Effect of Nutrients, Dietary Supplements and Vitamins on Cognition: a Systematic Review and Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

Background

Observational studies have suggested that various nutrients, dietary supplements, and vitamins may delay the onset of age-associated cognitive decline and dementia. We systematically reviewed recent randomized controlled trials investigating the effect of nutritional interventions on cognitive performance in older non-demented adults.

Methods

We searched MEDLINE, CINAHL, Embase, and the Cochrane Library for articles published between 2003 and 2013. We included randomized trials of ≥ 3 months' duration that examined the cognitive effects of a nutritional intervention in non-demented adults > 40 years of age. Meta-analyses were done when sufficient trials were available.

Results

Twenty-four trials met inclusion criteria (six omega-3 fatty acids, seven B vitamins, three vitamin E, eight other interventions). In the meta-analyses, omega-3 fatty acids showed no significant effect on Mini-Mental State Examination (MMSE) scores (four trials, mean difference 0.06, 95% CI -0.08 – 0.19) or digit span forward (three trials, mean difference -0.02, 95% CI -0.30 – 0.25), while B vitamins showed no significant effect on MMSE scores (three trials, mean difference 0.02, 95% CI -0.22 – 0.25). None of the vitamin E studies reported significant effects on cognitive outcomes. Among the other nutritional interventions, statistically significant differences between the intervention and control groups on at least one cognitive domain were found in single studies of green tea extract, Concord grape juice, chromium picolinate, beta-carotene, two different combinations of multiple vitamins, and a dietary approach developed for the control of hypertension.

Conclusions

Omega-3 fatty acids, B vitamins, and vitamin E supplementation did not affect cognition in non-demented middle-aged and older adults. Other nutritional interventions require further evaluation before their use can be advocated for the prevention of age-associated cognitive decline and dementia.

Key words: nutrition, micro-nutrients, macro-nutrients, dementia

INTRODUCTION

By 2050, the number of individuals with dementia worldwide is projected to reach 135 million.(1) Dementia, a devastating condition, adversely affects the cognitive abilities, independence, and quality of life of those affected and leads to health costs equivalent to those of heart disease and cancer.(2) In 2012, the World Health Organization declared dementia a public health priority.(3)

The mechanisms underlying the development of age-associated cognitive decline and dementia are felt to be operant 10–15 years or more before the development of clinical symptoms.(4,5) Recent reports suggest that there is a decline in the age-specific prevalence of dementia,(6-8) providing indirect evidence of potentially modifiable risk factors.(5) Effective strategies that can ameliorate the anticipated

dramatic growth in the number of individuals affected by dementia brought on by population aging are needed.[3,5] In the absence of curative treatment,[9] preventing or postponing the onset of dementia is of critical importance.[5] A five-year delay in the development of Alzheimer's disease (the most common neurodegenerative cause of late-life dementia) would reduce its prevalence by 50%.[10]

While to date no interventions have been shown to conclusively decrease the risk of age-associated cognitive decline or the development of Alzheimer's disease,[9] there is a large body of evidence from observational studies suggesting that vitamins, nutrients, and dietary supplements (e.g., omega-3 fatty acids,[11,12] folic acid,[13] vitamins B6,[13] B12,[13] C,[14,15] D,[16] and E[14,15] may delay the onset of age-associated cognitive decline and various forms of dementia including Alzheimer's disease.[17,18] A variety of mechanisms including correction of metabolic derangements or dietary deficiencies have been proposed by which they may affect cognitive health.[19]

The purpose of this systematic review is to summarize the findings of recent randomized controlled trials (RCTs) investigating the cognitive impact of nutritional interventions (e.g., nutrients [including macro-nutrients, vitamins, or minerals], diet, dietary supplement, fortified food, or medical food) of three months or longer in middle-aged and older (> 40 years) non-demented adults. We performed meta-analyses of the effects where possible.

METHODS

The approach outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*[20] was followed and the reporting was done in accordance with *PRISMA* (*Preferred Reporting Items for Systematic Reviews and Meta-Analyses*).[21]

Data Sources and Search Strategy

Literature searches were performed in June 2013 on MEDLINE, Embase, CINAHL, and the Cochrane Database of Systematic Reviews. For the MEDLINE search, the Medical Subject headings (MeSH) terms (exploded) *Delirium*, *Dementia*, *Amnestic*, and *Cognitive Disorders* with the subheading "prevention and control" were combined with the terms *Nutrition Assessment*, *Nutrition Therapy*, *Diet*, *Micronutrients* and *Food,* plus *Nutrition* as a keyword. Delirium, dementia, and other related terms were searched with the diet therapy subheading as a separate set. A supporting keyword search was also done: (cognition disorder* or Alzheimer* or mild cognitive decline) AND (food* or diet* or nutrition* or apolipoprotein* or lipoprotein* or micronutrient* or mineral*). Searches were limited to meta-analyses, systematic reviews, or RCTs performed on middle-aged and/or older human study populations and published between 2003 and June 2013. Other systematic reviews surveyed the literature prior to 2006.[22-24] Our systematic review was intended to update this prior work. We wanted to focus on those nutritional interventions attracting the greatest current interest. A concern we had in including older studies was the change that that has occurred in typical food intake over the last 20+ years[25] as there is evidence that baseline dietary intake may impact on the effect that dietary supplements have on cognitive function. The other databases were searched by similar strategies using terms from their specific thesauri. The search was not limited to articles written in any specific language. The full search strategy is attached in Appendix 1. Other articles included in our systematic review were either known by the authors or identified by manually searching the bibliographies of retrieved articles.

