[New 2015]

Nutritional interventions for people with dementia or cognitive impairment. [New 2015]

SCOPING QUESTION: Do nutritional interventions for people with dementia or cognitive impairment reduce the progression of cognitive decline?

BACKGROUND

The association of diet and nutrients with cognitive function, impairment and dementia has received a lot of attention in the past (Caracciolo et al., 2014; Ogawa, 2014). Some micronutrient deficiencies are potentially harmful to the brain and mechanistic evidence suggests that micro- and macro-nutrients, as well as dietary patterns, can interact with the neurodegenerative, inflammatory, oxidative stress and vascular processes that underlying dementia.

Experimental evidence from RCTs provides the best evidence base on the efficacy of interventions aimed at reducing cognitive decline in people with dementia. Studies on the potential effects of dietary supplements and nutrients on cognitive function have been conducted in people with dementia or cognitive impairment to determine whether these interventions can reduce the progression of cognitive decline (Caracciolo et al., 2014). However, dementia-related pathology likely predates the clinical onset of the disease by up to two decades, and disease modifying treatment is thought to be potentially effective before the symptomatic onset of dementia, during the long prodromal phase of the disease (Alzheimer's Disease International [ADI], 2014). RCTs carried out in cognitively healthy subjects at high risk of dementia typically assess whether interventions may preserve cognitive performance on cognitive tests over a relatively short period of time (from weeks to several months). These studies may provide indirect evidence on the efficacy of nutritional interventions aimed at reducing the progression of cognitive decline in those with dementia and may be important for secondary prevention, such as the delay of the onset of clinical symptoms irrespective of the underlying brain pathology. This latter body of evidence is also considered in the present scoping question and will be interpreted accounting for indirectness.

The evidence is herein presented according to the nutritional interventions aimed at preventing or reducing the progression of dementia and cognitive impairment in people with dementia or cognitive impairment. A selection of micro- (e.g., vitamins) and macro-nutrients (e.g., fatty acids), and dietary patterns have been considered consistent with the framework adopted in the 2014 Alzheimer Disease International (ADI) report on 'Nutrition and Dementia', in which up to date evidence from both observational and experimental studies has been systematically reviewed and critically appraised (Prince et al., 2014).

[New 2015]

PART 1: EVIDENCE REVIEW

Population/ Intervention / Comparison / Outcome (PICO)

1. **Population:** Older adults with cognitive impairment (including dementia)
2. **Interventions:** Dietary supplements (specifically micro- and macro-nutrients, including B vitamins, antioxidants, omega-3 and ginkgo); Mediterranean diet
1. **Comparison:** Placebo
2. **Outcomes:**
1. **Critical –** Cognitive decline
2. **Important** – Memory, executive functions, attention, activities of daily living

Search strategy

The following databases were used to identify studies for this review: Pubmed (1966 to August 2014); Embase (1960 to August 2014); and the Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials (until August 2014). The search was then pruned to include studies from the last 10 years (2004 to 2014). In order to identify relevant systematic reviews, the following search strategy was used:

1. (meta analysis[Publication Type] OR meta analysis[Title/Abstract] OR meta analysis[MeSH Terms] OR review[Publication Type] OR search*[Title/Abstract]). The following additional terms were used: ("Dementia"[Mesh] OR dementia[Title/Abstract] OR dementia[Text Word] OR Alzheimer Disease[Title/Abstract]) AND ("Nutrition Therapy"[Mesh] OR (nutrition[TIAB] AND therapy [TIAB]) OR "Nutrition Therapy"[TIAB] OR "Medical Nutrition Therapy" [TIAB] OR "Diet Therapy"[Mesh] OR "Diet Therapy"[TIAB] OR "dietary supplements" [TIAB] OR "dietary supplement" [TIAB] OR antioxidants [TIAB] OR ginkgo [TIAB] OR "w-3 PUFAs" [TIAB] OR "b vitamins"[TIAB] OR "mediterranean diet") AND ("cognition"[MeSH Terms] OR "cognition"[TIAB] OR "cognitive decline"[TIAB] OR "cognitive impairment" [TIAB])

In order to identify relevant primary studies the following search strategy was used:

2. (randomized controlled trial[Publication Type] OR randomized[Title/Abstract]). The following additional terms were used: ("Dementia"[Mesh] OR dementia[Title/Abstract] OR dementia[Text Word] OR Alzheimer Disease[Title/Abstract]) AND ("Nutrition Therapy"[Mesh] OR (nutrition[TIAB] AND therapy [TIAB]) OR "Nutrition Therapy"[TIAB] OR "Medical Nutrition Therapy" [TIAB] OR "Diet Therapy"[Mesh] OR "Diet Therapy"[TIAB] OR "dietary supplements" [TIAB] OR "dietary supplement" [TIAB] OR antioxidants [TIAB] OR ginkgo [TIAB] OR "w-3 PUFAs" [TIAB] OR "b vitamins"[TIAB] OR "mediterranean diet") AND ("cognition"[MeSH Terms] OR "cognition"[TIAB] OR "cognitive decline"[TIAB] OR "cognitive impairment" [TIAB]).

The search was updated until 19 August 2014.

Included in GRADE tables or footnotes

B Vitamins

- de Jager CA, Oulhaj A, Jacoby R, Refsum H, Smith AD (2012). Cognitive and clinical outcomes of homocysteine-lowering B-vitamin treatment in mild cognitive impairment: a randomized controlled trial. International Journal of Geriatric Psychiatry.27(6):592-600. doi:10.1002/gps.2758.

- Eussen SJ, de Groot LC, Joosten LW, Bloo RJ, Clarke R, Ueland PM, Schneede J, Blom HJ, Hoefnagels WH, van Staveren WA (2006). Effect of oral vitamin B-12 with or without folic acid on cognitive function in older people with mild vitamin B-12 deficiency: a randomized, placebo-controlled trial. The American Journal of Clinical Nutrition.84(2):361-370.

- Kwok T, Lee J, Law CB, Pan PC, Yung CY, Choi KC, Lam LC (2011). A randomized placebo controlled trial of homocysteine lowering to reduce cognitive decline in older demented people. Clinical Nutrition.30(3):297-302. doi:10.1016/j.clnu.2010.12.004.

- Malouf R and Grimley Evans J (2008). Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people. Cochrane Database of Systematic Reviews.4:CD004514. doi:10.1002/14651858.CD004514.pub2.

- Malouf R and Grimley Evans J (2003). Vitamin B6 for cognition. Cochrane Database of Systematic Reviews.4: CD004393.

- Malouf R and Areosa Sastre A (2003). Vitamin B12 for cognition. Cochrane Database of Systematic Reviews.3: CD004394.

- Walker JG, Batterham PJ, Mackinnon AJ, Jorm AF, Hickie I, Fenech M, Kljakovic M, Crisp D, Christensen H (2012). 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. American Journal of Clinical Nutrition.95(1):194-203. doi:10.3945/ajcn.110.007799.

Vitamin E

- Farina N, Isaac MG, Clark AR, Rusted J, Tabet N (2012). Vitamin E for Alzheimer's dementia and mild cognitive impairment. Cochrane Database of Systematic Reviews.11:CD002854. doi:10.1002/14651858.CD002854.pub3.

Omega – 3

- Rondanelli M, Opizzi A, Faliva M, Mozzoni M, Antoniello N, Cazzola R, Savarè R, Cerutti R, Grossi E, Cestaro B (2012). Effects of a diet integration with an oily emulsion of DHA-phospholipids containing melatonin and tryptophan in elderly patients suffering from mild cognitive impairment. Nutritional Neuroscience.15(2): 46-54. doi:10.1179/1476830511Y.0000000032.

- Sinn N, Milte CM, Street SJ, Buckley JD, Coates A, Petkov J, Howe PRC (2012). 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. British Journal of Nutrition.107(11):1682-1693. doi:10.1017/S0007114511004788.

- Sydenham E, Dangour AD, Lim WS (2012). Omega 3 fatty acid for the prevention of cognitive decline and dementia. Cochrane Database of Systematic Reviews.6:CD005379. doi:10.1002/14651858.CD005379.pub3.

Ginkgo

- Birks J, Grimley Evans J (2009). Ginkgo biloba for cognitive impairment and dementia. Cochrane Database of Systematic Reviews.1:CD003120.

- Ihl R (2013). Effects of Ginkgo biloba extract EGb 761 ® in dementia with neuropsychiatric features: review of recently completed randomised, controlled trials. International Journal of Psychiatry in Clinical Practice.17(Suppl 1):8-14. doi:10.3109/13651501.2013.814796.

- Jiang L, Su L, Cui H, Ren J, Li C (2013). Ginkgo biloba extract for dementia: a systematic review. Shanghai Arch Psychiatry.25(1):10-21. doi:10.3969/j.issn.1002-0829.2013.01.005.

