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Original Study

Nutritional Strategies in the Management of Alzheimer Disease: Systematic Review With Network Meta-Analysis

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A B S T R A C T

Background: Alzheimer disease (AD) is the major cause of dependency and disability in the elderly. Numerous studies have sought to achieve its prevention and/or management examining a role for modifiable risk factors, such as nutrition. This work aims to investigate the effects of food and/or nutrients in the management of AD at different stages.

Methods: Electronic databases were searched for clinical trials examining the effect of nutrient intervention in individuals with AD, compared with placebo, published up to 2014. The outcomes investigated were neuropsychological assessment scales, neuroimaging, and biomarkers. The Cochrane tool was employed to assess risk of bias. Pairwise meta-analyses were performed in a random-effect model by estimating the weighted mean differences with 95% confidence interval (CI) for each outcome measure. The Network meta-analysis was undertaken on cognitive outcome.

Results: Selected studies used antioxidants, B-vitamins, inositol, medium-chain triglyceride, omega-3, polymeric formulas, polypeptide, and vitamin D. AD outcome measurements were mainly restricted to cognitive state and functional abilities. Estimate treatment effects from pairwise meta-analyses showed large but nonsignificant effect in the supplementation with proline-rich polypeptide [weighted mean difference 6.93 (95% CI −3.04, 16.89); $P = .17$] and B-vitamins [weighted mean difference 0.52 (95% CI −0.05, 1.09); $P = .07$) on cognitive function measured by the Mini-Mental State Examination. The other nutrients supplementation did not show any significant effect on any outcome measures.

Conclusions: Isolated nutrient supplementations show no convincing evidence of providing a significant benefit on clinical manifestations or neuropathology of AD. During the initial stages of AD, nutrient supplementation did not show any effect when delivered individually, probably because of their synergistic function on brain, at different domains.

Dementias are caused by different brain modifications that disrupt multiple cortical functions, leading to intellectual and cognitive impairments; dementia constitutes one of the major causes of disabilities and dependence in aging.[1,2] Alzheimer disease (AD), the most common form of dementia, is characterized by progressive synaptic loss, dysfunction, and neuronal death, and vascular toxicity, triggered by the deposition of pathologic inducers of lesions in the brain tissue, amyloid β peptide (Aβ), and hyperphosphorylated tau protein.[2] The neuropathogenesis of AD has been associated with mitochondrial dysfunction, inflammation, abnormal accumulation of transition metals, and oxidative stress. The brain is susceptible to oxidative damage, which in turn increases Aβ production and deposition, promotes the phosphorylation of tau and the consequent neuropathology, creating a vicious cycle that boosts the beginning and progression of AD.[3,4] Therapies attempting to counteract these lesions have not achieved permanent successful results.[5] Thus, investigating strategies that may prevent or delay the progression of dementia is a matter of the utmost importance.[6]

Extensive research has indicated that nutritional adjustments have strong effects on health and might have a preventive effect in

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neurodegenerative diseases.[7] Some dietary components or patterns (folate, fish, antioxidants, coffee, Mediterranean diet, among others) have been identified as protective factors against the development of AD. In addition, some nutrition-related conditions (hyperhomocysteine, hypertension, frailty, and type 2 diabetes mellitus) increase the risk for AD, suggesting that effective dietary interventions may reduce the growing incidence of this disease.[8,9] The beneficial effects of nutrients in AD may imply a safe, cost-effective, easy to administer and socially acceptable approach.[10]

Herein, we hypothesize that clinical and neuropathologic manifestations of AD can be counteracted, at least partially, through the ingestion of specific nutrients, foods and/or dietary patterns. Many studies on the influence of nutrients in cognitive impairment have been reported over the last few years, demonstrating the need for the systemic discussion of these data.[11] Although some systematic reviews regarding specific nutrients related to AD exist in the literature, none of these evaluated simultaneously the effects of the ingestion of nutrients, foods, and dietary patterns. As such, this systematic review and meta-analysis aims to gather, organize, critically assess, and quantitatively measure the evidence examining the use of nutrients, foods, and/or dietary patterns, in the management of AD at different stages; we addressed whether nutrition interventions are capable of slowing down the progress or decreasing some symptoms of AD, and whether exists any therapeutic association between consumption of specific nutrients, food, or dietary patterns with the pathologic manifestations of AD in the elderly.

Methods

This study was performed in accordance with the Cochrane Handbook for the Systematic Review of Interventions[12] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[13] Studies were organized into groups according to the type of nutrient.

Eligibility Criteria

Inclusion criteria for eligible studies are summarized in Table 1.

Sources and Search Strategy

Electronic databases (the Cochrane Controlled Trial Registered, EMBASE, PubMed, Virtual Health Library and Web of Science) were exhaustively searched for potentially relevant studies, up to December 2014. The search strategy was built by crossing key search terms with the Boolean operator "AND" for each component of the review question (clinical condition, type of intervention and type of study). Key search terms are shown in Supplementary Table 1.

Data Extraction and Quality Assessment

The first author screened and evaluated primary studies by title and abstract for inclusion. Studies that matched clinical condition, intervention, and study design of interest were selected and documented. Duplicate studies were identified simultaneously in the database searches. Afterward, a second author accessed the study records to evaluate them for inclusion. Final decisions on study inclusion were reached in a consensus meeting. The first author retrieved and perused the full texts of preliminary relevant reports identified in the preceding step for compliance with eligibility criteria and data extraction. Clinical trials were characterized according to the recommendations of the Cochrane Collaboration.[12] The quality of studies was independently evaluated by two authors using the Cochrane Risk of Bias Tool.[12] The assessment was categorized by domains (selection bias, performance bias, detection bias, attrition bias, reporting bias, and other sources of bias) specifying the source of bias and grading domains as "low," "unclear," or "high" risk. The final assessment of bias for the inclusion of studies was determined by the risk of the main domains for this study: selection bias, performance bias, and attrition bias. Disagreements were resolved by a second consensus meeting. Articles classified as high risk were excluded. The overall assessment was presented in a risk of bias summary figure using the RevMan software.[14] The quality of evidence and strength of recommendation was determined according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, which is based on the risk of bias, inconsistency, indirectness, imprecision and publication bias of included studies. To assess imprecision, the optimal information size) calculated at http://www.stat.ubc.ca/~rollin/stats/ssize/b2.html.[15]