Study Selection

Two of the authors independently screened the titles and abstracts of each of the articles identified in the search for possible inclusion in our systematic review. Articles were selected for full-text review if they met the following criteria: (i) RCT where participants were allocated to either a dietary intervention (e.g., nutrient [including macro-nutrients, vitamins, or minerals], diet, dietary supplement, fortified food, or medical food) or a control arm; (ii) all participants were 40 years of age or older and judged to have normal cognition or mild cognitive impairment (note: if it was not explicitly noted that all cases of diagnosed or suspected dementia were excluded, a study was not selected for full-text review); (iii) intervention duration three or more months (to exclude studies that dealt with the acute effects of nutritional interventions); and, (iv) included cognition as an outcome measure. Discrepancies were resolved either by consensus or the involvement of a third author if necessary.

Full-text articles were reviewed independently by two of the authors for their eligibility of inclusion in the systematic review. Study quality, based on the procedures used for randomization, allocation concealment and blinding,[20] and excluding persons with an underlying condition that could affect cognition, was considered during the study selection process.

Data Extraction

Full-text articles selected for inclusion had the following information extracted: authors, country where the study was done, date of publication, information on specific inclusion and exclusion criteria, sample size, proportion of total sample that was female, proportion of total sample completing the study, mean age, other characteristics of the study population, nutritional intervention used (including information on dose and frequency of a supplement), duration of study, intervention and control adherence, outcome measures, and results. We focused on examining the outcome measure(s) results as reported for the entire group. As mean (standard deviation [SD]) change in the cognitive

outcome(s) from baseline was frequently not reported, we noted the final mean value, SD, and number of participants in each group. If a trial had two or more intervention arms, combining their data was considered if the arms were judged similar (e.g., they used the same nutritional intervention except for dosage)[20] and the same control group was utilized. This was done with one study[26] where we pooled two intervention arms (moderate and higher dosages of the same nutritional intervention).

Two authors extracted the data independently with any disagreements resolved by consensus or the involvement of a third author if necessary.

Assessment of the Risk for Bias in Included Studies

Two of the authors independently assessed and rated the trials for their risk of bias based on criteria derived from the *Cochrane Handbook for Systematic Reviews of Interventions*.[20] The methods used for randomization and blinding were examined. A low risk of bias was considered present when the approach taken was deemed adequate for both randomization and blinding, moderate if the approach taken was either unclear or only partially met the pre-determined criteria for adequacy, and high risk when these pre-determined criteria were not met. Disagreements were resolved by consensus or the involvement of a third author if necessary.

Data Analysis

A meta-analysis was done if three or more studies examined the same intervention with the same outcome measure. We did not encounter any situations where two studies examined the same intervention with the same outcome measure where a meta-analysis could have been performed. A fixed effect model was used. A summary measure of the mean difference with a 95% confidence interval (CI) was calculated. Statistical analysis for heterogeneity was assessed using chi-square test for heterogeneity and the I^2 statistic to quantify total variation across studies attributable to heterogeneity. Meta-analysis results are presented as forest plots. Funnel plots of the meta-analyses were visually inspected to look for evidence of publication bias, but statistical testing was not done because of the small number (< 10 / meta-analysis) of included studies. Statistical analyses were performed using the software program Review Manager (Review Manager 5.2; The Nordic Cochrane Centre, Copenhagen, Denmark).

RESULTS

Study Characteristics

Two hundred and sixty citations, excluding duplicate entries, were identified as potentially relevant. After the initial screening of titles and abstracts, 49 full-text articles were retrieved for detailed review (Figure 1). Twenty-four articles met our inclusion criteria for the systematic review (Appendix 2 lists retrieved full-text articles excluded from the systematic review). While most studies had multiple cognitive outcomes, ten had a single or designated primary outcome.

Six trials examined the effects of omega-3 fatty acid supplementation (Table 1). Among these studies, there was a large amount of heterogeneity with regards to the dosage used (400 mg to 2200 mg) and duration of the intervention (6 months to 3.3 years). Three found a modest beneficial effect on memory and/or executive functioning,[27-29] while the other three reported none.[26,30,31]

Meta-analyses of omega-3 fatty acid studies were performed for the outcomes of MMSE scores and digit span forward results (Figure 2(a) and (b)). The summary mean difference for MMSE scores was non-significant at 0.06 (95% CI -0.08 to 0.19, $p = .40$), and the summary mean difference for digit span forward was non-significant at -0.02 (95% CI -0.30 to 0.25, $p = .87$).

Seven trials investigated the effects of various combinations of folate, B6 and/or B12 vitamins (Table 2). There was substantial heterogeneity between trials with regards to dose, intervention duration (12 weeks to 6.6 years), participant health status (suffering from or at risk for cardiovascular disease to healthy community-dwelling individuals), and cognitive outcomes assessed. Inconsistent results were seen with some studies reporting modest benefits in at least one cognitive domain,[32-35] while others found no effect.[36-38]

Three studies were pooled to examine the impact on MMSE scores of folate combined with vitamins B6 and/or B12 (Figure 3). The summary mean difference for MMSE scores was non-significant at 0.02 (95% CI -0.22 to 0.25, $p = .90$).

Three trials investigated vitamin E supplementation (Table 3). They were relatively large (769 to 6377 participants) [39-41] and of long duration (3 to 9.6 years). One trial was limited to participants with amnestic mild cognitive impairment. [39] No statistically significant effect on any of the cognitive outcomes examined was found.[39-41]

Among the other nutritional interventions examined (Table 4), statistically significant differences between the intervention and control groups on at least one cognitive domain were found for green tea extract,[42] Concord grape juice,[43] chromium picolinate,[44] beta-carotene,[45] two different combination therapies including multiple vitamins,[46,47] and a dietary approach developed for the control of hypertension. [48] No beneficial effects were found for calcium carbonate combined with vitamin D3.[49]

A variety of approaches were used to assess adherence to the nutritional interventions including counting capsules,[26,27,31,32,35,37,42-44,47] weighing pills,[49] questionnaires,[33,45] diaries,[32,46] interviews,[34,49] and/or blood analyses.[28,30,37,38] All studies reporting on adherence described it as good or better (e.g., consumption of 2/3+ of all capsules) with the intervention.[30,31,33,35,37,40,41,49] Two studies did not attempt to assess adherence.[29,48]

