): 16 (2) years Baseline cog: NR	Continued estrogen-based hormone therapy (17 beta-estradiol or conjugated equine estrogen) for 2 years after an average of 10 years of use	Discontinuation of estrogen therapy for 2 years after an average of 10 years of use	2 years	Biomarkers [PET scan to assess changes on regional cerebral metabolism]
{Espeland 2013; Espeland 2010; Espeland 2004; Coker 2009; Resnick 2009; Resnick 2009; Shumaker 2004; (Women's Health Initiative sub-	2947	Community dwelling postmenopausal women aged 65-80 years, free of probable dementia at enrollment 45% aged 65-69 37% aged 70-74 18% aged 75+ 100% female 85% White Education 31% ≤ high school	Estrogen (conjugated equine estrogen 0.625 mg) daily	Placebo daily	Varied 5.7 – 8+ years	Diagnosis [Incidence of Probable Dementia] [Incidence of MCI] Biomarkers [MRI: Total Brain Volume] [MRI: Ventricle Volume] [MRI: Hippocampal Volume] [MRI: Frontal Lobe Volume] [MRI: White and Gray Matter (outside of basal ganglia)] [MRI: Basal Ganglia] [MRI: Total Brain Lesion Volume] Screening [3MS] [TICS] Executive/Attention/Processing Speed [Digit Span Forward] [Digit Span Backward] [Oral Trail Making Test Part A] [Oral Trail Making Test Part B] Memory [Benton Visual Retention Test]

studies) Medium		42% > some college 27% ≥ college Mean 3MSE (SD): 94.6 (4.8)				[California Verbal Learning Test] [East Boston Memory Test] Language [Primary Mental Abilities-Verbal] [Verbal Fluency] Visuospatial [Card Rotations Test] Motor [Finger Tapping, Dominant Hand] [Finger Tapping, Non-Dominant Hand]
Gorenstein 2011 [2] RCT Brazil Medium	65	Healthy, postmenopausal hysterectomized women aged 40-59 years Mean age: 26.5 100% female Race not reported Mean education (SD): 9.1 (4) years Baseline cog: NR	Estrogen (conjugated equine estrogens 0.625 mg/day) for 6 months	Placebo for 6 months	6 months	Executive/Attention/Processing Speed [Digit Span Forward] [Digit Span Backward [DSST] [3-min Reasoning Test, Correct] [3-min Reasoning Test, Time] Memory [Paired Associate Learning Test, Easy] [Paired Associate Learning Test, Difficult] [Immediate Verbal Recall] [Delayed Verbal Recall] [Free Recall of Words]
HRT-estrogen + progestin						
{Espeland 2013; Espeland 2010; Espeland 2004; Coker 2009; Resnick 2009; Shumaker 2004; Shumaker 2003} RCT (Women's Health Initiative – Memory Study and Study of Cognitive Aging) USA Medium	4532	Community dwelling postmenopausal women aged 65-80 years, free of probable dementia at enrollment 45% aged 65-69 37% aged 70-74 18% aged 75+ 100% female 85% White Education 31% ≤ high school 42% > some college 27% ≥ college Mean 3MSE (SD): 94.7 (4.5)	Estrogen (conjugated equine estrogen 0.625 mg) daily with progestin (medroxyprogesterone acetate 2.5 mg) daily	Placebo daily	Average 7 years	Diagnosis [Incidence of Probable Dementia] [Incidence of MCI] Biomarkers [MRI: Total Brain Volume] [MRI: Ventricle Volume] [MRI: Hippocampal Volume] [MRI: Frontal Lobe Volume] [MRI: White and Gray Matter (outside of basal ganglia)] [MRI: Basal Ganglia] [MRI: Total Brain Lesion Volume] Screening [3MS] [TICS] Executive/Attention/Processing Speed [Digit Span Forward] [Digit Span Backward] [Oral Trail Making Test Part A] [Oral Trail Making Test Part B] Memory [Benton Visual Retention Test] [California Verbal Learning Test] [East Boston Memory Test] Language [Primary Mental Abilities-Verbal] [Verbal Fluency] Visuospatial [Card Rotations Test] Motor [Finger Tapping, Dominant Hand] [Finger Tapping, Non-Dominant Hand]
Davison 2013 [3] RCT	23	Healthy postmenopausal	Estrogen (oral estradiol + progestin (drospirenone)	Placebo for 6 months	6 months	Executive/Attention/Processing Speed [Groton Maze Learning Task] [CogState

Australia Medium	13 (MRI)	women aged 49-55 years] Mean age: 53 100% women Race: NR Race: NR Baseline global cog: NR	for 6 months			Identification] [CogState Detection Speed] [Mental Rotation] Memory [Groton Maze Recall] [CogState International Shopping List, Learn] [CogState International Shopping List, Recall] [CogState Continued Paired Associate Learning] Visuospatial [Mental Rotation]
Alhola 2010 [4] RCT Finland High	32	Premenopausal (aged 45-51 years) and postmenopausal (aged 58-70 years) women Mean age pre-menop (SD): 48 (1.5) Mean age post-menop (SD): 63 (2.5) 100% female Race NR Mean education (years): 15 years Mean MMSE (SD): 27 (1.5)	Estrogen + progestin daily for 6 months	Placebo daily for 6 months	6 months	Executive/Attention/Processing speed [Verbal Functions, Similarities] [Digit Span] [Counting] [Digit Symbol] [CogniSpeed, SRT] [CogniSpeed, 2-CRT] [CogniSpeed, 10-CRT] [CogniSpeed, Subtraction] [CogniSpeed, Verification] [CogniSpeed, Vigilance] [Stroop Congruence] [Stroop Incongruence] [PASAT, Easy, Correct] [PASAT, Easy, Correct Consecutive] [PASAT, Difficult, Correct] [PASAT, Difficult, Correct Consecutive] [Shared Attention Dual Task Efficiency, Cancellation] [Shared Attention Dual Efficiency, Counting] [Shared Attention Dual Task Smaller Percentage, Efficiency] Memory [RAVLT, Trial 1] [RAVLT, Trial 2] [RAVLT, Trial 3] [RAVLT, Immediate Recall] [RAVLT, Delayed Recall] [Benton Visual Retention, Immediate Recall] [Benton Visual Retention, Delayed Recall] Visuospatial [Block Design] [Cancellation]
Maki 2009 [5] RCT USA High	66	Midlife women aged 61-87 years with ≥ 35 weekly hot flashes Mean age (SD): 53 (4.5) years 100% female 45% White Education: NR Baseline cog: NR	Estrogen + progestin (0.625 mg conjugated equine estrogen + 2.5 mg medroxyprogesterone acetate) for 1 year	Placebo for 1 year	1 year	Executive/Attention/Processing Speed [Digit Span Forward] [Digit Span Backward] [Brief Test of Attention] [Finding As Test] Memory [CVLT, Total Learning] [CVLT, Short-Delay Free Recall] [CVLT, Long-Delay Free Recall] [Logical Memory Subtest-WMS – Immediate Total Score] [Logical Memory Subtest-WMS – Delayed Total Score] [BVRT] Language [Letter Fluency Test] Visuospatial [Modified Card Rotations Test]
Tierney 2009 [6] RCT Canada Medium	142	Older postmenopausal women with normal to mildly impaired memory functioning (**about 28% had**	Estrogen + progestin (1 mg 17-B estradiol daily and 0.35 mg norethindrone 3 days/week) for 2 years	Placebo daily for 2 years	2 years	Memory [CVLT, Short Delay Recall]

		MCI at baseline) Mean age (SD)75 (6) years 100% female 90% White Education mean (SD): 13 (3) years) Mean MMSE (SD): 28 (1.5)				
HRT-DHEA						
Kritz-Silverstein 2008 [7] USA RCT Medium	225	Healthy men and women aged 55 to 85 years Mean age (SD): 68 (8) years 53% female Race: NR Mean education (SD): 16 (2.4) years Median 3MS (IQR): 96 (5)	Oral dehydroepiandrosterone (DHEA) supplementation 50 mg/day for 1 year	Placebo daily for 1 year	1 year	Screening [MMSE] Executive/Attention/Processing Speed [Trails B] Memory [Word List] [Word List Recall] Language [Verbal Fluency] [Boston Naming]
HRT-Testosterone						
Vaughn 2007 [8] RCT USA High	69	Men aged 65 to 83 years without evidence of cognitive impairment and baseline testosterone levels below 350 ng/dL Mean age: NR 0% female Race: NR Education: NR Baseline cognition: mean NR but all participants had baseline MMSE scores ≥ 28	Testosterone enanthate 200 mg intramuscularly every 2 weeks or testosterone enanthate 200 mg intramuscularly every 2 weeks plus finasteride 5 mg/day orally	Placebo (sesame oil injections) plus placebo pill daily	3 years	Executive/Attention/Processing Speed [Digit Span Forward] [Digit Span Backward][Trails A] [Trails B] Memory [Benton Visual Retention Test # Correct] [Benton Visual Retention Test [# Errors] [Selective Reminding Test, Total Recall] [Selective Reminding Test, Long-Term Storage] [Selective Reminding Test, Consistent Long-Term Retrieval] [Selective Reminding Test, Delayed Recall] [Selective Reminding Test, # of Intrusions] Visuospatial [Judgment of Line Orientation]
Kenny 2002 [9] RCT USA	67	Men aged 65-87 years with low biotesterone levels	Testosterone (transdermal testosterone patch 2-2.5 mg daily)	Placebo patch	1 year	Executive/Attention/Processing Speed [Digit Span] [Digit Symbol] [Trailmaking A] [Trailmaking B]

High		Mean age (SD): 75.5 (4.5) years 0% female Race: NR 65% ≥ college Baseline global cog: NR				
Selective estrogen receptor modulator (SERM)						
Yaffe 2005 [10] RCT USA Medium	5386	Postmenopausal women with osteoporosis Mean age (SD): 68 (7) years 100% female 95% white Mean education (SD): 12 (4) years Baseline global cognition: NR	Raloxifene 60 mg or 120 mg daily for 3 years	Oral placebo daily	3 years	Diagnosis [MCI] [Alzheimer's Disease] [Any Type of Dementia] [Dementia or MCI]
Nickelsen 1998 [11] RCT USA Medium	143	Postmenopausal women aged 45-75 years with osteoporosis Mean age: 68 years 100% female Race: NR Education: NR Baseline global cog: NR	Raloxifene 60 mg or 120 mg daily for 1 year	Placebo for 1 year	1 year	Executive/Attention/Processing Speed [Walter Reed Performance Assessment Battery (PAB) 2-Letter Search] [Walter Reed PAB: 6-Letter Search] [Walter Reed PAB: 4-Choice Serial Reaction Time] Memory [MAC Battery: Name-Face Association, Total Acquisition] [MAC Battery: Name-Face Association, Delayed Recall] [MAC Battery: First-Last Name Association, Delayed Recall] [MAC Battery: First-Last Name Association, Total Acquisition] [MAC Battery: Facial Recognition, Number Before 1st Error] [Telephone Number Recall, Before Interference] [Telephone Number Recall, After Interference]
Soy						

Henderson 2012 [12] RCT USA Low	350	Healthy postmenopausal women aged 45-92 years Mean age (SD): 61 (7) years 100% female 63% White 60% college graduate Baseline global cognition: NR	Soy (isoflavone rich soy protein 25 g) daily for 2.5 years	Milk protein-matched placebo for 2.5 years	2.5 years	Multidomain Composite [Cognitive Composite, (components not described] Executive/Attention/Processing Speed [Executive/Expressive/Visuospatial Factor Composite: Symbol Digit Modalities Test, TMT B, Shipley Abstraction, Letter-Number Sequencing, Block Design, Judgment of Line Orientation, Category Fluency, Boston Naming Test] [Symbol Digit Modalities Test] [TMT B] [Shipley Abstraction] [Letter-Number Sequencing] Memory [Verbal Episodic Memory, List Learning Factor: CVLT Immediate & Delayed Recall] [CVLT, Immediate Recall] [CVLT, Delayed Recall] [Visual Episodic Memory Factor: East Boston Memory Test, Immediate & Delayed Recall] [East Boston Memory Test, Immediate Recall] [East Boston Memory Test, Delayed Recall] [Visual Episodic Memory Factor: Faces I and II] [Faces I] [Faces II] Language [Category Fluency] [Boston Naming Test] Visuospatial [Block Design] [Judgment Of Line Orientation]
Gleason 2009 [13] RCT USA Medium	30	Older women aged 62-89 years without dementia Mean age (SD): 74 (7) years 100% female Race: NR Mean education (SD): 16.5 (3) years Mean MMSE (SD): 29 (1)	Soy isoflavonea 100 mg/d for 6 months	Matching placebo tablets for 6 months	6 months	Executive/Attention/Processing Speed [Stroop Color Word Test] [Trail Making Test B] [Mazes] [Language Fluency, Letter (Also in Language]] Memory [Buschke Selective Reminding Test] [Buschke Selective Reminding Test, Total of Learning Trials – Words] [Buschke Selective Reminding Test, Learning Slope, Trial 5 vs. Trial 1] [Delayed Recall, Words] [Paragraph Recall Test, Total Immediate Recall] [Paragraph Recall Test, Total Delayed Recall] [Rey Complex Figure Test, Immediate Recall] [Rey Complex Figure Test, Delayed Recall] [Visual Spatial Learning Test, Total Correction Positions + Designs] [Visual Spatial Learning Test, Learning Slope Position + Design, Trial 5 Vs. Trial 1] [Visual Spatial Learning Test, Learning Slope Incorrect Designs] Language [Boston Naming] [Language

						Fluency, Letter] [Language Fluency, Category] Visuospatial [Rey Complex Figure Test] [Grooved Pegboard
Ho 2007 [14] RCT China Medium	191	Generally healthy community-dwelling women aged 55-76 years Mean age (SD): 65 (6) years 100% female Race: NR 30% secondary education 17% postsecondary education Mean MMSE (SD): 28 (1.9)	Soy (soy-derived isoflavones 80 mg) daily for 6 months	Identical appearing placebo daily for 6 months	6 months	Screening [MMSE] Multidomain Composite [Composite Cognitive Score, including all cognitive test scores] Executive/Attention/Processing Speed [Color Trail I] [Color Trail II] [Digit Symbol – WAIS] Memory [Hong Kong List Learning Test (HKLLT), Trials 1-5] [HKLLT, Short Delay Recall] [HKLLT, Long Delay Recall] [Visual Reproduction I] [Visual Reproduction II] [Visual Reproduction, Copy] Language [Boston Naming Test] [Verbal Fluency, Categories] Motor [Finger Tapping, Right] [Finger Tapping, Left]
Kritz-Silverstein 2003 [15] RCT USA Low	56	Women aged 55 to 74 years in good health, postmenopausal at least 2 years and not using estrogen therapy Mean age (SD): 60 (5) years 100% female 86% White Mean education (SD): 15 (2.5) years Mean MMSE (SD): 29 (1.2)	Soy (soy-extracted isoflavones (110 mg) daily for 6 months	Identical appearing placebo daily for 6 months	6 months	Executive/Attention/Processing Speed [Trails A] [Trails B] Memory [Logical Memory I, Immediate] [Logical Memory II, Delayed] Language [Category Fluency]

3MSE=Modified Mini Mental Status Examination; CRT=; CVLT=California Verbal Learning Test; DSST=Digit Symbol Substitution Test; MCI=Mild Cognitive Impairment; MMSE= Mini Mental Status Exam; MRI=Magnetic resonance imaging; NR=; PASAT=; PET=positron emission tomography; RAVLT=Rey's Auditory Verbal Learning Test; RCT=Randomized Controlled Trial; SD=Standard Deviation; TICS=Telephone Interview Cognitive Status; TMT=Trails Making Test (B); WAIS=Wechsler Adult Intelligence Scale

Appendix Table K2. Summary risk of bias assessments: hormone interventions vs. inactive controls in adults with normal cognition

Study	Overall Risk of Bias Assessment	Rationale
HRT-estrogen efficacy		
Rasgon 2014 [1]	High	Unclear randomization procedures; 30% attrition without correction to account for possible bias
Coker 2009[16] Espeland 2004 {Espeland 2004} Shumaker 2004 [17] Resnick 2009 {Resnick, 2009 Resnick 2009 {Resnick 2009}	Medium	Medium attrition and detection bias
Gorenstein 2011 [2]	Medium	Medium attrition
Espeland 2010 [18]	High	Participants from 2 dissimilar studies combined for analysis; original studies already included in review
HRT-estrogen + progestin efficacy		
Espeland 2013 [19] Espeland 2004 [17] Shumaker 2004 [17] Shumaker 2003 (Shumaker 2003} Resnick 2009 [20] Resnick 2009 [20]	Medium	Attrition
Davison 2013 [3]	Medium	Attrition (19%); possible detection bias
Alhola 2010 [4]	High	Attrition (>25%) from original randomization
Maki 2009 [5]	High	High attrition without appropriate analysis
Tierney 2009 [6]	Medium	Performance bias
HRT-testerone efficacy		
Kenny 2002 [9]	High	Randomization not well described; high attrition (34%)
DHEA efficacy		
Kritz-Silverstein 2008 [7]	Medium	Medium selection and attrition biases
SERM efficacy		
Yaffe 2014 [21]	Medium	Randomization poorly described; medium selection and attrition
Nickelsen 1998 [11]	Medium	High attrition
Soy efficacy		
Henderson 2012 [12]	Low	
Gleason 2009 [13]	Medium	Randomization not well described; medium attrition; possible detection bias
Ho 2007 [14]	Medium	Medium detection bias
Kritz-Silverstein 2003 [15]	Low	

Appendix Table K3. Characteristics of eligible studies: hormone interventions vs. active controls in adults with normal cognition

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]
HRT-estrogen + progestin vs. tibolone						
Pan 2003 [22] RCT Taiwan Medium	50	Healthy postmenopausal women Mean age (SD): 52 (4) years 100% female Race: NR Mean MMSE (SD): 26.6 (2.3)	Estrogen + progestin (conjugated equine estrogen 0.625 mg/day + metheylprogresterone acetate 5 mg/day) for 6 months	Tibolone 2.5 mg/day for 6 months	6 months	Screening [MMSE] [Cognitive Abilities Screening Instrument]
HRT-Estrogen + testosterone vs. estrogen						
Moller 2013 [23] Moller 2010 [24] RCT crossover Sweden Medium	50	Women aged 45-60 years with surgically-induced menopause Mean age (SD): 54 (2.9) years 100% female Race: NR Baseline global cognition: NR	Estrogen + testosterone (estradiol valerate 2 mg/day + testosterone undecanoate 40 mg/day) for 6 months	Estrogen (estradiol valerate 2 mg/day) plus placebo	6 months	Executive/Attention/Processing Speed [Digit Symbol – WAIS, used To assess "cognitive fatigue," = difference between the # of digits produced during the first 30 seconds and last 30 seconds of a 90 second session] [Digit Symbol, Free Recall Of Words] [Digit Symbol, Paired Recall Of Symbols] [Digit Symbol, % Spatial Errors] Memory [Logical Story, Immediate Recall] [Logical Story, Delayed Recall]
SERM Tamoxifen vs. Raloxifene						
Legault 2009 [25] RCT USA High	1498	Healthy postmenopausal women aged 65+ with increased risk	Tamixofen 20 mg/d daily for up to 5 years	Raloxifene 60 mg daily for up to 5 years	Up to 5 years	Screening [3MS] Executive/attention/processing speed [Digits Forward] [Digits Backward] Memory [Benton Visual Retention Test]

		of breast cancer, without dementia Mean age (SD): 70 (4.2) years 100% female 94% White 34% some college 34% college graduate 67% 3MSE ≤ 95 23% 3MSE 90-94 10% 3MSE < 90				[California Verbal Learning Test] Language [Primary Mental Abilities-Verbal] [Verbal Fluency, Letter] [Verbal Fluency, Semantic] Visuospatial [Card Rotations] Motor [Finger Tapping]
SERM/HRT - Tamoxifen or Raloxifene vs. CEE						
Espeland 2010[18] RCT USA High	6461 (WHI & Co-STAR trial participants)	Women aged 65-80 years who participated in the WHI or CoSTAR trials Age, years (approx.) 65-59: 51% 70-74: 34% 75+: 15% 100% female % white: 90% Education: 7% < high school 25% high school graduate 38% some college 30% college grad Baseline 3MS (SD): 95 (4.25)	Congugated equine estrogen 0.625 with or without medroxyprogesterone for at least 3 years	Tamoxifen (20 mg/d) or raloxifene (60 mg/d) for at least 3 years (There were also Placebo arms in both trials included in the analysis)	Mean follow-up: 4.6 years (range 1-8) years	Screening [3MS]

3MS=Modified Mini Mental Status; BVRT=Benton Visual Retention Test; CVLT=California Verbal Learning Test; MMSE= Mini Mental Status Exam; NR=not reported; RCT=Randomized Controlled Trial; SD=Standard Deviation; WAIS=Wechsler Adult Intelligence Scale

Appendix Table K4. Summary risk of bias assessments: hormone interventions vs. active controls in adults with normal cognition

HRT-estrogen vs. estrogen + progestin		
Pan 2003 [22]	Medium	20% attrition without analysis to correct for potential bias
HRT-estrogen vs. estrogen + testosterone		
Moller 2010 [24] Moller 2013 [23]	Medium	Attrition 12% without analysis to correct for possible bias
SERM Tamoxifen vs. Raloxifene		
Legault 2009 [25]	High	High attrition
Raloxifene vs. CEE		
Espeland 2010 [18]	High	Considerable variation in study populations included in analysis

Appendix Table K5. Strength of evidence assessments: hormone therapies in adults with normal cognition

Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Direct-ness	Precision	Consistency	Reporting Bias	Optional Compo-nents	SOE
HRT-estrogen									
Dementia	1 (2947)	1 of 2 tests show statistically significant differences between groups (favoring placebo) (p=0.04) Shumaker 2004 Probable Dementia: Not significant HR: 1.49 [0.83, 2.66] Probable Dementia or Mild Cognitive Impairment: C>I HR: 1.38 [1.01, 1.89]	Medium	Direct	Precise	Unknown	Undetected	NA	Low
MCI	NR	Shumaker 2004 MCI: Not significant HR: 1.34 [0.95, 1.89]	Medium	Direct	Precise	Unknown	Undetected	NA	Low
Screening	1 (2947)	1 of 1 test favors C Espeland 2004 Mean difference in change from baseline 3MSE scores, estrogen group minus placebo (p=0.04): Mean (95% CI): -0.26 (-0.52 to 0)	Medium	Indirect	Precise	Unknown	Undetected	NA	Low
Multidomain Composite	NR								
Executive/ Attention/ Processing Speed	2 (585)	1 of 8 tests favor I	Medium	Indirect	Imprecise	Consistent	Undetected	NA	Insufficient
Memory	2 (585)	1 of 10 tests favor I	Medium	Indirect	Imprecise	Consistent	Undetected	NA	Insufficient

Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Direct-ness	Precision	Consistency	Reporting Bias	Optional Compo-nents	SOE
HRT-estrogen + progestin									
Dementia	1 (4532)	1 of 2 tests show statistically significant differences between groups <u>Shumaker 2003</u> Probable Dementia: C>I HR: 2.05 [1.21, 3.48] Probable Dementia or MCI: NS HR: 1.37 [0.99, 1.89]	Medium	Direct	Precise	Unknown	Undetected	NA	Low
MCI	1 (4532)	No statistically significant differences between groups MCI: NS HR: 1.07 [0.74, 1.55]	Medium	Direct	Precise	Unknown	Undetected	NA	Low
Screening	1 (4532)	No statistically significant difference between groups. <u>Espeland 2004</u> Mean difference in change from baseline 3MSE scores, estrogen group minus placebo: Mean (95% CI): -0.18 (-0.37 to 0)	Medium	Indirect	Precise	Unknown	Undetected	NA	Low
Multidomain Composite	NR								

Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Direct-ness	Precision	Consistency	Reporting Bias	Optional Compo-nents	SOE
Executive/ Attention/ Processing Speed	2 (1439)	1 of 6 tests was statistically significant in favor of placebo	Medium	Indirect	Imprecise	Consistent	Undetected	NA	Low
Memory	4 (1613)	4 of 25 tests favor C (16%) 1 of 25 favors I (4%)	Medium	Indirect	Imprecise	Consistent	Undetected	NA	Low
SERM									
Dementia	1 (5386)	Yaffe 2005 Relative risk of cognitive impairment, SERM (60 & 120 mg doses) vs. placebo (no significant results) Alzheimer's disease NS (either group) RR (60 mg): 0.82 [0.39, 1.71] RR (120 mg): 0.52 [0.22, 1.21] Any type of dementia NS (either group) RR (60 mg): 0.90 [0.47, 1.74] RR (120 mg): 0.91 [0.47, 1.76] Dementia or MCI NS (either group) RR (60 mg): 1.12 [0.84, 1.49] RR (120 mg): 0.73 [0.53, 1.01]	Medium	Direct	Precise	Unknown	Undetected	NA	Low
MCI	1 (5386)	Yaffe 2005 Relative risk of cognitive impairment,	Medium	Direct	Precise	Unknown	Undetected	NA	Low/ insufficient

Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Direct-ness	Precision	Consistency	Reporting Bias	Optional Compo-nents	SOE
		SERM (60 & 120 mg doses) vs. placebo MCI: Significant (p=0.04) at 120 mg dose; not significant at 60 mg I>C (lower risk in SERM group) RR (60 mg): 1.18 [0.85, 1.64] RR (120 mg): 0.67 [0.46, 0.98]							
Screening	NR								
Multidomain Composite	2 (541)	0 of 2 (no differences)	Medium	Indirect	Imprecise	Consistent	Undetected	NA	Insufficient
Executive function/attention/ processing speed	NR								
Memory	NR								
Soy									
Dementia	NR								
MCI	NR								
Screening	Insuf-ficient study size								Insufficient
Multidomain Composite	2 (541)	0 of 3 (no differences)	Medium	Indirect	Imprecise	Consistent	Undetected	NA	Insufficient
Executive/ Attention/ Processing Speed	4 (631)	2 of 14 tests favor C	Medium	Indirect	Insufficient	Consistent	Undetected	NA	Low

Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Direct-ness	Precision	Consistency	Reporting Bias	Optional Compo-nents	SOE
Memory	4 (631)	5 of 27 tests favor I 1 of 27 tests favors C	Medium	Indirect	Insufficient	Consistent	Undetected	NA	Low
Adverse Effects									

HR=; MCI=mild cognitive impairment; NR=not repoted; NS=; RR=

Appendix Table K6. Characteristics of eligible studies: hormone interventions vs. inactive controls in adults with MCI

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]
HRT-testosterone						
Cherrier 2010 [28] RCT USA Medium	22	Men aged 60-90 years with both MCI and low serum testosterone levels Mean age (SD): 70.5 (8) years 0% female Race NR Education NR Mean 3MSE (SD) 92.5 (6.7)	Testosterone gel 50-100 mg/d with a target total T level of 500 to 900 ng/dL	Placebo gel daily for 6 months	6 months	Executive/Attention/Processing Speed [Letter-Number Sequencing, Total Score] [Letter-Number Sequencing, Span] [Computerized Simple Reaction Time, 2=Second Interval] [Computerized Simple Reaction Time, 5-Second Interval] [Computerized Choice Reaction Time, 2-Second Interval] [Computerized Choice Reaction Time, 5-Second Interval] [Mental Rotation] Memory [RAVLT, Immediate] [RAVLT, Short Delay] [RAVLT, Long Delay] [Story Recall, Immediate] [Story Recall, Delay] [Visual Spatial Learning Test, Immediate] [Visual Spatial Learning Test, Delay] Language [Verbal Fluency] Visuospatial [Route Test, Immediate] [Route Test, Delay] [Complex Design Construction]
Soy						
Kato-Kataoka 2010 [29] RCT Japan Medium	78	Peopled aged 50-69 years with MCI Mean age (SD): 60 (1) years 48% female Japanese Mean education (SD): 14 (0.4) years Mean MMSE (SD) 27.8 (0.4)	Soybean derived phosphatidylerine (Soy-PS) 100 mg or 300 mg daily for 6 months	Placebo for 6 months	6 months	Screening [MMSE] [Hasegawa Dementia Scale] Memory [Rivermead Behavioral Memory Test]

MCI=Mild Cognitive Impairment; NR=not reported; RAVLT=Rey's Auditory Verbal Learning Test; RCT=Randomized Controlled Trial; SD=Standard Deviation

Appendix K Table K6. Summary risk of bias assessments: hormone interventions vs. inactive controls in adults with MCI

HRT-testosterone		
Cherrier 2015 [28]	Medium	
Soy		
Kato-Kataoka 2010 [29]	Medium	

References for Appendix K

1. Rasgon NL, Geist CL, Kenna HA, et al. Prospective randomized trial to assess effects of continuing hormone therapy on cerebral function in postmenopausal women at risk for dementia. PLoS One. 2014;9(3):e89095. doi: 10.1371/journal.pone.0089095. PMID: 24622517.

2. Gorenstein C, Renno J, Jr., Vieira Filho AH, et al. Estrogen replacement therapy and cognitive functions in healthy postmenopausal women: a randomized trial. Arch Womens Ment Health. 2011 Oct;14(5):367-73. doi: 10.1007/s00737-011-0230-6. PMID: 21732218.

3. Davison SL, Bell RJ, Robinson PJ, et al. Continuous-combined oral estradiol/drospirenone has no detrimental effect on cognitive performance and improves estrogen deficiency symptoms in early postmenopausal women: a randomized placebo-controlled trial. Menopause. 2013 Oct;20(10):1020-6. doi: 10.1097/GME.0b013e318287474f. PMID: 23591255.

4. Alhola P, Tuomisto H, Saarinen R, et al. Estrogen + progestin therapy and cognition: a randomized placebo-controlled double-blind study. J Obstet Gynaecol Res. 2010 Aug;36(4):796-802. doi: 10.1111/j.1447-0756.2010.01214.x. PMID: 20666948.

5. Espeland MA, Shumaker SA, Limacher M, et al. Relative effects of tamoxifen, raloxifene, and conjugated equine estrogens on cognition. J Womens Health (Larchmt). 2010 Mar;19(3):371-9. doi: 10.1089/jwh.2009.1605. PMID: 20136553.

6. Tierney MC, Oh P, Moineddin R, et al. A randomized double-blind trial of the effects of hormone therapy on delayed verbal recall in older women. Psychoneuroendocrinology. 2009 Aug;34(7):1065-74. doi: 10.1016/j.psyneuen.2009.02.009. PMID: 19297102.

7. Kritz-Silverstein D, von Muhlen D, Laughlin GA, et al. Effects of dehydroepiandrosterone supplementation on cognitive function and quality of life: the DHEA and Well-Ness (DAWN) Trial. J Am Geriatr Soc. 2008 Jul;56(7):1292-8. doi: 10.1111/j.1532-5415.2008.01768.x. PMID: 18482290.

8. Vaughan C, Goldstein FC, Tenover JL. Exogenous testosterone alone or with finasteride does not improve measurements of cognition in healthy older men with low serum testosterone. J Androl. 2007 Nov-Dec;28(6):875-82. doi: 10.2164/jandrol.107.002931. PMID: 17609296.

9. Kenny AM, Bellantonio S, Gruman CA, et al. Effects of transdermal testosterone on cognitive function and health perception in older men with low bioavailable testosterone levels. J Gerontol A Biol Sci Med Sci. 2002 May;57(5):M321-5. PMID: 11983727.

10. Yaffe K, Krueger K, Cummings SR, et al. Effect of raloxifene on prevention of dementia and cognitive impairment in older women: the Multiple Outcomes of Raloxifene Evaluation (MORE) randomized trial. Am J Psychiatry. 2005 Apr;162(4):683-90. doi: 10.1176/appi.ajp.162.4.683. PMID: 15800139.

11. Nickelsen T, Lufkin EG, Riggs BL, et al. Raloxifene hydrochloride, a selective estrogen receptor modulator: safety assessment of effects on cognitive function and mood in

postmenopausal women. Psychoneuroendocrinology. 1999 Jan;24(1):115-28. PMID: 10098223.

12. Henderson VW, St John JA, Hodis HN, et al. Long-term soy isoflavone supplementation and cognition in women: a randomized, controlled trial. Neurology. 2012 Jun 5;78(23):1841-8. doi: 10.1212/WNL.0b013e318258f822. PMID: 22665144.

13. Gleason CE, Carlsson CM, Barnet JH, et al. A preliminary study of the safety, feasibility and cognitive efficacy of soy isoflavone supplements in older men and women. Age Ageing. 2009 Jan;38(1):86-93. doi: 10.1093/ageing/afn227. PMID: 19054783.

14. Adapt Research Group. Results of a follow-up study to the randomized Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT). Alzheimer's & Dementia. 2013 Nov;9(6):714-23. doi: http://dx.doi.org/10.1016/j.jalz.2012.11.012. PMID: 23562431.

15. Kritz-Silverstein D, Von Muhlen D, Barrett-Connor E, et al. Isoflavones and cognitive function in older women: the SOy and Postmenopausal Health In Aging (SOPHIA) Study. Menopause. 2003 May-Jun;10(3):196-202. PMID: 12792289.

16. Coker LH, Hogan PE, Bryan NR, et al. Postmenopausal hormone therapy and subclinical cerebrovascular disease: the WHIMS-MRI Study. Neurology. 2009 Jan 13;72(2):125-34. doi: 10.1212/01.wnl.0000339036.88842.9e. PMID: 19139363.

17. Espeland MA, Rapp SR, Shumaker SA, et al. Conjugated equine estrogens and global cognitive function in postmenopausal women: Women's Health Initiative Memory Study. JAMA. 2004 Jun 23;291(24):2959-68. doi: 10.1001/jama.291.24.2959. PMID: 15213207.

18. Espeland MA, Brunner RL, Hogan PE, et al. Long-term effects of conjugated equine estrogen therapies on domain-specific cognitive function: results from the Women's Health Initiative study of cognitive aging extension. J Am Geriatr Soc. 2010 Jul;58(7):1263-71. doi: 10.1111/j.1532-5415.2010.02953.x. PMID: 20649689.

19. Espeland MA, Shumaker SA, Leng I, et al. Long-term effects on cognitive function of postmenopausal hormone therapy prescribed to women aged 50 to 55 years. JAMA Intern Med. 2013 Aug 12;173(15):1429-36. doi: 10.1001/jamainternmed.2013.7727. PMID: 23797469.

20. Beydoun MA, Beason-Held LL, Kitner-Triolo MH, et al. Statins and serum cholesterol's associations with incident dementia and mild cognitive impairment. J. Epidemiol. Community Health. 2011 2011/11;65(11):949-57. doi: 10.1136/jech.2009.100826.

21. Cukierman-Yaffe T, Bosch J, Diaz R, et al. Effects of basal insulin glargine and omega-3 fatty acid on cognitive decline and probable cognitive impairment in people with dysglycaemia: a substudy of the ORIGIN trial. Lancet Diabetes Endocrinol. 2014 Jul;2(7):562-72. doi: 10.1016/S2213-8587(14)70062-2. PMID: 24898834.

22. Pan HA, Wang ST, Pai MC, et al. Cognitive function variations in postmenopausal women treated with continuous, combined HRT or tibolone. A comparison. J Reprod Med. 2003 May;48(5):375-80. PMID: 12815913.

23. Moller MC, Radestad AF, von Schoultz B, et al. Effect of estrogen and testosterone replacement therapy on cognitive fatigue. Gynecol Endocrinol. 2013 Feb;29(2):173-6. doi: 10.3109/09513590.2012.730568. PMID: 23095007.

24. Moller MC, Bartfai AB, Radestad AF. Effects of testosterone and estrogen replacement on memory function. Menopause. 2010 Sep-Oct;17(5):983-9. doi: 10.1097/gme.0b013e3181dc2e40. PMID: 20555288.

25. Legault C, Maki PM, Resnick SM, et al. Effects of tamoxifen and raloxifene on memory and other cognitive abilities: cognition in the study of tamoxifen and raloxifene. J Clin Oncol. 2009 Nov 1;27(31):5144-52. doi: 10.1200/JCO.2008.21.0716. PMID: 19770382.

26. Shumaker SA, Legault C, Kuller L, et al. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. JAMA. 2004 Jun 23;291(24):2947-58. doi: 10.1001/jama.291.24.2947. PMID: 15213206.

27. Shumaker SA, Legault C, Rapp SR, et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. JAMA. 2003 May 28;289(20):2651-62. doi: 10.1001/jama.289.20.2651. PMID: 12771112.

28. Cherrier MM, Anderson K, Shofer J, et al. Testosterone treatment of men with mild cognitive impairment and low testosterone levels. Am J Alzheimers Dis Other Demen. 2015 Jun;30(4):421-30. doi: 10.1177/1533317514556874. PMID: 25392187.

29. Kato-Kataoka A, Sakai M, Ebina R, et al. Soybean-derived phosphatidylserine improves memory function of the elderly Japanese subjects with memory complaints. J Clin Biochem Nutr. 2010 Nov;47(3):246-55. doi: 10.3164/jcbn.10-62. PMID: 21103034.

Appendix L. Vitamin Interventions

Appendix Table L1. Characteristics of eligible studies: vitamins in adults with normal cognition

Study Design Country RoB	N=	Population Inclusion Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Duration	Comparison	Outcome timing	Outcome Domain [Instrument]
Multivitamins						
Chew 2015[1] Age-related Eye Disease Study 2 RCT USA High	3501	Adults at risk for developing late age-related macular degeneration Age 73 Female 58% White 97% Black 1% Asian <1% American Indian <1% Native Hawaiian or Pacific Islander <1% Other <1% Education ≤ High school 29% ≥ Some college 49% Postgrad 22% Baseline cognition: TICS 33	Vitamin C (500 mg) Vitamin E (400 IU) Beta carotene (15 mg) Zinc (80 or 25 mg) daily for 5 years	No beta carotene or no zinc	5 years	Brief Cognitive Test Performance [TICS-m] Multidomain Neuropsychological Performance [composite of all cognitive tests included in battery plus Delayed recall of the WMS-III Recall paragraph] Executive/attention/processing [Animal Category, Letter Fluency, Alternating Fluency, Digits Backward] Memory [WMS-III Logical Memory Part I and II, Recall paragraph] Language [Animal Category, Letter Fluency, Alternating Fluency]
Grodstein 2013[2] Physicians' Health Study II RCT USA Medium: followup 1 and 3 High: followup 3	5947	Substudy of Physicians' Health Initiative recruited men physicians without serious disease aged 65+ 65-74 72% 75-84 26%	Multivitamin (Centrum Silver) daily for approximately 13 years	Placebo	8.5 years (mean)	Brief Cognitive Test Performance [TICS] Multidomain Neuropsychological Performance [Composite z-score (TICS, EBMT, TICS 10-word list delayed recall, and category fluency)] Memory [Composite z-score (TICS and EBMT immediate and delayed word recall)]

Study **Design** **Country** **RoB**	**N=**	**Population** **Inclusion** **Age (mean)** **Sex (% female)** **Race (% White)** **Education (mean years)** **Baseline Cognition**	**Intervention** **Duration**	**Comparison**	**Outcome timing**	**Outcome** **Domain [Instrument]**
and 4 (time in years NR)		85+ 2% Female 0% Race NR Education 100% medical school Baseline cognition TICS 34				Language [Category fluency]
Kesse-Guyot 2011[3] Supplementation in Vitamins and Mineral Antioxidants 2011 RCT France High	4447	Healthy adults aged 45-60 Age 52 Female 48% Race NR Education: Primary 21% Secondary 40% University 39% Baseline cognition NR	Vitamin C (120 mg) Vitamin E (30 mg) Beta carotene (6 mg) Selenium (100 µg) Zinc (20 mg) daily for 6 years	Placebo	6 years	Executive/attention/processing speed [Trail Making Test, digit span forwards & backwards] Memory [RI-48] Language [verbal fluency, semantic fluency, phonetic fluency]
McNeill 2007[4] Mineral and Vitamin Intervention Study RCT Scotland Low-medium	910	Aged 65+ and not taken vitamins, minerals or fish oil in prior 3 months Age 72 Female 48% Race NR Education: 7 years Baseline cognition NR	Supplement containing 11 vitamins & 5 minerals: Vitamin A (800 µg) Vitamin B_{12} (1 µg) Folic acid (200 µg) Vitamin C (60 mg) Vitamin D (5 µg) Vitamin E (10 mg) Thiamin (1.4 mg) Riboflavin (1.6 mg) Niacin (18 mg) Pantothenic acid (6 mg) Pyridoxine (2 mg) Iron (14 mg) Iodine (150 µg) Copper (0.75 mg)	Placebo	1 year	Executive/attention/processing speed [digit span forwards] Language [verbal fluency test]

Study Design Country RoB	**N=**	**Population Inclusion Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition**	**Intervention Duration**	**Comparison**	**Outcome timing**	**Outcome Domain [Instrument]**
			Zinc (15 mg) Manganese (1 mg) daily for 1 year			
Wolters 2005[5] RCT Germany Low-medium	220	Healthy women aged 60+ not taking vitamins in prior 2 months Age 63 Female 100% Race NR Education: No secondary school 35% Grammar school 43% High school grad 22% Baseline cognition NR	Vitamin C (150 mg) Vitamin E (36 mg) Beta carotene (9 mg) Magnesium (50 mg) Niacin (34 mg) Pantothenic acid (16 mg) Riboflavin (3.2 mg) Thiamine (2.4 mg) Folic acid (400 µg) Biotin (200 µg) Selenium (60 µg) Cobalamin (9 µg) daily for 6 months	Placebo	6 months	Executive/attention/processing speed [WAIS-III symbol search subtest, Kurztest fuer Allgemeine Intelligenz] Memory [Berliner Amnesie Test]
Heart Protection Study 2002 RCT UK Medium	20,536	Aged 40-80 with substantial risk of death from coronary heart disease in next 5 years. Some were concurrently taking simvastatin, which was the primary study drug. Age 70+: 28% Female 25% Race NR Education NR Baseline cognition NR	Vitamin E (600 mg) Vitamin C (250 mg) Beta carotene (20 mg) daily for 5 years	Placebo	5 Years	Diagnosis [dementia, MCI] Brief Cognitive Test Performance [TICS-m]

Study Design Country RoB	**N=**	**Population Inclusion Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition**	**Intervention Duration**	**Comparison**	**Outcome timing**	**Outcome Domain [Instrument]**
Smith 1999[6] RCT UK High	110	Healthy adults aged 60-80 and with MMSE 18+ Age 67 Female 54% Race NR Education NR Baseline cognition NR	Vitamin C (500 mg) Vitamin E (400 mg) Beta carotene (2 mg) daily for 1 year	Placebo	1 year	Executive/attention/processing speed [Logical Reasoning Task, Simple Reaction Time Task, Repeated-digits Vigilance Task, Focused Attention Task, Categoric Search Task] Memory [Free Recall Task, Delayed Recognition Memory Task]
Vitamin B						
van der Zwaluw 2014[7] B-vitamins for the Prevention of Osteoporotic Fractures RCT Netherlands Low-medium	2919	Aged 65+ with elevated homocysteine levels, able to make own decisions and compliant Age 74 Female 50% Race NR Education: Low 51% Medium 21% High 26% Baseline cognition: MMSE 28	Folic acid (400 mg) Vitamin B_{12} (500 mg) Daily for 2 years	Placebo	2 years	Brief Cognitive Test Performance [MMSE] Executive/Attention/processing speed [Composite: Attention and working memory (Digit span forwards & backwards), Composite: Information Processing Speed (Trails A, Stroop I & II), Composite: Executive functioning (Trails B, Stroop Interference, Verbal fluency), Digit span forwards & backwards, Trails A & B, Stroop I & II and Interference, Symbol digit modalities] Memory [Composite: Episodic memory (RAVLT immediate recall, decay, recognition), RAVLT immediate recall, decay, recognition] Language [Verbal Fluency Test]
Walker 2012[8] RCT Australia Low-medium	900	Age 60-74 with elevated psychological distress, did not exercise or take vitamins	Folic acid (400 µg) Vitamin B_{12} (100 µg) Daily for 2 years	Placebo	2 years	Brief Cognitive Test Performance [TICS-m] Executive/attention/processing speed [TICS-m orientation/calculation & attention] Memory [TICS-m immediate & delayed recall

Study Design Country RoB	**N=**	**Population Inclusion Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition**	**Intervention Duration**	**Comparison**	**Outcome timing**	**Outcome Domain [Instrument]**
		Age 66 Female 60% Race NR Education 14 years Baseline cognition: TICS-m 27				and semantic memory]
Andreeva 2011[9] Supplementation with Folate, vitamins B_6 and B_{12} and/or Omega-3 fatty acids RCT France Low	1248	Age 45-70 with heart disease Age 61 Female 58% Race NR Education: Less than high school diploma 37% Baseline cognition: Isaac set test: 35.8	Folate (0.56 mg) Vitamin B_6 (3 mg) Vitamin B_{12} (0.02 mg) Daily for 4 years	Placebo	4 years	Brief Cognitive Test Performance [TICS-m French version] Memory [TICS-m memory & recall]
Brady 2009[10] VA HOST RCT USA High	659	Veterans aged 21+ with advanced chronic kidney disease Age 64 Female 2% White 49% Black 37% Hispanic 11% Other 3% Education NR Baseline cognition: TICS 32	Folic acid (40 mg) Vitamin B_6 (100 mg) Vitamin B_{12} (2 mg) Daily for 6 years	Placebo	1 year	Brief Cognitive Test Performance [TICS]
McMahon 2006[11] RCT New Zealand Low-medium	276	Age 65+ with healthy cognition Age 74 Female 44% Race NR	Folate (1000 µg) Vitamin B_{12} (500 µg) Vitamin B_6 (10 mg) Daily for 2 years	Placebo	2 years	Brief Cognitive Test Performance [MMSE] Executive/attention/processing speed [Raven's Progressive Matrices, Trails B]

Study Design Country RoB	N=	Population Inclusion Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Duration	Comparison	Outcome timing	Outcome Domain [Instrument]
		Education: <3 years secondary 35% ≧3 years secondary 11% Tertiary 54% Baseline cognition: MMSE 29				Memory [RAVLT, paragraph recall (WMS)] Language [Category word Fluency, National Adult Reading Test, Controlled Oral Word Association Test of the Multilingual Aphasia Examination]
Vitamin E						
Kang 2009[12] The Women's Antioxidant and Cardiovascular Study RCT USA Low-medium: followup 1-3 High: followup 4 (exact time in years NR)	2824	Women aged 40+ with CVD or 3+ coronary risk factors who are part of the larger RCT; this sub-study included women aged 65+ Age 69 Female 100% Race NR Education: Technical nursing degree 70% Bachelor's or higher 30% Baseline cognition NR	Vitamin E (402 mg) Every other day for 9 years	Placebo	5.4 years (4 follow up calls)	Brief Cognitive Test Performance [TICS] Multidomain Neuropsychological Performance [Composite (TICS, TICS 10 word list delayed, East Boston Memory Test immediate & delayed, category fluency test)] Memory [Composite (TICS 10 word list delayed, East Boston Memory Test immediate & delayed)] Language [Category Fluency test]
Kang 2006[13] Women's Health Study RCT USA Low-medium	6377	Women age 65+ Age 72 Female 100% Race NR Technical nursing degree 68% Bachelor's or higher	Vitamin E (600 IU) Every other day for 10 years	Placebo	4 years	Brief Cognitive Test Performance [TICS] Multidomain Neuropsychological Performance [Composite (TICS, TICS 10 word list delayed, East Boston Memory Test immediate & delayed, category fluency test)]

Study Design Country RoB	N=	Population Inclusion Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Duration	Comparison	Outcome timing	Outcome Domain [Instrument]
		32% Baseline cognition: TICS 34				Memory [Composite (TICS 10 word list delayed, East Boston Memory Test immediate & delayed)] Language [Category Fluency test]
Vitamin C						
Kang 2009[12] The Women's Antioxidant and Cardiovascular Study RCT USA Low-medium: followup 1-3 High: followup 4 (exact time in years NR)	2824	Women aged 40+ with CVD or 3+ coronary risk factors who are part of the larger RCT; this sub-study included women aged 65+ Age 69 Female 100% Race NR Education: Technical nursing degree 70% Bachelor's or higher 30% Baseline cognition NR	Vitamin C (500 mg) Daily for 9 years	Placebo	5.4 years (4 follow up calls)	Brief Cognitive Test Performance [TICS] Multidomain Neuropsychological Performance [Composite (TICS, TICS 10 word list delayed, East Boston Memory Test immediate & delayed, category fluency test)] Memory [Composite (TICS 10 word list delayed, East Boston Memory Test immediate & delayed)] Language [Category Fluency test]
Vitamin D + Calcium						
Rossom 2012[14] Women's Health Initiative Calcium and Vitamin D Trial RCT USA	4143	Participants in the Women's Health Initiative Memory Study Age 71 Female 100% Race:	Calcium carbonate (1000 mg) Vitamin D_3 (400 IU) Daily for 8 years Optional use of calcium (1000 mg)	Placebo	7.8 years (mean)	Diagnosis [probable dementia or MCI] Brief Cognitive Test Performance [MMSE-m] Executive/attention/processing speed [digit span forwards & backwards]

Study Design Country RoB	N=	Population Inclusion Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Duration	Comparison	Outcome timing	Outcome Domain [Instrument]
Low-medium: 7 years High: 8 years		White 88% Black 6% Hispanic 3% Asian 2% Native American 1% Education: <High school 7% High school grad 22% >High school 40% College grad 31% Baseline cognition: MMSE-m 95	Vitamin D (600 mg)			Memory [California Verbal Learning Test, Benton Visual Retention Test] Language [letter & category fluency, primary abilities vocabulary] Motor [finger tapping] Visuospatial [card rotations]
Beta carotene						
Kang 2009[12] The Women's Antioxidant and Cardiovascular Study RCT USA Low-medium: followup 1-3 High: followup 4 (exact time in years NR)	2824	Women aged 40+ with CVD or 3+ coronary risk factors who are part of the larger RCT; this sub-study included women aged 65+ Age 69 Female 100% Race NR Education: Technical nursing degree 70% Bachelor's or higher 30% Baseline cognition NR	Beta carotene (50 mg) Every other day for 9 years	Placebo	5.4 years (4 follow up calls)	Brief Cognitive Test Performance [TICS] Multidomain Neuropsychological Performance [Composite (TICS, TICS 10 word list delayed, East Boston Memory Test immediate & delayed, category fluency test)] Memory [Composite (TICS 10 word list delayed, East Boston Memory Test immediate & delayed)] Language [Category Fluency test]