- Lovera JF, Kim E, Heriza E, Fitzpatrick M, Hunziker J, Turner AP, Adams J, Stover T, Sangeorzan A, Sloan A, Howieson D, Wild K, Haselkorn J, Bourdette D (2012). Ginkgo biloba does not improve cognitive function in MS: a randomized placebo-controlled trial. Neurology.79(12):1278-1284. doi:10.1212/WNL.0b013e31826aac60.

- McCarney R, Fisher P, Iliffe S, van Haselen R, Griffin M, van der Meulen J, Warner J (2008). Ginkgo biloba for mild to moderate dementia in a community setting: a pragmatic, randomised, parallel-group, double-blind, placebo-controlled trial. International Journal of Geriatric Psychiatry.23(12):1222-1230. doi:10.1002/gps.2055.

- Vellas B, Coley N, Ousset PJ, Berrut G, Dartigues JF, Dubois B, Grandjean H, Pasquier F, Piette F, Robert P, Touchon J, Garnier P, Mathiex-Fortunet H, Andrieu S (2012). Long-term use of standardised Ginkgo biloba extract for the prevention of Alzheimer's disease (GuidAge): A randomised placebo-controlled trial. Lancet Neurology. 11(10):851-859. doi:10.1016/S1474-4422(12)70206-5.

Mediterranean diet

- Martínez-Lapiscina EH, Clavero P, Toledo E, Estruch R, Salas-Salvadó J, San Julián B, Sanchez-Tainta A, Ros E, Valls-Pedret C, Martinez-Gonzalez MÁ (2013). Mediterranean diet improves cognition: the PREDIMED-NAVARRA randomised trial. Journal of Neurology, Neurosurgery & Psychiatry. 84(12)1318-1325. doi:10.1136/jnnp-2012-304792.
- Sofi F, Abbate R, Gensini GF, Casini A (2010). Accruing evidence on benefits of adherence to the Mediterranean diet on health: an updated systematic review and meta-analysis. The American Journal of Clinical Nutrition.92(5): 1189–1196. doi:10.3945/ajcn.2010.29673.

PICO Table

Intervention	Comparison	Outcomes	Systematic reviews used for GRADE	Justification for systematic review used	Relevant GRADE Table
B VITAMINS					
Vitamin B12	Placebo	Cognitive decline Memory Executive functions Attention	Malouf and Areaosa Sastre (2003)	Systematic reviews relevant to the area	Table 1
Folic acid	Placebo	Cognitive decline Memory Executive functions Attention	Malouf and Grimley Evans (2008)		Table 3
Folic acid + vitamin B12	Placebo	Cognitive decline	Malouf and Grimley Evans (2008)		Table 2
Vitamin B6	Placebo	Memory Executive functions Cognitive decline	Malouf and Grimley Evans (2003)		Table 4
Antioxidants					
Vitamin E	Placebo	Cognitive decline	No systematic review with meta-analysis was found.		N/A

			Evidence was derived and narratively summarized from Farina et al. (2012).		
Omega-3	Placebo		Sydenham et al. (2012)	Recent systematic review relevant to the area	Table 5
Ginkgo	Placebo	Cognitive decline Activities of daily living	Jiang L et al. (2013)	Recent systematic reviews relevant to the area	Table 6
		Cognitive decline Behavioural symptoms Activities of daily living	Ihl R (2013)		Table 6
		Cognitive decline	Birks et al. (2009)		Table 7
Mediterranean diet	Placebo	Cognitive decline	Sofi F et al. (2010)	Recent systematic review relevant to the area	Table 8

Narrative description of studies that went into the analysis

B Vitamins

B12

The Cochrane review carried out by Malouf and Areosa Sastre (2003) included three randomized placebo-controlled trials (Fourniere et al., 1997; Seal et al., 2002; Hvas et al., 2004). Two of these studies enrolled older people with dementia (i.e., Alzheimer's disease) and low blood levels of vitamin B12 (Fourniere et al., 1997; Seal et al., 2002). The third study enrolled patients with vitamin B12 deficiency regardless of cognitive function (Hvas et al., 2004). The number of participants ranged from 11 to 140, for a total of 182. The interventions were compared to placebo. The duration of the studies ranged from 4-20 weeks (1-5 months). In one study, the treatment was given for 4 weeks with the outcome assessed in 12-week/3-month follow up). The authors of this Cochrane systematic review concluded that there was no evidence of the efficacy of vitamin B12 supplementation for cognitive function.

Folic acid (with or without vitamin B12)

The Cochrane review carried out by Malouf and Grimley Evans (2008) on folic acid with or without vitamin B12 comprised searches and assessment of primary studies updated to July 2008 and included eight randomized placebo-controlled trials. Four of these trials enrolled people with dementia, Alzheimer's disease or moderate to severe cognitive decline, while the other four enrolled healthy participants. The number of participants ranged from 11 to 818, for a total of 1523 subjects. The intervention was folic acid compared to placebo or folic acid plus vitamin B12 compared to placebo. The duration of the studies ranged from 4 to 30 weeks. The authors of this Cochrane systematic review concluded that there is insufficient evidence to determine whether folic acid is beneficial for cognitive function in those with or without dementia.

Eussen et al. (2006) conducted a double-blind placebo-controlled clinical trial on 195 subjects aged 70 years or older in order to study the effect of oral supplementation with vitamin B12 alone or in combination with folic acid. Cognitive function was assessed before and after 24 weeks of treatment using an extensive neuropsychological battery that included tests of various cognitive domains. There was no improvement in cognitive function in those who received the oral supplement containing vitamin B12 alone or in combination with folic acid. Conversely, performance on memory tests improved in those assigned to the placebo group.

B6

The Cochrane review carried out by Malouf and Grimley Evans (2003) included two randomized placebo-controlled trials in which the effect on cognitive function of supplementation with vitamin B6 was compared to placebo in healthy older people. The studies included 211 healthy women and 76 healthy men and had a duration of 5 and 12 weeks respectively (Deijen et al., 1992; Bryan et al., 2002). No trials of vitamin B6 involving people with cognitive impairment or dementia were found. This review found no evidence for short-term benefit from vitamin B6 for cognitive function.

Other RCTs

Walker et al. (2012) randomized 909 healthy older adults with elevated level of distress to B9+B12 supplementation or placebo. The study had a duration of two years and the primary outcome of interest was prevention of cognitive decline.

Kwok et al. (2011) randomized 140 subjects with mild to moderate Alzheimer disease or vascular dementia to receive 1 mg of vitamin B12 (methylcobalamin) and 5 mg of folic acid, or placebo once daily for 24 months . There were no significant differences in cognitive decline over the 24 months follow-up between groups measured with the Mattis dementia rating scale (MDRS), regardless of the homocysteine lowering effects of the vitamin compounds.

de Jager et al. (2012) randomized 266 participants with MCI to receive B-vitamins (folic acid, 0.8mg/day; B12 (cyanocobalamin), 0.5mg/day; B6 (pyridoxine HCL), 20mg /day) or placebo for two years. Cognitive measures were secondary endpoints. The authors found significant benefit of the B-vitamin treatment among participants with baseline homocysteine above the median (11.3mmol/L) in global cognition (Mini Mental State Examination (MMSE), P<0.001), episodic memory (Hopkins Verbal Learning Test–delayed recall, P=0.001) and semantic memory (category fluency, P=0.037). Clinical benefit occurred in the B-vitamin group for those in the upper quartile of homocysteine at baseline in global clinical dementia rating score (P=0.02) and IQCODE score (P=0.01).

Antioxidants (Vitamin E and cocoa)

Vitamin E
The Cochrane review carried out by Farina et al. (2012) included three randomized placebo-controlled trials. No meta-analysis was performed because outcome measures were too heterogeneous to be directly compared and results could not be pooled. The authors concluded that there is no evidence of efficacy of vitamin E in the treatment of people with Alzheimer's disease.

However, results in the RCT carried out in people with dementia by Sano et al. (1996) show some positive effects. The trial recruited 341 patients with Alzheimer's disease of moderate severity from 23 centres in the United States of America. Four groups were compared on a number of primary endpoints over two years: those who received vitamin E supplementation only (2000IU/day); selegiline only (a monoamine oxidase inhibitor); vitamin E and selegiline combined; or placebo. The primary cognitive endpoint was progression to severe dementia (i.e., CDR[i] 3.0), secondary outcomes included change in ADAS-Cog[ii] and MMSE scores (which were not assessed in the Cochrane review).

Omega-3

The Cochrane review carried out by Sydenham et al. (2012) included three randomized placebo-controlled trials. They studied the efficacy of various dosages of omega-3 long-chain (LC) poly-saturated fatty acids (PUFAs) (namely, eicosapentaenoic acid, EPA and docosahexaenoic acid [DHA]) in preventing incident dementia, or in preventing or slowing cognitive decline. All of the trials were conducted in cognitively healthy adults (aged 60 years or more). One study included people who had a clinically diagnosed myocardial infarction up to ten years before the start of the study and the primary outcome was mortality from a subsequent heart attack during the study period. The number of participants ranged from 302 to 2911, for a total of 4080. The duration of the studies ranged from 6 to 40 months. The interventions were compared to placebo (i.e., high-oleic sunflower oil, omega-9 rich olive oil, margarine).