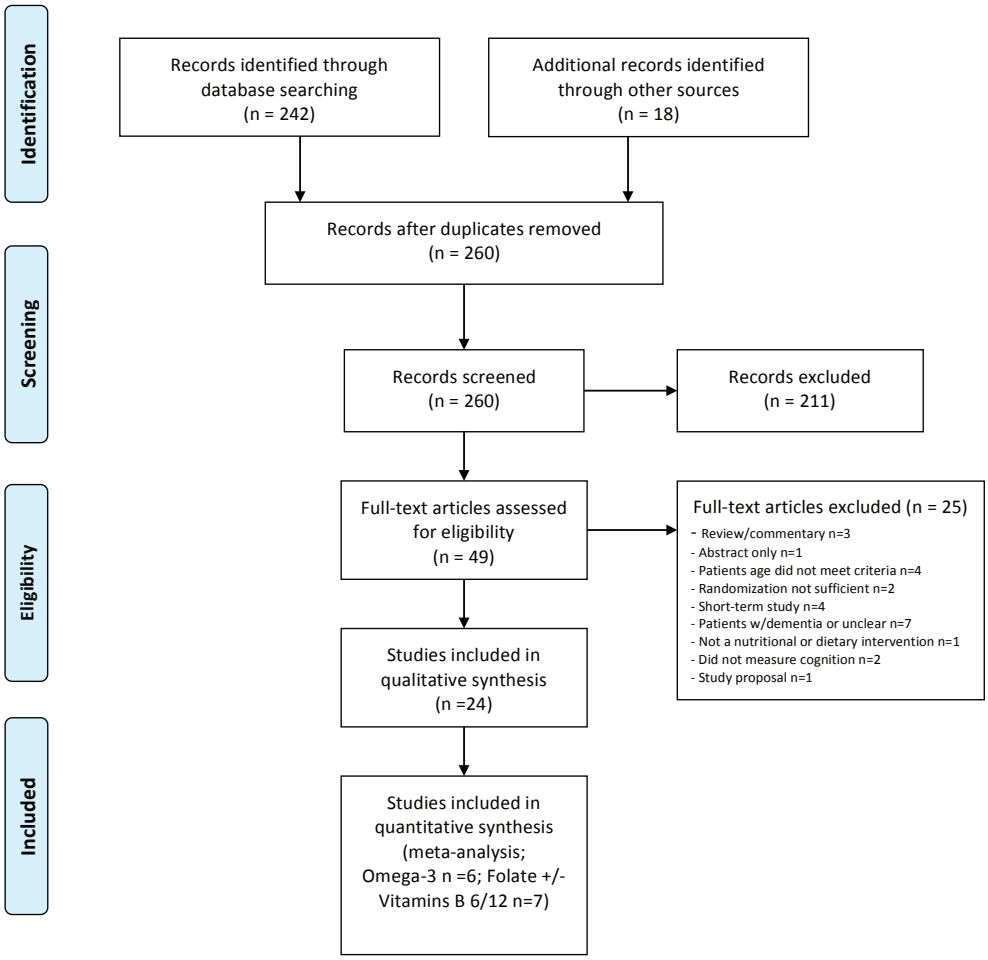


FIGURE 1. Literature search flow diagram

Risk of Bias and Evidence of Publication Bias

Ten trials were considered low,[26-28,31,34-39] ten moderate,[29,32,33,40-42,46-49] and four high risk[30,43-45] of bias (Tables 1–4). Funnel plots for each meta-analysis were visually inspected and showed no evidence of publication bias.

DISCUSSION

This systematic review and meta-analysis presents data on recent RCTs of the cognitive impact of nutritional interventions in non-demented middle-aged and older adults. Our main finding is that there is no convincing evidence of benefit for any of the nutritional interventions included in this review. Meta-analyses of two nutritional interventions, omega-3 fatty acids, and select B vitamins (folate, B6 and/or B12) didn't demonstrate significant effects. The promising results of generally small single studies with moderate to high risk of bias reporting on other nutritional interventions will require confirmation.

In general, observational studies have been more positive than experimental ones. For example, though several observational studies[50-53] suggest that a high intake of omega-3 might lead to improve cognition, the RCTs examined showed no benefit[26,30,31] or at most a modest one.[27-29] Observational studies can lead to erroneous conclusions and must be interpreted cautiously.[54] The risk of a confounding variable leading to the groups being compared (e.g., those following a particular diet versus those not) differing in their probability of the outcome of interest (e.g., developing cognitive problems) for reasons other than the intervention is a major limitation with them. This can occur if one is unaware of potential confounders, does not measure them, or does not measure them adequately. In many circumstances, to more firmly establish causality, a RCT is required.

Biologically plausible mechanisms are present for most of the nutritional interventions examined. Omega-3 fatty acids play a critical role in central nervous system development, structure, and function.[55] Folate, vitamin B6, and/or vitamin B12 are considered essential for normal brain function as we