µg=micrograms; IU=internal units; mg=milligrams; CVD=; EBMT=; MCI=mild cognitive impairment; MMSE=Mini Mental Status Exam; NR=not reported; RAVLT=Rey's Auditory Verbal Learning; RCT=Randomized Controlled Trial; RI=; TICS=Telephone Interview Cognitive Status; WMS=Wechsler Memory Scale

Appendix Table L2. Characteristics of eligible studies: vitamins vs. active control in adults with normal cognition

Study Design Country RoB	N=	Population Inclusion Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Duration	Comparison	Outcome timing	Outcome Domain [Instrument]
Vitamin B + omega-3 vs. omega-3						
Andreeva 2011[9] Supplementation with FOLate, vitamins B_6 and B_{12} and/or Omega-3 fatty acids RCT France Low	1259	Age 45-70 with heart disease Age 61 Female 58% Race NR Education: Less than high school diploma 37% Baseline cognition: Isaac set test: 35.8	Folate (0.56 mg) Vitamin B_6 (3 mg) Vitamin B_{12} (0.02 mg) Daily for 4 years	Eicosapentaenoic acid/docosahexanoic acid (600 mg)	4 years	Brief Cognitive Test Performance [TICS-m French version] Memory [TICS-m memory & recall]
Andreeva 2011[9] Supplementation with FOLate, vitamins B_6 and B_{12} and/or Omega-3 fatty acids RCT France Low	1246	Age 45-70 with heart disease Age 61 Female 58% Race NR Education: Less than high school diploma 37% Baseline cognition: Isaac set test: 35.8	Folate (0.56 mg) Vitamin B_6 (3 mg) Vitamin B_{12} (0.02 mg) Daily for 4 years Taken with omega-3 Eicosapentaenoic acid/docosahexanoic acid (600 mg) Daily for 4 years	Eicosapentaenoic acid/docosahexanoic acid (600 mg)	4 years	Brief Cognitive Test Performance [TICS-m French version] Memory [TICS-m memory & recall]
Vitamin E + statin vs. placebo						
Carlsson 2002[15] RCT - crossover USA Medium	41	Adults aged 70+ with high cholesterol Age 76 Female 68% Race NR Education NR Baseline cognition	Vitamin E (400 IU) Pravastatin (20 mg) Daily for 6 months	Vitamin E alone (400 IU) for 6 months	1 year	Executive/attention/processing speed [digit symbol coding]

		NR				

µg=micrograms; IU=internal units; mg=milligrams; NR=not reported; RCT=randomized controlled trial; TICS=Telephone Interview for Cognitive Status

Appendix Table L3. Summary risk of bias assessments: vitamins in adults with normal cognition

Study	Overall Risk of Bias Assessment	Rationale
Multivitamins		
Chew 2015[1]	High	Randomization methods unclear, reported attrition (19%) conflicting with related publication, concurrent intervention not controlled for.
Grodstein 2013[2]	Medium at followup 2 High at followup 3+	Randomization and blinding methods adequate, attrition 11% at second followup (medium), 31% at third followup (high) and 60% and final followup (high) with no missing data imputation, independent outcome assessor unclear.
Kesse-Guyot 2006[3]	High	Randomization unclear, attrition 35% with no missing data imputation.
McNeill 2007[4]	Low-medium	Randomization and blinding methods adequate, attrition unclear but likely 15%, ITT, all outcomes reported.
Wolters 2005[5]	Low-medium	Randomization and blinding methods unclear, comparable outcome assessment timing between groups, blinding likely adequate, concurrent interventions unclear.
Heart Protection Study 2002[16, 17]	Medium	Randomization methods adequate, attrition unclear but used survival analyses, outcome assessor blinding and independence unclear, ITT.
Smith 1999[6]	High	Randomization methods unclear, attrition not reported, blinding methods adequate, ITT not reported.
Vitamin B		
van der Zwaluw 2014[18, 19]	Low-medium	Randomization methods adequate, attrition 24% with no missing data imputation, outcome assessor not independent, all outcomes reported.
Walker 2012[8]	Low-medium	Randomization methods adequate, blinding unclear, attrition 16% at two year followup and no missing data imputation, outcome assessor independence unclear.
Andreeva 2011[9]	Low-medium	Adequate randomization and blinding, low attrition in this followup study, ITT.
Brady 2009[10]	High	Attrition 25-27% and no missing data imputation.

Study	Overall Risk of Bias Assessment	Rationale
McMahon 2006[11]	Low-medium	Randomization and blinding methods adequate, outcome assessor independence unclear, ITT not reported.
Vitamin E		
Kang 2009[12]	Low-medium at followup 3 High at final followup	Attrition 12% at third followup (medium) and 20% by final followup (high), outcome assessment timing not comparable between groups, ITT unclear.
Kang 2006[13]	Low-medium	Randomization unclear, attrition 20% and no missing data imputation, outcome assessment timing unclear.
Carlsson 2002[15]	Medium	Randomization and blinding methods unclear, adequate outcome assessment tools, ITT.
Vitamin C		
Kang 2009[12]	Low-medium at followup 3 High at final followup	Attrition 12% at third followup (medium) and 20% by final followup (high), outcome assessment timing not comparable between groups, ITT unclear.
Vitamin D + Calcium		
Rossom 2012[14]	Low-medium at followup 7 High at followup 8	Randomization and blinding methods adequate, outcome assessor independent, ITT, all outcomes reported.
Beta carotene		
Kang 2009[12]	Low-medium at followup 3 High at final followup	Attrition 12% at third followup (medium) and 20% by final followup (high), outcome assessment timing not comparable between groups, ITT unclear.

Appendix Table L4. Strength of evidence assessments: vitamins in adults with normal cognition

Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
Multivitamin vs. placebo k=4; n=27,613									
Dementia	1 (20,536)	1 test showed no statistically significant improvement Heart Protection Study 2002[16, 17] Dementia diagnosis 0.3% vs 0.3%	Medium	Direct	Unclear	Unknown	Suspected	NA	Low
MCI	1 (20,536)	1 test showed no statistically significant improvement Heart Protection Study 2002[16, 17] MCI diagnosis 23.7% vs 24.2%	Medium	Direct	Unclear	Unknown	Suspected	NA	Low
Brief Cognitive Test Performance Grodstein 2013[2]: Followup 2 (time NR)	2 (26,483)	2 tests showed no statistically significant improvement Grodstein 2013[2] TICS, between groups difference from longitudinal models of mean cognitive performance 0.10 (-0.05 to 0.24) Heart Protection Study 2002[16, 17] TICS-m, between groups mean difference at followup (time NR) 0.02 (SE 0.07)	Medium	Indirect	Imprecise	Consistent	Suspected	NA	Insufficient
Multidomain Neuropsychological Performance	1 (5947)	1 test showed no statistically significant improvement	Medium	Indirect	Precise	Unknown	Undetected	NA	Low

Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
Grodstein 2013[2]: Followup 2 (time NR)		Grodstein 2013[2] Composite z-score, between groups difference from longitudinal models of mean cognitive performance -0.01 (-0.05 to 0.03)							
Executive/ Attention/ Processing Speed McNeill 2007[4]: 1 year Wolters 2005[5] 6 months	2 (1130)	3 tests showed no statistically significant improvement McNeill 2007[4] Digit span forwards, mean difference -0.1 (-0.3 to 0.2) Wolters 2005[5] Kurztest fuer Allgemeine Intelligenz, between groups change from baseline* -1 [NR] WAIS-III symbol search, between groups change from baseline* 0 [NR]	Low-medium	Indirect	Unclear	Consistent	Undetected	NA	Low
Memory Grodstein 2013[2]: Followup 2 (time NR) Wolters 2004: 6 months	2 (6167)	2 tests showed no statistically significant improvement Grodstein 2013[2] Composite z-score, between groups difference from longitudinal models of mean cognitive performance 0.00 (-0.05 to 0.04)	Medium	Indirect	Unclear	Consistent	Undetected	NA	Low

Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
		Wolters 2005[5] Berliner Amnesit Test, between groups change from baseline* -0.8 [NR]							
Adverse Effects		NR							
Vitamin B vs. placebo k=4; n=4,904									
Dementia		NR							
MCI		NR							
Brief Cognitive Test Performance van der Zwaluw 2014[18, 19]: 2 years Walker 2012[8]: 2 years Andreeva 2011[9]: 4 years McMahon 2006[11]: 2 years	4 (4904)	2 of 4 tests showed statistically significant improvement with intervention, but effect size not clinically meaningful van der Zwaluw 2014[18, 19] MMSE, between groups change from baseline* -0.4 [NR] p=0.05 Walker 2012[8] TICS-m total, time by intervention effect size 0.17 [NR] p=0.03 Andreeva 2011[9] TICS-m total (French), between groups difference at followup* -0.4 [NR] p>0.1 McMahon 2006[11] MMSE, adjusted	Low-medium	Indirect	Imprecise	Consistent	Suspected	NA	Low

Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
		between groups change from baseline -0.09 [-0.30 to 1.13] p=0.42							
Multidomain Neuropsychological Performance	NR								
Executive/ Attention/ Processing Speed	3 (4095)	1 of 13 tests showed statistically significant improvement with control, but effect size not clinically meaningful van der Zwaluw 2014[18, 19] Executive functioning composite, between groups change from baseline* 0.07 [NR] p>0.1 Attention/working memory composite, between groups change from baseline* -0.03 [NR] p>0.1 Information processing speed composite, between groups change from baseline* -0.01 [NR] p>0.1 Digit span forwards, between groups change from baseline* -0.1 [NR] p>0.1 Digit span backwards, between groups change from baseline* 0.0 [NR] p>0.1	Low-medium	Indirect	Unclear	Consistent	Suspected	NA	Low

Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
		Trails B/A, between groups change from baseline* 0.0 [NR] p>0.1 Stroop I&II, between groups change from baseline* 0.4 [NR] p>0.1 Stroop Interference, between groups change from baseline* -1.6 [NR] p>0.1 Symbol digit modalities, between groups change from baseline* -0.1 [NR] p>0.1 <u>Walker 2012[8]</u> TICS-m orientation/calculation NR; NS TICS-m attention NR; NS <u>McMahon 2006[11]</u> Trails B, adjusted between groups change from baseline 1.08 [1.02 to 1.14] p<0.01 Raven's Progressive Matrices, adjusted between groups change from baseline -0.31 [-0.81 to 0.19] p=0.22							
Memory	2 (2148)	2 of 11 tests showed statistically significant	Low-medium	Indirect	Unclear	Consistent	Suspected	NA	Low

Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
Walker 2012[8]: 2 years Andreeva 2011[9]: 4 years		improvement with intervention, but effect size not clinically meaningful Walker 2012[8] TICS-m immediate recall, time by intervention effect size 0.15 (p=0.05) TICS-m delayed recall, time by intervention effect size 0.18 (p=0.01) TICS-m semantic memory NR Andreeva 2011[9] TICS-m memory (French), between groups difference at followup* 0.0 [NR] p>0.1 TICS-m recall (French), between groups difference at followup* -0.1 [NR] p>0.1 McMahon 2006[11] RAVLT, adjusted between groups change from baseline -0.35 [-0.85 to 0.14] p=0.16 WMS paragraph recall, adjusted between groups change from baseline -0.88 [-1.98 to 0.21]							

Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
		p=0.12							
Adverse Effects		NR							
Vitamin E vs. placebo k=2; n=9,201									
Dementia		NR							
MCI		NR							
Brief Cognitive Test Performance Kang 2009[12]: Followup 3 (~4 years) Kang 2006: 4 years	2 (9201)	2 tests showed no statistically significant improvement Kang 2009[12] TICS, between groups change from baseline -0.08 [-0.37 to 0.21] p=0.61 Kang 2006[13] TICS, between groups change from baseline 0.04 [-0.12 to 0.21]	Low-medium	Indirect	Precise	Consistent	Suspected	NA	Moderate
Multidomain Neuropsychological Performance	2 (9201)	2 tests showed no statistically significant improvement Kang 2009[12] Composite, between groups change from baseline z-score -0.02 [-0.09 to 0.05] p=0.55 Kang 2006[13] Composite, between groups change from baseline z-score 0.00 [-0.04 to 0.04]	Low-medium	Indirect	Precise	Consistent	Suspected	NA	Moderate
Executive/ Attention/ Processing Speed		NR							
Memory	2 (9201)	2 tests showed no	Low-medium	Indirect	Precise	Consistent	Suspected	NA	Moderate

Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
		statistically significant improvement Kang 2009[12] Composite, between groups change from baseline z-score -0.01 [-0.08 to 0.06] p=0.61 Kang 2009[12] Composite, between groups change from baseline z-score 0.01 [-0.03 to 0.05]							
Adverse Effects	1 (2824)	Kang 2009[12] None	Low-medium	Direct	Unclear	Unknown	Suspected	NA	Insufficient
Vitamin C vs. placebo k=1; n=2,824									
Dementia		NR							
MCI		NR							
Brief Cognitive Test Performance ~4 years	1 (2824)	1 test showed no statistically significant improvement TICS, between groups change from baseline 0.15 [-0.14 to 0.44] p=0.31	Low-medium	Indirect	Imprecise	Unknown	Suspected	NA	Low
Multidomain Neuropsychological Performance	1 (2824)	1 test showed no statistically significant improvement Composite, between groups change from baseline z-score 0.05 [-0.01 to 0.12] p=0.1	Low-medium	Indirect	Imprecise	Unknown	Suspected	NA	Low
Executive/ Attention/ Processing Speed		NR							

Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
Memory	1 (2824)	1 test showed statistically significant improvement with vitamin C, but effect size was not clinically meaningful. Composite, between groups change from baseline z-score 0.07 [0.00 to 0.13] p=0.05	Low-medium	Indirect	Imprecise	Unknown	Suspected	NA	Low
Adverse Effects	1 (2824)	No adverse effects were reported, but no statistics were presented	Low-medium	Direct	Unclear	Unknown	Suspected	NA	Insufficient
Vitamin D + calcium vs. placebo k=1; n=4,143									
Dementia	1 (4,143)	1 test showed no statistically significant difference Incidence of probable dementia or MCI (pooled), hazard ratio 0.94 (0.72 to 1.24) p=0.68	Low-medium	Direct	Precise	Unknown	Suspected	NA	Low
MCI	1 (4,143)	See above							
Brief Cognitive Test Performance 7 years	1 (4,143)	1 test showed no statistically significant improvement MMSE-m, unadjusted between group change from baseline -0.05 (SE 0.17) p=0.77	Low-medium	Indirect	Imprecise	Unknown	Suspected	NA	Insufficient
Multidomain Neuropsychological Performance		NR							

Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
Executive/ Attention/ Processing Speed	1 (4,143)	1 test showed no statistically significant improvement Digit span forwards and backwards (pooled), adjusted standardized between groups change from baseline 0.02 (SE 0.04) p=0.46	Low-medium	Indirect	Precise	Unknown	Suspected	NA	Low
Memory	1 (4,143)	2 tests showed no statistically significant improvement California Verbal Learning Test, adjusted standardized between groups change from baseline -0.05 (SE 0.04) p=0.15 Benton Visual Retention Test, adjusted standardized between groups change from baseline -0.02 (SE 0.04) p=0.66	Low-medium	Indirect	Imprecise	Consistent	Suspected	NA	Low
Adverse Effects		NR							
Beta carotene vs. placebo k=1; n=2,824									
Dementia		NR							
MCI		NR							
Brief Cognitive Test Performance ~4 years	1 (2824)	1 test showed no statistically significant improvement TICS, between groups change from baseline 0.14 [-0.15 to 0.43]	Low-medium	Indirect	Imprecise	Unknown	Suspected	NA	Low

Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
		p=0.35							
Multidomain Neuropsychological Performance	1 (2824)	1 test showed no statistically significant improvement Composite, between groups change from baseline z-score 0.01 [-0.06 to 0.07] p=0.82	Low-medium	Indirect	Precise	Unknown	Suspected	NA	Low
Executive/ Attention/ Processing Speed		NR							
Memory	1 (2824)	1 test showed no statistically significant improvement Composite, between groups change from baseline z-score 0.02 [-0.04 to 0.09] p=0.50	Low-medium	Indirect	Precise	Unknown	Suspected	NA	Low
Adverse Effects	1 (2824)	No adverse effects were reported, but no statistics were presented	Low-medium	Direct	Unclear	Unknown	Suspected	NA	Insufficient

*calculated by EPC

MCI=mild cognitive impairment; MMSE= Mini Mental Status Exam; NR=not reported; RAVLT=Rey's Auditory Verbal Learning Test; TICS=Telephone Interview Cognitive Status; WAIS=Wechsler Adult Intelligence Scale

Appendix Table L5. Strength of evidence assessments: vitamins vs. active control in adults with normal cognition

Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
Vitamin B vs. omega-3 k=1; n=1,259									
Dementia	NR								
MCI	NR								
Brief Cognitive Test Performance 4 years	1 (1259)	1 test showed no statistically significant improvement with vitamin B over omega-3 TICS-m total (French), between groups difference at followup* -0.1 [NR] p>0.1	Low-medium	Indirect	Unclear	Unknown	Suspected	NA	Low
Multidomain Neuropsychological Performance	NR								
Executive/ Attention/ Processing Speed	NR								
Memory	1 (1259)	2 tests showed no statistically significant improvement with vitamin B over omega-3 TICS-m memory (French), between groups difference at followup* 0.0 [NR] p>0.1 TICS-m recall (French), between groups difference at followup* 0.0 [NR] p>0.1	Low-medium	Indirect	Unclear	Consistent	Suspected	NA	Low
Adverse Effects	NR								
Vitamin B + omega-3 vs.									

Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
omega-3 k=1; n=1246									
Dementia	NR								
MCI	NR								
Brief Cognitive Test Performance 4 years	1 (1246)	1 test showed no statistically significant improvement with vitamin B + omega-3 over omega-3 TICS-m total (French), between groups difference at followup* 0.1 [NR] p>0.1	Low-medium	Indirect	Unclear	Unknown	Suspected	NA	Low
Multidomain Neuropsychological Performance	NR								
Executive/ Attention/ Processing Speed	NR								
Memory	1 (1246)	2 tests showed no statistically significant improvement with vitamin B + omega-3 over omega-3 TICS-m memory (French), between groups difference at followup* -0.1 [NR] p>0.1 TICS-m recall (French), between groups difference at followup* 0.1 [NR] p>0.1	Low-medium	Indirect	Unclear	Consistent	Suspected	NA	Low
Adverse Effects	NR								
Vitamin E + statin vs. placebo k=1; n=41									
Dementia	NR								

Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
MCI	NR								
Brief Cognitive Test Performance	NR								
Multidomain Neuropsychological Performance	NR								
Executive/ Attention/ Processing Speed 6 months	1 (41)	1 test showed statistically significant changes between Vitamin E + pravastatin and placebo. Digit symbol coding, between groups difference at followup* 0.73 [NR] p>0.1	Medium	Indirect	Unclear	Unknown	Suspected	NA	Insufficient
Memory	NR								
Adverse Effects	NR								

MCI=mild cognitive impairment; NR=not reported; TICS=Telephone Interview Cognitive Status

Appendix Table L6. Characteristics of eligible studies: vitamins vs. inactive control in adults with MCI

Study Design Country RoB	N=	Population Inclusion Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Duration	Comparison	Outcome timing	Outcome Domain [Instrument]
Multivitamins						
Naeini 2014[20] RCT Iran Low-medium	256	Adults aged 60-75 with MCI (MMSE 21-26) Age 67 Female 53% Race NR Education: Primary 16% Secondary 11% Diploma 40% University degree 33% Baseline cognition: MMSE 24	Vitamin E (300 mg) Vitamin C (400 mg) Daily for 1 year	Placebo	1 year	Brief Cognitive Test Performance [MMSE]
Vitamin B						
Remington 2015[21] RCT USA High	34	Community-dwelling adults with MCI Age 66 Female NR Race NR Education: 15 years Baseline cognition NR	Folic acid (400 µg) Vitamin B_{12} (6 µg) Vitamin E (30 IU) SAM (400 mg) ALCAR (500 mg) NAC (600 mg) Two doses daily for 6 months	Placebo	6 months	Brief Cognitive Test Performance [Mattis Dementia Rating Scale] Visuospatial [Clock drawing test (CLOX-1)]
Smith 2010[22] deJager 2012[23] Duouad 2013[24] RCT UK Low-medium	266	Adults aged 70+ diagno-sed with MCI (Peterson's criteria) Age 77 Female 47% Race NR Mean years of education: 15 Baseline cognition: MMSE 28 TICS 25	Folic Acid (0.8 mg) Vitamin B_6 (20 mg) Vitamin B_{12} (0.5 mg) Daily for 2 years	Placebo	2 years	Biomarkers [posterior brain atrophy, rate of atrophy] Brief Cognitive Test Performance [MMSE] Memory [Hopkins Verbal Learning Test] Language [Category fluency test] Visuospatial [Clock drawing]

Study Design Country RoB	N=	Population Inclusion Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Duration	Comparison	Outcome timing	Outcome Domain [Instrument]
Vitamin E						
Petersen 2005[25] RCT USA Low-medium	516	Adults aged 55-90 with degenerative amnestic MCI Age 73 Female 47% Race NR Education NR Baseline cognition: MMSE 27	Vitamin E (2000 IU) Daily for 3 years (study included a donepezil arm)	Placebo	3 years	Diagnosis [possible or probable Alzheimer's disease, Clinical Dementia Rating sum of boxes (Alzheimer's disease)] Brief Cognitive Test Performance [MMSE] Multidomain Neuropsychological Performance [ADAS-Cog] Executive/attention/processing speed [From composite battery; presumed to be Symbol digit backwards, Symbol Digit modalities, number cancellation, maze tracing] Memory [From composite battery; presumed to be New York University paragraph recall test] Language [From composite battery; presumed to be Boston Naming Test, category fluency] Visuospatial [From composite battery; presumed to be clock drawing]

µg=micrograms; ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive Subscale; Clox-1= Clock drawing test; IU=internal units; MCI=mild cognitive impairment; mg=milligrams; MMSE= Mini Mental Status Exam; RCT=randomized controlled trial

Appendix Table L7. Summary risk of bias assessments: vitamins in adults with MCI

Study	Overall Risk of Bias Assessment	Rationale
Multivitamins		
Naeini 2014[20]	Low-medium	Randomization methods unclear, blinding methods adequate, attrition low, ITT not reported.
Vitamin B		
Remington 2015[21]	High	Randomization methods unclear, attrition 45% at 6 month followup with no missing data imputation.
Douaud 2013[24]	Low-medium	Randomization and blinding methods adequate, attrition low, all outcomes reported.
de Jager 2012[23]	Low-medium	Randomization methods adequate, attrition 16% for cognitive outcomes and no missing data imputation, blinding methods likely adequate, all outcomes reported.
Smith 2010[22]	Low-medium	Randomization and blinding methods adequate, attrition low for primary outcome and medium for secondary outcomes, ITT, comparable outcome assessment timing between groups.
Vitamin E		
Petersen 2005[25]	Low-medium	Randomization and blinding methods adequate, attrition 30% but performed appropriate sensitivity analyses, ITT.

Appendix Table L8. Strength of evidence assessments: vitamins vs. inactive control in adults with MCI

Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
Vitamin E vs. placebo k=1; n=516									
Dementia 3 years	1 (516)	2 tests showed no statistically significant decrease in diagnosis of Alzheimer's disease with vitamin E, Diagnosis, between groups probability of progression to Alzheimer's disease HR=1.02 [0.74 to 1.41] p=0.91 CDR sum of boxes, between groups change from baseline (z-score)* 0.03 [NR] p>0.1	Medium	Direct	Imprecise	Consistent	Undetected	NA	Low
Brief Cognitive Test Performance	1 (516)	1 test showed no statistically significant improvement with vitamin E MMSE, between groups change from baseline (z-score)* 0.55 [NR] p>0.1	Medium	Indirect	Imprecise	Unknown	Undetected	NA	Insufficient
Multidomain Neuropsychological Performance	1 (516)	1 test showed no statistically significant improvement with vitamin E ADAS-Cog, between groups change from baseline (z-score)* 0.85 [NR] p>0.1	Medium	Indirect	Imprecise	Unknown	Undetected	NA	Insufficient
Executive/ Attention/ Processing Speed	1 (516)	1 composite test showed no statistically significant	Medium	Indirect	Imprecise	Unknown	Undetected	NA	Insufficient

Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
		improvement with vitamin E Composite, between groups change from baseline (z-score)* 0.0 [NR] p>0.1							
Memory	1 (516)	1 composite test showed no statistically significant improvement with vitamin E Composite, between groups change from baseline (z-score)* -0.03 [NR] p>0.1	Medium	Indirect	Imprecise	Unknown	Undetected	NA	Insufficient
Adverse Effects	1 (516)	No significant difference between groups for withdrawals 28% vs. 25%* Relative risk* 1.10 [0.83 to 1.46] p=0.52	Medium	Direct	Imprecise	Unknown	Undetected	NA	Low

*calculated by EPC

ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive Subscale; MMSE= Mini Mental Status Exam; NR=not reported

References for Appendix L

1. Chew EY, Clemons TE, Agron E, et al. Effect of Omega-3 Fatty Acids, Lutein/Zeaxanthin, or Other Nutrient Supplementation on Cognitive Function: The AREDS2 Randomized Clinical Trial. JAMA. 2015 Aug 25;314(8):791-801. doi: 10.1001/jama.2015.9677. PMID: 26305649.