Other RCTs

Rondanelli et al. (2012) conducted an RCT in 25 long-term care facilities residents with mild cognitive impairment aged 70 years or older to assess the efficacy of a dietary supplement (i.e., DHA, EPA, soy phospholipids, tryptophan, vitamin E and melatonin) on cognitive performance. Cognitive assessments were performed at baseline and after 12 weeks of treatment. The authors reported significant improvements in the intervention group on cognitive impairment, MMSE score and semantic fluency compared to placebo group; however, no adjustment for multiple comparisons was performed and chance may explain results in view of the very small sample size.

Sinn et al. (2012) conducted a 6-month RCT to investigate the benefits of supplementing a diet with n-3 PUFA, DHA and EPA for depressive symptoms, quality of life (QOL) and cognition in 50 patients (aged 65 years or more) who met criteria of mild cognitive impairment at baseline. Although cognitive function did not improve in the intervention group compared to the control group, depressive symptom scores were significantly reduced after 6 months

of high-EPA and high-DHA supplementation compared with placebo. Of the cognitive outcomes, significant improvements were only detected on fluid thinking ability and some trends for improvement were found for executive function.

Ginkgo biloba

In a recent systematic review conducted by Jiang et al. (2013), the authors include six RCTs of a minimum duration of 22 weeks on the effect of *Ginkgo biloba* in patients with dementia in their meta-analysis on a total of nearly 2000 participants. The reviewers identified considerable heterogeneity of effect. In one trial (Napryeyenko et al., 2007), the treatment effect size was more than twice that of any other trial and this was accordingly omitted from the meta-analysis. The other major source of heterogeneity was the mean patient age. Overall, treatment effect sizes for both cognitive decline (Syndrom Kurz Test [SKT], ADAS-cog and MMSE) and activities of daily living were of small size, but statistically significant in favour of gingko. Stratified analysis revealed a moderate and more clinically significant effect size in favour of *Ginkgo biloba* for trials with a mean patient age of 75 years or under, but no effect in trials with a mean patient age of over 75 years. However, the authors found evidence of publication bias and remarked that the RCTs were not independent. All of those included in the meta-analyses were directly or indirectly sponsored by the makers of EGb 761®, a standardised gingko extract; therefore, likelihood of bias was considered to be high.

Another recent systematic review (Ihl, 2013) focuses on the efficacy of *Ginkgo biloba* extract EGb 761® in older patients with Alzheimer or vascular dementia with neuropsychiatric features (with a composite score of 6 or more on the Neuropsychiatric Inventory (NPI) behavioural domain). Four RCTs were identified, with 1924 patients randomized. Three trials compared EGb 761® 120mg/day or 240mg/ day to placebo, while one used donepezil as an active control. The duration of randomized treatment was 22 or 24 weeks. In each placebo-controlled trial, EGb 761 ® was significantly superior for cognitive and neuropsychiatric outcomes, as well as for activities of daily living. The reviewer comments that the results support the efficacy of EGb 761® in age-related dementia with neuropsychiatric features and that the medication was safe and well tolerated. This review includes the Napryeyenko et al. (2007) study excluded (as an extreme outlier) from the Jiang et al. (2013) meta-analysis. All of the included trials were sponsored by the manufacturer of EGb 761®, a fact not mentioned in the review. The sole author of the review acknowledges that he has "received grants/research support or was involved as consultant, speaker or in advisory boards or received authors honoraria within the last three years from Schwabe (the makers of EGb 761®)" (p. 11) alongside 26 other companies.

A previously published Cochrane review carried out by Birks et al. (2009) aimed to assess the efficacy and safety of *Ginkgo biloba* for dementia and also included studies on participants with any cognitive impairment. There were 36 RCTs included studying patients with dementia or cognitive decline. The number of participants ranged from 14 to 513, for 4457 patients in total. The duration of the studies varied from 3-52 weeks, with the majority being of 12-weeks duration. The authors of the review concluded that evidence on any potential benefit of *Ginkgo* for people with dementia is inconsistent and unreliable. The overall quality of primary studies was poor, with small sample sizes and likely publication bias.

Other RCTs

McCarney et al. (2008) conducted a community-based, pragmatic, randomised, double-blind, parallel-group trial where 176 participants were randomized to a standardized extract of *Ginkgo biloba* (120mg/day) or a placebo control for 6 months. Primary outcomes were cognitive functioning (ADAS-Cog) and participant and carer-rated quality of life (QOL-AD). The investigators reported no evidence that a standard dose of high purity *Ginkgo biloba* confers benefits on these outcomes in mild-moderate dementia over 6 months. Although considered to meet inclusion criteria for the Jiang et al. (2013) review, results were not incorporated in the meta-analysis on the grounds that before and after treatment mean scores were not provided and standardized treatment effects could not be calculated. McCarney et al. (2008) was the only trial in the Jiang et al. (2013) review that had been conducted without support from the manufacturers of standardized *Gingko* supplement. In fact, treatment effects could be calculated using methods recommended by the Cochrane collaboration and these were therefore included in a revised set of meta-analyses carried out for this mhGAP evidence review.

Lovera et al. (2012) randomized 120 subjects with multiple sclerosis to receive *Ginkgo biloba* extract (120mg twice daily) or placebo for 12 weeks. Neuropsychological tests used to assess cognitive functions included PASAT[iii], Stroop interference, COWAT[iv], CVLT-II[v] delayed free recall. Treatment with *Ginkgo* extract did not improve cognitive performance in people with multiple sclerosis.

Vellas et al. (2012) randomized 2854 older adults with memory complaints to receive *Ginkgo biloba* extract or placebo for 5 years. The primary outcome was conversion to probable Alzheimer's disease in participants who received at least one dose of study medicationor placebo. The authors found that the long-term use of standardized *Ginkgo biloba* extract did not reduce the risk of progression to Alzheimer's disease compared to placebo.

Mediterranean diet

The review by Sofi et al. (2010) includes 7 prospective studies conducted on healthy subjects to investigate the effects of adherence to the Mediterranean diet on health status. The sample size of the studies varied from 50 to 2391 subjects and the follow up range was 4.5 – 20 years.

Other RCTs

Martínez-Lapiscina et al. (2013) conducted an RCT assessing 522 participants at high vascular risk after a nutritional intervention comparing two MedDiets (supplemented with either extra-virgin olive oil (EVOO) or mixed nuts) compared to a low-fat control diet. Global cognitive performance was examined by MMSE and Clock Drawing Test (CDT) after 6.5 years of nutritional intervention. Data are available for 224 patients randomized to Mediterranean diet + EVOO, 166 randomized to Mediterranean diet + Nuts and 132 TO control.

GRADE Tables

B Vitamins

Table 1. Vitamin B12 vs. placebo for reducing cognitive decline

Authors: I Bighelli
Question: In older adults with cognitive impairment, are vitamin B12 dietary supplements effective to reduce the progession of cognitive decline compared to placebo?
Bibliography: Malouf R, Areosa Sastre A (2003). Vitamin B12 for cognition. Cochrane Database of Systematic Reviews.3:CD004394.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin B12 dietary supplements	Placebo	Relative (95% CI)	Absolute		
Cognition I (follow-up mean 3 months; measured with: MMSE; Better indicated by higher values)												
1[1]	Randomzsed trials	Serious[2]	No serious inconsistency[3]	Serious[4]	Serious[5]	None	65	69	-	MD 0.10 higher (0.59 lower to 0.79 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Cognition II (follow-up mean 5 months; measured with: ADAS-Cog; Better indicated by lower values)												
1[6]	Randomzsed trials	Serious[2]	No serious inconsistency[3]	No serious indirectness	Very serious[7]	None	6	5	-	MD 0.04 higher (5.95 lower to 6.03 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Cognition III (follow-up mean 3 months; measured with CAMCOG[vi]; better indicated by lower values)												
1[8]	Randomzsed trials	Serious[2]	No serious inconsistency[3]	Serious[4]	Serious[5]	None	65	69	-	MD 0.60 lower (2.15 lower to 0.95 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Memory - Immediate recall (follow-up mean 3 months; measured with word learning test; better indicated by higher values)												

1[9]	Randomzsed trials	Serious[2]	No serious inconsistency[3]	No serious indirectness	Serious[10]	None	65	69	-	MD 0.20 lower (0.69 lower to 0.29 higher)	⨁⨁⨁◯ LOW	IMPORTANT
Memory - Delayed recall (follow-up mean 3 months; measured with word learning test; better indicated by higher values)												
1[11]	Randomzsed trials	Serious[2]	No serious inconsistency[3]	No serious indirectness	Serious[10]	None	65	69	-	MD 0.50 lower (1.01 lower to 0.01 higher)	⨁⨁⨁◯ LOW	IMPORTANT
Executive functions												
0	No evidence available					None	-	-	-	-		IMPORTANT
Attention												
0	No evidence available					None	-	-	-	-		

[1] From Analysis 1.4 of Malouf and Areosa Sastre's (2003) Cochrane Review.
[2] Allocation concealment is described as unclear.
[3] Not applicable: only one study was included in this analysis.
[4] The question being addressed by the guideline panel has a different population than that included in this study (i.e., this study does not include subjects with cognitive impairment, but only healthy subjects).
[5] The number of individuals included in the trial is small (n=134); the 95% confidence intervals are relatively broad and range from appreciable benefit to appreciable harm.
[6] From Analysis 1.1 of Malouf and Areosa Sastre's (2003) Cochrane Review.
[7] The number of individuals included in the trial is very low (n=11); the 95% confidence interval ranges from appreciable benefit to appreciable harm.
[8] From Analysis 1.3 of Malouf and Areosa Sastre's (2003) Cochrane Review.
[9] From Analysis 1.5 of Malouf and Areosa Sastre's (2003) Cochrane Review.
[10] The number of individuals included in the trial is low (n=134); the 95% confidence interval ranges from appreciable harm to no effect.
[11] From Analysis 1.6 of Malouf and Areosa Sastre's (2003) Cochrane Review.