Statistical Analysis

We run different pairwise meta-analyses of continuous variables for each outcome and nutrient intervention using the method of the inverse variance in a random effect model (DerSimonian and Laird method) to calculate the estimative of treatment effect, the weighted mean difference (WMD), and its 95% confidence interval (CI). All outcome measures were estimated based on the change from baseline to follow-up.[16] The heterogeneity was appraised with the I^2 statistic (low <40%; moderate 30%–60%; substantial 50%–90%; and considerable heterogeneity 75%–100%) and the χ^2 test with significance (P value) at the level of .10. Heterogeneity was explored and explained if significant (I^2 >30% and χ^2 $P < .10$). Statistical analyses were carried out using the software Review Manager (RevMan) v 5.3.[14] A Network Meta-analysis (NMA) was performed for cognitive outcome measure in a Bayesian framework using Markov Chain Monte Carlo method with a random effect model (mean difference with 95% credible interval) using ADDIS release 1.16.6[17] to analyze the consistency and

Table 1
Eligibility Criteria PICOS

	Inclusion Criteria	Exclusion Criteria
Participants	AD at any stage with or without chronic diseases; aged over 60 y old; both sexes; any race/ethnicity or geographic location.	Healthy participants; mild cognitive decline or other types of non-Alzheimer dementia; familial AD initiated before 50 y old or related to other genetic diseases (eg, trisomy of chromosome 21).
Interventions	Any type of nutrient, food, special diet, or dietary pattern at all doses or ingested amounts without restriction on the duration of intervention; with or without medication as cointervention.	Other different than nutrient or food interventions
Comparisons	Placebo or control	
Outcomes	Primary: neuropsychological scales and structural, functional, or other methods of neuroimaging. Secondary: biochemical biomarkers of AD and oxidative stress and/or inflammatory biomarkers in CSF or plasma.	Plasma nutrient levels, nutritional status, or food intake without any direct association with disease status or progression.
Study design	Blinded clinical trials completed and published from the beginning of the databases up to 2014	Nonhuman animal model studies, in vivo, or in vitro. Full-texts published in languages other than English, Portuguese, or Spanish.

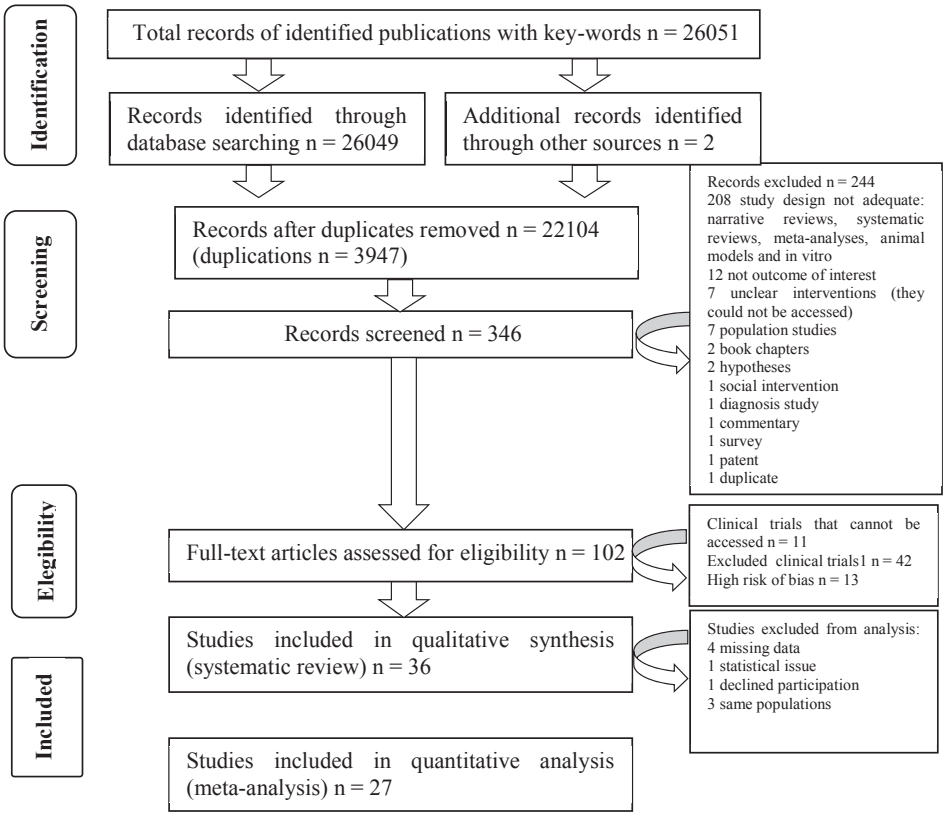
inconsistency of relative effects and estimate the rank probability of an intervention to be the best treatment, the second best, and so on. The model generated 50,000-simulation iterations (4 chains) to provide an accurate estimate of the statistical model.[18]

Trials that assessed outcomes with different scales to the selected ones were not included in the statistical analysis. Sensitivity analysis was performed to evaluate the degree of reliability of results in situations of uncertain decisions or assumptions about the data.[12] Unpublished data necessary to undertake meta-analysis was made available by authors on request; however, some authors did not respond to our request. Then, we used the strategies proposed by the Cochrane Handbook[12] described in details in the Supplementary Material.

Results

Characterization of Included Studies

The systematic search identified 26,051 records in all databases at first (Supplementary Table 2). The Figure 1 shows the PRISMA flow diagram for the identification process and study selection. Ninety-one clinical trials were thoroughly assessed by the eligibility criteria and the Cochrane risk of bias tool. Following the perusal of full-texts, 42 clinical trials were excluded because of the following reasons: 7 unsuitable study design, 22 participants did not meet clinical condition, 3 ongoing studies, 6 duplicate, and 4 not outcomes of the interest. Of clinical trials that matched the eligibility criteria, 13 were classified as high risk of bias by the Cochrane's tool and excluded, with a total of 36 trials left for inclusion in the systematic review. Of included studies, 30 were double-blind randomized controlled trial, 2 pilot studies, 1 crossover clinical trial, and 2 secondary analyses of double-blind randomized controlled trial. Sample sizes ranged from 11 to 561 participants. The mean age of participants was 74.6 years (range 66.5–81.6 years). In most studies, the diagnosis of AD was based on that of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer Disease and Related Disorders Association criteria, and the Diagnostic and Statistical Manual of Mental Disorders third or fourth edition. Interventions compared an active treatment with a placebo group; they were classified into 9 types of nutrient interventions: 4 antioxidants, 1 carbohydrate, 1 lipid, 2 micronutrients, 8 polymeric formula, 2 polypeptide, 8 omega-3, 3 B-vitamins, 1 vitamin D, and 5 vitamin E. From these, 19 studies used medication as co-intervention, generally acetylcholinesterase inhibitors. The shortest duration was 4 weeks, and the longest 24 months. To evaluate clinical and neuropathologic manifestations of AD, there were identified 4 types of neuropsychological outcome measures: behavioral disturbances, cognitive, functional, and global performance; measured through different assessment scales.[19] Given that most studies used a common assessment scale for neuropsychological outcomes, we used these scales as the primary outcome measure, the Mini-Mental State Examination (MMSE)[20] to assess cognition, the Alzheimer Disease Cooperative Study Activities of Daily Living[21] to assess functional capacity, the Neuropsychiatric Inventory[22] to assess behavioral disturbances, and the Clinical Dementia Rating Scale Sum of boxes[23] to assess global performance. Four studies assessed brain imaging using different outcome measures methodically incomparable among them; therefore, it was not possible to perform a statistical analysis. Among the secondary outcomes we