2. Grodstein F, O'Brien J, Kang JH, et al. Long-term multivitamin supplementation and cognitive function in men: a randomized trial. Ann Intern Med. 2013 Dec 17;159(12):806-14. doi: 10.7326/0003-4819-159-12-201312170-00006. PMID: 24490265.

3. Kesse-Guyot E, Fezeu L, Jeandel C, et al. French adults' cognitive performance after daily supplementation with antioxidant vitamins and minerals at nutritional doses: a post hoc analysis of the Supplementation in Vitamins and Mineral Antioxidants (SU.VI.MAX) trial. Am J Clin Nutr. 2011 Sep;94(3):892-9. doi: 10.3945/ajcn.110.007815. PMID: 21775560.

4. McNeill G, Avenell A, Campbell MK, et al. Effect of multivitamin and multimineral supplementation on cognitive function in men and women aged 65 years and over: a randomised controlled trial. Nutr J. 2007;6:10. doi: 10.1186/1475-2891-6-10. PMID: 17474991.

5. Wolters M, Hickstein M, Flintermann A, et al. Cognitive performance in relation to vitamin status in healthy elderly German women-the effect of 6-month multivitamin supplementation. Prev Med. 2005 Jul;41(1):253-9. doi: 10.1016/j.ypmed.2004.11.007. PMID: 15917019.

6. Smith A, Clark R, Nutt D, et al. Anti-oxidant vitamins and mental performance of the elderly. Human Psychopharmacology-Clinical and Experimental. 1999 Oct;14(7):459-71. doi: Doi 10.1002/(Sici)1099-1077(199910)14:7<459::Aid-Hup128>3.0.Co;2-0. PMID: WOS:000083485200003.

7. van de Rest O, van der Zwaluw NL, Tieland M, et al. Effect of resistance-type exercise training with or without protein supplementation on cognitive functioning in frail and pre-frail elderly: secondary analysis of a randomized, double-blind, placebo-controlled trial. Mech Ageing Dev. 2014 Mar-Apr;136-137:85-93. doi: 10.1016/j.mad.2013.12.005. PMID: 24374288.

8. Walker JG, Batterham PJ, Mackinnon AJ, et al. Oral folic acid and vitamin B-12 supplementation to prevent cognitive decline in community-dwelling older adults with depressive symptoms--the Beyond Ageing Project: a randomized controlled trial. Am J Clin Nutr. 2012 Jan;95(1):194-203. doi: 10.3945/ajcn.110.007799. PMID: 22170358.

9. Andreeva VA, Kesse-Guyot E, Barberger-Gateau P, et al. Cognitive function after supplementation with B vitamins and long-chain omega-3 fatty acids: ancillary

findings from the SU.FOL.OM3 randomized trial. Am J Clin Nutr. 2011 Jul;94(1):278-86. doi: 10.3945/ajcn.110.006320. PMID: 21593490.

10. Brady CB, Gaziano JM, Cxypoliski RA, et al. Homocysteine lowering and cognition in CKD: the Veterans Affairs homocysteine study. Am J Kidney Dis. 2009 Sep;54(3):440-9. doi: 10.1053/j.ajkd.2009.05.013. PMID: 19628319.

11. McMahon JA, Green TJ, Skeaff CM, et al. A controlled trial of homocysteine lowering and cognitive performance. N Engl J Med. 2006 Jun 29;354(26):2764-72. doi: 10.1056/NEJMoa054025. PMID: 16807413.

12. Kang JH, Cook NR, Manson JE, et al. Vitamin E, vitamin C, beta carotene, and cognitive function among women with or at risk of cardiovascular disease: The Women's Antioxidant and Cardiovascular Study. Circulation. 2009 Jun 2;119(21):2772-80. doi: 10.1161/CIRCULATIONAHA.108.816900. PMID: 19451353.

13. Kang JH, Cook N, Manson J, et al. A randomized trial of vitamin E supplementation and cognitive function in women. Arch Intern Med. 2006 Dec 11-25;166(22):2462-8. doi: 10.1001/archinte.166.22.2462. PMID: 17159011.

14. Rossom RC, Espeland MA, Manson JE, et al. Calcium and vitamin D supplementation and cognitive impairment in the women's health initiative. J Am Geriatr Soc. 2012 Dec;60(12):2197-205. doi: 10.1111/jgs.12032. PMID: 23176129.

15. Carlsson CM, Papcke-Benson K, Carnes M, et al. Health-related quality of life and long-term therapy with pravastatin and tocopherol (vitamin E) in older adults. Drugs Aging. 2002;19(10):793-805. PMID: 12390056.

16. Heart Protection Study Collaborative G. MRC/BHF Heart Protection Study of antioxidant vitamin supplementation in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet. 2002 Jul 6;360(9326):23-33. doi: 10.1016/S0140-6736(02)09328-5. PMID: 12114037.

17. Heart Protection Study Collaborative G. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet. 2002 Jul 6;360(9326):7-22. doi: 10.1016/S0140-6736(02)09327-3. PMID: 12114036.

18. van der Zwaluw NL, Dhonukshe-Rutten RA, van Wijngaarden JP, et al. Results of 2-year vitamin B treatment on cognitive performance: secondary data from an RCT. Neurology. 2014 Dec 2;83(23):2158-66. doi: 10.1212/WNL.0000000000001050. PMID: 25391305.

19. van der Zwaluw NL, van de Rest O, Tieland M, et al. The impact of protein supplementation on cognitive performance in frail elderly. Eur J Nutr. 2014 Apr;53(3):803-12. doi: 10.1007/s00394-013-0584-9. PMID: 24045855.

20. Naeini AM, Elmadfa I, Djazayery A, et al. The effect of antioxidant vitamins E and C on cognitive performance of the elderly with mild cognitive impairment in Isfahan, Iran: a double-blind, randomized, placebo-controlled trial. Eur J Nutr. 2014 Aug;53(5):1255-62. doi: 10.1007/s00394-013-0628-1. PMID: 24326981.

21. Remington R, Lortie JJ, Hoffmann H, et al. A Nutritional Formulation for Cognitive Performance in Mild Cognitive Impairment: A Placebo-Controlled Trial with an Open-Label Extension. J Alzheimers Dis. 2015 01 Oct;48(3):591-5. doi: 10.3233/JAD-150057. PMID: 26402075.

22. Smith AD, Smith SM, de Jager CA, et al. Homocysteine-lowering by B vitamins slows the rate of accelerated brain atrophy in mild cognitive impairment: a randomized controlled trial. PLoS One. 2010;5(9):e12244. doi: 10.1371/journal.pone.0012244. PMID: 20838622.

23. de Jager CA, Oulhaj A, Jacoby R, et al. Cognitive and clinical outcomes of homocysteine-lowering B-vitamin treatment in mild cognitive impairment: a randomized controlled trial. Int J Geriatr Psychiatry. 2012 Jun;27(6):592-600. doi: 10.1002/gps.2758. PMID: 21780182.

24. Douaud G, Refsum H, de Jager CA, et al. Preventing Alzheimer's disease-related gray matter atrophy by B-vitamin treatment. Proc Natl Acad Sci U S A. 2013 Jun 4;110(23):9523-8. doi: 10.1073/pnas.1301816110. PMID: 23690582.

25. Petersen RC, Thomas RG, Grundman M, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. N Engl J Med. 2005 Jun 9;352(23):2379-88. doi: 10.1056/NEJMoa050151. PMID: 15829527.

Appendix M. Antihypertension Treatment

Appendix Table M1. Characteristics of eligible studies: antihypertension interventions in adults with normal cognition

Study Design Country RoB	**N=**	**Population Inclusion Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cog**	**Intervention (INT) Mode Components Frequency Duration**	**Comparison Mode Components Frequency Duration**	**Outcome measurement timing**	**Outcome (Instrument)**
Efficacy						
ACE and *Thiazide* *k = 2*						
Peters 2008[1] (HYVET-COG) RCT Multinational Medium	3,845	Adults aged ≥80 years with an average sitting systolic blood pressure between 160 mmHg and 200 mmHg and an average standing systolic blood pressure ≥140 mmHg, and a sitting diastolic blood pressure of ≤110 mmHg. Normal cognition. Mean age (SD): 83.5 (3.1) 61% Female Race: NR 27% no education 28% primary education 29% secondary education 12% higher education 3% more than higher education Median MMSE (range): 26 (15 – 30)	Indapamide 1.5 mg with optional perindopril (2mg up to 4 mg)	Matching-placebo	2.2 years mean follow up	Diagnosis [committee-reported diagnosis of dementia] Global cognition Screening [MMSE, cognitive decline defined as MMSE <24 or a decline of >3 MMSE points in a year] Adverse events [number of events]
ADVANCE Collaborative Group 2007[2] RCT Multinational Low	11,140	Adults diagnosed with type 2 diabetes at the age ≥30 years, and were aged ≥55 years at study entry. Patients also need to have a history of cardiovascular disease or at risk for cardiovascular disease. Normal cognition.	Combined perindopril (2 mg up to 4 mg) and indapamide (0.625 mg up to 1.25 mg) and open label perindopril up to 4 mg	Matching-placebo and open label perindopril up to 4 mg.	4.3 yeas mean follow up	Diagnosis Global cognition Screening [MMSE] Adverse Events [number with serious drug reactions]

		Mean age (SD): 66 (7) 43% Female Race: NR Education: NR Median MMSE (range): NR				
ARB *k = 3*						
Anderson 2011[3] (TRANSCEND trial) RCT Multinational Medium	5926	Adults aged ≥55 years with evidence of coronary artery, peripheral vascular, or cerebrovascular disease or diabetes with end-organ damage, intolerance to ACE inhibitors, and normal cognition. Mean age (SD): 66.9 43% Female 61% European ethnic origin 62% ≥9 years of education Median MMSE (IRQ): 29 (27 – 30)	Telmisartan 80 mg daily	Placebo daily	56 months median follow up	Global Cognition Screening [cognitive decline - drop of 3 or more MMSE points]
Saxby 2008[4] (single center in SCOPE trial) RCT United Kingdom Medium	257	Hypertensive adults aged 70 to 89 years with systolic blood pressure of 160 to 179 mmHg and diastolic blood pressure of 90 to 99 mmHg and normal cognition. Mean age (SD): 76 (4) 54% Female Race: NR Mean years education (SD): 10 (2) Mean MMSE (SD): 29 (1)	Candesartan (8 mg – 16 mg) daily with hydrochlorothiazide 12.5 mg added as needed. When target blood pressure not achieved (<160/90 mmHg) other drugs added as needed.	Placebo daily and hydrochlorothiazide 12.5 mg added as needed. When target blood pressure not achieved (<160/90 mmHg) other drugs added as needed.	44 months mean follow up	Global Cognition Screening [MMSE] Executive/attention/processing speed [processing speed composite measure, attention composite measure, executive function composite measure][a] Memory [episodic memory composite measure, working memory composite measure][a]
Lithell 2003[5] Skoog 2005[6] (SCOPE trial) RCT Multinational Medium	4937	Hypertensive adults aged 70 to 89 years with systolic blood pressure of 160 to 179 mmHg and diastolic blood pressure of 90 to 99 mmHg and normal cognition with results stratified by low (MMSE 24 – 28) and high (29 – 30) cognitive function. Mean age (SD): 76 (NR) 64% female Race: NR	Candesartan (8mg – 16 mg) daily with hydrochlorothiazide 12.5 mg added as needed. When target blood pressure not achieved (<160/90 mmHg) other drugs added as needed.	Placebo daily and hydrochlorothiazide 12.5mg added as needed. When target blood pressure not achieved (<160/90 mmHg) other	44 months mean follow up	Diagnosis Global Cognition Screening [MMSE]

		10% less than primary school education 44% primary school education 40% more than primary school education 6% University education Mean MMSE (SD): 28.5 (NR)		drugs added as needed.		
Beta Blocker						
Perez-Stable 2000[7] RCT United States High	312	Adults aged 18 to 59 with diastolic blood pressure between 90 and 104 mmHg and normal cognition.	Propranolol (40 mg first three days then 80 mg daily as tolerated then increased up to 400 mg daily)	Placebo daily	12 months	Executive/attention/processing speed [[Stimulus Evaluation/Response Selection, Continuous Performance Task, Digit Symbol Substitution Task] Memory [California Verbal Learning Test]
Bird 1990[8, 9] RCT United Kingdom Medium	2401	Adults aged 65 to 74 with systolic blood pressure of 160 to 209 mmHg and diastolic blood pressure of <114 mmHg, and normal cognition. Mean age (SD): 70.3 (2.7) 58% Female Race: NR Education: NR Cognition: NR	Atenolol 50 mg daily	Placebo daily	9 months	Executive/attention/processing speed [Trail Making Test] Memory [Paired Associated Learning Test]
Combination therapy						
Forette 2002[10] (Syst-Eur trial 1 & 2) RCT and open-label follow up Multinational Medium	3228	Adults aged >60 years with systolic blood pressure of 160 to 219 mmHg and diastolic blood pressure <95 mmHg and normal cognition. Median age (range): 68 (60-92) Sex: NR Race: NR Mean age (SD) on leaving school: 16.7 (4.5) Cognition: NR	Antihypertensive stepwise therapy with titration with goal of lowering systolic blood pressure by 20 mmHg or below 150 mmHg (step 1: nitrendipine 10 -40 mg daily; step 2: enalapril 5 – 20 mg daily; step 3: hydrochlorothiazide 12.5 – 25 mg daily)	Placebo daily (in open-label phase offered active treatment)	3.9 years median follow up	Diagnosis Global Cognition Screening [MMSE]
Forette 1998[11] (Syst-Eur trial 1) RCT Multinational	3162	Adults >60 years with systolic blood pressure of 160 to 219 mmHg and diastolic blood pressure <95 mmHg and normal cognition.	Antihypertensive stepwise therapy with titration with goal of lowering systolic blood pressure by 20	Placebo daily	2 years median follow up	Diagnosis Global Cognition Screening [MMSE]

Medium		Mean age (SD): 69.9 (6.4) Sex: NR Race: NR Mean age (SD) on leaving school: 16.2 (4.4) Median MMSE (range): 29 (15-30)	mmHg or below 150 mmHg (step 1: nitrendipine 10 -40 mg daily; step 2: enalapril 5 – 20 mg daily; step 3: hydrochlorothiazide 12.5 – 25 mg daily)			
Applegate 1994[12, 13] (SHEP trial) RCT United States High	4736	Adults >60 years with systolic blood pressure of 160 to 220 mmHg and diastolic blood pressure <90 mmHg and normal cognition. Mean age (range): 72 (60 – 94) 57% Female 86% White Mean years of education (SD): 11.7 (NR) 0.4% Evidence of cognitive impairment	Step therapy: step 1: chlorthalidone (12.5 – 25 mg); step 2: atenolol (25 – 50 mg) or reserpine (0.05 – 0.1 mg).	Placebo daily	5 year average follow up	Diagnosis Global Cognition Screening [SHORT-CARE Dementia] Executive/attention/processing speed [Digit Symbol] Memory [Addition Test Finding A's Test, Delayed Recognition Span Test] Language [Boston Naming Test] Visuospatial [Letter Sets Test]
Gurland 1988[14] (SHEP feasibility trial) RCT United States Medium	551	Adults >60 years with systolic blood pressure >160 mmHg and diastolic blood pressure <90 mmHg and normal cognition. Mean Age: NR Sex: NR 83% White Education: NR Cognition: NR	Step therapy: step 1: chlorthalidone; step 2: reserpine, metoprolol, or hydralazine)	Placebo	1 year	Diagnosis Executive/attention/processing speed [Trail Making, Digit Symbol, composite battery[b]]
Comparative Effectiveness ARB versus ACE						
Hajjar 2013[15] RCT United States Medium	53	Adults aged ≥60 years with systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or receiving antihypertensive medications and normal cognition. Mean age (SD): 72 (7) 57% Female 70% White 19% ≤High school	I_1:Lisinopril 10 mg with titration to 40 mg I_2: Candesartan 8 mg with titration to 32 mg I_3: Hydrochlorothiazide 12.5 mg with titration to 25 mg If systolic blood		6 months	Executive/attention/processing speed [Trail Making Tests, Digit Span Test]] Memory [Hopkins Verbal Learning Tests-Revised] Adverse Events [Hospitalizations]

		Mean MMSE (SD): 26 (2)	pressure of less than 140 mmHG and diastolic blood pressure of less than 90 mmHG not get then long-acting nifedipine (30 mg increased to 90 mg) was added followed by long-acting metoprolo (12.5 mg to 50 mg).			
Andrerson 2011[3] (ONTARGET trial) RCT Multinational Medium	17118	Adults aged ≥55 with evidence of coronary artery, peripheral vascular, or cerebrovascular disease or diabetes with end-organ damage, and normal cognition. Mean age (SD): 66 (7.2) 27% Female 73% European ethnic origin 67% ≥ 9 years of education Median MMSE (IRQ): 29 (27 – 30)	Ramipril 5mg (increased to 10 mg after 2wks) daily	Telmisartan 80 mg daily	56 months median follow up	Global Cognition Screening [cognitive decline - drop of 3 or more MMSE points]
Forgari 2006[16] RCT open-label Italy Low	160	Adults aged 61 to 75 with systolic blood pressure >140 mmHg diastolic blood pressure ≥95 and <110 mmHg, and normal cognition. Mean age (SD): 68 (5.5) 54% Female Race: NR Education: NR Cognition: NR	Telmisartan 80 mg and hydrochlorothiazide 12.5 mg daily	Lisinopril 20 mg and hydrochlorothiazide 12.5mg daily	6 months	Executive/attention/processing speed [Trail Making B] Memory [Word-list Memory Test, Word-list Recall Test, Word-list Recognition Test] Language [Boston Naming Test, Name Animals]
Comparative Effectiveness ARB versus Thiazide						
Hajjar 2013[15] RCT United States Medium	53	Adults aged ≥60 years with systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or receiving antihypertensive medications and normal cognition. Mean age (SD): 72 (7)	I_1:Lisinopril 10 mg with titration to 40 mg I_2: Candesartan 8 mg with titration to 32 mg I_3: Hydrochlorothiazide 12.5 mg with titration		6 months	Executive/attention/processing speed [Trail Making Tests, Digit Span Test] Memory [Hopkins Verbal Learning Tests-Revised] Adverse Events [Hospitalizations]

		57% Female 70% White 19% ≤High school Mean MMSE (SD): 26 (2)	to 25 mg If systolic blood pressure of less than 140 mmHG and diastolic blood pressure of less than 90 mmHG not get then long-acting nifedipine (30 mg increased to 90 mg) was added followed by long-acting metoprolo (12.5 mg to 50 mg).			
Tedesco 1999[17] RCT Italy Low	69	Adults aged 30 to 73 with mild-to-moderate essential hypertension: diastolic blood pressure of 90 to 114 mmHg and normal cognition. Mean age (SD): 55 (11) 48% Female Race: NR Mean years education (SD): 9.1 (4) Mean MMSE (SD): 23 (3)	Losartan 50 mg daily	Hydrochlorothiazide de 25 mg daily	26 months	Global Cognition Screening [MMSE]
Comparative Effectiveness – Unique comparisons						
Williamson 2014[18] (ACCORD BP trial) RCT United States Medium	1439	Middle-aged and older adults with diabetes at high risk of cardiovascular events and systolic blood pressure of 130 to 180 mmHg and normal cognition. Mean age (SD): 62 (5.8) 55% Female 66% White 13% <High school 26% High school graduate 36% Some college 25% college graduate or more Median MMSE (25th and 75th percentile): 28 (26-29)	Intensive intervention (systolic blood pressure <120 mm Hg)	Standard therapy (systolic blood pressure <140 mm Hg)	40 months	Global Cognition Screening [MMSE] Executive/attention/processing speed [modified Stroop Color-Word Test, Digit Symbol Test] Memory [Rey Auditory Verbal Learning]
Hajjar 2013[15]	53	Adults aged ≥60 years with	I_1:Lisinopril 10mg with		6 months	Executive/attention/processing speed [Trail

RCT United States Medium		systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or receiving antihypertensive medications and normal cognition. Mean age (SD): 72 (7) 57% Female 70% White 19% ≤High school Mean MMSE (SD): 26 (2)	titration to 40 mg I_2: Candesartan 8 mg with titration to 32 mg I_3: Hydrochlorothiazide 12.5mg with titration to 25 mg If systolic blood pressure of less than 140 mmHG and diastolic blood pressure of less than 90mmHG not get then long-acting nifedipine (30 mg increased to 90 mg) was added followed by long-acting metoprolo (12.5 mg to 50 mg).			Making Tests, Digit Span Test]] Memory [Hopkins Verbal Learning Tests-Revised] Adverse Events [Hospitalizations]
Sato 2013[19] (CAMUI trial) RCT open-label Japan Low	142	Hypertensive adults aged ≥65 years that had not attained the blood pressure goal (systolic blood pressure <140 mmHg and or diastolic blood pressure >90 mmHg) with monotherapy with typical dosage of ARB and normal cognition. Mean age (SD): 74 (6.2) Sex: NR Race: NR Education: NR Mean MMSE (SD): 26.7 (3)	Combined losartan 50mg and hydrochlorothiazide 12.5 mg daily in quarterly visits if blood pressure goals not obtained titration was undertaken	Combined amlodipine 5mg and typical dosage of a angiotensin receptor blocker daily during quarterly visits if blood pressure goals not obtained titration was undertaken	12 months	Global Cognition Screening [MMSE]
Andrerson 2011[3] (ONTARGET trial) RCT Multinational Medium	17078	Adults aged ≥55 years with evidence of coronary artery, peripheral vascular, or cerebrovascular disease or diabetes with end-organ damage, and normal cognition. Mean age (SD): 66 (7.2) 27% Female 73% European ethnic origin 67% ≥ 9 years of education Median MMSE (IRQ): 29 (27 – 30)	Ramipril 5mg (increased to 10mg after 2wks) daily	Combined ramipril 5 mg (increased to 10mg after 2wks) daily and telmisartan 80 mg daily	56 months median follow up	Global Cognition Screening [cognitive decline - drop of 3 or more MMSE points]

Forgari 2003[20] RCT Italy Low	120	Adults aged 75 to 89 with mild to moderate essential hypertension: systolic blood pressure <200 mmHg and diastolic blood pressure of 90 to 105 mmHg. Normal cognition. Mean age (SD): 83 (4.3) 56% Female Race: NR Mean years education (SD): 8.6 (4.1) Cognition: NR	Atenolo 50 mg with titration to 100 mg	Losartan 50 mg with titration to 100 mg	6 months	Memory [Word-list Test, Memory Word Recall Test] Language [Word-list Frequency] Adverse Events
Yodfat 1996[21] RCT Israel Low	368	Males aged 40 to 65 with essential hypertension: diastolic blood pressure of 95 to 105 mmgHg. Normal cognition. Mean age (SD): 52 (7.6) 100% Male Race: NR Education: NR Cognition: NR	I_1:Isradipine 1.25 mg twice a day (dose doubled if normotension not achieved at 4 weeks and if normotension not achieved at 6 weeks captopril 25mg daily) I_2: Methyldopa 250 mg twice a day (dose doubled if normotension not achieved at 4 weeks and if normotension not achieved at 6 weeks captopril 25 mg daily)	placebo twice a day	12 months	Language [Semantic Memory] Adverse Events [life-threatening events, adverse reaction]
Bird 1990[8] RCT United Kingdom Medium	2446	Adults aged 65 to 74 with systolic blood pressure of 160 to 209 mmHg and diastolic blood pressure of <114 mmHg, and normal cognition. Mean age (SD): 70.3 (2.7) 58% Female Race: NR Education: NR Cognition: NR	I_1: Atenolol 50mg daily I_2: Moduretic (hydrochlorothiaz ide 25mg and amiloride 2.5mg) daily	Placebo	9 months	Executive/attention/processing speed [Trail Making Test] Memory [Paired Associated Learning Test]
Goldstein 1990[22] RCT United States	690	Men aged >60 with mild-to-moderate hypertension and normal cognition.	Hydrochlorothiazide 25mg once or twice a day if target blood pressure not	Hydrochlorothiazide 50mg once or twice a day if target blood	1 year	Executive/attention/processing speed [Trail Making Test, Symbol digit, Time Estimation, Digit Span] Memory [Benton Visual Retention Test,

High		Mean Age: NR 100% Male Race: NR Mean years of education (SD): 10.6 (NR) Cognition: NR	achieved (<90 mmHg and ≤5 mmHg decline from baseline) randomly assigned to additional therapy (hydralazine 50-200 mg daily, methyldopa 550-2,000 mg daily, metoprolol 100-400 mg daily, and reserpine 0.05-0.25mg daily).	pressure not achieved (<90 mmHg and ≤5 mmHg decline from baseline) randomly assigned to additional therapy (hydralazine 50-200mg daily, methyldopa 550-2,000 mg daily, metoprolol 100-400 mg daily, and reserpine 0.05-0.25mg daily).		Immediate and Delayed Logical Memory, Paired Associate Learning, 3-word short-term memory, complex cognition composite, memory composite] Language[Token Test, Controlled word production] Motor [Halstead Finger Tapping, motor speed composite] Visuospatial [Hooper Visual Organization]

[a] Saxby 2008[4] evaluated a composite measures of episodic memory (composed of immediate word recall, immediate word recognition, delayed word recall, delayed word recognition, picture recognition), attention (composited simple reaction time, number vigilance, choice reaction time), working memory (composted of spatial memory, numeric working memory), speed of cognition (composed of reaction time scores from episodic memory recognition tasks, attention, and working memory tasks), and executive function (composed of trail making A & B, verbal fluency for letters F, A, and S, verbal fluency for category animals).
[b] Gurland 1988[14] evaluated a composite executive/attention/processing speed measure composed of SHORT-CARE dementia, Trail Making, and Digit Symbol test.