Table 2. Folic acid + vitamin B12 vs. placebo for reducing cognitive decline

Authors: I Bighelli
Question: In older adults with cognitive impairment is folic acid + vitamin B12 dietary supplements effective for reducing the progression of cognitive decline compared to placebo?
Bibliography: Malouf R, Grimley Evans J (2008). Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people. Cochrane Database of Systematic Reviews.4:CD004514.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Folic acid + vitamin B12 dietary supplements	Placebo	Relative (95% CI)	Absolute		
Cognition I (follow-up mean 12 weeks; measured with MMSE; better indicated by higher values)												
1[1]	Randomized trials	No serious risk of bias	No serious inconsistency[2]	No serious indirectness	Serious[3]	None	72	66	-	MD 0.39 higher (0.43 lower to 1.21 higher)[4]	⨁⨁⨁◯ MODERATE	CRITICAL
Cognition II (follow-up mean 12 weeks; measured with ADAS-Cog; better indicated by lower values)												
1[5]	r Randomized trials	No serious risk of bias	No serious inconsistency[2]	No serious indirectness	Very serious[6]	None	72	61	-	MD 0.41 higher (1.25 lower to 2.07 higher)	⨁◯◯◯ LOW	CRITICAL
Memory (better indicated by lower values)												
0	No evidence available					None	0	-	-	MD 0 higher (0 to 0 higher)[7, 8]		IMPORTANT
Executive Functions												
0	No evidence available					None	-	-	-	MD 0 higher (0 to 0 higher)[8]		IMPORTANT
Attention												
0	No evidence available					None	-	-	-	MD 0 higher (0 to 0 higher)[8]		IMPORTANT

[1] From Analysis 4.1 of Malouf et al.'s (2008) Cochrane Review.
[2] Not applicable: only one study was included in this analysis.
[3] The number of individuals included in the trial is small (n=138); 95% confidence intervals are relatively broad and range from no effect to appreciable benefit.
[4] Kwok et al. (2012) did not find a significant difference in MMSE scores between subjects receiving vitamins B9+B12 and subjects receiving placebo.
[5] From Analysis 4.2 of Malouf et al.'s (2008) Cochrane Review..
[6] The number of individuals included in the trial is small (n=132); 95% confidence intervals are relatively broad and range from no effect to appreciable benefit.
[7] Walker et al. (2012) found an improvement in immediate recall (mean=0.242, 95% CI [0.01; 0.48]) and delayed recall (mean=0.308, 95% CI [0.06; 0.55]) (measured with TICS-M[vii]) for vitamin B9+B12 supplementation compared to placebo.
[8] Eussen et al. (2006) found a significant improvement in memory performance in the placebo group compared to the vitamin B12 supplementation group (composite score obtained computing z-scores of six tests of delayed and immediate memory recall); there were no significant differences in tests of attention (digit span forward) and executive function (including Stroop test, trail making test and verbal fluency).

Table 3. Folic acid vs. placebo for reducing cognitive decline

Authors: I Bighelli
Question: In older adults with cognitive impairment is folic acid effective for reducing the progression of cognitive decline compared to placebo?
Bibliography: Malouf R, Grimley Evans J (2008). Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people. Cochrane Database of Systematic Reviews.4:CD004514.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Folic acid	Placebo	Relative (95% CI)	Absolute		
Cognition (follow-up mean 24 weeks; measured with MMSE; better indicated by higher values)												
1[1]	Randomized trials[2]	No serious risk of bias	No serious inconsistency[3]	No serious indirectness	Very serious[4]	None	23	18	-	MD 0.13 lower (1.96 lower to 1.7 higher)	⨁⨁◯◯ LOW	CRITICAL
Memory - Delayed recall (follow-up mean 9 weeks; measured with Randt Memory Test; better indicated by higher values)												
1[5]	Randomized trials[6]	No serious risk of bias	No serious inconsistency[3]	No serious indirectness	Very serious[7]	None	16	13	-	MD 7.38 higher (8.58 lower to 23.34 higher)	⨁⨁◯◯ LOW	IMPORTANT
Memory - Cognitive Efficiency (follow-up mean 9 weeks; measured with Randt Memory Test; better indicated by lower values)												
1[8]	Randomized trials[6]	No serious risk of bias	No serious inconsistency[3]	No serious indirectness	Very serious[7]	None	16	13	-	MD 0.57 higher (1.97 lower to 3.11 higher)	⨁⨁◯◯ LOW	IMPORTANT
Executive Functions (follow-up mean 24 weeks; measured with DDST [2viii]; better indicated by lower values)												

1[9]	Randomized trials[2]	No serious risk of bias	No serious inconsistency[3]	No serious indirectness	Very serious[4]	None	23	18	-	MD 0.26 higher (4.12 lower to 4.64 higher)	⨁⨁◯◯ LOW	IMPORTANT
Attention (follow-up mean 9 weeks; measured with Randt Memory Test - attention efficiency; better indicated by lower values)												
1[10]	Randomized trials[6]	No serious risk of bias	No serious inconsistency[3]	No serious indirectness	Very serious[11]	None	16	13	-	MD 1.05 higher (0.17 lower to 2.27 higher)	⨁⨁◯◯ LOW	IMPORTANT

[1] From Analysis 1.1 of Malouf et al.'s (2008) Cochrane Review.
[2] Folic acid dosage = 1mg/day.
[3] Not applicable: only one study was included in this analysis.
[4] The number of individuals included in the trial is very low (n=41); the 95% confidence interval ranges from appreciable benefit to appreciable harm.
[5] From Analysis 3.2 of Malouf et al.'s (2008) Cochrane Review.
[6] Folic acid dosage = 15mg/day,
[7] The number of individuals included in the trial is very low (n=29); the 95% confidence interval ranges from appreciable benefit to appreciable harm.
[8] From Analysis 3.5 of Malouf et al.'s (2008) Cochrane Review.
[9] From Analysis 1.2 of Malouf et al.'s (2008) Cochrane Review.
[10] From Analysis 3.6 of Malouf et al.'s (2008) Cochrane Review.
[11] The number of individuals included in the trial is very low (n=29); 95% confidence interval ranges from no effect to appreciable benefit.

Table 4. Vitamin B6 vs. placebo for reducing cognitive decline

Authors: I Bighelli
Question: In older adults with cognitive impairment is vitamin B6 effective for reducing the progression of cognitive decline compared to placebo?
Bibliography: Malouf R, Grimley Evans J (2008). Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people. Cochrane Database of Systematic Reviews.4:CD004514.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Vitamin B6**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Cognition												
0	No evidence available					None	-	-	-	-		CRITICAL
Memory - Immediate recall (follow-up mean 5 weeks; measured with RAVLT[ix] 1-5; better indicated by higher values)												

1[1]	Randomized trials	No serious risk of bias	No serious inconsistency[2]	Very serious[3]	Very serious[4]	None	12	21	-	MD 2.21 lower (11.4 lower to 6.98 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Memory - Delayed recall (follow-up mean 5 weeks; measured with RAVLT 6; better indicated by higher values)												
1[1]	Randomized trials	No serious risk of bias	No serious inconsistency[2]	Very serious[3]	Very serious[4]	None	12	21	-	MD 0.32 lower (3.49 lower to 2.85 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Executive Functions I (follow-up mean 5 weeks; measured with Digit Span-Backwards; better indicated by higher values)												
1[5]	Randomized trials	No serious risk of bias	No serious inconsistency[2]	Very serious[3]	Very serious[4]	None	12	21	-	MD 0.48 lower (2.73 lower to 1.77 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Executive Functions II (follow-up mean 5 weeks; measured with Stroop Test; better indicated by lower values)												
1[6]	Randomized trials	No serious risk of bias	serious[2]	Very serious[3]	Very serious[7]	None	12	21	-	MD 0.06 lower (0.5 lower to 0.38 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Executive Functions III (follow-up mean 5 weeks; measured with Verbal Fluency – Initial Letter; better indicated by higher values)												
1[8]	Randomized trials	No serious risk of bias	No serious inconsistency[2]	Very serious[3]	Very serious[4]	None	12	21	-	MD 2.08 lower (10 lower to 5.84 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Attention												
0	No evidence available					None	-	-	-	-		IMPORTANT
Associated Recognition Task (follow-up mean 12 weeks; measured with Associated Recognition Task; better indicated by lower values)												
1[9]	Randomized	No serious risk of bias	No serious inconsistency[2]	Very serious[3]	Very serious[10]	None	38	38	-	MD 1.02 lower (2.4 lower to 0.36 higher)	⨁◯◯◯ VERY LOW	IMPORTANT