* Excluded clinical trials: 6 duplicated studies, 8 healthy population, 14 mild cognitive impairment population or no Alzheimer dementia, 4 no outcomes of interest, 3 ongoing studies, 7 study design

Fig. 1. PRISMA flow diagram; illustration of the stages of study.*

Table 2
Characteristics of Clinical Trials Eligible for Systematic Review

First Author, Year of Publication (Country)	Study Design (Name of Study)	Principal Health Problem	Mean Age in Years	Sex	Final Sample Size	Intervention	Duration	Co-interventions	Main Outcomes	Main Findings	Risk of Bias
B-Vitamin Complex											
Ford et al, 2010 (Australia)[31]	Randomized, double-blind controlled clinical trial (Health in Men Study)	Cognitive impairment and dementia	79	M = 100%	241	400 μg B12, 2 mg folic acid, and 25 mg B6, 1 capsule daily.	2 y	Not reported	ADAS-cog, MMSE, Digit cancellation test, CDT CAMDEX, TICS, SF36 −mental health, SF36 −vitality, social functioning, role emotional.	This trial found no difference in cognition between vitamins and placebo groups, however there was a lower decline in specific cognitive domains, verbal memory and attention, in the vitamins group. The risks of cognitive impairment and dementia were not significantly reduced across 8 years of follow-up.	Low
Connelly et al, 2008 (United Kingdom)[32]	Double-blind placebo-controlled study	Probable AD, NINCDS-ADRDA criteria	76.27	M/F = 12/29	41	1 mg of folic acid or placebo daily	6 mo	Dpz n = 35, Riv n = 12, Gal n = 10.	MMSE, IADL, Social Behavior (SB), DSST, Combined IADL/SB	A significant change was found between groups in combined scale of IADL and SB, but not in cognition, as measured by the MMSE.	Low
Sun et al, 2007 (Taiwan)[33]	Randomized, double-blind, placebo controlled trial	Mild to moderate AD	75	M/F = 45 / 44	63	Mecobalamin (0.5 mg) in addition to folic acid and pyridoxine hydrochloride and multivitamin supplement.	26 wk	AchE-I Dpz (all participants), Riv (multivitamin group n = 1)	ADAS-Cog, MMSE, CASI, ADL Index, IADL Scale	Although levels of homocysteine were reduced, patients with mild to moderate AD and normal serum levels of vit B12 and folic acid did not exhibit significant differences between multivitamin intervention and placebo in cognition or functional performance at 26 wk.	Low
Aisen et al, 2008 (USA)[34]	Multicenter, randomized, double-blind 2-group parallel design controlled clinical trial (VITAL)	Probable AD, NINDS-ADRDA criteria	76.3	F = 229 (56.0%)	344	Folic acid 5mg/d, vitamin B12 1mg/d and vitamin B6 25 mg/d vs placebo.	18 mo	Stable use (for at least 3 mo) of AchE-Is and Mem was allowed	ADAS-cog, MMSE, CDR sob, ADCS-ADL, NPI	High-dose B-vitamins intervention decreased levels of serum homocysteine but an important beneficial effect on any outcome measurement was not reached.	Low
Vitamin D											
Stein et al, 2011 (Australia)[35]	Double-blinded Randomized Controlled Trial	Mild to moderate AD	77.5 (Median)	F/M = 15/ 17	31	Low-dose vitamin D2 (1000 IU), 2 capsules, 3 times/d. High-dose vitamin D2 (6000 IU). Human insulin: Humulin-R 100 IU per mL. Three sprays per nostril (total 60 IU insulin) 4 times/d. Compared with placebo	low-dose during 8 wk, followed by a high-dose for 8 additional wk	Dpz n = 16, Riv n = 1, Gal n = 8 and Gal plus Mem n = 1	ADAS-cog, WMS, GDS, DAD, DAD sub-scores of activities of daily living	Vitamin D supplementation did not lead to benefits in cognition or functional performance, even after adding a high-dose to ongoing low-dose supplementation. No benefit from acute nasal insulin or over 48 h in a subgroup.	Unclear

Vitamin E

Dysken et al, 2014 (USA)[36]	Double-blind, placebo-controlled, parallel-group, randomized clinical trial	Mild to moderate AD	78.77	M = 594	561	dl- α-tocopherol acetate 1000 IU twice a d, Mem 10 mg twice a d, α-tocopherol plus Mem vs placebo.	4 y	Dpz n = 304, Gal n = 194, Riv n = 18	ADCS-ADL, MMSE, ADAS-cog, NPI, CAS, Dependence Scale level.	α- tocopherol was effective in slowing the functional decline of patients with mild to moderate AD taking an AChEI and was also effective in reducing caregiver burden. Neither memantine nor the combination of alpha tocopherol and memantine showed clinical benefits in these patients.	Low
Sano et al, 1997 (USA)[37]	Double-blind, placebo-controlled, paralleled group, randomized, multicenter trial (Alzheimer's Disease Cooperative Study)	Moderate probable AD	73.37	F (%) = 65.5 Selegiline 67.8 α-tocopherol 65.9 Selegilin + α-tocopherol 60.0	318	Selegiline 5 mg twice a d, dl-α-tocopherol 1000 IU twice a d, selegiline plus α-tocopherol vs placebo	2 y	Not reported	MMSE, ADAS, BDS, Equivalent Institutional Service, Dependence Scale, BRSD	In patients with AD treated with α-tocopherol; significant delay in institutionalization, deterioration of functional performance, and the need for care. There was no improvement in cognitive test scores in any of the treatment groups. Both selegiline and α-tocopherol delay functional deterioration.	Unclear
Thomas et al, 2001 (Italy)[38]	26-week study, randomized in double-blind branches (DPZ vs vitamin E) and in an open controlled study (Riv).	Probable AD, DSM-IV and the NINCDS-ADRDA criteria	66.12	M/F = 53/67	54	Vit E: 2000 IU single dose. DPZ: single dose 5 mg/d/1 mo and 10 mg/d/ remaining mo. Riv: 1.5 mg/d /1st mo; 3 mg/d 2 mo; 6 mg/d 3 mo; 9 mg/d 4 mo; 12 mg/d following mo vs placebo.	6 mo	Not reported	MMSE, ADAS-cog, WAIS, NPI, P300 Recordings	Vitamin E supplementation did not yield improvements in P300 or neuropsychological test results.	Unclear
Onofrj et al, 2002 (Italy)[39]	Double-blinded Randomized Controlled Trial	Mild and with moderate −severe AD	65.97	M/F (27/33)	60	Vitamin E 2000 IU single dose vs DPZ single dose 5 mg/d/during 14 d of titration and 10 mg/d/ remaining mo. Divided into group I (mild AD) and group II (moderate to severe AD)	6 mo	Not reported	MMSE, ADAS-cog, WAIS, P300 Recordings	Vitamin E Group II demonstrated a more severe deterioration in P3 and neuropsychological outcome measures, compared with DPZ Group II.	Unclear
Lloret et al, 2009 (Spain)[40]	Prospective, double blind, placebo controlled study.	Probable AD, NINCDS-ADRA criteria	Not reported	Not reported	33	vitamin E (800 IU per d), or placebo	6 mo	Cholinesterase drugs	MMSE, BDS, CDT, GSSG, plasma MDA	This trial showed that AD patients did not respond equally to antioxidant treatment. There were two groups of patients: "respondents" and "nonrespondents". In respondents, vitamin E treatment reduced GSSG levels and maintained cognition. The nonrespondent group of patients did not reduce oxidative level nor improve their cognitive functions.	Unclear