TABLE 1.
Studies of omega-3 fatty acid supplementation on cognitive function

First Author (year)	*Study Population (n)*	*Design and Duration*	*Intervention*	*Outcome Measure*	*Results*	*Risk of Bias*
Geleijnse *et al.*[30]	*N*=2,911 coronary heart disease patients (22% women); 60–80 yrs.	RCT; 40 mths.	20 g of a margarine that contained either a supplement (400 mg/d of EPA–DHA at a ratio of 3:2, 2 g/d of ALA, 400 mg/d of EPA–DHA plus 2 g/d of ALA (EPA–DHA 1 ALA)) or a placebo (i.e., non-supplemented margarine)	Global (MMSE)	↔ Global cognitive decline (Mean ± SD: PLA=28.2±1.7 vs. Omega-3 =28.3±1.6)	High
Lee *et al.*[27]	*N*=36; (27 women); >60 yrs.; low SES with MCI	RCT; 12 mths.	3 x/d 430 mg of DHA and 150 mg of EPA/d or an isocaloric placebo (0.6 g linoeic acid)	Memory (Auditory Verbal Learning Test and Digit span backward), executive function, attention, psychomotor speed, and global (MMSE)	↑ Digit Span (Mean (95%CI): PLA = 8.0 (6.877 -9.113) vs. Omega-3 = 9.6 (8.437-10.749); VR-I (PLA = 23.1 (19.154-26.952) vs. Omega-3 = 29.2 (25.207-33.269); RAVLT delayed recall (PLA = 5.0 (3.587-6.312) vs. Omega-3 = 8.1 (6.645-9.462); ↔ MMSE (PLA = 26.5 (25.6-27.4) vs. Omega-3 = 26.6 (25.7-27.6); RAVLT immediate recall (PLA = 40.1 (37.384-42.785) vs. Omega-3 = 45.5 (42.706-48.291); VR-II (PLA = 18.0 (12.943-23.143) vs. Omega-3 = 20.8 (15.564-26.110); CDT (PLA = 7.8 (7.145-8.436) vs. Omega-3 (7.8 (7.142- 8.477); Digit Symbol substitution (PLA = 4.9 (3.254-6.634) vs. Omega-3 = 5.5 (3.723-7.218)	Low
Van de Rest *et al.*[26]	N=302 (45% women); > 65 yrs. (mean=70 yrs.)	RCT; 26 wks.	1,800 mg/d EPA–DHA, 400 mg/d EPA–DHA or placebo (high-oleic sunflower oil)	Cognitive domains of attention, sensorimotor speed, memory, and executive function	↔ Mean ± SD: Trail Making part A (PLA = 40.9±16.2 vs. Low Omega-3 = 42.3±14.0 vs. High Omega-3 = 43.4±15.1); Trail Making Test Part B – Part A / Part A (PLA = 0.66±0.51 vs. Low Omega-3 = 0.62±0.46 vs. High Omega-3 = 0.73±0.62); 15 Word Learning-immediate recall – 75 words (PLA = 44.8±9.4 vs. Low Omega-3 = 46.1±10.1 vs. High Omega-3 = 44.9±9.9); Digit span Forward (PLA = 8.5±2.0 vs. Low Omega-3 = 8.6±1.8; High Omega-3 = 8.6±2.0)	Low risk

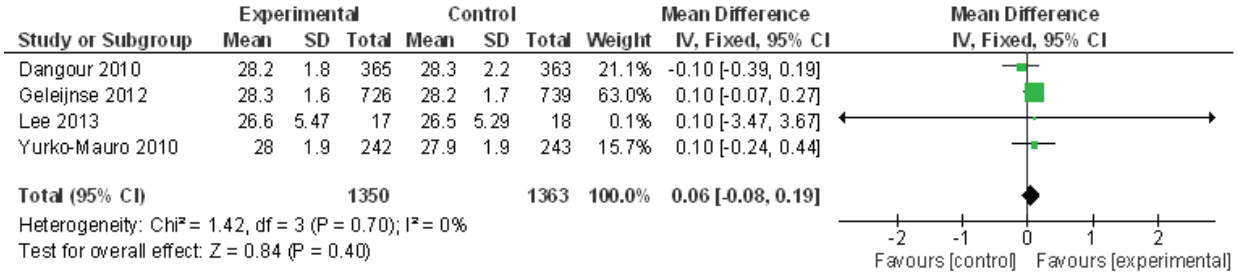
TABLE 1.
Continued

First Author (year)	*Study Population (n)*	*Design and Duration*	*Intervention*	*Outcome Measure*	*Results*	*Risk of Bias*
Dangour *et al.*[31]	N=867 (45% women); 70-79 yrs.	RCT; 2 yrs.	200 mg EPA plus 500 mg DHA/d or placebo (olive oil)	Primary: California Verbal Learning Test (CVLT) Secondary: Cognitive domains for global cognitive function, memory, processing speed, executive function, global delay score	↔ Mean ± SD: Primary: CVLT (PLA = 24.4±6.4 vs. Omega-3 = 24.1±6.7) on any secondary cognitive outcome	Low risk
Yurko-Mauro *et al.*[28]	N=485 (58% women); ≥ 55 yrs.	RCT; 24 wks.	900 mg/d DHA or placebo (50% corn oil and 50% soy oil)	Primary: CANTAB Paired Associate Learning - visuospatial learning, and episodic memory Secondary: CANTAB Pattern and Verbal Recognition memory, CANTAB Stockings of Cambridge, CANTAB spatial working memory, Frequency of forgetting-10 scale, MMSE	↑ Mean ± SD: CANTAB Paired Associate Learning (PLA = 9.7±10.4 vs. Omega-3 = 8.8±9.9); ↑ Verbal Recognition memory -immediate (PLA = 10.9±1.4 vs. Omega-3 = 11.0±1.4) and delayed (PLA = 10.7±1.8 vs. Omega-3 = 10.7±1.8) and Stockings of Cambridge - Executive function (PLA = 3.7±1.3 vs. Omega-3 = 3.5±1.3); ↔ on any other cognitive outcome: VRM free recall (PLA = 5.8±2.1 vs. Omega-3 = 5.8±2.1); PRM delayed, number correct (PLA = 8.8±1.8 vs. Omega-3 = 8.6±2.0); MMSE (PLA = 27.9±1.9 vs. Omega-3 = 28.0±1.9)	Low
Witte *et al.*[29]	N=65 (31% women); 50-75 yrs.	RCT; 26 wks.	2.2 g/d (1320 mg EPA plus 880 mg DHA) or placebo (sunflower oil)	Executive function (phonemic fluency, semantic fluency, TMT-B/TMT-A, Stroop) and memory (AVLT learning, delayed recall, recognition, digit span backwards)	↑ Executive function#; ↔ memory# (Data presented as a figure).	Moderate

↑ = significantly better ($p<.05$) in the omega-3 condition; ↔ = no difference between omega-3 and control conditions; # = corrected for multiple comparisons; RCT = randomized controlled trial; EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid; ALA = alpha-linolenic acid; SES = socio-economic status; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; CVLT = California Verbal Learning Test; CANTAB = Cambridge neuropsychological test automated battery; TMT-A = Trail Making Test part A; TMT-B = Trail Making Test part B; AVLT = auditory verbal learning task.