Speed of processing (follow-up mean 5 weeks; measured with Symbol Search; better indicated by higher values)												
1[11]	Randomized trials	No serious risk of bias	No serious inconsistency[2]	Very serious[3]	Very serious[4]	None	12	21	-	MD 0.06 higher (3.61 lower to 3.73 higher)	⨁⨁⨁◯ VERY LOW	IMPORTANT

[1] From Analysis 1.3 of Malouf et al.'s (2003) Cochrane Review.
[2] Not applicable: only one study was included in this analysis.
[3] The question being addressed by the guideline panel has a different population than that included in the systematic review (i.e., this review does not include subjects with cognitive impairment, but healthy subjects).
[4] The number of individuals included in the comparison is very low (n=33); the 95% confidence interval ranges from appreciable benefit to appreciable harm.
[5] From Analysis 1.2 of Malouf et al.'s (2003) Cochrane Review.
[6] From Analysis 1.4 of Malouf et al.'s (2003) Cochrane Review.
[7] The number of individuals included in the comparison is very low (n=33); the 95% confidence interval ranges from no effect to appreciable benefit.
[8] From Analysis 1.4 of Malouf et al.'s (2003) Cochrane Review.
[9] From Analysis 2.3 of Malouf et al.'s (2003) Cochrane Review.
[10] The number of individuals included in the comparison is very low (n=76); the 95% confidence interval ranges from appreciable benefit to no effect.
[11] From Analysis 1.1 of Malouf et al.'s (2003) Cochrane Review.

Omega-3

Table 5. Omega-3 dietary supplements vs. placebo for reducing cognitive decline

Authors: I Bighelli
Question: In older adults with cognitive impairment are Omega-3 dietary supplements effective for reducing the progression of cognitive decline compared to placebo?
Bibliography: Sydenham E, Dangour AD, Lim WS (2012). Omega 3 fatty acid for the prevention of cognitive decline and dementia. Cochrane Database of Systematic Reviews.6:CD005379. doi:10.1002/14651858.CD005379.pub3.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Omega-3 dietary supplements**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Cognition (follow-up 24 - 40 months; measured with MMSE; better indicated by higher values)												
2[1]	Randomized trials	No serious risk of bias	Serious[2]	Very serious[3]	No serious imprecision[4]	None	2231	990	-	MD 0.07 lower (0.25 lower to 0.1 higher)[5]	⨁⨁⨁◯ VERY LOW	CRITICAL

Memory - Immediate recall (follow-up 6 - 24 months; measured with word learning test; better indicated by lower values)												
2[6]	Randomized trials	No serious risk of bias	No serious inconsistency	Very serious[3]	No serious imprecision[7,8]	None	571	472	-	SMD[x] 0.01 higher (0.11 lower to 0.14 higher)[9]	⨁⨁⨁◯ LOW	IMPORTANT
Memory - Delayed recall (follow-up 6 - 24 months; measured with word learning test; better indicated by lower values)												
2[10]	Randomized trials	No serious risk of bias	No serious inconsistency	Very serious[3]	No serious imprecision[11]	None	571	472	-	SMD 0.04 lower (0.16 lower to 0.09 higher)[12]	⨁⨁⨁◯ LOW	IMPORTANT
Memory - Word Recognition (follow-up 6 - 24 months; measured with word learning test; better indicated by lower values)												
2[13]	Randomized trials	No serious risk of bias	No serious inconsistency	Very serious[3]	No serious imprecision[14]	None	570	472	-	SMD 0.04 higher (0.08 lower to 0.16 higher)	⨁⨁⨁◯ LOW	IMPORTANT
Executive Functions I (follow-up 6 - 24 months; measured with Verbal Fluency - Numbers of animals named; better indicated by lower values)												
2[15]	Randomized trials	No serious risk of bias	No serious inconsistency	Very serious[3]	No serious imprecision[16]	None	570	472	-	SMD 0.06 higher (0.06 lower to 0.18 higher)[17]	⨁⨁⨁◯ LOW	IMPORTANT
Executive Functions II (follow-up 6 - 24 months; measured with Digit Span Forward; better indicated by lower values)												
2[18]	Randomized trials	No serious risk of bias	No serious inconsistency	Very serious[3]	No serious imprecision[19]	None	560	458	-	MD 0.03 higher (0.25 lower to 0.31 higher)[20]	⨁⨁⨁◯ LOW	IMPORTANT
Executive Functions III (follow-up 6 - 24 months; measured with Digit Span Backward; better indicated by lower values)												
2[21]	Randomized trials	No serious risk of bias	No serious inconsistency	Very serious[3]	No serious imprecision[22]	None	557	458	-	MD 0.12 higher (0.12 lower to 0.36 higher)[23]	⨁⨁⨁◯ LOW	IMPORTANT
Attention												
0	No evidence available					None	-	-	-	-		IMPORTANT

[1] From Analysis 1.1 of Sydenham et al.'s (2012) Cochrane Review.
[2] Heterogeneity exceeds 50% (I-squared = 53%) and visual investigation of forest plot suggests some degree of heterogeneity.
[3] The question being addressed by the guideline panel has a different population than that included in the systematic review (i.e., this review does not include subjects with cognitive impairment, but only healthy subjects).
[4] 95% CI includes no effect and does not include appreciable benefit nor appreciable harm [-0.25, 0.10].

[5] In the RCT by Rondanelli et al. (2012), a significant effect of the intervention was found in slowing the decline in MMSE score over time (absolute difference placebo -2.17, supplement + 1.01, P=0.0011).
[6] From Analysis 2.1 of Sydenham et al.'s (2012) Cochrane Review. One study and two arms (with high and low dosages of omega-3, considered separately) of another study (Van de Rest, 2008) are compared.
[7] No explanation was provided.
[8] 95% CI includes no effect and does not include appreciable benefit nor appreciable harm [-0.11, 0.14].
[9] In the RCT by Rondanelli et al. (2012), the measures of long-term memory did not show a significant difference between treatments, although on the RAVLT there was an improvement from baseline immediate recall with intervention (mean change from baseline = 4.60) compared with a worsening of 4.86 points in the placebo group.
[10] From Analysis 2.2 of Sydenham et al.'s (2012) Cochrane Review. One study and two arms (with high and low dosages of omega-3, considered separately) of another study (Van de Rest, 2008) are compared.
[11] 95% CI includes no effect and does not include appreciable benefit nor appreciable harm [-0.16, 0.09].
[12] Sinn et al. (2012) did not find an improvement in delayed recall (measured with RAVLT) for EPA compared to control (mean=0.53, 95% CI [-1.35; 2,42]), nor for DHA compared to control (mean=0.36, 95% CI [-1,43; 2,14])
[13] From Analysis 2.3 of Sydenham et al.'s (2012) Cochrane Review. One study and two arms (with high and low dosages of omega-3, considered separately) of another study (Van de Rest, 2008) are compared.
[14] 95% CI includes no effect and does not include appreciable benefit nor appreciable harm [-0.08, 0.16].
[15] From Analysis 3.1 of Sydenham et al.'s (2012) Cochrane Review. One study and two arms (with high and low dosages of omega-3, considered separately) of another study (Van de Rest, 2008) are compared.
[16] 95% CI includes no effect and does not include appreciable benefit nor appreciable harm [-0.06, 0.18].
[17] In the RCT by Rondanelli et al., 2012, a positive trend for the semantic verbal fluency in the intervention group was found (placebo mean difference= -0.35, intervention mean difference =+1.73, P=0.060
[18] From Analysis 4.1 of Sydenham et al.'s (2012) Cochrane Review. One study and two arms (with high and low dosages of omega-3, considered separately) of another study (Van de Rest, 2008) are compared.
[19] 95% CI includes no effect and doesn't include appreciable benefit nor appreciable harm [-0.25, 0.31].
[20] Sinn et al. (2012) did not find an improvement in Digits Forward for EPA compared to control (mean=0.47, 95% CI [-2,32; 1.08]), nor for DHA compared to control (mean=0.12, 95% CI [-1,49; 1.73])
[21] From Analysis 4.2 of Sydenham et al.'s (2012) Cochrane Review. One study and two arms (with high and low dosages of omega-3, considered separately) of another study (Van de Rest, 2008) are compared.
[22] 95% CI includes no effect and does not include appreciable benefit nor appreciable harm [-0.12, 0.36].
[23] Sinn et al. (2012) did not find an improvement in Digits Backwad for EPA compared to control (mean= -0.74, 95% CI [-2,24; 0.77]), nor for DHA compared to control (mean=-1.20, 95% CI [-2,63; 0.23])