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Table 2 (*continued*)

First Author, Year of Publication (Country)	Study Design (Name of Study)	Principal Health Problem	Mean Age in Years	Sex	Final Sample Size	Intervention	Duration	Co-interventions	Main Outcomes	Main Findings	Risk of Bias
Antioxidants											
Ringman et al, 2012 (USA)[41]	Randomized, double blind, placebo-controlled study	Mild to moderate AD	73.5	F = 63%	30	2 g or 4 g of curcumin in four 500 mg capsules twice daily vs placebo.	24 wk, with an open-label extension to 48 wk.	AchE-Is (93%) and Mem (77%)	ADAS-Cog, NPI, MMSE, ADCS-ADL; plasma levels of: Ab1-40, Ab1-42; CSF levels of: Ab1-42, T-tau, P-tau, F2-IsoPs	There were no significant effects of treatment on change in plasma Ab1-40 and Ab1-42, CSF Ab1-42, CSF tau or p-tau or F2-IsoPs; neither on neuropsychological outcome measures.	Low
Adair et al 2001 (USA)[42]	double-blind fashion	Probable AD, NINCDS-ADRDA criteria	Not reported	Data not shown	43	50 mg/kg/d of NAC (N-acetylcysteine) vs placebo.	6 mo	Not reported	MMSE, ADL, BNT, Gesture to Command, WMS Figure Reproduction (immediate)	Active treatment with NAC failed to reach significant change in the cognitive and functional performance outcome measures. Effective results in reducing oxidative stress were observed.	Unclear
J.M. Rubio-Perez and J.M. Morillas-Ruiz, 2013 (Spain)[43]	double-blind study with cross-sectional and longitudinal analysis	Probable AD at different stages, NINCDS-ADRDA criteria	77.75	F/M = Patients 35/13 (AD initial phase 17/7; AD moderate phase 18/6), control 40/12	100	Antioxidant Beverage (AB) rich in polyphenolic antioxidants (10.16% apple concentrate, 0.42% lemon concentrate, 0.16% green tea extract, 0.08% apple extract) vs 200 mL Placebo beverage (PB) daily	8 mo	Not reported	Biomarkers of inflammation (IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IFN-γ, TNF-α, MCP-1)	The AB significantly decreased serum levels of the pro-inflammatory cytokines IL-2, IFN-γ and TNF-α in the early stage of AD, but did not affect serum levels of the anti-inflammatory cytokines IL-4 and IL-10	Unclear
Galasko et al, 2012 (USA)[44]	Double-blind, placebo-controlled clinical trial.	Mild to moderate AD	72.73	F = 78	62	800 IU Vitamin E, 200 mg vitamin C, and 600 mg alpha-lipoic acid (α-LA) into three capsules, 1 capsule, 3 times/d. CoQ 400 mg, as a wafer, 2 wafers 3 times/d; vs placebo capsules and placebo wafer.	16 wk	AChE-I , Mem, Concomitant vitamin or supplement (allowed only if contained vitamin E, vitamin C, α-LA, or CoQ in quantities much lower than the doses used in this trial).	F2-IsoPslevel CSF, Ab-42 level, Tau level, P-tau181, MMSE, ADL	These antioxidants did not affect biomarkers in CSF; suggesting that this combination did not improve indices of clinical or biochemical manifestations in AD. E/C/ALA significantly reduced CSF F2-isoprostane levels; however, clinical benefits derived from this reduction remain uncertain. Researchers detected increased cognitive decline in the E/C/ALA.	Unclear
Copper											
Kessler et al, 2008 II (Germany)[45]	monocentric, prospective, double-blind, placebo-controlled, parallel-group randomized design	Probable AD, NINCDS −ADRDA criteria	69.92	M/F = 29/39	57	Cu orotate 51.62 mg (8 mg Cu) once daily.	12 mo	5−10 mg Dpz daily	CSF Ab42, Tau level, P-Tau level	An analysis of CSF biomarker demonstrates that long-term oral intake of Cu can be excluded as a risk factor for AD. CSF Ab42 levels declined significantly at the end of the period of intervention.	Unclear
Kessler et al, 2008 (Germany)[46]	Monocenter, prospective, double-blind, placebo-controlled, parallel-group randomized design	Probable AD, NINCDS-ADRDA criteria	69.5	M/F = 25/32	57	51.62 mg Cu-(II)-orotate-dihydrate (8 mg Cu) once daily.	12 mo	5−10 mg Dpz 2 mo before recruitment and during the study.	ADAS-cog, MMSE	Long-term oral intake copper supplementation is well-tolerated and did not show an influence on cognitive outcome measures.	Unclear