MMSE= Mini Mental Status Exam; NR=not reported; RCT=randomized controlled trial; SD=Standard Deviation; TMT=Trails Making Test

Appendix Table M2. Summary risk of bias assessments: antihypertensives in adults with normal cognition

Study	Overall Risk of Bias Assessment	Rationale
ACE and Thiazide versus Placebo		
Peters 2008[1]	Medium	Attrition 19%
ADVANCE Collaborative Group 2007 [2]	Low	
ARB versus Placebo		
Anderson 2011[3]	Medium (TRANSCEND)	Attrition 12%
Saxby 2008[4]	Medium	Attrition 13%
Lithell 2003 [5], Skoog 2005[6]	Medium	Attrition 32%
Beta Blocker versus Placebo		
Perez-Stable 2000[7]	High	Attrition 34%
Bird 1990[8]	Medium	Attrition 11%
Combination Therapy versus Placebo		
Forette 2003 [10]	Medium	Attrition unclear and outcome assessor not independent
Forette 1998[11]	Medium	Attrition 14%
Applegate 1994[12, 13]	High	Attrition 25%
Gurland 1988[14]	Medium	Attrition 12%
ARB versus ACE		
Anderson 2011[3]	Medium (ONTARGET)	Attrition 12%
Hajjar 2013[15]	Medium (6 month outcomes) High (12 month outcomes)	Medium: Attrition 11% High: Attrition 42%
Fogari 2006[16]	Low	
ARB versus Thiazide		
Hajjar 2013[15]	Medium (6 month outcomes) High (12 month outcomes)	Medium: Attrition 11% High: Attrition 42%
Tedesco 1999[17]	Low	
Comparative Effectiveness –		

Study	Overall Risk of Bias Assessment	Rationale
Unique Comparisons		
Williamson 2014[18]	Medium High (MIND substudy)	Medium (ACCORD BP trial): Attrition 13% High (ACCORD BP MIND trial): Attrition 24% among those in the intensive intervention
Hajjar 2013[15]	Medium (6 month outcomes) High (12 month outcomes)	Medium: Attrition 11% High: Attrition 42%
Sato 2013[19]	Low	
Anderson 2011[3]	Medium (ONTARGET)	Attrition 12%
Fogari 2003[20]	Low	
Yodfat 1996[21]	Medium	Attrition 19%
Bird 1990[8]	Medium	Attrition 11%
Goldstein 1990[22]	High	Attrition 52%

Appendix Table M3. Strength of evidence assessments: antihypertensives in adults with normal cognition

Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
Antihypertension (ACE and Thiazide)									
Dementia	2 (14,985)	0 of 2 tests show statistically significant improvement Peters 2008 (HYVET-COG)[1] Diagnosis HR: 0.86 [0.67 to 1.09] ADVANCE Collaborative Group 2007 [2] Relative risk reduction diagnosis: -4% [-64% to 33%]	Medium	Direct	Imprecise	Consistent	Suspect	NA	Low
MCI	NR								Insufficient
Biomarkers	NR								Insufficient

Screening Tools	2 (14,985)	0 of 3 tests show statistically significant improvement Peters 2008 (HYVET-COG))[1] Cognitive decline (MMSE <24 or a decline of >3 MMSE points in a year HR: 0.93 [0.82 to 1.05] Mean MMSE change score in indapamide and perindopril 0.07 (SD 4.0) versus placebo -1.1 (SD 3.9) p = 0.08 ADVANCE Collaborative Group 2007 [2] Relative risk reduction cognitive function: 2% [-9% to 12%]	Medium	Indirect	Precise	Consistent	Suspect	NA	Moderate
Multidomain Composites	NR								Insufficient
Executive/Attention / Processing Speed	NR								Insufficient
Memory	NR								Insufficient

Serious Adverse Events	2 (14,985)	1 of 2 tests show statistically fewer adverse events Peters 2008 (HYVET-COG)[1] Number of adverse events in indapamide and perindopril (358) vs placebo (448) p <0.001 ADVANCE Collaborative Group 2007 [2] Number of adverse drug reactions in perindopril and indapamide (47) and placebo (31).	Medium	Direct	Precise	Unknown	Suspect	NA	Low
Antihypertension (ARBs)									
Dementia	1 (4937)	0 of 1 tests show statistically significant improvement Lithell 2003 [5] and Skoog 2005[6] (SCOPE) Dement events per 1000 patient years candesartan (6.8) vs control (6.3) p > 0.20	Medium	Direct	Precise	Unknown	Suspect	NA	Low
MCI	NR								Insufficient
Biomarkers	NR								Insufficient
Screening Tools	2 (10,863)	0 of 3 tests show statistically significant improvement: Anderson 2011[3] (TRANSCEND) OR cognitive decline (drop of 3 or more MMSE points) Telmisartan vs placebo 1.10 [0.95 to 1.27] Saxby 2008[4] (single center	Medium	Indirect	Precise	Consistent	Suspect	NA	Moderate

		in SCOPE) Difference in mean change from baseline to closeout visit (MMSE) candesartan (baseline 28.7 to closeout visit 28.3) vs placebo (baseline 28.9 to closeout visit 28.5) p-value = 0.94 for change in MMSE between groups. Lithell 2003 [5] and Skoog 2005[6] (SCOPE) Difference in mean change (MMSE) candesartan vs placebo 0.15 [-0.08 to 0.38]							
Multidomain Composites	NR								Insufficient
Executive/Attention / Processing Speed	1 (257)	1 of 3 tests show statistically significant improvement with Intervention	Medium	Indirect	Unknown	Inconsistent	Suspect	NA	Insufficient
Memory	1 (257)	1 of 2 tests show statistically significant improvement with Intervention Saxby 2008[4] (single center in SCOPE) Coefficient (SD) for decline in episodic memory for candesartan 0.14 (1.38) and placebo -0.22 (1.21). p = 0.04. Coefficient (SD) for decline in working memory for candesartan 0.0014 (0.012) and placebo 0.0010 (0.012). p = 0.90.	Medium	Indirect	Unknown	Inconsistent	Suspect	NA	Insufficient
Serious Adverse Events	1 (5,926)	Lithell 2003 [5] and Skoog 2005[6] (SCOPE) No difference adverse	Medium	Direct	Unknown	Unknown	Suspect	NA	Insufficient

		events reported between groups							
Antihypertension (Beta blocker)									
Dementia	NR								Insufficient
MCI	NR								Insufficient
Biomarkers	NR								Insufficient
Screening Tools	NR								Insufficient
Multidomain Composites	NR								Insufficient
Executive Function	1 (1859)	0 of 1 tests show statistically significant improvement with Intervention	Medium	Indirect	Unknown	Unknown	Suspect	NA	Insufficient
Memory	1 (1859)	0 of 2 tests show statistically significant improvement with Intervention	Medium	Indirect	Unknown	Inconsistent	Suspect	NA	Insufficient
Serious Adverse Events	NR								Insufficient
Antihypertension (Combination therapy)									
Dementia	2 (3779)	Forette 1998 [11] (Syst-Eur 1) Forette 2002[10] (Syst-Eur 1 & 2) 2011 RR 0.50 (95%CI, 0.24-1.00) reduction in the rate of dementia for treatment vs. placebo	Medium	Direct	Imprecise	Unknown	Suspect	Low	Insufficient
MCI	NR								Insufficient
Biomarkers	NR								Insufficient
Global Cognition	1 (3228)	0 of 2 tests show statistically significant improvement: Forette 2002[10] (Syst-Eur 1 & 2) 2011 Change in MMSE score at year 1 [treatment 0.10 (SD 1.44) control 0.16 (SD 1.52); p = 0.28], year 2 [treatment 0.17 (SD 1.64)	Medium	Indirect	Precise	Consistent	Suspect	NA	Low

		control 0.15 (SD 1.69); p = 0.75], year 3 [treatment 0.17 (SD 1.82) control 0.14 (SD 1.85); p = 0.73] Forette 1998[11] (Syst-Eur 1) MD MMSE 0.07 [-0.09 to 0.23]							
Executive Function	1 (551)	1 of 3 tests show statistically significant improvement	Medium	Indirect	Imprecise	Inconsistent	Suspect	NA	Insufficient
Memory	NR								Insufficient
Serious Adverse Events	NR								Insufficient
Antihypertension (ARB versus ACE)									
Dementia	NR								Insufficient
MCI	NR								Insufficient
Biomarkers	NR								Insufficient
Screening Tools	1 (17,118)	0 of 1 test show statistical significant improvement Anderson 2011[3] (ONTARGET) cognitive decline (drop of 3 or more MMSE points) telmisartan vs ramipril RR 0.97 [0.89 to 1.06]	Medium	Indirect	Precise	Unknown	Suspect	NA	Low
Multidomain Composites	NR								
Executive Function	1 (160)	0 of 1 test show statistically significant improvement	Medium	Indirect	Unknown	Unknown	Suspect	NA	Insufficient
Memory	1 (160)	1 of 2 tests show statistically significant improvement	Low	Indirect	Unknown	Unknown	Suspect	NA	Insufficient
Serious adverse events	1 (160)	0 of 1 test show statistically significant difference Forgari 2006[16] No difference in adverse events	Low	Direct	Unknown	Unknown	Suspect	NA	Insufficient
ARB versus									

Thiazide									
Dementia	NR								Insufficient
MCI	NR								Insufficient
Biomarkers	NR								Insufficient
Global Cognition	NR								Insufficient
Executive Function	NR								Insufficient
Memory	NR								Insufficient
Serious adverse events	2 (122)	0 of 2 test show statistically significant difference Hajjar 2013[15] No difference in adverse events Tedesco 1999 [17] No difference in adverse events	Medium	Direct	Unknown	Unknown	Suspect	NA	Insufficient
Unique Comparisons with ≥ 500									
Intensive blood pressure control **(**systolic blood pressure <120 mm Hg) versus standard blood pressure control (standard therapy (systolic blood pressure <140 mm Hg))									
Dementia	NR	NR							Insufficient
MCI	NR	NR							Insufficient
Biomarkers	NR	NR							Insufficient
Screening Tools	1 (1439)	0 if 1 test show statistically significant difference Williamson 2014[18] (ACCORD BP trial) MD MMSE 0.05 [-0.20 to 0.29]	Medium	Indirect	Precise	Unknown	Suspect	NA	Low
Multidomain Composites	NR								
Executive Function	1 (1439)	0 of 2 tests show	Medium	Indirect	Imprecise	Consistent	Suspect	NA	Low

		statistically significant difference							
Memory	1 (1439)	0 of 1 test show statistically significant difference	Medium	Indirect	Precise	Unknown	Suspect	NA	Low
Serious adverse events	NR								Insufficient
(I_1) Ramipril up to 10 mg daily vs. (I_2) combined ramipril up to 10 mg daily and telmisartan 80 mg daily									
Dementia	NR								Insufficient
MCI	NR								Insufficient
Biomarkers	NR								Insufficient
Screening Tools	1 (17,078)	0 if 1 test shows statistically significant difference Anderson 2011[3] (ONTARGET) OR cognitive decline (drop of 3 or more MMSE points) combined ramipril and telmisartan vs. ramipril 0.95 [0.88 to 1.04]	Medium	Indirect	Precise	Unknown	Suspect	NA	Low
Multidomain Composites	NR								Insufficient
Executive Function	NR								Insufficient
Memory	NR								Insufficient
Serious adverse events	NR								Insufficient

MCI=mild cognitive impairment; MMSE= Mini Mental Status Exam; NR=not reported; SD=Standard Deviation

Appendix Table M4. Characteristics of eligible studies: antihypertension interventions in adults with MCI

Study **Design** **Country** **RoB**	**N=**	**Population** **Inclusion** **Age (mean)** **Sex (% female)** **Race (% White)** **Education (mean years)** **Baseline Cog**	**Intervention (INT)** **Mode** **Components** **Frequency** **Duration**	**Comparison** **Mode** **Components** **Frequency** **Duration**	**Outcome measurement timing**	**Outcome (Instrument)**
Starr 1996[23], 2005[24] (HOPE trail) RCT United Kingdom Medium	81	Adults aged 70 to 85 with median systolic blood pressure of 160 to 220 mmHg and diastolic blood pressure of 100 to 120 mmHg, or median systolic blood pressure of 180 to 220 mmHg and diastolic blood pressure of ≥85 mmHg. Mild cognitive impairment. Mean age (range): 76.1 (70-84) 65% Female Race: NR Education: NR Mean MMSE (range): 26.1 (20-28)	Captopril 12.5mg twice a day	Bendrofluazide 2.5 mg once a day	26 weeks	Executive/attention/processing speed [Trail Making A, Ravens Colored Progressive Matrices] Memory [Logical Memory Immediate, Delayed Memory Immediate, Anomalous Sentences Repetition Test, Paired Associated Learning]

MMSE= Mini Mental Status Exam; NR=not reported; RCT=randomized controlled trial

Appendix Table M5. Summary risk of bias assessments: antihypertension in adults with mild cognitive impairment

Study	Overall Risk of Bias Assessment	Rationale
Starr 1996[23], 2005[24]	Medium	Attrition 12%

References for Appendix M

1. Peters R, Beckett N, Forette F, et al. Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial. Lancet Neurology. 2008 Aug;7(8):683-9. doi: http://dx.doi.org/10.1016/S1474-4422(08)70143-1. PMID: 18614402.

2. Patel A, Group AC, MacMahon S, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet. 2007 Sep 8;370(9590):829-40. PMID: 17765963.

3. Anderson C, Teo K, Gao P, et al. Renin-angiotensin system blockade and cognitive function in patients at high risk of cardiovascular disease: analysis of data from the ONTARGET and TRANSCEND studies. Lancet Neurology. 2011 Jan;10(1):43-53. doi: http://dx.doi.org/10.1016/S1474-4422(10)70250-7. PMID: 20980201.

4. Saxby BK, Harrington F, Wesnes KA, et al. Candesartan and cognitive decline in older patients with hypertension: a substudy of the SCOPE trial. Neurology. 2008 May 6;70(19 Pt 2):1858-66. doi: http://dx.doi.org/10.1212/01.wnl.0000311447.85948.78. PMID: 18458219.

5. Lithell H, Hansson L, Skoog I, et al. The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. Journal of Hypertension. 2003 May;21(5):875-86. PMID: 12714861.

6. Skoog I, Lithell H, Hansson L, et al. Effect of baseline cognitive function and antihypertensive treatment on cognitive and cardiovascular outcomes: Study on COgnition and Prognosis in the Elderly (SCOPE). American Journal of Hypertension. 2005 Aug;18(8):1052-9. PMID: 16109319.

7. Perez-Stable EJ, Halliday R, Gardiner PS, et al. The effects of propranolol on cognitive function and quality of life: a randomized trial among patients with diastolic hypertension. American Journal of Medicine. 2000 Apr 1;108(5):359-65. PMID: 10759091.

8. Bird AS, Blizard RA, Mann AH. Treating hypertension in the older person: an evaluation of the association of blood pressure level and its reduction with cognitive performance. Journal of Hypertension. 1990 Feb;8(2):147-52. PMID: 2162877.

9. Prince MJ, Bird AS, Blizard RA, et al. Is the cognitive function of older patients affected by antihypertensive treatment? Results from 54 months of the Medical Research Council's trial of hypertension in older adults. BMJ. 1996 Mar 30;312(7034):801-5. PMID: 8608285.

10. Forette F, Seux ML, Staessen JA, et al. The prevention of dementia with antihypertensive treatment: new evidence from the Systolic Hypertension in Europe (Syst-Eur) study.[Erratum appears in Arch Intern Med. 2003 Jan 27;163(2):241.]. Archives of Internal Medicine. 2002 Oct 14;162(18):2046-52. PMID: 12374512.

11. Forette F, Seux ML, Staessen JA, et al. Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. Lancet. 1998 Oct 24;352(9137):1347-51. PMID: 9802273.

12. Applegate WB, Pressel S, Wittes J, et al. Impact of the treatment of isolated systolic hypertension on behavioral variables. Results from the systolic hypertension in the elderly program. Archives of Internal Medicine. 1994 Oct 10;154(19):2154-60. PMID: 7944835.

13. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. JAMA. 1991 Jun 26;265(24):3255-64. PMID: 2046107.

14. Gurland BJ, Teresi J, Smith WM, et al. Effects of treatment for isolated systolic hypertension on cognitive status and depression in the elderly. Journal of the American Geriatrics Society. 1988 Nov;36(11):1015-22. PMID: 3171039.

15. Hajjar I, Hart M, Chen YL, et al. Antihypertensive therapy and cerebral hemodynamics in executive mild cognitive impairment: results of a pilot randomized clinical trial. Journal of the American Geriatrics Society. 2013 Feb;61(2):194-201. doi: http://dx.doi.org/10.1111/jgs.12100. PMID: 23350899.

16. Fogari R, Mugellini A, Zoppi A, et al. Effect of telmisartan/hydrochlorothiazide vs lisinopril/hydrochlorothiazide combination on ambulatory blood pressure and cognitive function in elderly hypertensive patients. Journal of Human Hypertension. 2006 Mar;20(3):177-85. PMID: 16306998.

17. Tedesco MA, Ratti G, Mennella S, et al. Comparison of losartan and hydrochlorothiazide on cognitive function and quality of life in hypertensive patients. American Journal of Hypertension. 1999 Nov;12(11 Pt 1):1130-4. PMID: 10604491.

18. Williamson JD, Launer LJ, Bryan RN, et al. Cognitive function and brain structure in persons with type 2 diabetes mellitus after intensive lowering of blood pressure and lipid levels: a randomized clinical trial. JAMA Intern Med. 2014 Mar;174(3):324-33. doi: 10.1001/jamainternmed.2013.13656. PMID: 24493100.

19. Sato N, Saijo Y, Sasagawa Y, et al. Combination of antihypertensive therapy in the elderly, multicenter investigation (CAMUI) trial: results after 1 year. J Hypertens. 2013 Jun;31(6):1245-55. doi: 10.1097/HJH.0b013e32835fdf60. PMID: 23492647.

20. Fogari R, Mugellini A, Zoppi A, et al. Influence of losartan and atenolol on memory function in very elderly hypertensive patients. Journal of Human Hypertension. 2003 Nov;17(11):781-5. PMID: 14578918.

21. Yodfat Y, Bar-On D, Amir M, et al. Quality of life in normotensives compared to hypertensive men treated with isradipine or methyldopa as monotherapy or in combination with captopril: the LOMIR-MCT-IL study. Journal of Human Hypertension. 1996 Feb;10(2):117-22. PMID: 8867566.

22. Goldstein G, Materson BJ, Cushman WC, et al. Treatment of hypertension in the elderly: II. Cognitive and behavioral function. Results of a Department of Veterans Affairs Cooperative Study. Hypertension. 1990 Apr;15(4):361-9. PMID: 2318518.

23. Starr JM, Whalley LJ, Deary IJ. The effects of antihypertensive treatment on cognitive function: results from the HOPE study. Journal of the American Geriatrics Society. 1996 Apr;44(4):411-5. PMID: 8636587.

24. Starr JM, Whalley LJ. Differential cognitive outcomes in the Hypertensive Old People in Edinburgh study. Journal of the Neurological Sciences. 2005 Mar 15;229-230:103-7. PMID: 15760627.

Appendix N. Lipid Lowering Treatment

Appendix Table N1. Characteristics of eligible studies: lipid lowering interventions in adults with normal cognition

Study **Design** **Country** **RoB**	**N=**	**Population** **Inclusion** **Age (mean)** **Sex (% female)** **Race (% White)** **Education (mean years)** **Baseline Cog**	**Intervention (INT)** **Mode** **Components** **Frequency** **Duration**	**Comparison** **Mode** **Components** **Frequency** **Duration**	**Outcome measurement timing**	**Outcome (Instrument)**
Efficacy						
Statins Versus Placebo						
Trompet 2010[1] RCT Multinational High	5804	Adults aged 70 to 82 years with preexisting vascular disease or at increased risk of vascular disease and normal cognition. Mean age (SD): 75 (3) 52% Female Race: NR Mean years of education (SD): 15.1 (2) Mean MMSE (SD): 28 (1.5)	Pravastatin	Placebo	42 months mean follow up	Global Cognition Screening [MMSE] Executive/attention/processing speed [Stroop-Color-Word Test, Letter-Digit Coding Test] Memory [15-Picture Learning test immediate and delayed]

Parale 2006 [2] Observational India High	97	Adults age ≥40 years with cardiovascular indications for statin use and normal cognition. Mean age (SD): 56.5 (8) 67% Female Race: NR Mean years education (SD): 11 (2.9) Mean MMSE (SD): 28.4 (1.8)	Atorvastatin 10 mg daily	Placebo	6 months	Global Cognition Screening [MMSE] Executive/attention/processing speed [Digit Symbol, Digit Span, Digit Vigilance, Trail Making B] Memory [Picture-Word Learning, Controlled Oral Word Association Test, Auditory Vigilance] Adverse Events
Muldoon 2004[3] RCT United States Medium	308	Adults aged 35 to 70 years with low-density lipoprotein cholesterol level between 160 and 220 mg/dL and normal cognition. Mean age (SD): 53.7 (9.1) 52% Female 86% White Mean years education (SD): 14.8 (3.4) Mean Digit Vigilance (errors), and Recurring Words (errors): 6.6, 81.84.	Simvastatin 10 mg daily or Simvastatin 40 mg daily	Placebo	6 months	Executive/attention/processing speed[a] [composite executive/attention/processing speed 1] Memory [memory composite 1, memory 2] Adverse Events
Heart Protection Study 2002[4] RCT United Kingdom Medium	20,536	Adults aged 40-80 years with total cholesterol concentrations ≥ 135 mg/dL and with substantial 5-risk of death from coronary heart disease and normal cognition. 28% > 70 years 28% Female Race: NR Education: NR Mean TICS-M (SD): 24.07 (NR)	Simvastatin 40 mg daily	Matching-placebo	5 years mean follow up	Diagnosis Global cognition Screening [Telephone Interview for Cognitive Status TICS-m] Adverse Events [hospitalizations]
Muldoon 2000[5] RCT United States	209	Adults aged 24 to 60 with hypercholesterolemia (serum low-density-lipoprotein cholesterol level ≥160 md/dL) and normal cognition.	Lovastatin 20 mg daily	Matching placebo	6 months	Executive/attention/processing speed[b] [composite measure of attention, composite of mental flexibility, composite measure of psychomotor speed]

Medium		Mean age (SD): 46.4 (8.9) 46% Female 88% White Mean years education (SD): 15 (3) Mean Digit Span (SD), Digit Symbol (SD), Trailing Making B (SD): 7 (1.3), 11.8 (2.5), 65 (21).				Executive/attention/processing speed[b] Memory [working memory composite, memory retrieval composite]
Santanello 1997 [6] RCT United States Medium	431	Adults aged ≥65 years with low-density lipoprotein-cholesterol >159 md/dL and < 221 mg/dL and normal cognition and MMSE ≥ 24. Mean age (SD): 71.2 (NR) 71% Female 24% White Education: NR Mean Digit Symbol Substation Score (SD): 41.86 (13.88)	(I_1) lovastatin 20 mg daily (I_2) lovastatin 40 mg daily	Placebo	6 months	Executive/attention/processing speed [Digit Symbol Substitution Task] Adverse Events [number of events]
Statin Plus Ezetimibe Versus Placebo						
Tendolkar 2010 [7] RCT Netherlands Low	34	Elderly stroke-free patients with chronic or paroxysmal atrial fibrillation and normal cognition. Mean age (SD): 74 (4) 24% Female Race: NR Education: NR Mean MMSE (SD): 27.4 (2)	Atorvastatin 20mg for 2 weeks then increased to 40mg, after 4 weeks ezetimibe 10mg was added. Standard anticoagulant therapy	Matching-placebo and standard anticoagulant therapy	1 year	Global Cognition Screening [MMSE] Executive/attention/processing speed [Digit Symbol Substitution Test, Memory [Dutch modified version of the Rey Adulatory Verbal Learning Test, Immediate and delayed word recall] Biomarker [Brain Volume Change]
Statin Plus Fenofibrate Versus Statin Plus Placebo						
Willamson 2014 [8] (ACCORD Lipid trial) RCT United States Medium	1538	Middle-aged and older adults with diabetes at high risk of cardiovascular events with low-density lipoprotein cholesterol levels of less than 100 mg/dL and normal cognition. Mean age (SD): 62.5 (5.7)	Fenofibrate plus statin	Placebo plus statin	40 months	Global Cognition Screening [MMSE] Executive/attention/processing speed [modified Stroop Color-Word Test, Digit Symbol Test] Memory [Rey Auditory Verbal Learning]

		38.9% Female 73% White 13% <High school 25% High school graduate 33% Some college 28% college graduate or more Median MMSE (25th and 75th percentile): 28 (26-29)				
Comparative Effectiveness						
Muldoon 2004[3] RCT United States Medium	189	Adults aged 35 to 70 years with low-density lipoprotein cholesterol level between 160 and 220 mg/dL and normal cognition. Mean age (SD): 53.7 (9.1) 52% Female 86% White Mean years education (SD): 14.8 (3.4) Mean Digit Vigilance (errors), and Recurring Words (errors): 6.6, 81.84.	Simvastatin 10 mg daily	Simvastatin 40 mg daily	6 months	Executive/attention/processing speed[a] [composite executive/attention/processing speed 1, composite executive/attention/processing speed 2] Memory [memory composite] Adverse Events
Carlsson 2002[9] RCT-Crossover United States Medium	41	Adults ≥70 years with low-density lipoprotein-cholesterol ≥140 mg/dl and tri-glyceride levels ≤140 mg/dl and normal cognition. Mean age (SD): 76.3 (4.3) 68% Female Race: NR Education: NR Mean Digit Symbol Substitution (SD): 42.45 (9.69)	Pravastatin 20 mg daily	Tocopherol 440 IU daily	6 months	Executive/attention/processing speed [Digit Symbol Substitution Task] Adverse Events [physical adverse events and hospitalizations]

[a]Muldoon 2004[3] grouped tests into composite measures and if there was a significant difference in the composite measure individual items were evaluated. The composite measures were: 1) composite executive/attention/processing speed 1: Elithorn mazes, digit vigilance, recurring words, grooved pegboard; 2) memory composite 1: mirror tracing, 4-word short term memory, 3) memory composite 1: digit symbol, stroop interference, trail making B, digit span, complex figure, letter rotation;

[b]Muldoon 2000[5] grouped tests into composite measures and if there was a significant difference in the composite measure individual items were evaluated. The composite measures were: 1) composite measure of attention: digit vigilance, letter rotation, digit span, recurring words; 2) composite measure of psychomotor speed: grooved pegboard, Elithorn Maze, Digit Symbol; 3) composite of mental flexibility: Strool Interference, Trail Making Digit Vigilance, Letter Rotation; 4) working memory composite: Associative Learning, Digit Span, 5) memory retrieval composite: Controlled Oral Word Association, Digit Symbol Recall, Verbal Recall, Complex Figure.