Ginkgo biloba

Table 6. *Gingko biloba* vs. placebo for reducing cognitive decline

Authors: M Prince
Question: Is *Gingko biloba* effective for reducing cognitive decline in people with dementia when compared to placebo?
Bibliography (systematic reviews):

- Jiang L, Su L, Cui H, Ren J, Li C (2013). Ginkgo biloba extract for dementia: a systematic review. Shanghai Arch Psychiatry.25(1):10-21. doi:10.3969/j.issn.1002-0829.2013.01.005.
- Ihl R (2013). Effects of Ginkgo biloba extract EGb 761 ® in dementia with neuropsychiatric features: review of recently completed randomised, controlled trials. International Journal of Psychiatry in Clinical Practice.17(Suppl.1):8-14. doi:10.3109/13651501.2013.814796.
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Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	***Gingko biloba***	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Any cognitive outcome, all trials included (follow up: range 22-26 months; assessed with Syndrom-Kurz test, MMSE, ADAS-Cog)												
8	Randomized trials	Very serious [2,3,4]	Very serious [5]	Not serious	Not serious	Publication bias strongly suspected strong association [1]	1294	1132	-	SMD 0.66 lower (1.15 lower to 0.17 lower)	⨁◯◯◯ VERY LOW	CRITICAL

Any cognitive outcome, two extreme outlier trials excluded (follow up: range 22-26 weeks; assessed with Syndrom-Kurz test, MMSE, ADAS-Cog)												
6	Randomized trials	Very serious [2,3,4]	Very serious [6]	Not serious	Not serious	Publication bias strongly suspected [1]	1071	899	-	SMD 0.24 lower (0.49 lower to 0.01 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Any disability outcome, all trials included (follow up: range 22-26 weeks; assessed with GERRI[xi], NAA)												
8	Randomized trials	Very serious [2,3,4]	very serious [7]	Not serious	Not serious	Publication bias strongly suspected [1]	1249	1064	-	SMD 0.3 lower (0.57 lower to 0.04 lower)	⨁◯◯◯ VERY LOW	IMPORTANT
Any disability outcome, one extreme outlier trial excluded [Napryeyenko et al., 2007] (follow up: range 22-26 weeks; assessed with GERRI, NAA)												
7	Randomized trials	Very serious [3,4]	Very serious [8]	Not serious	Not serious	Publication bias strongly suspected [1]	1051	867	-	SMD 0.19 lower (0.37 lower to 0.004 lower)	⨁◯◯◯ VERY LOW	IMPORTANT
Neuropsychiatric symptoms, all trials included (follow up: range 22-26 weeks; assessed with NPI[xii] total score)												
4	Randomized trials	very serious [3]	Very serious [9]	Not serious	Serious [10]	None	643	646	-	MD 2.99 lower (7.06 lower to 1.07 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Neuropsychiatric symptoms, one extreme outlier trial excluded (Napryeyenko et al., 2007) (follow up: range 22-26 weeks; assessed with NPI total score)												
3	Randomized trials	Serious [3]	Very serious [11]	Not serious	Serious [10]	None	445	449	-	MD 1.62 lower (3.99 lower to 1.07 higher)	⨁◯◯◯ VERY LOW	IMPORTANT

1. Suggestion of publication bias from funnel plot, in favour of studies favouring *Gingko biloba* over placebo (see Jiang et al., 2013).
2. All but one of the included studies was sponsored by the manufacturer of a widely used *Gingko* standardized preparation.
3. Attrition bias is a significant problem in four of the studies (see Jiang et al., 2013).
4. Heterogeneity (Isq) = 96.9%, with two extreme outliers (Mazza et al., 2006; Napryeyenko et al., 2007).
5. Heterogeneity (lsq)= 86.6%.
6. Heterogenity (Isq)=88.2%.
7. Heterogeneity (Isq)=71.6%.
8. Heterogeneity (Isq)=90.8%.
9. Wide confidence intervals ranging from substantial effect in favour of *Gingko* to moderate effect favouring placebo.
10. Heterogeneity (Isq)=79.7%.

Table 7. *Gingko biloba* vs. placebo for reducing cognitive decline

Authors: I Bighelli
Question: In older adults with cognitive impairment (with or without a diagnosis of dementia) is Ginkgo biloba effective for reducing the progression of cognitive decline compared to placebo?
Bibliography: Birks J, Grimley Evans J (2009). Ginkgo biloba for cognitive impairment and dementia. Cochrane Database of Systematic Reviews.1:CD003120.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	***Ginkgo biloba***	**Placebo**	**Relative (95% CI)**	**Absolute**		
Cognition I (follow-up 22-26 weeks; measured with ADAS-Cog; better indicated by lower values)												
3[1]	Randomized trials	No serious risk of bias	Serious[2]	No serious indirectness	Serious[3]	None	0[4]	-	-	MD 0.03 lower (0.77 lower to 0.71 higher)[5]	⨁⨁◯◯ LOW	CRITICAL
Cognition II (follow-up mean 12 weeks; measured with speed of learning test, SKT, Crichton Memory Impairment sub-test, Wechslet digit symbol, Benton digit span; better indicated by lower values)												
5[6]	Randomized trials	No serious risk of bias	Very serious[7]	No serious indirectness	No serious imprecision	None	129	121	-	SMD 0.65 lower (1.22 to 0.09 lower)	⨁⨁◯◯ LOW	CRITICAL
Cognition III (follow-up 22-26 weeks; measured with speed of learning test, SKT, Crichton Memory Impairment sub-test, Wechslet digit symbol, Benton digit span; better indicated by lower values)												
6[8]	Randomized trials	No serious risk of bias	Serious[9]	No serious indirectness	No serious imprecision	None	563	396	-	SMD 0.04 lower (0.14 lower to 0.06 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Memory and Attention (follow-up 22-26 weeks; measured with SKT; better indicated by lower values)												
4[10]	Randomized trials	No serious risk of bias	Very serious[11]	No serious indirectness	No serious imprecision	None	409	366	-	MD 3.57 lower (3.94 to 3.2 lower)[12]	⨁⨁◯◯ LOW	IMPORTANT
Executive Functions												
0	No evidence available					None	-	-	-	-		IMPORTANT

Attention												
0	No evidence available					None	-	-	-	-		IMPORTANT

[1] From Analysis 1.13.3 of Birks et al.'s (2009) Cochrane Review.
[2] I^2=66%.
[3] The 95% confidence interval ranges from appreciable benefit to appreciable harm.
[4] Number of patients not reported.
[5] Vellas et al., 2012 did not find a significant difference in the conversion to probable Alzheimer's disease (HR= 0.84, 95% CI [0.60; 1.18]) in participants randomized to *Ginkgo* compared to placebo.
[6] From Analysis 1.11.3 of Birks et al.'s (2009) Cochrane Review.
[7] I^2 = 77%.
[8] From Analysis 1.15.6 of Birks et al.'s (2009) Cochrane Review.
[9] I^2 = 57%.
[10] From Analysis 1.13.3 of Birks et al.'s (2009) Cochrane Review.
[11] I^2= 96%.
[12] Lovera et al. (2012) did not find an improvement in delayed recall as measured with CVLT-II (mean = 0.0, 95% CI [-0.3; 0.3]) in multiple sclerosis subjects randomized to *Ginkgo* compared to placebo.

Mediterranean diet

Table 8. Mediterranean diet vs. placebo for reducing cognitive decline

Authors: I Bighelli
Question: In older adults with cognitive impairment is Mediterranean diet effective for reducing the progression of cognitive decline compared to placebo?
Bibliography:

- Sofi F, Abbate R, Gensini GF, Casini A (2010). Accruing evidence on benefits of adherence to the Mediterranean diet on health: an updated systematic review and meta-analysis. The American Journal of Clinical Nutrition.92(5): 1189–1196. doi:10.3945/ajcn.2010.29673.
- Martínez-Lapiscina EH, Clavero P, Toledo E, Estruch R, Salas-Salvadó J, San Julián B, Sanchez-Tainta A, Ros E, Valls-Pedret C, Martinez-Gonzalez MÁ (2013). Mediterranean diet improves cognition: the PREDIMED-NAVARRA randomised trial. Journal of Neurology, Neurosurgery & Psychiatry. 84(12)1318-1325. doi:10.1136/jnnp-2012-304792.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Mediterranean diet**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Cognition (follow-up 4.5 - years; assessed with incidence of neurodegenerative diseases)												