Range of scores of each outcome tool: MMSE = 0–30, Digit Span = 1–19, VR-I = 0–11. VR-II = 0–41, RAVLT delayed recall = 0–15, RAVLT immediate = 0–75, Digit Symbol Substitution = 1–19, CDT = 0–10, Digit Span Forward = 1–16, CVLT = 0–30, CANTAB PAL = 21 potential outcome measures, CANTAB VRM = 5 potential outcome measures, CANTAB Stockings of Cambridge = 3 potential outcome measures, TMT-A, TMT-B, Stroop are timed in seconds. Higher scores indicate better performance except for TMT-A, TMT-B, and Stroop (i.e., more time to complete the tasks represents poorer performance).

A



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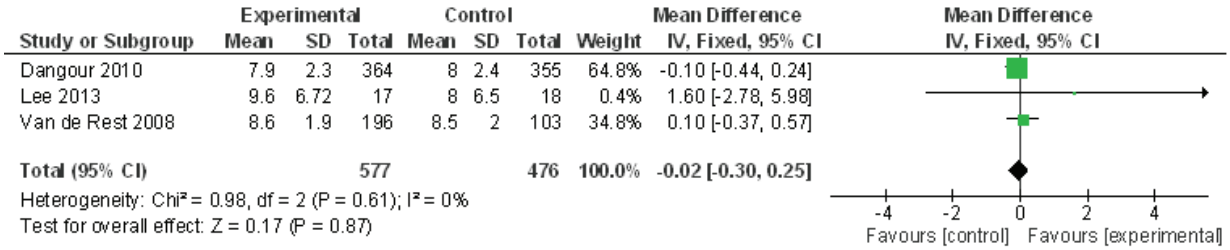

FIGURE 2. Meta-analyses of polyunsaturated omega-3 studies for the outcomes of (A) Mini-Mental State Examination (MMSE) score and (B) digit span forward

age[56] as a result of their effect on homocysteine metabolism[56,57] and other mechanisms.[58,59] Vitamin E and several of the other nutrients examined are felt to have anti-oxidant effects. Long-term oxidative stress has been implicated in the pathogenesis of cognitive decline and dementia.[60] Consumption of anti-oxidants, such as vitamin E, could potentially decrease free radical mediated damage in neuronal cells and reduce beta amyloid toxicity.[61] An *in vitro* model of green tea extract was found to attenuate cell death induced by beta amyloid.[62] Insulin resistance is associated with cognitive impairment,[63] and chromium may improve insulin sensitivity.[64] Determining, though, how much weight to give these purported mechanisms is difficult, cannot be done in isolation from other forms of evidence (e.g., clinical studies), and ultimately is often subjective.[65]

B vitamins have attracted particular interest as a possible nutritional intervention.[56] Folate acts as a donor of methyl groups in a reaction catalyzed by the enzyme methionine synthase to produce methylcobalamin, which is required for methylation of homocysteine to methionine.[56] B-vitamin deficiency leads to an increase in blood concentrations of homocysteine.[66] High intra-neuronal levels of homocysteine could disturb brain metabolism and cause cognitive impairment.[56] Additionally, folate increases nitric oxide availability in the brain,[58] and deficiency of this molecule impairs DNA repair in neurons and sensitizes neurons to oxidative damage and the toxicity of amyloid beta-peptide.[59] A cohort study of 965 older adults demonstrated a lower incidence of Alzheimer's disease in the highest quartile of total dietary folate intake after controlling for other factors.[67] We identified seven RCTs investigating the influence of B vitamins on cognition (Table 2). Our meta-analysis showed no significant effect of supplementation on MMSE scores. One study did show better cognitive performance with active therapy but only in women with low baseline dietary folate intake.[33] Future RCTs should consider initial nutritional status, as benefits may be limited to those with relative deficiencies.[33]

Our findings are congruent with the previous systematic reviews. While Manders *et al*.,[22] in an examination of the available literature on the cognitive effects of nutritional supplements in older individuals concluded that their use might lead to improvements without causing any harm, the two more recent systematic reviews on this topic found little if any evidence of a beneficial effect.[23,24]

A number of systematic reviews have dealt with specific nutritional interventions. One examined population-based cohort studies of anti-oxidant nutrients and reported a possible effect on age-related cognitive decline though the available evidence was limited.[68] Recent Cochrane systematic reviews concluded that both omega-3[69] and folate (± vitamin B12)[70] had no consistent beneficial effect on cognitive functioning in healthy older individuals.

Limitations of this review include the limited extent and quality of the available literature. Even when there are a number of studies dealing with the same nutritional intervention, the results do not necessarily show a consistent picture. While this may be due to differences in study population and/or outcome measures, an issue requiring attention is the variability in the composition, dose, duration, and timing (during the participant's life span) of the intervention. For example, the ratio of omega-6 to -3 may be an important consideration for omega-3 trials.[71] There is increasing evidence that a

TABLE 2.
Studies of B vitamins (vitamin B6, vitamin B12, and folate) on cognitive function