MMSE= Mini Mental Status Exam; NR=not reported; RCT=randomized controlled trial; SD=Standard Deviation; TICS=Telephone Interview Cognitive Status

Appendix Table N2. Summary risk of bias assessments: lipid lowering treatment in adults with normal cognition

Study	Overall Risk of Bias Assessment	Rationale
Willamson 2014 Williamson 2014[8] (ACCORD Lipid trial)	Low (ACCORD Lipid-MIND trial) High (ACCORD Lipid-MIND MRI sub-trial)	Low (ACCORD Lipid-MIND trial) High (ACCORD Lipid MIND MRI sub-trial): Attrition 21%
Tendolkar 2012[7]	Low	
Trompet 2010[1]	High	Attrition 25%
Parale 2006 [2]	High	Method of randomization and performance bias
Muldoon 2004[3]	Medium	Reporting bias
Heart Protection Study 2002[4]	Medium	Attrition unclear, detection bias
Muldoon 2000[5]	Medium	Reporting bias
Santanello 1997 [6]	Medium	Attrition 15%
Carlsson 2002{Carlsson, 2002 #475	Medium	Attrition 12%

Appendix Table N3. Strength of evidence assessments: lipid lowering interventions in adults with normal cognition

Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
Statins Versus Placebo									
Dementia	1 (20,536)	0 of 1 tests shows statistically significant improvement: Heart Protection Study 2002{ Heart Protection Study Collaborative Group, 2002 #476 Number in statins versus placebo who developed dementia during follow up: 31 [0.3%] vs. 31 [0.3%]	Medium	Direct	Unknown	Unknown	Suspect	NA	Insufficient
MCI	NR								Insufficient
Biomarkers	NR								Insufficient
Screening	1 (20,536)	0 of 1 tests shows statistically significant improvement: Heart Protection Study 2002{ Heart Protection Study Collaborative Group, 2002 #476 Mean difference TICS-m [SE]: 0.02 [0.07] Percent of participant classified as cognitively impaired statins versus placebo: 23.7% vs. 24.2%	Medium	Indirect	Unknown	Unknown	Suspect	NA	Insufficient
Multidomain Composites									
Executive/Attention/ Processing Speed	3 (948)	0 of 4 tests shows statistically significant improvement for statins. 3 of 4 tests shows statically	Medium	Indirect	Imprecise	Inconsistent	Suspect	NA	Low

		significant improvement for placebo. Muldoon 2004[3] Mean difference composite executive/attention/processing speed [CI]: 0.18 [0.07 to 0.29] Muldoon 2000[5] Mean difference in change composite executive/attention/processing speed [95% CI]: 0.18 [0.06 to 0.31] Mean difference in change composite psychomotor speed [95% CI]: 0.17 [0.05 to 0.28] Santanello 1997[6] Mean change Digit Symbol Substitution [SD] placebo 0.33 [13.06], lovastatin 20 mg -0.80 [13.28], and lovastatin 40 mg 1.66 [8.98]. P-value for difference between groups 0.66							
Memory	2 (517)	0 of 4 tests shows statistically significant improvement for statins. 1 of 4 tests shows statically significant improvement for placebo.	Medium	Indirect	Imprecise	Inconsistent	Suspect	NA	Insufficient
Serious Adverse Events	2 (20,967)	1 of 17 test shows a statistically significant difference: Heart Protection Study 2002{ Heart Protection	Medium	Direct	Unknown	Consistent	Suspect	NA	Insufficient

		Study Collaborative Group, 2002 #476 Number of hospitalization in statins versus placebo. NS Santanello 1997{Santanello, 1997 #480} Abdominal pain %: placebo 4.4, lovastatin 20 mg 5.8, lovastatin 40 mg 9.6. P-value for difference between groups <0.01 For 15 other common symptoms no difference reported.							
Fenofibrate plus statin versus placebo plus statin									
Dementia	NR								Insufficient
MCI	NR								Insufficient
Biomarkers[a]	NR								Insufficient
Screening	1 (1,538)	0 of 1 tests shows statistically significant improvement: Williamson 2014 [8] (ACCORD Lipid trial) Mean difference MMSE 0.07 [95% CI]: [-0.17 to 0.31]	Low	Indirect	Precise	Unknown	Suspect	NA	Low
Multidomain Composites									
Executive/Attention/ Processing Speed	1 (1,538)	0 of 2 tests shows statistically significant improvement	Low	Indirect	Imprecise	Consistent	Suspect	NA	Low
Memory	1 (1,538)	0 of 1 tests shows statistically significant	Low	Indirect	Precise	Unknown	Suspect	NA	Low

		improvement							
Serious Adverse Events	NR								Insufficient

[a] Williamson 2014 [8] (ACCORD Lipid trial) reported total brain volume but data was excluded from analysis due to high risk of bias (attrition 21%).

MCI=mild cognitive impairment; NR=not reported

References for Appendix N

1. Trompet S, van Vliet P, de Craen AJ, et al. Pravastatin and cognitive function in the elderly. Results of the PROSPER study. J Neurol. 2010 Jan;257(1):85-90. doi: 10.1007/s00415-009-5271-7. PMID: 19653027.

2. Parale GP, Baheti NN, Kulkarni PM, et al. Effects of atorvastatin on higher functions. Eur J Clin Pharmacol. 2006 Apr;62(4):259-65. doi: 10.1007/s00228-005-0073-z. PMID: 16489473.

3. Muldoon MF, Ryan CM, Sereika SM, et al. Randomized trial of the effects of simvastatin on cognitive functioning in hypercholesterolemic adults. Am J Med. 2004 Dec 1;117(11):823-9. doi: 10.1016/j.amjmed.2004.07.041. PMID: 15589485.

4. Heart Protection Study Collaborative G. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet. 2002 Jul 6;360(9326):7-22. doi: 10.1016/S0140-6736(02)09327-3. PMID: 12114036.

5. Muldoon MF, Barger SD, Ryan CM, et al. Effects of lovastatin on cognitive function and psychological well-being. Am J Med. 2000 May;108(7):538-46. PMID: 10806282.

6. Santanello NC, Barber BL, Applegate WB, et al. Effect of pharmacologic lipid lowering on health-related quality of life in older persons: results from the Cholesterol Reduction in Seniors Program (CRISP) Pilot Study. J Am Geriatr Soc. 1997 Jan;45(1):8-14. PMID: 8994481.

7. Tendolkar I, Enajat M, Zwiers MP, et al. One-year cholesterol lowering treatment reduces medial temporal lobe atrophy and memory decline in stroke-free elderly with atrial fibrillation: evidence from a parallel group randomized trial. Int J Geriatr Psychiatry. 2012 Jan;27(1):49-58. doi: 10.1002/gps.2688. PMID: 21308791.

8. Williamson JD, Launer LJ, Bryan RN, et al. Cognitive function and brain structure in persons with type 2 diabetes mellitus after intensive lowering of blood pressure and lipid levels: a randomized clinical trial. JAMA Intern Med. 2014 Mar;174(3):324-33. doi: 10.1001/jamainternmed.2013.13656. PMID: 24493100.

9. Carlsson CM, Papcke-Benson K, Carnes M, et al. Health-related quality of life and long-term therapy with pravastatin and tocopherol (vitamin E) in older adults. Drugs Aging. 2002;19(10):793-805. PMID: 12390056.

Appendix O. NSAIDs

Appendix Table O1. Characteristics of eligible studies: NSAIDs in adults with normal cognition

Study Design Country RoB	N=	Population Inclusion Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention	Comparison	Outcome Timing	Outcome Domain [Instrument]
ADAPT Group RCT USA 8 years Medium 5 years Medium 4 years 2008: Medium 2007: Medium	8 years 2117 5 years 2071 4 years 2528	Adults aged 70+ with normal cognition and at least 1 first-degree relative with AD-like dementia **Age** (median) 70-74: 55% 75-79: 32% 80-84: 11% 85+: 2% **Sex** 46% **Race** White: 97% Black: 2% Hispanic: 1% **Education** Less than high school: 4% High school degree: 20% College, no degree: 27% College degree: 19% Postgrad: 30% **Baseline cognition** (median) Adjusted 3MS: 95.0	Celecoxib (200 mg BID) or naproxen (220 mg BID)	Placebo	8 years[1] 5 years[2] 4 years[3, 4]	8 years Diagnosis [Alzheimer's disease] 5 years Diagnosis [Alzheimer's disease] Biomarkers [CSF tau : Ab1-42] 4 years Diagnosis [Alzheimer's disease] Global Cognition [3MS; composite (Hopkins Verbal Learning Test-Revised, informant-rated Dementia Severity Rating Scale, Digit Span, Naming supermarkets, Rivermead Behavioral Memory Test)] Executive/Attention/Processing Speed [Digit Span] Memory [Hopkins Verbal Learning Test; Rivermead Behavioral Memory Test]
Small, 2008[5] RCT USA High	88	Middle-aged and older volunteers with normal cognition and self-reported age-related memory complaints **Age** 58 **Sex** 38% **Race** NR **Education** (mean years) 15 **Baseline cognition** (median)	Celecoxib 200 mg or 400 mg QD	Placebo	1.5 years	Executive/Attention/Processing Speed [Trails A and B; WAIS-III Digit Symbol Substitution; Stroop Interference Kaplan version; F.A.S. Letter Fluency Test] Memory [Buschke Selective Reminding Test total and delayed

Study **Design** **Country** **RoB**	**N=**	**Population** **Inclusion** **Age (mean)** **Sex (% female)** **Race (% White)** **Education (mean years)** **Baseline Cognition**	**Intervention**	**Comparison**	**Outcome Timing**	**Outcome Domain [Instrument]**
		MMSE: 29.2				recall; Wechsler Memory Scale-3rd Edition WMS-III Verbal Paired Associations I; Benton Visual Retention Test] Language [Boston Naming Test; Animal Naming Test] Visuospatial [WAIS-III Block Design Test, Rey-Osterreich Complex Figure Test copy]
Kang, 2007[6] RCT USA Medium	6377	Normal cognition, women aged 65+ participating in healthy study **Age** 72 **Sex** 100% **Race** NR **Education** Licensed vocational or registered nurse/associates degree: 67% Bachelors/masters/doctorate degree: 33% **Baseline cognition** TICS: 34	Aspirin (100 mg QAD)	Placebo	10 years	Global cognition [TICS; composite (TICS, category fluency, 10 words list immediate and delayed recall, East Boston Memory Test)] Memory [composite (10 words list immediate and delayed recall, East Boston Memory Test)]

3MS=Modified Mini-Mental State Examination; BID=twice daily; NP=Neuropsychological; NR=not reported; QAD=every other day; QD=every day; SD=Standard Deviation; RCT=Randomized Controlled Trial;

Appendix Table O2. Summary risk of bias assessments: NSAIDs in adults with normal cognition

Study	Overall Risk of Bias Assessment	Rationale
ADAPT Group, 2013[1]	Medium	Attrition 39% but use survival and sensitivity analyses; unclear if concurrent interventions
ADAPT Group, 2011[2]	Medium	Attrition 18% but use survival analysis; participant and outcome assessor blinding methods unclear
ADAPT Group, 2008[3]	Medium	Attrition 20%; unclear if concurrent interventions
ADAPT Group, 2007[4]	Low	Attrition 15% but use survival analysis; unclear if concurrent interventions
Small, 2008[5]	High	Attrition 44%
Kang, 2007[6]	Medium	Attrition 29%; outcome assessor independence unclear; unclear if concurrent interventions

Appendix Table O3. Strength of evidence assessments: NSAIDs in adults with normal cognition

Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Direct-ness	Precision	Consistency	Reporting Bias	Optional Components	SOE
Aspirin vs. Placebo k=1[6]									
Dementia	NR								
MCI	NR								
Screening Tests 10 years	1 (6377)	0 of 1 tests showed no statistically significant difference. TICS, mean difference from baseline -0.02 [-0.19 to 0.14]	Medium	Indirect	Precise	Unknown	Undetected	NA	Low
Multidomain Composite 10 years	1 (6377)	0 of 1 tests showed no statistically significant difference. Composite, mean difference from baseline 0.0 [-0.04 to 0.04]	Medium	Indirect	Precise	Unknown	Undetected	NA	Low
Executive/ Attention/ Processing Speed	NR								
Memory 10 years	1 (6377)	0 of 1 test showed no statistically significant difference. Composite, mean difference from baseline -0.02 [-0.06 to 0.02]	Medium	Indirect	Precise	Unknown	Undetected	NA	Low
Adverse Effects	NR								
Non-aspirin (Celecoxib 200 mg BID; Naproxen 220 mg BID) **vs. Placebo k=1[1-4]**									
Dementia 8 years	1 (2117)	0 of 2 tests at longest follow-up showed no significant difference.	Medium	Direct	Precise	Unknown	Undetected	NA	Low

Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Direct-ness	Precision	Consistency	Reporting Bias	Optional Components	SOE
		Adjusted HR for Alzheimer's disease Celecoxib: 1.03 [0.72 to 1.50] p=0.86 Naproxen: 0.92 [0.62 to 1.35] p=0.66							
MCI	NR								
Screening Tools 4 years	1 (2528)	0 of 2 tests showed no statistically significant difference. Adjusted 3MS, generalized estimating equation regression vs placebo (B coefficient) Celecoxib: -0.20 [-0.47 to 0.07] p=0.14 Naproxen: -0.19 [-0.47 to 0.09] p=0.19	Medium	Indirect	Imprecise	Unknown	Undetected	NA	Insufficient
Multidomain Composite 4 years	1 (2528)	0 of 2 tests showed no statistically significant difference. Composite, generalized estimating equation regression vs placebo (B coefficient) Celecoxib: -0.004 [-0.04 to 0.03] p=0.84 Naproxen: -0.03 [-0.07 to 0.01] p=0.09	Medium	Indirect	Precise	Unknown	Undetected	NA	Low
Executive/ Attention/ Processing Speed 4 years	1 (2528)	0 of 4 tests show no statistically significant improvement with intervention Digit Span Forward, generalized estimating equation regression vs placebo (B coefficient)	Medium	Indirect	Imprecise	Consistent	Undetected	NA	Low

Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Direct-ness	Precision	Consistency	Reporting Bias	Optional Components	SOE
		Celecoxib: -0.05 [-0.19 to 0.09] p=0.48 Naproxen: -0.03 [-0.17 to 0.11] p=0.69 <u>Digit Span Backward, generalized estimating equation regression vs placebo (B coefficient)</u> Celecoxib: 0.03 [-0.11 to 0.18] p=0.64 Naproxen: -0.09 [-0.23 to 0.05] p=0.22							
Memory 4 years	1 (2528)	0 of 6 tests show no statistically significant improvement with intervention <u>Hopkins Verbal Learning Test, generalized estimating equation regression vs placebo (B coefficient)</u> Celecoxib: 0.12 [-0.06 to 0.30] p=0.20 Naproxen: -0.04 [-0.23 to 0.16] p=0.70 <u>Rivermead Behavioral Memory Test, generalized estimating equation regression vs placebo (B coefficient)</u> Celecoxib: -0.06 [-0.29 to 0.18] p=0.64 Naproxen: -0.13 [-0.37 to 0.11] p=0.28 <u>Brief Visuospatial Memory Test-Revised, generalized estimating</u>	Medium	Indirect	Imprecise	Consistent	Undetected	NA	Low

Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Direct-ness	Precision	Consistency	Reporting Bias	Optional Components	SOE
		equation regression vs placebo (B coefficient) Celecoxib: 0.05 [-0.14 to 0.23] p=0.62 Naproxen: -0.07 [-0.26 to 0.12] p=0.45							
Adverse Effects	NR								

3ME=Modified Mini-Mental State Examination; MCI= mild cognitive impairment; NP=Neuropsychological; NR=not reported; RCT=Randomized Controlled Trial; SD=Standard Deviation;

Appendix Table O4. Characteristics of eligible studies: NSAIDs in adults with MCI

Study **Design** **Country** **RoB**	**N=**	**Population** **Inclusion** **Age (mean)** **Sex** **Race** **Education** **Baseline Cog**	**Intervention**	**Comparison**	**Outcome** **Timing**	**Outcome** **Domain [Instrument]**
Thal, 2005[7] RCT USA High	1457	People aged 65+ with 8+ years of education and met criteria for MCI **Age** 75 **Sex** 32% **Race** NR **Education** (years) <11: 10% 12-17: 77% 18+: 13% **Baseline cognition** MMSE: 27.4 ADAS-Cog: 9.3	Rofecoxib 25 mg QD	Placebo	4 years	Global cognition [MMSE; ADAS-Cog] Memory [Buschke Selective Reminding Test (summed and delayed)]

3ME=Modified Mini-Mental State Examination; BID=twice daily; NP=Neuropsychological; NR=not reported; QD=daily; SD=Standard Deviation; RCT=Randomized Controlled Trial;

Appendix Table O5. Summary risk of bias assessments: NSAIDs in adults with MCI

Study	Overall Risk of Bias Assessment	Rationale
Thal, 2005[7]	High	Attrition 45%

References for Appendix O

1. Adapt Research Group. Results of a follow-up study to the randomized Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT). Alzheimer's & Dementia. 2013 Nov;9(6):714-23. doi: http://dx.doi.org/10.1016/j.jalz.2012.11.012. PMID: 23562431.

2. Breitner JC, Baker LD, Montine TJ, et al. Extended results of the Alzheimer's disease anti-inflammatory prevention trial. Alzheimer's & Dementia. 2011 Jul;7(4):402-11. doi: http://dx.doi.org/10.1016/j.jalz.2010.12.014. PMID: 21784351.

3. Adapt Research Group, Martin BK, Szekely C, et al. Cognitive function over time in the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT): results of a randomized, controlled trial of naproxen and celecoxib. Archives of Neurology. 2008 Jul;65(7):896-905. doi: http://dx.doi.org/10.1001/archneur.2008.65.7.nct70006. PMID: 18474729.

4. Adapt Research Group, Lyketsos CG, Breitner JC, et al. Naproxen and celecoxib do not prevent AD in early results from a randomized controlled trial. Neurology. 2007 May 22;68(21):1800-8. PMID: 17460158.

5. Small GW, Siddarth P, Silverman DH, et al. Cognitive and cerebral metabolic effects of celecoxib versus placebo in people with age-related memory loss: randomized controlled study. American Journal of Geriatric Psychiatry. 2008 Dec;16(12):999-1009. doi: http://dx.doi.org/10.1097/JGP.0b013e31818cd3a4. PMID: 19038899.

6. Kang JH, Cook N, Manson J, et al. Low dose aspirin and cognitive function in the women's health study cognitive cohort. BMJ. 2007 May 12;334(7601):987. PMID: 17468120.

7. Thal LJ, Ferris SH, Kirby L, et al. A randomized, double-blind, study of rofecoxib in patients with mild cognitive impairment. Neuropsychopharmacology. 2005 Jun;30(6):1204-15. PMID: 15742005.