5[1]	Observational studies	No serious risk of bias	No serious inconsistency	Very serious[2]	No serious imprecision	None	-[3]	-	RR 0.87 (0.81 to 0.94)[4]	-	⨁⨁⨁◯ VERY LOW	CRITICAL
								0%		-		
Memory												
0	No evidence available					None	-	-	-	-		IMPORTANT
Executive Functions												
0	No evidence available					None	-	-	-	-		IMPORTANT
Attention												
0	No evidence available					None	-	-	-	-		IMPORTANT
All-cause mortality (assessed with all-cause mortality)												
9[5]	Observational studies	No serious risk of bias	No serious inconsistency	Very serious[2]	No serious imprecision	None	-[3]	-	RR 0.92 (0.9 to 0.94)	-	⨁⨁⨁◯ VERY LOW	IMPORTANT
								0%		-		

[1] From Figure 4 of Rosi et al. (2010).
[2] The question being addressed by the guideline panel has a different population than that included in the systematic review (i.e., this review does not include subjects with cognitive impairment, but healthy subjects).
[3] Data not reported in the publication.
[4] In the RCT by Martinez-Lapiscina.et al. (2013), 60 cases of incident MCI (18 in Mediterranean Diet+EVOO; 19 in Mediterranean Diet+Nuts; 23 low-fat diet) and 35 cases of incident dementia (12 in Mediterranean Diet + EVOO; 6 in Mediterranean Diet + Nuts; 17 in low-fat diet) were diagnosed after 6.5 years of nutritional intervention. They also found a significant increase in MMSE score for the 224 patients randomized to Mediterranean diet + EVOO (mean=+0.62, 95% CI [+0.18; +1.05]) and the 166 randomized to Mediterranean diet + Nuts (mean=+0.57, 95% CI [+0.11; +1.03]), comparing to 132 controls.
[5] From Figure 1 of Rosi et al. (2010).

Evidence not mentioned in GRADE tables (including footnotes)

Multivitamin supplementation

Hankey et al. (2013) randomized 8164 patients with stroke or transient ischemic attack to double-blind treatment with B-vitamin tablets (i.e., folic acid, 2mg; vitamin B6, 25mg; vitamin b12, 500µg/day) or placebo in the VITAmins TO Prevent Stroke (VITATOPS) trial. The subjects were followed for up to 3.4 years. The data on MMSE were used for a secondary analysis and were available for 3089 patients. Although the vitamin tablets lowered mean plasma total homocysteine, results showed that B vitamins had no effect on the incidence of cognitive impairment or cognitive decline (e.g., difference in MMSE between group was 0.03; 95% CI: -0.13 to 0.19).

Galasko et al. (2012) assessed the effect of a multi-vitamin supplementation (Vitamin E, 800IU/day; Vitamin C, 500mg/ day; alpha-lipoic acid, 900mg/day) in a 16-week trial. The authors found a potential harmful effect of the multi-vitamin supplementation and reported that cognitive decline was significantly accelerated in those who received this supplementation compared to controls.

B Vitamins

In a recent meta-analysis Clarke et al. (2014) investigated the effect of lowering homocysteine level on cognitive function and cognitive aging. The authors included 22 RCTs conducted in participants with and without cognitive impairment or dementia or other diseases at baseline. The intervention of interest was lowering of homocysteine level usually obtained with long treatment with B12 vitamin in association or not with other vitamins. In their meta-analysis the authors found no significant association between homocysteine lowering and any cognitive outcome measure considered in the primary studies.

Antioxidants

Dysken et al. (2014) reported the results of the **TEAM-AD VA** collaborative study. This was a double-blind, placebo-controlled, parallel-group, RCT conducted in 613 patients with mild to moderate Alzheimer's disease taking acetylcholinesterase inhibitors (AChEIs). The trial had a factorial design that compared the effect of vitamin E (2000 IU/day), memantine (20mg/day), their combination or placebo over a mean follow-up of 2.3 years. The main cognitive endpoint was clinical progression (measured with the ADCS-ADL Inventory[xiii] score). Although differences in secondary cognitive outcomes were not significant across groups, the authors found that those who received vitamin E experienced a slower functional decline, with no evidence of potential harm.

Desideri et al. (2012) enrolled 90 elderly individuals with mild cognitive impairment randomized to consume once daily for 8 weeks a drink containing three different dosages of cocoa flavanols per day. They found no difference between the three treatment groups in MMSE scores. Results in Trail Making Test A and Trail Making Test B were significantly better in subjects assigned to high flavanols and intermediate flavanols in comparison with those

assigned to low flavanols. Similarly, verbal fluency test score was significantly better in subjects assigned to high flavanols in comparison with those assigned to low flavanols.

Grodstein et al. (2013) enrolled 5947 male physicians aged 65 years or older randomized to receive intervention (including β-carotene, vitamin E, ascorbic acid or a multivitamin) or placebo. No difference was found in mean cognitive change over 12 years of follow-up between the multivitamin and placebo groups or in the mean level of cognition at any of the assessments.

PART 2: FROM EVIDENCE TO RECOMMENDATIONS

Summary of evidence table

Outcome	Vitamin B12 *(MD [95% CI], quality)*	Folic acid *(MD [95% CI], quality)*	Folic acid + vitamin B12 *(MD [95% CI], quality)*	Vitamin E *(OR or MD [95% CI], quality)*	Vitamin B6 *(MD [95% CI], quality)*	Omega-3 *(MD [95% CI], quality)*	*Ginkgo biloba* *(MD [95% CI], quality)*	Mediterranean diet *(RR [95% CI], quality)*
Dementia progression (RCTs in those with dementia)				OR =0.49 (0.25 to 0.96) for increased severity, In favour of Vitamin E (2000 IU total daily), LOW quality WMD = 3.15 units (0.92 to 5.39) ADCS-ADL Inventory scores In favour of vitamin E, LOW quality		No significant changes in ADAS-cog and CDR-sum of the box p > .41 Between arms, LOW quality	SMD -0.66 (-1.15 to -0.17) in favour of Gingko (bias, inconsistency) (SKT, ADAS-Cog, MMSE) VERY LOW quality However, after excluding two extreme outlier trials SMD -0.24 (-0.49 to +0.01) (bias, inconsistency in SKT, ADAS-Cog, MMSE), VERY LOW quality	
Cognition short-term	*(Measured with MMSE*) MD 0.10 (-0.59 to +0.79) (3 months), VERY LOW quality		MD 0.39 (-0.43 to +1.21) (12 weeks), MODERATE quality			MD - 0.07 (-0.25 to +0.10), VERY LOW quality	MD 0.65 lower (1.22 to 0.09 lower) (12 weeks), LOW quality MD 0.41 (-0.87 to -+0.05) (12 weeks) In favour of *Ginkgo biloba* (ADAS-cog), VERY LOW quality	

	(Measured with CAMCOG) MD 0.60 lower (2.15 lower to 0.95 higher) VERY LOW quality		*(Measured with ADAS-COG)* MD 0.41 higher (1.25 lower to 2.07 higher) LOW quality					
Cognition long-term	MD 0.04 (-5.95 to +6.03) (5 months) VERY LOW quality	MD -0.13 (-1.96 to +1.7) (24 weeks) LOW quality	WMD = -0.6 (-2.2 to +0.9) CAMCOG total score				MD -0.03 (-0.77 to 0.71) (22-26 weeks) LOW quality HR[xiv] 0.84 (0.60 to 1.18) Dementia risk in at risk older adults MODERATE quality	RR 0.87 (0.81 to 0.94) (4.5 years) VERY LOW quality
Memory	Immediate recall: MD -0.20 (-0.69 to +0.29) LOW quality Delayed recall: MD - 0.50 (-1.01 to 0.01) LOW quality	MD +7.38 (-8.58 to +23.34) LOW quality	WMD -0.2 (-0.7 to + 0.3) (15 word learning test immediate)		Immediate recall: MD - 2.21 (-11.4 to +6.98) VERY LOW quality Delayed recall: MD - 0.32 (-3.49 to 2.85) VERY LOW quality	Immediate recall: SMD 0.01 (-0.11 to +0.14) LOW quality Delayed recall: SMD - 0.04 (-0.16 to 0.09) LOW quality	- 3.57 (-3.94 to -3.2) In favour of *Ginkgo,* VERY LOW quality	

Evidence to recommendation table

Benefits	*In people with dementia* There is very limited evidence on the efficacy of either B vitamins (including folate), omega-3 or the Mediterranean diet in reducing the progression of dementia (both cognitive and functional outcomes). Evidence on the potential beneficial effects of *Ginkgo biloba* is highly dependent upon trials sponsored by the leading manufacturer of standardized preparations, with very high levels of heterogeneity between studies and potential publication bias in favour of *Gingko*, including in all trials. However, after excluding two extreme outlier trials, the effect is no longer statistically significant.