Inositol										
Barak et al, 1996 (Israel)[47]	double-blind controlled crossover trial	Dementia of the Alzheimer type, DSM-III-R	81.6	F = 100%	11	Inositol 6 gm daily or placebo (dextrose)	4 wk (8 wk cross-over)	No medications allowed, except for oxazepam up to 15 mg/ d, or an equivalent benzodiazepine if the patients had been taking it before the study.	CAMDEX-CAMCOG Subscales	A trend of effect of inositol on cognitive function, as measured by the CAMCOG was not statistically significant. In an analysis by cognitive domains, a significant improvement in language and orientation was detected during inositol treatment.	Unclear
Omega-3 PUFA											
Faxén-Irving et al, 2013 (Sweden)[48]	Randomized double blind placebo-controlled study	Mild to moderate AD	72.75	M/F = 84/90	174	Four 1-g capsules daily, of 430 mg of DHA and 150 mg of EPA, or placebo (1 g of corn oil, including 0.6 g of linoleic acid). 4 mg of tocopherol were added to each capsule.	12 mo	Dpz, Gal, Riv, Antidepressants Neuroleptics Herbal medication	MMSE, Plasma and CSF TTR, hs-CRP	Omega−3 supplementation seemingly maintained the levels of TTR in plasma. Plasma TTR correlated with MMSE and inversely with ADAS-Cog; authors suggest a potential mechanism for probable positive effects of omega−3 on cognition.	Low
Freund-Levi et al, 2009 (Sweden)[49]	Part of a larger randomized, double-blind placebo-controlled trial (OmegAD Trial)	AD, DSM-IV criteria	70.25	F = n-3FA 8 (44%), Pbo 6 (30%)	35	Four 1-g capsules daily, of 430 mg of DHA and 150 mg of EPA, or placebo (1 g of corn oil, including 0.6 g of linoleic acid). 4 mg of tocopherol were added to each capsule.	6 mo	Acetylsalicylic acid, omega-3FA 4, Placebo 2. All patients in the present study were on standard treatment with AchE-Is	CSF Ab−42, T-tau, CSF P-tau level, IL-6 in plasma and CSF, TNF-α in CSF, TNF-α in Plasma, hs-CRP in plasma	Treatment with n-3 FAs resulted in no effects on CSF and plasma inflammatory markers nor on dementia biomarkers, compared with placebo. The concomitant treatment with AChEIs may have masked a smaller anti-inflammatory effect of the n-3 FAs.	Unclear
Freund-levi et al, 2008 (Sweden)[50]	Randomized, double-blind, placebo-controlled clinical trial	Mild tomoderate AD	72.75	F = 90	174	Four 1-g capsules daily, of 430 mg of DHA and 150 mg of EPA, or placebo (1 g of corn oil, including 0.6 g of linoleic acid). 4 mg of tocopherol were added to each capsule.	12 mo	Dpz, Gal, Riv, Antidepressants Neuroleptics Herbal medication	NPI, MADRS, DAD, Caregivers burden	Supplementation of 1.7 g DHA and 0.6 g EPA given daily for 6 mo to patients with mild to moderate AD did not seem to influence neuropsychiatric behavior, functional ability or on caregiver's burden, except for possible positive effects on depressive symptoms in non-APOEv4 carriers and agitation symptoms in APOEv4 carriers.	Unclear

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Table 2 (*continued*)

First Author, Year of Publication (Country)	Study Design (Name of Study)	Principal Health Problem	Mean Age in Years	Sex	Final Sample Size	Intervention	Duration	Co-interventions	Main Outcomes	Main Findings	Risk of Bias
Freund-Levi et al, 2006 (Sweden)[51]	Randomized, double-blind, placebo-controlled clinical trial.	Mild to moderate AD	72.75	F = 90	174	Four 1-g capsules daily, of 430 mg of DHA and 150 mg of EPA, or placebo (1 g of corn oil, including 0.6 g of linoleic acid). 4 mg of tocopherol were added to each capsule.	12 mo	Dpz, Gal, Riv, Antidepressant agents, Neuroleptic agents, Statin drugs.	MMSE, ADAS-cog, CDR Global Score, CDR Scale Sum of Boxes	Supplementation with omega-3 could not exert an influence on cognitive functions. However, in a very mild AD subgroup analysis, a significant difference in the MMSE was found - while the supplemented group maintained its score, the placebo demonstrated a decline.	Unclear
Quinn et al, 2010 (USA)[52]	Randomized, double-blind, placebo-controlled trial	Mild to moderate AD	76	F = 210 (52.2%)	298	Algal DHA capsules 1 g twice per d vs placebo.	18 mo	AchE-Is use at baseline. Mem use at baseline	ADAs-cog, CDR, MMSE, ADCS-ADL, NPI, Quality of Life AD scale. Rate of brain atrophy by volumetric MRI	Results from this study showed no benefit of DHA supplementation on any outcome measure. In a subgroup analysis, paired MRI scans displayed no effect on change in the volume of total brain, hippocampus, or ventricles.	Low
Shinto et al, 2014 (USA)[53]	3-arm, parallel group, randomized, double-blind, placebo-controlled pilot clinical trial	Probable AD, NINCDS-ADRDA criteria	75.93	F/M = 21/18	34	Omega-3: fish oil concentrate in the triglyceride form at 3 gr/d (DHA 675 mg and EPA 975 mg/d. Omega-3 + LA group: LA in the racemic form at 600 mg/d in one tablet. Placebo LA: no LA. Placebo oil: soybean oil with 5% fish oil.	12 mo	AchE-Is or Mem (Pbo 77% ω-3 92% ω-3+LA 77%), vitamin E, and ginkgo biloba.	F2-IsoPs, ADAS-cog, MMSE, ADL, IADL	The combination of omega-3 with α-lipoic acid resulted in benefits for slowing cognitive and functional decline. These findings did not occur in the omega-3 group. F2-IsoPs levels did not change between groups at 12 mo. The combination appears to be safe at the doses evaluated.	Low
Chiu et al, 2008 (Taiwan)[54]	Randomized double-blind placebo-controlled study	Mild or moderate AD, Amnesic MCI	75.25	F % Omega-3 65.0 Placebo 46.7	29	3 capsules of omega-3 twice/d (EPA 1080 mg and DHA 720 mg). Placebo capsules twice/d with olive oil esters.	24 wk	0.2 mg/g Tertiary-butyl hydroquinone, 2 mg/g and tocopherols.	ADAS-cog, CIBIC-plus, MMSE, HDRS.	Omega-3 appeared to benefit global performance in mild or moderate AD and MCI, but not cognition. The effect omega-3 on cognitive function by the ADAS-cog was negative in AD patients, but significantly improved in the MCI.	Unclear
Kotani et al, 2006 (Japan)[55]	Pilot clinical study	MCI, modified criteria of Petersen et al, 1999. Organic brain lesions and early AD, NINCDS-ADRDA and NINDSAIREN criteria.	64.2	F/M = 20/19	39	40 mg/capsule of ARA and DHA, and 0.16 mg/capsule of asthaxanthin (antioxidant of PUFA). Placebo: 40 mg/capsule of olive oil (oleic acid). Six capsules/d of ARA and DHA, or olive oil.	90 d	Not reported	RBANS	Authors reported notable memory improvements in patients with organic brain lesion or MCI, but not in the AD group	Unclear