Appendix P. Antidementia Drugs

Appendix Table P1. Characteristics of eligible studies: antidementia interventions in adults with normal cognition

Study Design Country RoB	N=	Population Inclusion Age (mean) Sex Race Education Baseline Cog	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
Cerebrolysin efficacy						
Gavrilova 2011[1] Observational Russia High	110	Adults aged 55 to 85 with an MMSE scores above 26, signs of cognitive deficit corresponding to stage 3 on the Global Deterioration Scale (GDS), and assessments of 0.5 on the Clinical Dementia Rating (CDR) scale Mean age: 67 years 74% Female Race: NR Education: NR Mean MMSE (SD): 28.6 (0.1) group 1 28.2 (0.1) group 2	Cerebrolysin (two courses per year for 3 years [lasting 4 weeks each] of 30ml cerebrolysin infusions in 100ml of physiological saline), or Cavinton (two courses per year for three years [lasting 4 weeks each] of 5 mg three times daily	Groups compared to one-another	3 years	Global Function [MMSE] Executive/attention/processing speed [Forward Number Naming] Executive/attention/processing speed [Reverse Number Naming] Executive/attention/processing speed [Frontal Dysfunction Battery] Executive/attention/processing speed [Wechsler Scale, Sound and Categorical Associations] Memory [Delayed 10-Word Reproduction] Visuospatial [Clock Drawing Test] Language [Boston Naming Test]
Donepezil efficacy						
Devi 2007[2] RCT USA Medium	28	Community-dwelling post-menopausal women aged 46 to 60 without depression Mean age: 54 100% Female 75% White	Donepezil 5mg daily for 6 weeks, then 10mg daily (if tolerated) for the remaining 20 weeks	Placebo daily for 26 weeks	26 weeks	Executive/attention/processing speed [WMS-III, Working Memory] Executive/attention/processing speed, Language [Controlled Oral Word Association] Memory [WMS-III, Logical Memory] Memory [Buschke Selective Reminding Test, list learning] Language [Boston Diagnostic Aphasia

Study Design Country RoB	N=	Population Inclusion Age (mean) Sex Race Education Baseline Cog	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
		Education: 100% ≥16 years Baseline global cog: NR				Examination, naming] Language [WAIS-III, Vocabulary]

Cognitive test abbreviations: 3MSE=Modified Mini Mental Status Examination; ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive Subscale; CVLT=California Verbal Learning Test; CDR=Change in Dementia Rating; COWA= Controlled Oral Word Association; MMSE=Mini-Mental State Examination; TMT=Trails Making Test (A & B); WAIS=Wechsler Adult Intelligence Scale; WMS= Wechsler Memory Scale

Other abbreviations: AD=Alzheimer's disease; DSM=Diagnostic and Statistical Manual of Mental Disorders (DSM); NINCDS-ADRDA=National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association; SD=Standard Deviation; RCT=Randomized Controlled Trial

Appendix Table P2. Summary risk of bias assessments: antidementia drug interventions in adults with normal cognition

Study	Overall Risk of Bias Assessment	Rationale
Antidementia		
Gavrilova 2011[1]	High	Systematic assignment instead of randomization. Attrition 20% with no sensitivity analysis
Devi 2007[2]	Medium	Attrition 14% in treatment group. Outcome assessor not independent

Appendix Table P3. Characteristics of eligible studies: antidementia interventions in adults with MCI

Study Design Country RoB	N=	Population Inclusion Age (mean) Sex Race Education Baseline Cog	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
Donepezil efficacy						
Doody 2009[4] Schuff 2011[3] (subset of Doody 2009)[4] RCT USA High	821	Healthy adults with MCI aged 45 to 90 who expressed a memory complaint representing a change from cognitive function Mean age: 70 45% Female 87% White Education: 0-7 years: <1% 8-15 years: 53% >15 years: 47% MMSE ≤ 28: 84%	Donepezil 5mg daily for 6 weeks, then 10mg daily for the remaining 42 weeks	Placebo daily for 48 weeks, with a 3-week single-blind run-in period	48 weeks	Biomarkers [MRI]: APC in hippocampal volume; changes in whole brain atrophy, ventricular atrophy, and cortical atrophy Global Cognition [ADAS-cog] Global Cognition [MMSE] Executive/attention/processing speed [Symbol Digit Modalities Test] Executive/attention/processing speed [WAIS-III, Digit Span Backwards]
Petrella 2009[5] RCT USA High	13	Healthy adults with MCI aged 55 to 90 with MMSE scores of at least 24 and without depressive symptoms Mean age: 68 Sex: NR Race: NR Mean education: 16 Mean MMSE (SD): 28.3 (1.7)	Donepezil 5mg daily for 6 weeks, followed by 10 mg daily for the remaining 4 months and 2 weeks	Placebo daily for 6 months	6 months	Biomarker [fMRI]: changes in dorsolateral prefrontal activation and ventrolateral prefrontal cortex activation Global Function [MMSE] Global Function [ADAS-cog] Executive/attention/processing speed [Digit Symbol] Executive/attention/processing speed [Digit Span Backwards] Memory [NYU Delayed Recall]
Petersen 2005[6] RCT USA Medium	769	Adults with amnestic MCI aged 55 to 90 with impaired memory, a Logical Memory Delayed-recall score	Donepezil 5mg daily for 6 weeks, followed by 10 mg daily for the remainder of the study	Placebo	3 years	Diagnosis [clinical criteria of the National Institute of Neurological and Communicative Diseases and Stroke and the Alzheimer's Disease and Related Disorders Association] Global Function [MMSE] Global Function [ADAS-cog original]

Study Design Country RoB	N=	Population Inclusion Age (mean) Sex Race Education Baseline Cog	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
		approximately 1.5 to 2 SD below an education-adjusted norm, a Clinical Dementia Rating (CDR) of 0.5, and a score of 24 to 30 on the MMSE Mean age: 73 46% Female Race: NR Education: NR Mean MMSE (SD): 27.27 (1.8) Mean ADAS-cog (SD): 11.26 (4.4) original 17.72 (6.1) modified				Global Function [ADAS-cog modified] Executive/attention/processing speed [composite measure] Language [composite measure] Memory [composite measure] Visuospatial [composite measure]
Salloway 2004[7] RCT USA High	270	Healthy adults aged 55 to 90 with MCI, a documented memory complaint, and MMSE scores ≥ 24, global Clinical Dementia Rating (CDR) score of 0.5 with memory box scores of 0.5 or 1, no more than two box scores other than memory rated as high as 1, and no box score rated greater than 1 Mean age: 72 42% Female 94% White	Donepezil 5mg daily for 42 days, then 10mg daily for the remainder of the study	Placebo daily for 2 years	2 years	Global Function [modified ADAS-cog] Executive/attention/processing speed [WMS-R, Digit Span Backwards] Executive/attention/processing speed [Symbol Digit Modalities Test] Executive/attention/processing speed [Maze test] Memory [NYU Paragraph Test] Language [modified Boston Naming Test] Language [Verbal Fluency]

Study Design Country RoB	N=	Population Inclusion Age (mean) Sex Race Education Baseline Cog	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
		Mean education: 15 Mean MMSE (SD): 27.5 (2.2) donepezil group 27.4 (2) placebo				
Donepezil & antidepressant efficacy						
Reynolds 2011[8] RCT USA High	130	Adults at least 65 years of age with normal cognition or MCI, and with remitted depression (a score of 15 or higher on the 17-item Hamilton Rating Scale for Depression)	Antidepressant pharmacotherapy with supportive depression care management (12 to 16 weeks), and donepezil (mean of) 7.8mg daily for 2 years	Placebo for 2 years	2 years	Global Function [composite=all tests below] Executive Function [composite=Stroop Neuropsychological Screening Test, Executive Interview, Trail Making Test B/A Ratio, and Wisconsin Card Sorting Test errors] Processing Speed [composite=Trail Making Test A, Digit Symbol, Grooved Pegboard] Memory [composite=Logical Memory Delayed Recall, Modified Rey-Osterreith Figure Delayed Recall, and California Verbal Learning Test Delayed Recall] Language [composite= Boston Naming Test, Spot-the-Word, Letter Fluency, and Animal Fluency] Visuospatial [composite=Modified Rey-Osterreith Figure copy, Simple Drawings, Block Design]
Rivastigmine efficacy						
Feldman 2007[9] RCT USA High	508	Adults aged 55 to 85 with MCI (defined by having a Global CDR score = 0.5, NYU Delayed Paragraph	Rivastigmine 1mg daily for 2 weeks, then 3-12mg daily (increases of 3mg at minimum of 4-week intervals) until end of study	Placebo daily for 4 years	Until diagnosis of AD, up to 4 years	Diagnosis [Time to Alzheimer's Disease] Global Cognition [MMSE]

Study Design Country RoB	N=	Population Inclusion Age (mean) Sex Race Education Baseline Cog	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
		Recall less than 9, 17-item HAM-D score less than 13, and HAM-D Item 1 [depressed mood] score =1) Mean age: 70 52% Female Race: NR Mean education: 11 Mean MMSE (SD): 27 (2.7)	or progression to AD; latter group could continue with starting dose of 3mg daily irrespective of treatment assignment			
Galantamine efficacy						
Peters 2012[12] RCT Germany High	232	Adults with amnestic MCI Mean age: 68 Sex: NR Race: NR Education: NR Mean MMSE (SD): 27.4 (2.2) glantamine group 27 (2.6) galantamine + memantine group 26.9 (2.1) placebo	Galantamine 8mg twice daily, galantamine (8mg) and memantine (10mg) twice daily	Placebo	2 years	Global Function [ADAS-cog]
Winblad 2008[11] Prins 2014[10] RCT (2) USA High	990	Adults at least 50 years of age with MCI, a CDR score of 0.5 and CDR memory score ≥0.5 Mean age: 70 45% Male 95% White Education: NR Median ADAS-	Galantamine 4 mg twice daily for 1 month, then 8 mg twice daily. If well tolerated, dose could be titrated to 12 mg twice daily, but could be lowered back to 8 mg twice daily after 1 month, if necessary. The dose selected at month 3 (8 or 12 mg twice daily) was fixed for	Placebo daily for 2 years	2 years	Biomarker [MRI]: hippocampal atrophy Diagnosis [CDR] Global Function [CDR-Sum of Boxes] Global Function [ADAS-cog/MCI] Executive, Processing Speed [Digit Symbol Substitution Test]

Study Design Country RoB	N=	Population Inclusion Age (mean) Sex Race Education Baseline Cog	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
		cog/MCI (range): 16 (2-54) galantamine 16 (2-61) placebo	the remainder of the study (23 months)			
	1058	Adults at least 50 years of age with a CDR score of 0.5 and CDR memory score ≥0.5 Mean age: 70 45% Male 95% White Education: NR Median ADAS-cog/MCI (range): 17 (1-57) galantamine 18 (2-63) placebo	Galantamine 4 mg twice daily for 1 month, then 8 mg twice daily for 1 month. If well tolerated, dose could be titrated to 12 mg twice daily, but could be lowered back to 8 mg twice daily after 1 month, if necessary. The dose selected at month 3 (8 or 12 mg twice daily) was fixed for the remainder of the study (23 months)	Placebo daily for 2 years	2 years	Global Function [ADAS-cog/MCI] Executive, Processing Speed [Digit Symbol Substitution Test]

ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive Subscale; MCI=mild cognitive impairment; MMSE= Mini Mental Status Exam; MRI= magnetic resonance imaging; NR=not reported; RCT=randomized controlled trial; SD=Standard Deviation; WAIS=Wechsler Adult Intelligence Scale; WMS=Wechsler Memory Scale

Appendix Table P4. Summary risk of bias assessments: antidementia drug interventions in adults with MCI

Study	Overall Risk of Bias Assessment	Rationale
Antidementia		
Doody 2009[4] Schuff 2011[3]	High	Attrition 39%
Petrella 2009[5]	High	Poor randomization. Attrition 13%
Petersen 2005[6]	Medium	Attrition 30% with sensitivity analysis
Salloway 2004[7]	High	Attrition 24%
Reynolds 2011[8]	High	Attrition 30% with sensitivity analysis; groups not described so not clear whether randomization held
Feldman 2007[9]	High	Attrition 35%
Peters 2012[12]	High	Method of randomization unclear. Attrition not clearly reported; likely greater than 50%.
Winblad 2008[11] Prins 2014[10]	High	Attrition 35%

Appendix P Table 5. Strength of evidence assessments: antidementia medication versus placebo control in adults with MCI

Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
Antidementia medication									
Dementia	1 (769)	No reduction in dementia diagnoses with donepezil Petersen 2005[6] (Donepezil) Hazard Ratio for risk of progression to AD (3 years): 0.8 [0.57 to 1.13]	Medium	Direct	Precise	Unknown	Undetected	N/A	Low
MCI	NR								
Biomarkers	NR								
Brief cognitive test performance	1 (769)	0 of 1 tests show statistically significant improvement at 3 years Petersen 2005[6] (Donepezil) Mean change from baseline in MMSE (SD) scores: Difference in mean [CI] change: -0.44 [-1.11 to 0.23]	Medium	Indirect	Precise	Unknown	Undetected	N/A	Low
Multidomain neuropsychological performance	1 (769)	0 of 2 tests show statistically significant improvement at 3 years Petersen 2005[6] (Donepezil) Mean change from baseline in ADAS-cog original (SD) scores: Difference in mean [CI] change: 0.06 [-1.07 to 1.19] Mean change from baseline in ADAS-cog (SD) modified scores: Difference in mean [CI] change: 0.6 [-0.79 to 1.99]	Medium	Indirect	Precise	Unknown	Undetected	N/A	Low
Executive/Attention/	1 (769)	0 of 1 tests show	Medium	Indirect	Imprecise	Unknown	Undetected	N/A	Insufficient

Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
Processing Speed		statistically significant improvement with Intervention							
Memory	1 (769)	0 of 1 tests show statistically significant improvement with Intervention	Medium	Indirect	Imprecise	Unknown	Undetected	N/A	Insufficient

AD=Alzheimer's disease; ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive Subscale; MCI=mild cognitive impairment; MMSE= Mini Mental Status Exam; SD=Standard Deviation

References for Appendix P

1. Gavrilova SI, Kolykhalov IV, Fedorova YB, et al. Potential of Preventive Treatment of Alzheimer's Disease: Results of a Three-Year Prospective Open Comparative Trial of the Efficacy and Safety of Courses of Treatment with Cerebrolysin and Cavinton in Elderly Patients with Mild Cognitive Impairment Syndrome. Neuroscience and Behavioral Physiology. 2011 May;41(4):391-8. doi: 10.1007/s11055-011-9427-4. PMID: 2011362050.

2. Devi G, Massimi S, Schultz S, et al. A double-blind, placebo-controlled trial of donepezil for the treatment of menopause-related cognitive loss. Gend Med. 2007 Dec;4(4):352-8. PMID: 18215726.

3. Schuff N, Suhy J, Goldman R, et al. An MRI substudy of a donepezil clinical trial in mild cognitive impairment. Neurobiol Aging. 2011 Dec;32(12):2318 e31-41. doi: 10.1016/j.neurobiolaging.2010.04.005. PMID: 20541841.

4. Doody RS, Ferris SH, Salloway S, et al. Donepezil treatment of patients with MCI: a 48-week randomized, placebo-controlled trial. Neurology. 2009 May 5;72(18):1555-61. doi: 10.1212/01.wnl.0000344650.95823.03. PMID: 19176895.

5. Petrella JR, Prince SE, Krishnan S, et al. Effects of donepezil on cortical activation in mild cognitive impairment: a pilot double-blind placebo-controlled trial using functional MR imaging. AJNR Am J Neuroradiol. 2009 Feb;30(2):411-6. doi: 10.3174/ajnr.A1359. PMID: 19001543.

6. Petersen RC, Thomas RG, Grundman M, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. N Engl J Med. 2005 Jun 9;352(23):2379-88. doi: 10.1056/NEJMoa050151. PMID: 15829527.

7. Salloway S, Ferris S, Kluger A, et al. Efficacy of donepezil in mild cognitive impairment: a randomized placebo-controlled trial. Neurology. 2004 Aug 24;63(4):651-7. PMID: 15326237.

8. Reynolds CF, 3rd, Butters MA, Lopez O, et al. Maintenance treatment of depression in old age: a randomized, double-blind, placebo-controlled evaluation of the efficacy and safety of donepezil combined with antidepressant pharmacotherapy. Arch Gen Psychiatry. 2011 Jan;68(1):51-60. doi: 10.1001/archgenpsychiatry.2010.184. PMID: 21199965.

9. Feldman HH, Ferris S, Winblad B, et al. Effect of rivastigmine on delay to diagnosis of Alzheimer's disease from mild cognitive impairment: the InDDEx study. Lancet Neurol. 2007 Jun;6(6):501-12. doi: 10.1016/S1474-4422(07)70109-6. PMID: 17509485.

10. Prins ND, van der Flier WA, Knol DL, et al. The effect of galantamine on brain atrophy rate in subjects with mild cognitive impairment is modified by apolipoprotein E genotype: post-hoc analysis of data from a randomized controlled trial. Alzheimers Res Ther. 2014 21 Jul;6(4):47. doi: 10.1186/alzrt275. PMID: 25478019.

11. Winblad B, Gauthier S, Scinto L, et al. Safety and efficacy of galantamine in subjects with mild cognitive impairment. Neurology. 2008 May 27;70(22):2024-35. doi: 10.1212/01.wnl.0000303815.69777.26. PMID: 18322263.

12. Peters O, Lorenz D, Fesche A, et al. A combination of galantamine and memantine modifies cognitive function in subjects with amnestic MCI. J Nutr Health Aging. 2012;16(6):544-8. PMID: 22659994.

Appendix Q. Diabetic Medication Treatment

Appendix Table Q1. Characteristics of eligible studies:diabetic medication treatments in adults with normal cognition

Study **Design** **Country** **RoB**	**N=**	**Population** **Inclusion** **Age (mean)** **Sex** **Race** **Education** **Baseline Cog**	**Intervention** **Mode** **Components** **Frequency** **Duration**	**Comparison** **Mode** **Components** **Frequency** **Duration**	**Outcome timing**	**Outcome** **Domain [Instrument]**
Glycemic control efficacy						
Cukierman-Yaffe 2014[1] (Substudy of ORIGIN trial) RCT Multinational Medium (High for outcomes at t5 for MMSE and t6 for DSS)	15077	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: 63 65% Male 59% White Mean MMSE (SD): 27.93 (2.74) MMSE group 27.50 (2.79) DSST group	Titrated basal insulin glargine targeting a fasting plasma glucose concentration of 5.3 mmol/L or lower – injected in evenings until target values achieved, then injected at least twice per week	Standard approaches to glycemic control (continuation of pre-randomization therapy)	Median 6.2 years	Diagnosis [MMSE<24, report forms] Global Function [MMSE] Executive/attention/processing speed [Digit Symbol Substitution]
Seaquist 2013[2] RCT (Substudy of ACCORD trial) USA Medium	2977	Adults aged 55 to 80 with type 2 diabetes, high HbA1c concentrations (>7.5%, >58 mmol/mol), and high risk for cardiovascular disease events Mean age: 63 47% Women 70% White Mean MMSE (IQR):	Intensive glycemic control targeting HbA1c to less than 6.0% for 40 months	Standard glycemic control targeting HbA1c to 7-7.9% for 40 months	40 months	Executive/attention/processing speed [Digit Symbol Substitution Test]

Study Design Country RoB	N=	Population Inclusion Age (mean) Sex Race Education Baseline Cog	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
		28 (26-29)				
Launer 2011[3] RCT (Substudy of ACCORD trial) USA Medium	2977	Adults aged 55 to 80 with type 2 diabetes, high HbA1c concentrations (>7.5%, >58 mmol/mol), and high risk for cardiovascular disease events Mean age: 63 47% Women 70% White Mean MMSE (IQR): 28 (26-29)	Intensive glycemic control targeting HbA1c to less than 6.0% for 40 months	Standard glycemic control targeting HbA1c to 7-7.9% for 40 months	40 months	Biomarker [MRI]: total brain volume Executive/attention/processing speed [Stroop Test] Executive/attention/processing speed [Digit Symbol Test] Memory [RAVLT]
Cheatham 2009[4] RCT USA High	42	Healthy overweight (BMI 25-29.9 kg/m^2) adults aged 20 to 42 without depression or diabetes Mean age: 35 Sex: NR Race: NR Education: NR Baseline global cog: NR	High glycemic load energy-restricted diet (116g/1000 kcal), or a low glycemic load energy-restricted diet (45g/1000 kcal) for 6 months	Groups compared to one-another	6 months	Executive/attention/processing speed [visual reaction time test] Executive/attention/processing speed, Motor [repeated acquisition test] Executive/attention/processing speed [scanning visual vigilance test] Language [grammatical reasoning test]
Luchsinger 2011[5] RCT USA High	2169	Adults at least 55 years of age with type 2 diabetes Mean age: 71 61% Female 52% White Education: 53% Elementary 29% High School	Diabetes case management (target HgbA1c was ≤7%, or ≤8% for participants with reduced life expectancy and/or severe hypoglycemic unawareness; BP goal was <130/85 mmHg, or <125/75 mmHg in the presence of proteinuria (>1g/24h) or renal	Usual care - care from primary care physicians without guidance from study personnel; primary care physicians were mailed diabetes care guidelines for 5 years	Up to 5 years (mean 3.5)	Global Cognition [Comprehensive Assessment and Referral Evaluation (CARE)-Diagnostic Scale]

Study Design Country RoB	N=	Population Inclusion Age (mean) Sex Race Education Baseline Cog	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
		16% College Baseline global cog: NR	insufficiency; in 2003 BP goal changed to <130/80 mmHg, except for proteinuria or renal insufficiency; LDL goals were < 130 mg/dl for primary prevention, and <100 mg/dl for those with cardiovascular disease) implemented by a diabetes nurse via telemedicine unit in participant's home in coordination with primary care physician for 5 years			
Lifestyle advice & glycemic control efficacy						
Koekkoek 2012[6] RCT Netherlands High	252	Adults aged 50 to 70 years with type II diabetes Mean age: 60 61% Female Race: NR Education: 10 years Baseline global cog: NR	Lifestyle advice (regarding diet, physical activity, and smoking); HbA1c level had to be kept <53 mmol/mol (a biguanide, prandial glucose regulator or sulphonylurea) and had to be altered when HbA1c was >48 mmol/mol., Antihypertensive treatment with an ACE inhibitor if needed, and blood pressure treatment with calcium channel blockers, thiazides or beta-blockers if needed (6 years)	Routine care (GPs were informed about diagnostic test results and patients received treatment according to the current guidelines of the Dutch College of GPs) for 6 years. Also reference group of spouses and acquaintances of the patients, without diabetes, was recruited and matched for age, sex, and education level	6 years	Executive/attention/processing speed [WAIS-III, Digit Span Forward] Executive/attention/processing speed [WAIS-III, Digit Span Backward] Executive/attention/processing speed [WAIS-III, Digit Symbol] Executive/attention/processing speed [Corsi block-tapping test forward] Executive/attention/processing speed [Corsi block-tapping test backward] Executive/attention/processing speed [Stroop Color Word Test I] Executive/attention/processing speed [Stroop Color Word Test II] Executive/attention/processing speed [Stroop Color Word Test III] Executive/attention/processing speed [Trail Making Test Part A] Executive/attention/processing speed [Trail Making Test Part B] Executive/attention/processing speed [Brixton

Study Design Country RoB	N=	Population Inclusion Age (mean) Sex Race Education Baseline Cog	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
						Spatial Anticipation Test] Memory [RAVLT, trials 1-5 and delayed recall and recognition] Memory [Location Learning Test, trials 1-5 and learning index and delayed trial] Memory [Complex Figure Test Delay] Language [Letter fluency] Language [Category fluency]

CARE=Comprehensive Assessment and Referral Evaluation; DSS= Digit Symbol Substitution; DSST= Digit Symbol Substitution Test; MMSE= Mini Mental Status Exam; NR=not reported; RAVLT= Rey's Auditory Verbal Learning Test; RCT= randomized controlled trial; SD= Standard Deviation

Appendix Table Q2. Summary risk of bias assessments: diabetic medication treatment in adults with normal cognition

Study	Overall Risk of Bias Assessment	Rationale
Glycemic control efficacy		
Cukierman-Yaffe 2014[1]	Medium (High for MMSE outcomes at year 5)	Attrition not clearly reported and sensitivity analysis performed only for the Digit Symbol Substitution cohort. Participants and outcome assessors not blinded
Seaquist 2013[2]	Medium (Table 4 and 5 analyses) High (other analyses)	Medium: Attrition not clearly reported. High: unclear if evaluations done by treatment assignment
Launer 2011[3]	Medium	Attrition 13%. Participants and outcome assessors not blinded
Luchsinger 2011[5]	High	Attrition not clearly reported. Participants not blinded
Cheatham 2009[4]	High	Method of randomization not clear. High attrition due to technical difficulties with encrypted data.
Lifestyle advice & glycemic control efficacy		
Koekkoek 2012[6]	High	Attrition 26%

Appendix Table Q3. Strength of evidence assessments: diabetic medication treatments versus standard of care/standard glycemic control in adults with normal cognition

Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
Antidiabetic									
Dementia	1 (12537)	0 of 1 tests show statistically significant improvement with intervention Cukierman-Yaffe 2014[1] Hazard ratio for incident cognitive impairment (composite of either incident dementia diagnosis of follow-up MMSE <24): 0.93 [0.86 to 1.0]	High	Direct	Precise	Unknown	Undetected	N/A	Low (due to study limitation of composite outcome with component of unequal importance, one of which is not clinical diagnosis and may be achieved due to chance)
MCI		NR							
Biomarkers	1 (2977)	1 of 2 tests show statistically significant improvement with intervention Launer 2011[3] Difference in decline in mean total brain volume: -13.0 vs. -17.7 cm3 (mean difference 4.6 cm^3 [2.0 to 7.3] (favors intervention) Difference in geometric mean abnormal white matter at follow-up: 1.10 cm^3 [1.02 to 1.19] (favors control)	Medium	Indirect	Precise	Inconsistent	Undetected	N/A	Insufficient
Brief cognitive test performance	2 (15514)	0 of 2 tests show statistically significant improvement: Cukierman-Yaffe 2014[1] Difference in least-squares	Medium	Indirect	Imprecise	Consistent	Undetected	N/A	Low

Outcome	# Trials (n)	Evidence Summary Summary statistics [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Optional Components	SOE
		mean raw MMSE score: 0.0037 [-0.0144 to 0.0217] Launer 2011[3] Difference in mean raw MMSE score: -0.01 [-0.18 to 0.16]							
Multidomain neuropsychological performance		NR							
Executive Function	2 (15514)	0 of 3 tests show statistically significant improvement with Intervention	Medium	Indirect	Imprecise	Consistent	Undetected	N/A	Low
Memory	1 (2977)	0 of 1 tests show statistically significant improvement with Intervention	Medium	Indirect	Imprecise	Unknown	Undetected	N/A	Low

MMSE=Mini Mental Status Exam

Appendix Table Q4. Characteristics of eligible studies: diabetic medication treatments in adults with MCI

Pioglitazone efficacy						
Hildreth 2015[7] RCT USA Low	78	Sedentary community-dwelling obese adults at least 55 years of age with MCI (90% had MCI) and without diabetes Mean age: 66 57% Female 88% White Education: 16 years Mean MMSE (SD): 28.4 (1.3) pioglitazone group 28.8 (1.3) placebo group	Pioglitazone 30mg daily for 1 month, then 45mg daily as tolerated for 5 months	Placebo for 6 months	6 months	Global Function [ADAS-cog] Executive/attention/processing speed [Stroop Test] Executive/attention/processing speed [Trail Making Test B] Executive/attention/processing speed [Digit Span Backwards] Executive/attention/processing speed [Digit Symbol Test] Executive/attention/processing speed [composite=comprised of above executive/attention/processing speed tests] Memory [RAVLT] Memory [Logical Memory II] Memory [Visual Reproduction] Memory [composite=comprised of above memory tests] Language [Boston Naming Test] Language [Category Fluency] Language [composite] Visuospatial [WAIS-R, Block Design] Visuospatial [WAIS-R, Block Design] Visuospatial [Clock Drawing Test] Visuospatial [composite=comprised of above visuospatial tests]

MCI=mild cognitive impairment; MMSE=Mini Mental Status Exam; RAVLT=Rey's Auditory Verbal Learning; RCT=randomized controlled trial; SD=Standard Deviation; WAIS=Wechsler Memory Scale

Appendix Table Q5. Summary risk of bias assessments: diabetic medication treatment in adults with MCI

Study	Overall Risk of Bias Assessment	Rationale
Antidiabetic		
Hildreth 2015	Low	

References for Appendix Q

1. Cukierman-Yaffe T, Bosch J, Diaz R, et al. Effects of basal insulin glargine and omega-3 fatty acid on cognitive decline and probable cognitive impairment in people with dysglycaemia: a substudy of the ORIGIN trial. Lancet Diabetes Endocrinol. 2014 Jul;2(7):562-72. doi: 10.1016/S2213-8587(14)70062-2. PMID: 24898834.