	There is limited evidence (from two multi-centre RCTs conducted in the USA) that vitamin E supplementation in people with dementia due to Alzheimer's disease may slow the clinical progression from mild to moderate severity. However, at present this evidence should be considered inconclusive. There was no evidence on the impacts on activities of daily living. *In those with cognitive impairment* There is limited, inconsistent and qualitatively poor evidence on the effects of vitamins B or E and omega-3 on cognitive decline and dementia incidence. Current evidence does not suggest any benefit, but at present this should be considered inconclusive. There is good quality and consistent evidence from two recent RCTs that supplementation with *Ginkgo biloba* does not reduce dementia risk in older adults with memory complaints. However, at present this evidence should be considered inconclusive. In older adults without cognitive impairment, preliminary indirect evidence from one RCT suggests that the Mediterranean diet may preserve cognitive function compared to a low fat diet over more than 6 years.
Harms	In people with dementia there is no direct evidence on the effect of B vitamins or omega-3 on adverse events, mortality or tolerability outcomes.
Summary of the quality of evidence	The quality of evidence varies from moderate to very low across the interventions considered.

Value and preferences	
In favour	Micronutrient deficiencies (mainly vitamin B12 and folate) should be investigated and treated in a timely manner in older adults with suspected dementia, since this can be a rare cause of secondary dementia. Such deficiencies should be further investigated and corrected, where found, in all older adults, given the associated risks of neurological sequelae and an increased risk of cardiovascular events.

Against	There are no major issues against the interventions considered.
Uncertainty or variability?	No major variability.

Feasibility (including resource use considerations)	Dietary vitamin B12 and B9 (i.e., folate) deficiencies are relatively common in low- and middle-income countries, but diagnosis is costly and unpractical in most of these settings. Supplementation with vitamin B12 and folate may be considered in patients with dementia to treat dietary vitamin deficiencies where suspected on clinical grounds. While most of the micronutrient supplements considered in this review are relatively cheap, their daily long-term use can be associated with significant cumulative costs for patients and/or health systems in resource-poor settings.
Uncertainty or variability?	No major uncertainty or variability.

Recommendation and remarks

Recommendation

In people with either cognitive impairment or dementia, supplementation with nutrients, or use of Gingko biloba extracts should not be considered to improve cognitive function, to reduce the risk of developing dementia or to slow the progression of dementia once established.
When feasible, dietary deficiencies should be investigated and monitored in those with dementia and appropriate supplementations should be provided.

Rationale: Current evidence does not suggest any benefit in people with dementia or those with cognitive impairment with micronutrient supplementation (vitamin B complex, vitamin E, Omega-3) or Ginkgo biloba extract or Mediterranean diet; the quality of evidence is very low and at present this should be considered inconclusive.

Remarks

None of the primary studies available have been carried out in low- and middle-income countries. Moreover, very few randomized controlled trials to date on supplementation have been carried out in the patients groups who are deficient in the relevant micronutrient.
Vitamin E supplementation in those with dementia and adherence to a Mediterranean diet in cognitively healthy older adults may have some potential benefits on cognitive function: however, further research is required.

Judgements about the strength of a recommendation

Factor	Decision
Quality of the evidence	□ High □ Moderate □ Low **X Very low**
Balance of benefits vs. harms	□ Benefits clearly outweigh harms **X Benefits and harms are balanced** □ Potential harms clearly outweigh potential benefits
Values and preferences	**X No major variability** □ Major variability
Resource use	**X Less resource-intensive** □ More resource-intensive
Strength	**CONDITIONAL**

OTHER REFERENCES

Bryan J, Calvaresi E, Hughes E (2002). Short-term folate, vitamin B-12 or vitamin B-6 supplementation slightly affects memory performance but not mood in women of various ages. The Journal of Nutrition.132(6):1345-1356.

Clarke R, Bennett D, Parish S, Lewington S, Skeaff M, Eussen SJ, Lewerin C, Stott DJ, Armitage J, Hankey GJ (2014). Effects of homocysteine lowering with B vitamins on cognitive aging: meta-analysis of 11 trials with cognitive data on 22,000 individuals. The American Journal of Clinical Nutrition.100(2): 657-666. doi:10.3945/ajcn.113.076349.

Caracciolo B, Xu W, Collins S, Fratiglioni L (2014). Cognitive decline, dietary factors and gut-brain interactions. Mechanisms of Ageing and Development.136-137:59-69. doi:10.1016/j.mad.2013.11.011.

Deijen J, Van der Beek E, Orlebeke J, Van den Berg H (1992). Vitamin B-6 supplementation in elderly men: effects on mood, memory, performance and mental effort. Psychopharmacology.109(4): 489-496.

Desideri G, Kwik-Uribe C, Grassi D, Necozione S, Ghiadoni L, Mastroiacovo D, Raffaele A, Ferri L, Bocale R, Lechiara MC (2012). 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.60(3): 794-801. doi:10.1161/HYPERTENSIONAHA.112.193060.

Dysken MW, Sano M, Asthana S, Vertrees JE, Pallaki M, Llorente M, Love S, Schellenberg GD, McCarten JR, Malphurs J (2014). Effect of vitamin E and memantine on functional decline in Alzheimer disease: the TEAM-AD VA cooperative randomized trial. The Journal of the American Medical Association.311(1): 33-44. doi:10.1001/jama.2013.282834.

Fourniere FDL, Ferry M, Cnockaert X, Chahwakilian A, Hugonot-Diener L, Baumann F, Nedelec C, Buronfosse D, Meignan S, Fauchier C (1997). Vitamin B12 deficiency and dementia: a multicenter epidemiologic and therapeutic study preliminary therapeutic trial. Semaine des Hopitaux de Paris.73(5): 133-139.

Galasko DR, Peskind E, Clark CM, Quinn JF, Ringman JM, Jicha GA, Cotman C, Cottrell B, Montine TJ, Thomas RG (2012). Antioxidants for Alzheimer disease: a randomized clinical trial with cerebrospinal fluid biomarker measures. Archives of Neurology.69(7): 836-841.

Grodstein F, O'Brien J, Kang JH, Dushkes R, Cook NR, Okereke O, Manson JE, Glynn RJ, Buring JE, Gaziano JM (2013). Long-Term Multivitamin Supplementation and Cognitive Function in MenA Randomized Trial. Annals of Internal Medicine.159(12): 806-814.

Hankey GJ, Ford AH, Yi Q, Eikelboom JW, Lees KR, Chen C, Xavier D, Navarro JC, Ranawaka UK, Uddin W, Ricci S, Gommans J, Schmidt R, Almeida OP, van Bockxmeer FM (2013). Effect of B vitamins and lowering homocysteine on cognitive impairment in patients with previous stroke or transient ischemic attack: a prespecified secondary analysis of a randomized, placebo-controlled trial and meta-analysis. Stroke 44(8):2232-1139. doi:10.1161/STROKEAHA.113.001886.

Hvas AM, Juul S, Lauritzen L, Nexø E (2004). No effect of vitamin B-12 treatment on cognitive function and depression: a randomized placebo controlled study. Journal of Affective Disorders.81(3):269-273.

Lovera, J., B. Bagert, K. Smoot, C. Morris, R. Frank, K. Bogardus, K. Wild, B. Oken, R. Whitman and D. Bourdette (2007). Ginkgo biloba for the improvement of cognitive performance in multiple sclerosis: a randomized, placebo-controlled trial. Multiple Sclerosis.13(3):376-385.

Ogawa S (2014). Nutritional management of older adults with cognitive decline and dementia. Geriatrics & Gerontology International.14(Suppl.2):17-22.

Prince MJ, Albanese E, Guerchet M, Prina M. Nutrition and Dementia - A review of available research. London, Alzheimer's Disease International, 2014.

Rondanelli M, Opizzi A, Faliva M, Mozzoni M, Antoniello N, Cazzola R, Savarè R, Cerutti R, Grossi E, Cestaro B (2012). Effects of a diet integration with an oily emulsion of DHA-phospholipids containing melatonin and tryptophan in elderly patients suffering from mild cognitive impairment. Nutritional Neuroscience.15(2):46-54. doi:10.1179/1476830511Y.0000000032.

Seal EC, Metz J, Flicker L, Melny J (2002). A Randomized, Double-Blind, Placebo-Controlled Study of Oral Vitamin B12 Supplementation in Older Patients with Subnormal or Borderline Serum Vitamin B12 Concentrations. Journal of the American Geriatrics Society.50(1):146-151.

[i] Clinical Dementia Rating (CDR)

[ii] Alzheimer's Disease Assessment Scale-cognitive (ADAS-Cog)

[iii] Paced Auditory Serial Addition Test (PASAT)

[iv] Controlled Oral Word Association Test (COWAT)
[v] California Verbal Learning Test – 2nd Edition (CVLT-II)
[vi] Cambridge Cognition Examination (CAMCOG)
[vii] Modified Telephone Interview for Cognitive Status (TICS-M)
[viii] Denver Developmental Screening Test (DDST)
[ix] Rey Auditory Verbal Learning Test (RAVLT)
[x] Standardized mean difference (SMD)
[xi] Geriatric Evaluation by Relative's Rating Instrument (GERRI)
[xii] Neuropsychiatric Inventory (NPI)
[xiii] Alzheimer's Disease Co-operative Study - Activities of Daily Living Inventory (ADCS-ADL Inventory)
[xiv] Hazard ratio (HR)