Medium-Chain Triglycerides											
Henderson ST et al, 2009 (USA)[56]	Randomized, double-blind, placebo-controlled, parallel-group study	Mild to moderate AD	76.85	M/F = 67/85	124	10 gr of medium chain triglycerides of glycerin and caprylic acid (AC-1202) in 30 gr powder sachets. First 7 d, one sachet/d. D 8, 2 sachets/d (20 g AC-1202), to 90 d.	90 d	AD medications: Dpz, Riv, Mem, Gal.	ADAS-Cog, MMSE, ADCS-CGIC	AC-1202 elevated serum ketone bodies in AD patients and led to a significant change in ADAS-Cog scores, compared with placebo after 45 d of supplementation. Further analysis revealed that this treatment was most remarkable in APOE4 (-) participants who were dosage compliant.	Unclear
Polymeric Formula											
Scheltens et al, 2010 (The Netherlands, Germany, United Kingdom, and United States)[57]	Double-blind, randomized, controlled, multicenter trial	Mild AD	73.7	M = 106	161	125 mL/d Fortasyn Connect: 300 mg EPA, 1200 mg DHA, 106 mg Phospholipids, 400 mg Choline, 625 mg UMP, 40 mg Vit E (alpha-TE), 80 mg Vit C, 60 μg selenium, 3 μg Vit B12, 1 mg Vit B6, 400 μg Folic acid.	12 wk, with possible extension of 12 wk.	Not reported	WMS, modified ADAS-cog, ADCS-ADL, NPI, Quality of life—AD, CIBIC-plus	This study showed no differences between the active and control group in cognitive, neuropsychiatric symptoms, function and global performance outcome measures. In a subgroup analysis with very mild AD, the active group presented a significant improvement in the memory domain compared with placebo.	Unclear (author declined participation)
Kamphuis et al, 2011 (The Netherlands, Germany, United Kingdom, and United States)[58]	Secondary analyses from a double-blind, randomized, controlled, multicenter, proof-of-concept trial	Mild AD	73.7	M = 106	161	125 mL/d Fortasyn Connect: 300 mg EPA, 1200 mg DHA, 106 mg Phospholipids, 400 mg Choline, 625 mg UMP, 40 mg Vit E (alpha-TE), 80 mg Vit C, 60 μg Selenium, 3 μg Vit B12, 1 mg Vit B6, 400 μg Folic acid.	12 wk, with possible extension of 12 wk.	Not reported	ADCS-ADL, MMSE	In this secondary analysis, a subgroup of patients with low baseline BMI in the active treatment was observed a significant improvement in the ADCS-ADL score at 12 wk compared with control, which means an improvement in functional performance.	Low
Kamphuis et al, 2011 (The Netherlands, Germany, United Kingdom, and United States)[59]	Secondary analyses from a double-blind, randomized, controlled, multicenter, proof-of-concept trial	Mild AD	73.7	M = 105	161	125 mL/d Fortasyn Connect: 300 mg EPA, 1200 mg DHA, 106 mg Phospholipids, 400 mg Choline, 625 mg UMP, 40 mg Vit E (alpha-TE), 80 mg Vit C, 60 μg Selenium, 3 μg Vit B12, 1 mg Vit B6, 400 μg Folic acid.	12 wk, with possible extension of 12 wk.	Not reported	13-item ADAS-cog	Supplementation with active product improved memory of patients with mild and very mild AD. An examination of the ADAS-cog score revealed a significant treatment effect in patients with a higher score at baseline, compared with patients with a high score compared with control.	Low

(*continued on next page*)

Table 2 (*continued*)

First Author, Year of Publication (Country)	Study Design (Name of Study)	Principal Health Problem	Mean Age in Years	Sex	Final Sample Size	Intervention	Duration	Co-interventions	Main Outcomes	Main Findings	Risk of Bias
Scheltens et al, 2014 (The Netherlands, Germany, Belgium, Spain, Italy, and France)[60]	Randomized, controlled, double-blind, parallel-group, multi-country trial (The Souvenir II study)	Probable AD	73.8	M = 132	238	125 mL/d Fortasyn Connect: 300 mg EPA, 1200 mg DHA, 106 mg Phospholipids, 400 mg Choline, 625 mg UMP, 40 mg Vit E (alpha-TE), 80 mg Vit C, 60 μg Selenium, 3 μg Vit B12, 1 mg Vit B6, 400 μg Folic acid.	24 wk	Drug naive	EEG, NTB memory domain, NTB executive function domain, NTB total composite, ADAS-cog orientation task, LDST.	A significant increase was found in the memory domain of the NTB in the active group. The functional connectivity analysis exhibited a significant difference in the delta band, but not in the other frequency bands, authors interpreted as a change in functional connectivity that support an enhancement of synapse formation by the active product in mild AD.	Low
Planas et al 2004 (Spain)[61]	Randomized double-blind placebo-controlled study	Probable AD, NINCDS-ADRDA criteria	74.61	M/F = 20/24	39	250 mL energy dense and protein-rich liquid supplement 2 times/d (total: 500 kcal/d, 45% carbohydrates, 25% fat, and 30% proteins)	6 mo	Not reported	Blandford scale, MMSE, Isaacs Set Test	After 6 mo of supplementation, beneficial effects were not detected on disease progression in groups, by assessing cognitive measurements and eating behavior disorders.	Unclear
Shah et al, 2013 (USA)[62]	24-week, double-masked, parallel, randomized, controlled clinical study (S-Connect study)	Probable AD, NINCDS-ADRDA criteria	76.7	F = Active 139 (52%) Control 135 (52%)	254	Fortasyn Connect or an iso-caloric control product that lacked Fortasyn Connect, as a 125 mL (125 kcal)/d.	24 wk	Duration of AD medication use (mo): Active 28.8 (22.9) Control 31.5 (28.7)	ADAS-cog, Cognitive test battery, ADCS-ADL Scale, CDR-sob	Results from this trial showed a cognitive decline, assessed by ADAS-cog, in both control and active group receiving souvenaid as an add-on intervention to AD medication.	Low
De Waal et al, 2014 (The Netherlands, Germany, Belgium, Spain, Italy, and France)[63]	A 24-week randomized, controlled, double-blind, parallel-group, multi-country study (Souvenir II study)	Probable AD, NINCDS-ADRDA criteria	73.3	M = Control 47 (50.5%) Active 45 (52.3%)	159	Fortasyn Connect (DHA, EPA, phospholipids, choline, UMP, vitamin B12, B6, and folate, vitamins C and E, and selenium), or an isocaloric control product that lacked Fortasyn Connect, as a 125mL/d.	24 wk	Drug naive	EEG Phase Lag Index (PLI)	A secondary analysis to measure local connectivity indicated a significant change in the beta band at the end of treatment duration in the active group, which remained stable, compared with control (which presented a decline).	Low
Remington, et al, 2015 (USA)[64]	A double-blind, multi-site, phase II study	Moderate to late-stage probable AD, NINCDS, and MMSE score of 11.9 ± 2.5	77.8	Not reported	106	Nutraceutical formulation (NF): folic acid (400 mg), B12 (6 mg), α-tocopherol (30 IU), SAM (400 mg), NAC (600 mg), and ALCAR (500 mg); vs placebo.	3–6 mo, following open-label extension to 9 mo	Not reported	DRS-2, CLOX-1, 12-item NPI, ADCS-ADL	Cognitive outcome measures exhibited an improvement in the NF group at 3 mo, and a decline of cognition in the placebo group. There were no significant differences between groups in functional performance or neuropsychiatric symptoms.	Low