2. Seaquist ER, Miller ME, Fonseca V, et al. Effect of thiazolidinediones and insulin on cognitive outcomes in ACCORD-MIND. J Diabetes Complications. 2013 Sep-Oct;27(5):485-91. doi: 10.1016/j.jdiacomp.2013.03.005. PMID: 23680059.

3. Launer LJ, Miller ME, Williamson JD, et al. Effects of intensive glucose lowering on brain structure and function in people with type 2 diabetes (ACCORD MIND): a randomised open-label substudy. Lancet Neurol. 2011 Nov;10(11):969-77. doi: 10.1016/S1474-4422(11)70188-0. PMID: 21958949.

4. Cheatham RA, Roberts SB, Das SK, et al. Long-term effects of provided low and high glycemic load low energy diets on mood and cognition. Physiol Behav. 2009 Sep 7;98(3):374-9. doi: 10.1016/j.physbeh.2009.06.015. PMID: 19576915.

5. Luchsinger JA, Palmas W, Teresi JA, et al. Improved diabetes control in the elderly delays global cognitive decline. J Nutr Health Aging. 2011 Jun;15(6):445-9. PMID: 21623465.

6. Koekkoek PS, Ruis C, van den Donk M, et al. Intensive multifactorial treatment and cognitive functioning in screen-detected type 2 diabetes--the ADDITION-Netherlands study: a cluster-randomized trial. J Neurol Sci. 2012 Mar 15;314(1-2):71-7. doi: 10.1016/j.jns.2011.10.028. PMID: 22093142.

7. Hildreth KL, Van Pelt RE, Moreau KL, et al. Effects of pioglitazone or exercise in older adults with mild cognitive impairment and insulin resistance: a pilot study. Dement Geriatr Cogn Dis Extra. 2015 Jan-Apr;5(1):51-63. doi: 10.1159/000371509. PMID: 25852732.

Appendix R. Other Interventions

Appendix Table R1. Characteristics of eligible studies: other interventions in adults with normal cognition

Study Design Country RoB	N=	Population Inclusion Age (mean) Sex Race Education Baseline Cog	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
Other Medications						
Newhouse 2012[1] RCT US Medium	74	Non-smoking adults ≥55 with MCI (determined by subjective and objective impairments in cognitive function) Age, Mean (SD) 76 (7.6) 39% Female Race NR Years of Education, Mean (SD) 15.9 (2.7) MMSE, Mean (SD) 27.4 (2.0)	Transdermal nicotine patch 15 mg/day for 6 months	Placebo	6 months	Diagnosis: CDR Multidomain Neuropsychological Performance [Cognitive Drug Research Battery] Executive, Attention, Processing Speed [Connors Continuous Performance Test] Immediate and Delayed Paragraph Recall Test (NYU version) Digit Symbol Substitution Task
Forlenza 2011[2] RCT Brazil Medium	45	Community-dwelling adults ≥60 diagnosed with amnestic MCI per Mayo criteria. Age, Mean (SD) 72.5 (5.9) Sex NR Race NR Years of Education, Mean (SD) 10.5 (5.3) ADAS-Cog Score, Mean (SD)	Lithium titrated to serum levels 0.25-0.5 mmol/l (lower than dose for affective disorders); daily doses for 12 months	Placebo	12 months	Diagnosis [Clinical Dementia Rating Scale, Sum of Boxes] Multidomain Neuropsychological Performance [ADAS-Cog] Executive, Attention, Processing Speed [Trails A Time (seconds)] Executive, Attention, Processing Speed [Trails B Time (seconds)] Memory [CERAD Delayed recall] Memory [CERAD Figure recall] Memory [Sequence of Letters and Numbers score] (Cognitive Performance outcomes compared only baseline to endpoint within group, not

Study Design Country RoB	N=	Population Inclusion Age (mean) Sex Race Education Baseline Cog	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
		10.9 (5.9)				between group) Biomarker [Amyloid-beta] Biomarker [Phosphorylated tau at threonine] Biomarker [Total tau]
Music Interventions						
Hars 2014[3] Secondary analysis of RCT Switzerland Medium	134	Adults ≥65 at increased risk of falling Age, Mean (SD) 75 (7) 96.5% Female Race NR Education, 15% primary, 67% middle, 18% highschool MMSE, Mean (SD) 26.1 (2.9)	Weekly 1 hour supervised group class; multitask exercises to rhythm	Inactive control	6 months	Brief Cognitive Test Performance [MMSE] Visuospatial [Clock drawing test] Executive, Attention, Processing Speed [Trails A Time (seconds)]
Bugos 2007[4] US RCT High	31	Musically naïve older adults Age, Mean (SD) 70.5 (5.6) 81% Females Race NR Years of Education, Mean (SD) 16.4 (NR) No baseline cognitive screen	Individualized piano instruction ½ hour per week and independent practice 3 hours per week for 6 months. (Music theory instruction component)	Inactive control	9 months	Multidomain Neuropsychological Performance [Wechsler Adult Intelligence Scale (WAIS)] Executive, Attention, Processing Speed [Trails A Time (seconds)] Executive, Attention, Processing Speed [Trails B Time (seconds)]
Sleep interventions						
Lucassen 2014[5] US RCT High	121	Short-sleeping (<6.5 hours/night), obese (BMI 30-55 kg/m2) adults Age, Mean (SD)	Sleep extension (up to 7.5 hours/night) with life-style modifications using personalized sleep plans	Continue current sleep habits; habits reviews every 2 months	Median 14 months	Wechsler Abbreviated Scale of Intelligence (WASI) Rey Complex Figure Test California Verbal Learning Test (CVLT-II) Grooved Peg Board Test (GPeg)

Study Design Country RoB	N=	Population Inclusion Age (mean) Sex Race Education Baseline Cog	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
		41.1 (7) 76% Female 60% Black Years of Education NR No baseline cognitive screen				Wisconsin Card Sort Test (WCST) Trail Making Test A and B Verbal Fluency Test (FAS)
Sun 2013[6] RCT China High	80	Adults ≥60 years with reduced sleep quality (Pittsburgh Sleep Quality Index >5) Age, Mean (SD) 69 (8) 74.7% Female Race NR 1.3% high school or above MMSE, Mean (SD) 24.2 (3.7)	Sleep hygiene educational pamphlet; guided progressive muscle relaxation tape (unclear frequency and duration; presumably daily for 12 months)	Sleep hygiene educational pamphlet	12 months	Brief Cognitive Test Performance [MMSE] Weschler Memory Scale (Chinese revised)
Social Engagement						
Lam 2015[7] RCT China High	276	Older adults with MCI (determined by subjective and objective impairments in cognitive function) and without dementia Age, Mean (SD) 75.4 (6.5) 78.2% Female Race NR Education Level (Years), Mean (SD)	Cognitive group (board games, reading/discussing newspapers) at least 3, 1-hr sessions/week	Social activities -At least 3, 1-hr sessions/week	12 months	Diagnosis [Clinical Dementia Rating Scale, Sum of Boxes] Multidomain Neuropsychological Performance [ADAS-Cog (Chinese version] Brief Cognitive Test Performance [MMSE] Memory [Delayed recall] Language [CVFT]

Study **Design** **Country** **RoB**	**N=**	**Population** **Inclusion** **Age (mean)** **Sex** **Race** **Education** **Baseline Cog**	**Intervention** **Mode** **Components** **Frequency** **Duration**	**Comparison** **Mode** **Components** **Frequency** **Duration**	**Outcome timing**	**Outcome** **Domain [Instrument]**
		3.9 (3.6) Catonese MMSE. Mean (SD) 25.6 (2.3)				
Mortimer 2012[8] RCT China High	74	Adults age 60-79 with an education-adjusted Chinese MMSE score greater than 26 Age, Mean (SD) 67.8 (5.8) 67% Female Race NR Years of Education, Mean (SD) 11.7 (3.4) Mattis Dementia Scale Score, Mean (SD) 137.6 (7.6)	Group social interaction for 1 hour 3 times per week at a neighborhood community center	Inactive control with 4 check-in calls over 40 weeks	40 weeks	Executive, Attention, Processing Speed [WAIS digit span (forward)[Executive, Attention, Processing Speed [WAIS digit span (backward)] Visuospatial [Bell cancellation test] Visuospatial , Memory [Rey Figure (copying)] Visuospatial , Memory [Rey Figure (recall)] Executive, Attention, Processing Speed [Stroop Test (word)] Executive, Attention, Processing Speed [Stroop Test (color)] Executive, Attention, Processing Speed [Stroop Test (color-word)] Memory [Auditory Verbal Learning Test (immed. recall)[Memory [Auditory Verbal Learning Test (delayed recall)] Memory [Auditory Verbal Learning Test (delayed recognition] Language [Category Verbal Fluency (animals)] Executive, Attention, Processing Speed [WAIS Similarities] Executive, Attention, Processing Speed [Trails A Time (seconds)] Executive, Attention, Processing Speed [Trails B Time (seconds)] Visuospatial [Clock drawing test] Language [Boston Naming Test (correct names)] Multidomain Neuropsychological Performance [Mattis Dementing Rating Scale (total score)] Executive, Attention, Processing Speed [Mattis Attention Score]

Study Design Country RoB	N=	Population Inclusion Age (mean) Sex Race Education Baseline Cog	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome timing	Outcome Domain [Instrument]
						Executive, Attention, Processing Speed [Mattis Initiation Score] Visuospatial Mattis Construction Score] Executive, Attention, Processing Speed Mattis Conceptualization Score] Memory [Mattis Memory Score] Biomarker [Whole brain volume (% of total intracranial volume)]

Cognitive test abbreviations: 3MSE=Modified Mini Mental Status Examination; ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive Subscale; CERAD=Consortium to Establish a Registry for Alzheimer's Disease; CVLT=California Verbal Learning Test; CDR=Change in Dementia Rating; COWA= Controlled Oral Word Association; MMSE=Mini-Mental State Examination; TMT=Trails Making Test (A & B); WAIS=Wechsler Adult Intelligence Scale; WMS= Wechsler Memory Scale

Other abbreviations: AD=Alzheimer's disease; DSM=Diagnostic and Statistical Manual of Mental Disorders (DSM); NINCDS-ADRDA=National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association; SD=Standard Deviation; RCT=Randomized Controlled Trial

Appendix Table R2. Summary risk of bias assessments: other interventions in adults with normal cognition and MCI

Study	Overall Risk of Bias Assessment	Rationale
Other Medications		
Newhouse 2012[1]	Medium	Method of randomization unclear. Likely selective outcome reporting
Forlenza 2011[2]	Medium	Method of randomization unclear.
Music		
Hars 2014[3]	Medium	Method of randomization unclear. 16% attrition with no sensitivity analysis.
Bugos 2007[4]	High	Method of randomization unclear. Attrition 21%.
Sleep		
Lucassen 2014[5]	High	Method of randomization unclear. Attrition 39%.
Sun 2013[6]	High	Attrition 51%
Social		
Lam 2015[7]	High	Method of randomization unclear. Attrition 22% at 8 months, 24% at 1 year.
Mortimer 2012[8]	High	Suspected selection bias due to modifications post-randomization.

References for Appendix R

1. Newhouse P, Kellar K, Aisen P, et al. Nicotine treatment of mild cognitive impairment: a 6-month double-blind pilot clinical trial. Neurology. 2012 Jan 10;78(2):91-101. doi: 10.1212/WNL.0b013e31823efcbb. PMID: 22232050.

2. Forlenza OV, Diniz BS, Radanovic M, et al. Disease-modifying properties of long-term lithium treatment for amnestic mild cognitive impairment: randomised controlled trial. Br J Psychiatry. 2011 May;198(5):351-6. doi: 10.1192/bjp.bp.110.080044. PMID: 21525519.

3. Hars M, Herrmann FR, Gold G, et al. Effect of music-based multitask training on cognition and mood in older adults. Age Ageing. 2014 Mar;43(2):196-200. doi: 10.1093/ageing/aft163. PMID: 24212920.

4. Bugos JA, Perlstein WM, McCrae CS, et al. Individualized piano instruction enhances executive functioning and working memory in older adults. Aging Ment Health. 2007 Jul;11(4):464-71. doi: 10.1080/13607860601086504. PMID: 17612811.

5. Lucassen EA, Piaggi P, Dsurney J, et al. Sleep extension improves neurocognitive functions in chronically sleep-deprived obese individuals. PLoS One. 2014;9(1):e84832. doi: 10.1371/journal.pone.0084832. PMID: 24482677.

6. Sun J, Kang J, Wang P, et al. Self-relaxation training can improve sleep quality and cognitive functions in the older: a one-year randomised controlled trial. J Clin Nurs. 2013 May;22(9-10):1270-80. doi: 10.1111/jocn.12096. PMID: 23574290.

7. Lam LC, Chan WC, Leung T, et al. Would older adults with mild cognitive impairment adhere to and benefit from a structured lifestyle activity intervention to enhance cognition?: a cluster randomized controlled trial. PLoS One. 2015 31 Mar;10(3):e0118173. doi: 10.1371/journal.pone.0118173. PMID: 25826620.

8. Mortimer JA, Ding D, Borenstein AR, et al. Changes in brain volume and cognition in a randomized trial of exercise and social interaction in a community-based sample of non-demented Chinese elders. J Alzheimers Dis. 2012;30(4):757-66. doi: 10.3233/JAD-2012-120079. PMID: 22451320.

Appendix S. Biomarkers

Appendix Table S1. Relationship between biomarkers and cognitive performance and incidence outcomes adults with normal cognition

Author Year Comparison N= Follow-up	Diagnosis	Biomarkers [specific biomarker]	BCT & MNP [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
Cognitive Training		**None reported**					
Physical Activity		**None reported**					
Nutraceuticals							
Omega 3							
Witte 2014[1] Omega 3 (fish oil LC-n3-FA) 2.2 grams daily vs placebo n=65 6 months		I>C [MRI - gray matter volume] NS [MRI - white matter integrity]		I>C [executive composite: phonemic & semantic fluency, TMT A&B, Stroop parts 1-3] NS [sensorimotor speed composite: TMT part A, Stroop A & B]	NS [memory composite: AVLT learning, delayed recall, recognition, digit span backward]	2 of 6 favor I	
Resveratrol							
Witte 2014[2] Resveratrol 200 mg daily n=46 6 months (Resveratrol is a member of a group of plant compounds called polyphenols with possible antioxidant properties)		NS [total gray matter volume] NS [HC microstructure I>C [functional capacity, HC frontal]] I>C [functional capacity, HC parietal] I>C [functional			I>C [memory composite: AVLT retention, delayed recall, recognition, learning ability, 5th learning trial] I>C [AVLT retention] NS [AVLT delayed recall] NS [AVLT recognition] NS [AVLT learning ability] NS [AVLT fifth learning trial]		

Author Year Comparison N= Follow-up	Diagnosis	Biomarkers [specific biomarker]	BCT & MNP [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
		capacity, HC occipital]					
Diet Types		**None Reported**					
Multimodal Interventions		**None Reported**					
Other Health / Lifestyle Interventions		**None Reported**					
HRT / SEM / Soy							
HRT- Estrogen							
Women's Health Initiative substudies Estrogen (conjugated equine estrogen 0.625 mg) daily n=2947 (Shumaker 2004)[1] n=883 (Resnick, 2009)[2] n=520 (Coker 2009)[3] n=520 (Resnick, 2009)[4] Mean follow-up 5.7 to total 9+ years	NS [Probable Dementia][1]	NS [MRI: Total Brain Volume][2]	NS Screening [3MS][4]	NS [Letter Fluency][24]	NS [BVRT Errors][4]	1 of 16 favors C	NS [Probable Dementia][1]
	NS [MCI][1]	NS [MRI: Ventricle Volume][2]		NS [Digits Forward][4]	NS [CLVT Total List A Trials][4]		
	C>I [Probable Dementia or MCI][1]	NS [MRI: Hippocampal Volume][2]		NS [Digits Backward][4]	NS [CVLT Total List B][4]		
		C>I [MRI: Frontal Lobe Volume][2]			NS [CVLT Short Delay Free][4]		
		NS [White & Gray Matter][3]			NS [CVLT Long Delay Free][4]		
		NS [Basal Ganglia][3]					
HRT – Estrogen + Progesterone							
Women's Health Initiative: Estrogen +	C>I [Probable Dementia][3]	NS [MRI: Total Brain Volume][2]				0 of 2 (no differences)	

Author Year Comparison N= Follow-up	Diagnosis	Biomarkers [specific biomarker]	BCT & MNP [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
progestin daily n=883 (Resnick, 2009)[2] n=4532 (Shumaker, 2003)[3] 5-7 years	NS [MCI][3]	NS [MRI: Ventricle Volume][2]					
Vitamins							
Vitamin B							
Douaud 2013[3] de Jager 2012de Jager, 2012 #372} Smith 2010[4] Vit B (folic acid + B12 + B6) n=266 MRI n=166 2 years		I>C [reduction of posterior atrophy]	NS [MMSE]		NS [Hopkins Verbal Learning Test]	1 of 3 favor I	NR
Antihypertensives		**None Reported**					
Statins							
Statins vs Placebo							
Tendolkar 2010 [5] Atorvastatin 20mg for 2 weeks then increased to 40mg, after 4 weeks ezetimibe 10mg was added. Standard anticoagulant therapy vs matching-placebo and standard anticoagulant therapy n = 34 1 year follow up		I>C [Left amygdala volume] NS [Right amygdala volume] NS [Left hippocampal volume] NS [Right hippocampal volume] NS [White matter lesion volume]	[MMSE]	I>C [Digit Symbol Substation]	NS [Dutch Modified version of the Rey Auditory Verbal Learning Immediate word recall] I>C [Dutch Modified version of the Rey Auditory Verbal Learning Delayed word recall]	2 of 8 favored I	NR

Author Year Comparison N= Follow-up	Diagnosis	Biomarkers [specific biomarker]	BCT & MNP [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
NSAIDs		**None Reported**					
Antidementia							
Donepazil vs Placebo							
Petrella 2009[6] Donepezil therapy vs. Placebo n=13 6 months		I>C [dorsolateral prefrontal activation] I>C [ventrolateral prefrontal cortex activation]	**Brief cognitive test performance NS [MMSE] Multidomain neuropsychological performance NS** [ADAS-cog]	NS [Digit Symbol] NS [Digit Span Backwards]	NS [NY Paragraph, delayed recall]	2 of 5 favor I	NS
Anti-Diabetics							
Glycemic Control vs Placebo							
ACCORD-MIND Trial Seaquist 2013[7]**Launer 2011**[8] Intensive glycemic control targeting HbA1c to less than 6.0% vs. standard glycemic control targeting HbA1c to 7-7.9% n=2977 40 months		I>C [total brain volume]	**Brief cognitive test performance** NS [MMSE]	NS [Stroop Test] NS [DSST]	NS [RAVLT]	1 of 5 favor I	I>C [mortality]
Other Drugs		Awatiting					
Forlenza 2011[9] Lithium titrated to serum levels 0.25-0.5 mmol/l vs placebo	NS [Convert to probable AD]	I>C [Amyloid-beta] NS [Total tau]					NS [ischemic stroke, death due to sepsis;

Author Year Comparison N= Follow-up	Diagnosis	Biomarkers [specific biomarker]	BCT & MNP [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
n=41 12 months		I>C [Phosphorylated tau]					neither deemed due to treatment]

[a] mean global composite z score composed of Digit Symbol Coding, HVLT immediate and delayed recall, n-back task, and reaction time on task switching and Flanker tasks; [b] composite z score of HVLT-R immediate and delayed word recall; [c] composite z score of of Flanker congruent and incongruent reaction times;
3MSE=Modified Mini-Mental State Examination; C=inactive control; DSST=Digit Symbol Substitution Test; DSy=Digit Symbol Coding; HVLT-R=Hopkins Verbal Learning Test; I=intervention; I=intervention; NS=no statistically significant difference; RAVLT=Rey Auditory Verbal Learning Test; Stroop=Modified Stroop;

Appendix Table S2. Relationship between biomarkers and cognitive performance and incidence outcomes adults with MCI

Author Year Comparison N= Follow-up	Diagnosis	Biomarkers [specific biomarker]	BCT & MNP [instrument]	Executive/Attention/ Processing Speed [instrument]	Memory [instrument]	Intermediate Outcomes Summary	Adverse Effects [specific adverse effect]
Cognitive Training		**Awaiting**					
Physical Activity		**None Reported**					
Neutraceuticals		**None Reported**					
Diet Types		**None Reported**					
Multimodal Interventions		**None Reported**					
Other Health / Lifestyle Interventions		Awaiting Tables					
HRT – SEM Soy		**NR**					
Vitamins		**None Reported**					
Antihypertensives		**None Reported**					
Statins							
NSAIDs		**None Reported**					
Antidementia		**None Reported**					

Anti-Diabetics		**None Reported**					
Other Drugs		Awaiting					

C=inactive control; **I**=intervention; $\mathbf{I_1}$=first intervention; $\mathbf{I_2}$=second intervention; **NS**=not significant

References for Appendix S

1. Witte AV, Kerti L, Hermannstadter HM, et al. Long-chain omega-3 fatty acids improve brain function and structure in older adults. Cerebral Cortex. 2014 Nov;24(11):3059-68. doi: http://dx.doi.org/10.1093/cercor/bht163. PMID: 23796946.

2. Witte AV, Kerti L, Margulies DS, et al. Effects of resveratrol on memory performance, hippocampal functional connectivity, and glucose metabolism in healthy older adults. Journal of Neuroscience. 2014 Jun 4;34(23):7862-70. doi: http://dx.doi.org/10.1523/JNEUROSCI.0385-14.2014. PMID: 24899709.

3. Douaud G, Refsum H, de Jager CA, et al. Preventing Alzheimer's disease-related gray matter atrophy by B-vitamin treatment. Proc Natl Acad Sci U S A. 2013 Jun 4;110(23):9523-8. doi: 10.1073/pnas.1301816110. PMID: 23690582.

4. Smith AD, Smith SM, de Jager CA, et al. Homocysteine-lowering by B vitamins slows the rate of accelerated brain atrophy in mild cognitive impairment: a randomized controlled trial. PLoS One. 2010;5(9):e12244. doi: 10.1371/journal.pone.0012244. PMID: 20838622.

5. Tendolkar I, Enajat M, Zwiers MP, et al. One-year cholesterol lowering treatment reduces medial temporal lobe atrophy and memory decline in stroke-free elderly with atrial fibrillation: evidence from a parallel group randomized trial. Int J Geriatr Psychiatry. 2012 Jan;27(1):49-58. doi: 10.1002/gps.2688. PMID: 21308791.

6. Petrella JR, Prince SE, Krishnan S, et al. Effects of donepezil on cortical activation in mild cognitive impairment: a pilot double-blind placebo-controlled trial using functional MR imaging. AJNR Am J Neuroradiol. 2009 Feb;30(2):411-6. doi: 10.3174/ajnr.A1359. PMID: 19001543.

7. Seaquist ER, Miller ME, Fonseca V, et al. Effect of thiazolidinediones and insulin on cognitive outcomes in ACCORD-MIND. J Diabetes Complications. 2013 Sep-Oct;27(5):485-91. doi: 10.1016/j.jdiacomp.2013.03.005. PMID: 23680059.

8. Launer LJ, Miller ME, Williamson JD, et al. Effects of intensive glucose lowering on brain structure and function in people with type 2 diabetes (ACCORD MIND): a randomised open-label substudy. Lancet Neurol. 2011 Nov;10(11):969-77. doi: 10.1016/S1474-4422(11)70188-0. PMID: 21958949.

9. Forlenza OV, Diniz BS, Radanovic M, et al. Disease-modifying properties of long-term lithium treatment for amnestic mild cognitive impairment: randomised controlled trial. Br J Psychiatry. 2011 May;198(5):351-6. doi: 10.1192/bjp.bp.110.080044. PMID: 21525519.