First author (year)	*Study Population (n)*	*Design and Duration*	*Intervention*	*Outcome Measure*	*Results*	*Risk of Bias*
Ford *et al.*[32]	N=299 hypertensive males; >75 yrs.	RCT (computer generated random permuted blocks); 2 yrs.	400 µg B12, 2 mg folic acid, and 25 mg B6 or placebo	Primary: ADAS-cog. Secondary: CVLT, MMSE, Digit Cancellation Test, Clock Drawing Test, TICS	Primary: (Mean change ± SD (PLA = -0.8±4.0 vs. B vitamins = -0.7±3.4) ↔ ADAS-cog Secondary: ↔ Clock Drawing Test, and MMSE; ↑ Digit Cancellation test @ 12 mths; ↑ CVLT @ 24 mths; ↔ in cognitive impairment and dementia risk over 8-yr follow-up	Moderate
Kang *et al.*[33]	N=2009 women with CVD or vascular risk factors	RCT; 6.6 yrs. of treatment and 5.4 yrs. of follow up	Folic acid 2.5 mg, Vitamin B6 50 mg, Vitamin B12 1 mg/d or placebo	Primary: Global cognitive composite score Secondary: Verbal memory composite score; TICS; Category Fluency	↔ Mean change in global score (95%CI): Cognitive decline = 0.03 (-0.03-0.08); ↔ Verbal memory; TICS; Category fluency Sub-group analysis: ↑ cognition in women with low baseline intake of B vitamins	Moderate
van Uffelen *et al.*[36]	N=152 (44% women); 70-80 yrs.; community dwelling	RCT; 1 yr.	2X2 factorial design: 2x/wk. moderate exercise; 2x/wk. low exercise with either 5 mg folic acid, 0.4 mg vitamin B12, 50 mg vitamin B6 or placebo	MMSE, Verbal Fluency Test, Digit symbol substitution test, and Abridged Stroop Color Word Test	↔ MMSE: Men: PLA = 29 (28-29) vs. B vitamins = 28 (27-30), Women: PLA = 29 (27-30) vs. B vitamins = 29 (27-30); AVLT 1-5 – words: Men: PLA = 31.5±9.3 vs. B vitamins = 29.1±8.9, Women: PLA = 31.2±6.6 vs. B vitamins = 33.7±10); DSST: Men: PLA = 38.1±9.1 vs. B vitamins = 36.2±12.1, Women: PLA = 33.5±7.7 vs. B vitamins = 36.6±10.3); Verbal Fluency Test: Men: PLA = 36.0±13.3 vs. B vitamins 31.8±10.3, Women: PLA = 36.7±12.1 vs. B vitamins = 33.8±10.1)	Low
Walker *et al.*[34]	N=900 with elevated psychological distress (60% women); 60-74 yrs.	RCT; 2 yrs.	400 µg folic acid + 100 µg vitamin B-12 or Placebo	Telephone interview for Cognitive Status-Modified (TICS-M), processing speed, and informant questionnaire on cognitive decline	↑ In cognitive function (immediate and delayed memory): Data presented as figures	Low
McMahon *et al.*[37]	N=276 (44% women); > 65 yrs.	RCT; 2 yrs.	Folate (1 mg) and vitamins B12 (500 µg) and B6 (10 mg) or placebo	Global cognition (MMSE); Rey Auditory Verbal Learning Test; Verbal and Semantic Fluency; Processing Speed; Reasoning Ability	↔ Mean ± SD: MMSE (PLA = 29.32±1.10 vs. B vitamins = 29.29±1.41); Wechsler Paragraph Recall test (PLA = 20.76±7.21 vs. B vitamins = 18.67±6.55); Category Word Fluency test (PLA = 68.78±13.71 vs. B vitamins = 65.72±14.96); Rey Auditory Verbal Learning (PLA 44.22±9.90 vs. B vitamins = 43.90±9.70); Raven's Progressive Matrices (PLA = 11.90±3.05 vs. B vitamins = 11.60±2.92); Controlled Oral Word Association (PLA = 41.00±12.44 vs. B vitamins = 40.11±14.08)	Low

TABLE 2.
Continued

First author (year)	*Study Population (n)*	*Design and Duration*	*Intervention*	*Outcome Measure*	*Results*	*Risk of Bias*
De Jager *et al.*[35]	N=223 (64% women); ≥70 yrs.	RCT; 2 yrs.	0.8 mg folic acid, 0.5 mg vitamin B12, 20 mg vitamin B6 or Placebo (vitamin free tablets)	MMSE, HVLT-DR; episodic memory, semantic memory, executive function (CLOX), and cognitive decline (IQCODE)	↔ MMSE, HVLT-DR or Category Fluency; ↑ Executive Function; ↓ Cognitive decline (i.e., slow the rate of cognitive decline): data presented for sub-analyses only.	Low
Stott *et al.*[38]	N=185 (52% women); > 65 yrs. with ischemic disease	RCT; 12 wks.	Folic acid (2.5 mg) plus vitamin B-12 (500 µg), vitamin B-6 (25 mg) and riboflavin (25 mg) or placebo	Letter Digit Coding Test; TICS-M	Mean change ± SD: ↔ Letter Digit Coding test (PLA = 1.0±3.2 vs. B vitamins = -1.2±5.6) and TICS-M (PLA = -0.4±2.7 vs. B vitamins = 0.7±3.8)	Low

↑ = significantly better (p<.05) in the B-vitamin condition; ↔ = no difference between B-vitamin and control conditions; ↓ = significantly lower (p<.05) in the B-vitamin condition; RCT = randomized controlled trial; ADAS-cog = Alzheimer's disease assessment scale – cognition; MMSE = Mini-Mental State Examination; TICS = telephone interview for cognitive status; TICS-M = telephone interview for cognitive status – modified; CVLT = California Verbal Learning Test; CVD = cardiovascular disease; HVLT-DR = Hopkins Verbal Learning Test – Delayed Recall; CLOX = Clock Drawing Task; IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly.
Range of scores of each outcome tool: ADAS-Cog = 0-70, CDR = 0-5, MMSE = 0-30, CVLT = 0-30, TICS-M = 0-30, AVLT immediate = 0-75, AVLT delayed = 0-15, DSST and Verbal Fluency Test = number of correct responses. Higher scores indicate better performance except for ADAS-cog.