Proline-Rich Polypeptide											
Leszek et al, 1999 (Poland)[65]	Double-blind placebo-controlled one-year trial	Mild, moderate and severe probable AD, DSM-III-R and NINCDS-ADRDA criteria	69.76	F/M = 34/12	42	Colostrinin (proline-rich polypeptide), one 100 μg tablet every second d. 100 mg Selenium tablets, vs placebo tablets.	1 year	Not reported	MMSE	The colostrinin group underwent a substantial positive effect on cognitive performance by the MMSE. The arm supplemented with selenium displayed a significant stabilization in 90% of patients, instead of an improvement in cognitive state, compared with placebo.	Unclear
Bilikiewicz and Gaus, 2004 (Poland)[66]	Placebo controlled, double-blind multicenter trial	Mild to moderate probable AD, DSM-IV and NINCDS-ADRDA	72.1	F 2/3	105	Colostrinin tablet 100 μg of active substance plus excipients (mannitol, magnesium stearate and sodium chloride) on alternate d interspersed with a placebo tablet on the even d.	15 wk followed by 15 wk open label	Not reported	ADAS-cog, CGIC, IADL, MMSE, GDS, Geriatric Depression Scale and ADAS-non cog.	The cognitive status was not significantly affected by this supplementation, as measured by the MMSE; however, it did attain an important benefit in the ADAS-cog and in the IADL on the FSA. The GIC showed no changes in any group. The overall benefit analysis in the full sample showed 40% patients stabilized or improved on Colostrinin at week 15 as opposed to only 21% on placebo.	Low

Ab, β-amyloid peptide; AChE-Is, acetylcholinesterase inhibitors; ADAS-cog, Alzheimer Disease Assessment Scale—cognitive subscale; ADCS-ADL, Alzheimer Disease Cooperative Study-activities of daily living; ADCS-CGIC, Alzheimer Disease Cooperative Study-clinician's global impression of change; ADL, activities of daily living; ARA, arachidonic acid; BDS, Blessed Dementia Scale; BNT, Boston Naming Test; BMI, body mass index; BRSD, Behavior Rating Scale for Dementia; CAMDEX, Cambridge Mental Disorders of the Elderly Examination; CAS, Caregiver Activity Survey; CASI, Cognitive Abilities Screening Instrument; CDR, clinical dementia rating; CDR-sob, clinical dementia rating-sum of boxes; CDT, clock drawing test; CIBIC, Clinician's Interview-Based Impression of Change Scale; CLOX, clox-drawing test; DAD, Disability Assessment in Dementia Questionnaire; DHA, docosahexaenoic acid; Dpz, donepezil; DRS, dementia rating scale; DSM-III/IV, Diagnostic and Statistical Manual of Mental Disorders third or fourth edition; DSST, Digit Symbol Substitution Test; EEG, electroencephalogram; EPA, eicosapentaenoic acid; F, female; F2-IsoPs, F2-isoprostanes; GSSG, oxidized glutathione; HDRS, Hamilton Depression Rating Scale; Hs-CRP, high sensitive C-reactive protein; IADL, instrumental activities of daily living; Gal, galantamine; GDS, Global Deterioration Scale; IL, interleukin; LDST, Letter Digit Substitution Test; M, male; MADRS, Montgomery Asberg Depression Rating Scale; MCI, mild cognitive impairment; MCP-1, monocyte chemotactic protein-1; MDA, malondialdehyde; Mem, memantine; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; NINCDS-ADRDA, Neurological and Communicative Disorders and Stroke-Alzheimer Disease and Related Disorders Association; NPI, Neuropsychiatric Inventory; NTB, Neuropsychological Test Battery; P-Tau, phosphor-tau; Riv, rivastigmine; PUFA, polyunsaturated fatty acid; RBANS, repeatable battery for the assessment of neuropsychological status index; SF36, Short Form 36; TICS, telephone interview of cognitive status; TNF-α, tumor necrosis factor; T-Tau, total tau; TTR, transthyretin; UMP, uridine monophosphate; WAIS, Wechsler Adult Intelligent Scale; WMS, Wechsler Memory Scale.

found biomarkers related to AD [Aβ-42[24], total tau (T-tau) and phosphorylated tau (P-tau) levels in cerebrospinal fluid (CSF)[25,26]]; inflammation/oxidative stress biomarkers [cytokines,[27] F2-isoprostanes (F2-IsoPs),[28] high sensitive C-reactive protein CSF levels[29,30] (Supplementary Table 3)]. Studies included in the systematic review and their main findings are summarized in Table 2.