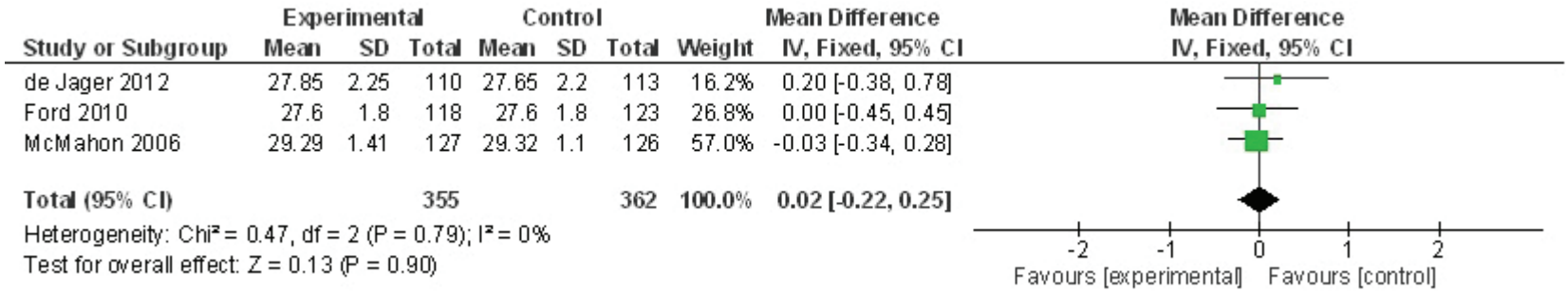

FIGURE 3. Meta-analysis of folate, B6, and B12 studies for the outcome of Mini-Mental State Examination (MMSE) score

TABLE 3.
Studies of vitamin E supplementation on cognitive function

First author (year)	*Study Population (n)*	*Design and Duration*	*Intervention*	*Outcome Measure*	*Results*	*Risk of Bias*
Kang *et al*.[41]	N=2824 women; > 65 yrs.; ≥ 3 coronary risk factors	RCT; 5.4 yrs. follow up time	Vitamin E 402 mg every other day + 500 mg of vitamin C daily and 50 mg of B-carotene every other day or placebo	Telephone interview for Cognitive Status-Modified (TICS-M)	↔ Rates of cognitive change; data presented as figures	Moderate
Kang *et al*.[40]	N= 6377 women; > 65 yrs.	RCT; follow up at ~5.6 yrs. and at ~9.6 yrs.	Vitamin E (600 IU) or placebo	Primary: Global composite score (TICS) Secondary: Verbal memory (TICS & East Boston Memory Test)	Mean ± SE: ↔ Global cognitive scores (PLA = 0.02±0.01 vs. Vitamin E = 0.02±0.01); ↔ verbal memory at both follow-ups	Moderate
Petersen *et al*.[39]	N=769 (46% women); 72.9±7.3 yrs.; Amnestic MCI	RCT; 3 yrs.	Vitamin E (2000 IU) or Donepezil (10 mg) or placebo	Primary: Possible or probably AD Secondary: MMSE; ADAS-Cog; global CDR; CDR sum of boxes; Global Deterioration Scale; New York University paragraph-recall test; the symbol digit modalities test; category-fluency test; a number cancellation test; Boston Naming Test; Digits-backward test; clock drawing test; maze-tracing task.	↔ Probability of progression from MCI to AD (hazard ratio, 1.02; 95% CI, 0.74 – 1.41); ↔ in any of the secondary outcome variables after 3 yrs.	Low

↔ = no difference between vitamin E and control conditions; RCT = randomized controlled trial; ADAS-cog = Alzheimer's disease assessment scale – cognition; MMSE = Mini-Mental State Examination; TICS = telephone interview for cognitive status; TICS-M = telephone interview for cognitive status – modified; AD = Alzheimer's disease; CDR = clinical dementia rating.

lifetime of accumulated exposures are predictive of cognitive function in late-life.[4] An intervention limited to later in the person's life may be beyond the critical period when it may be beneficial. More thought about the influence of the specific characteristics of the intervention is needed during the planning stage of these studies. Also relatively neglected is assessing the initial nutritional status of participants. Benefits may be limited to those with relative deficiencies.[72] In one of the B vitamin studies reviewed,[33] better cognitive performance was seen with active therapy but only in women with low baseline dietary folate intake. Another issue might be the relative insensitivity of the outcome measures utilized (e.g., MMSE).

Recent research suggests that considering the person's "whole" diet may be needed to better understand the nutrient-cognition link.[73] Supplements cannot replicate the complexity of natural food and provide all its potential benefits. Conducting rigorous long-term studies of the effect of diet on cognition will be a difficult challenge.[74] One of the dietary approaches that might be considered is caloric restriction. This may have a beneficial impact by increasing insulin sensitivity.[75] One of our included studies examined a dietary approach developed for hypertension.[48] Risk factors for Alzheimer's disease and vascular dementia overlap with those for heart disease.[4,76] A recent meta-analysis of observational studies found high adherence to a Mediterranean diet was associated with a lower risk of developing cognitive impairment,[77,78] but no interventional studies that met our inclusion criteria were found. While the PREDIMED-Navarra investigators found small but statistically significant differences in favour of those assigned to a Mediterranean diet supplemented with

TABLE 4.
Studies of other nutritional or dietary supplements on cognitive function

First author (year)	*Study Population (n)*	*Design and Duration*	*Intervention*	*Outcome Measure*	*Results*	*Risk of Bias*
Park *et al.*(42)	N=91 (73% women); subjective memory complaints including those with MCI	RCT (balanced blocked randomization); 16 wks.	360 mg of Green Tea Extract and 60 mg of L-theanine or placebo (maltodextrin and lactose)	MMSE-Korean; Rey-Kim memory test; Stroop color-word reading test	Mean change ± SD: ↔ Stoop (PLA = 0.67±2.41 vs. Green Tea Extract = 2.47±12.25); Rey-Kim Memory Test (PLA = 11.26±9.10 vs. Green Tea Extract = 10.60±10.51)	Moderate
Krikorian *et al.*[43]	N=12; (33% women); 78.2±5.0 yrs.	RCT; 12 wks.	100% Concord grape juice (~6-9 mL/kg) or isocaloric placebo	Verbal (CVLT) and non-verbal memory (SPALT)	↑verbal learning (PLA = 33.2 vs. Concord juice = 38.6); ↔ recall PLA = 5.0 vs. Concord juice = 7.2)	High
Smith *et al.*[48]	N=124 (64% women); hypertensive; 52.3±9.6 yrs.	RCT; 4 mths	Dietary Approaches to Stop Hypertension (DASH), DASH + weight management, or usual diet	Trail making test B-A, Stroop interference, Digit span, Verbal Fluency test, Verbal paired associations, Word Association, and Psychomotor speed	↑ Executive function-memory-learning and psychomotor speed on DASH + weight management; ↑ psychomotor speed on DASH alone: Data presented as figures	Moderate
Krikorian *et al.*[44]	N=26 (54% women); 71± 6 yrs.	RCT; 3 mths	Chromium picolinate (1000 mcg) or placebo	Clinical Dementia Rating; CVLT	↔ Learning rate and retention; ↑ semantic interference on learning, recall, and recognition memory tasks: Data presented as figures	High
Grodstein *et al.*[45]	N=5956 (n=1904 mean treatment time = 1 yr. [new recruits]; n=4052 mean treatment time = 18 yrs. [continuing recruits]); > 65 yrs.	RCT; New recruits (1 yr.); Continuing participants (18 yrs.)	B-carotene every other day (50 mg) or placebo	Primary: Global composite score (global cognition, verbal memory, and category fluency) Secondary: Verbal memory score	New recruits: (1 yr. treatment) ↔ Global composite score and verbal fluency Continuing Participants (18 yrs. treatment): ↑ global composite score and verbal memory in the continuing participants (PLA = -0.024±0.71 vs. Beta Carotene = 0.023±0.69)	High

TABLE 4.
Continued

First author (year)	*Study Population (n)*	*Design and Duration*	*Intervention*	*Outcome Measure*	*Results*	*Risk of Bias*
Rossom *et al.*[49]	N=4143; 71 yrs. (65-80); women	RCT; Mean follow-up of 7.8 yrs.	2 tablets/d (1,000mg of calcium carbonate and 400 IU of vitamin D3) or placebo	Primary: development of dementia or MCI	Primary: ↔ Incidence of cognitive impairment (Hazard ratio: 1.11, 95% CI, 0.71 – 1.74 for dementia)	Moderate
				Secondary: 3MSE, Digit Span Forward and backwards, Primary Mental Abilities Vocabulary Test, Card Rotation Test, Letter and Semantic fluency test, California Verbal Learning Test, the Benton Visual Retention Test, and Finger Tapping Test	Secondary: ↔ 3MSE; ↔ on any domain-specific cognitive scores	
Wolters *et al.*[46]	N=220 women; 60-91 yrs.	RCT; 6 mths	Vitamin and mineral capsule (150 mg vitamin C, 50 mg magnesium, 36 mg vitamin E, 34 mg niacin, 16 mg pantothenic acid, 9 mg B-carotene, 3.4 mg pyridoxine, 3.2 mg riboflavin, 2.4 mg thiamine, 400 µg folic acid, 200 µg biotin, 60 µg selenium, and 9 µµg cobalamin) or placebo (soy oil)	Symbol search test, Wechsler Adult Intelligence Scale, and pattern recognition and intelligence	Mean (5-95th percentiles): ↔ Pattern recognition (PLA = 7.4 (5.0-10.0) vs. multi-vitamin = 7.6 (5.0-10.0)) and intelligence (PLA = 110 (90.0-129) vs. multi-vitamin = 109 (93.4-131)); ↑ symbol search test (PLA = 33.0 (23-42) vs. multi-vitamin = 35.0 (25-48)	Moderate
Macpherson *et al.*[47]	N=56 women; 64-82 yrs.	RCT; 16 wks.	Multivitamin (contains folic acid, B6, B12), antioxidant and mineral formula with added herbal and antioxidant plant extracts (Swiss Women's Ultivite 50+) or placebo	Primary: memory and attention composite score Secondary: Simple Reaction Time; Complex Reaction Time; Immediate and Delayed Recognition Memory; Stroop Congruent; Contextual Recognition Memory; CVLT-II	Primary data is presented as figures. ↑ Spatial working memory; ↔ any other cognitive test	Moderate

↑ = significantly better ($p<.05$) in the experimental condition; ↔ = no difference between conditions; RCT = randomized controlled trial; MMSE = Mini-Mental State Examination; IU = international units; MCI = mild cognitive impairment; TICS-M = telephone interview for cognitive status – modified; CVLT = California Verbal Learning Test.

extra-virgin olive oil on several cognitive measures after an average of 6.5 years,[79,80] cognitive testing was not done at baseline. As a result, change in cognition in response to the intervention could not be evaluated. As well, the testing was done only on sub-groups of participants randomized at one PREDIMED recruitment site. Other components of a healthy lifestyle, such as exercise, may be important modulators of the relationship between dietary intake and cognition.[81] Their influence should also be considered in future research.

Much of the research demonstrating a potential link between nutrition and cognition is observational, done on animals, or *in vitro* and may not be relevant to clinical practice. Our meta-analyses demonstrated no overall effect of omega-3 fatty acids or select B-vitamin supplementation on cognition. Green tea extract, chromium, anti-oxidants, and the DASH (Dietary Approaches to Stop Hypertension) diet deserve further exploration but cannot be recommended at this juncture. Future research should utilize rigorous study methods that incorporate baseline dietary assessments, consider potential modulation by other components of a healthy lifestyle, and use common and robust outcome measures.

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CONFLICT OF INTEREST DISCLOSURES

The authors have no competing interests to declare.

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