Risk of Bias Assessment of Included Studies

The general grading of risk of bias graph is presented in Supplementary Figure 1 and Supplementary Figure 2. Studies graded as high risk of bias in the domain selection bias were excluded. In performance bias, 61.1% of included studies described the method of

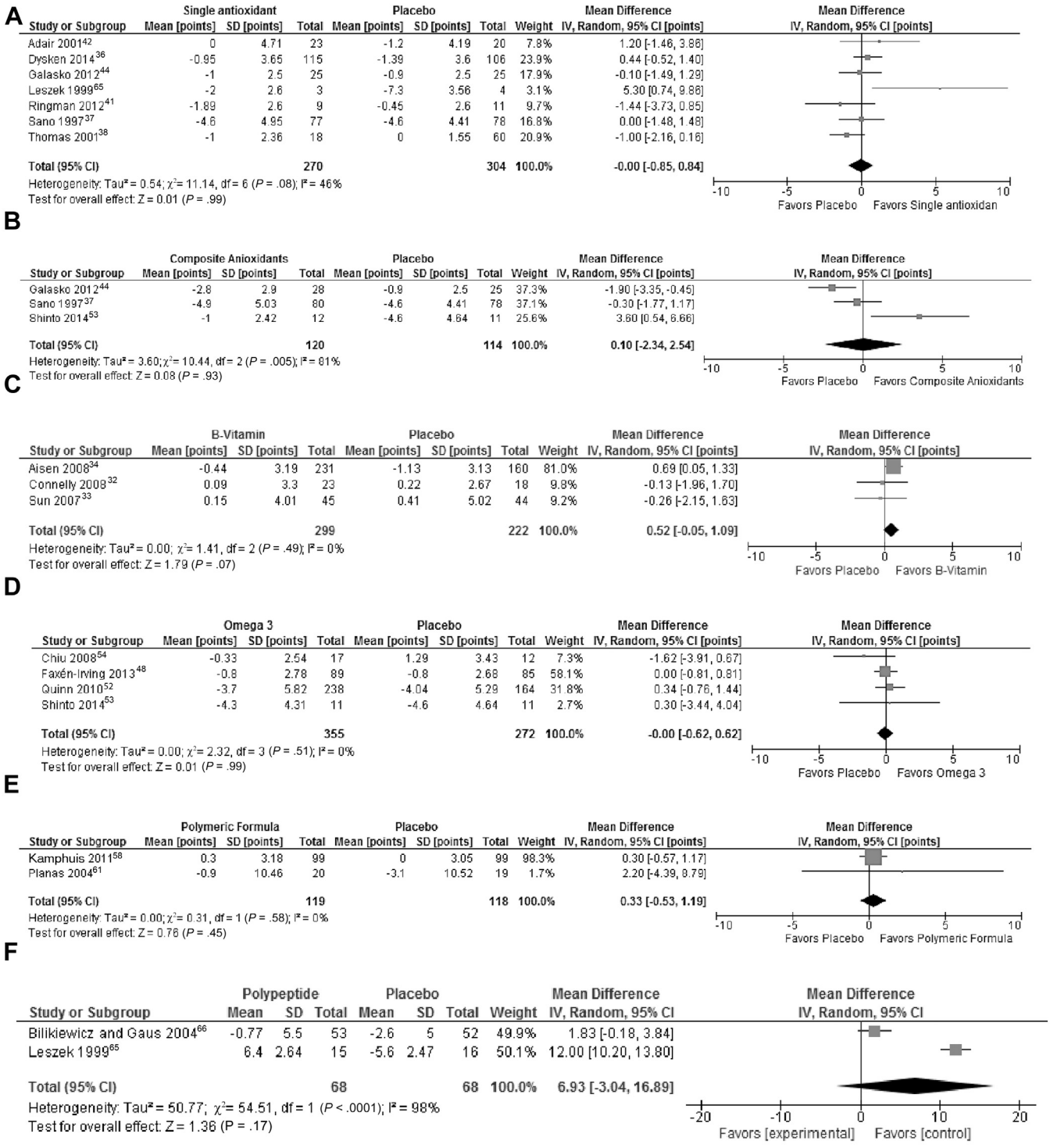


Fig. 2. Random-effects meta-analysis of the data on the effects of different nutrition interventions on cognitive outcomes.

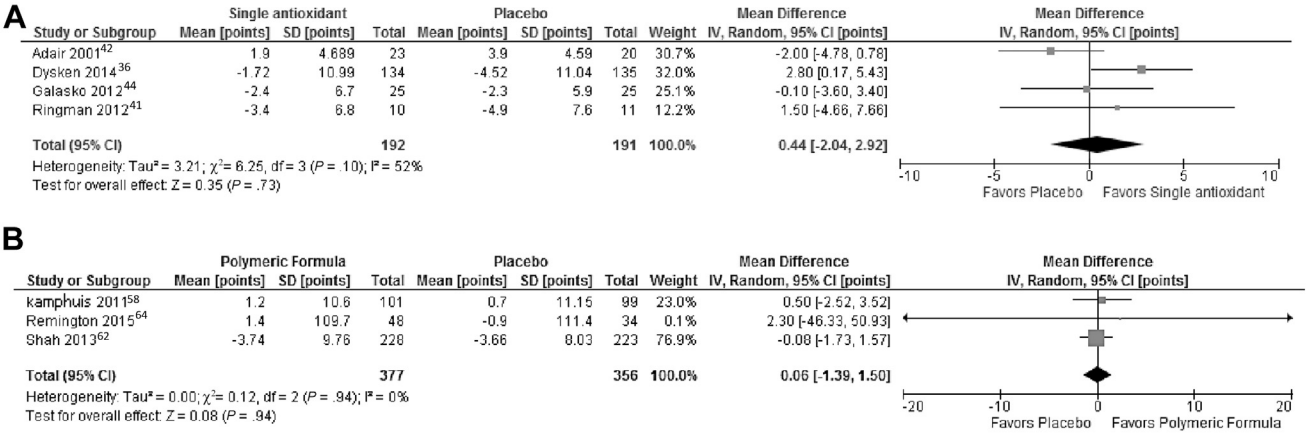


Fig. 3. Random-effects meta-analysis of the data on the effects of different nutrition interventions on functional outcomes.

blinding of both participants and personnel; nonblinded studies were excluded. In reporting bias, 19.4% studies with missing results were classified as high risk of bias and excluded from the analysis.

Intervention Effects

Studies with missing data[40,45,46,55,57] or evaluating similar outcomes in the same population and intervention[48,52-54] were excluded from analysis (Supplementary Table 4).

Pair-Wise Meta-Analysis

Effect of nutrition interventions on cognitive outcomes

The analysis of nutrient interventions for cognition in AD, using the MMSE, showed that patients supplemented with B-group vitamins, in co-intervention with acetylcholinesterase inhibitors and memantine, an important tendency favoring intervention group was detected on cognitive status at 6 months [WMD 0.52 (95% CI −0.05, 1.09) $P = .07$] (Figure 2C).[32–34] Also, Colostrinin, a proline-rich polypeptide, showed a nonsignificant large effect on cognition [WMD 6.93 (95% CI −3.04,16.89) $P = .17$), though with a significant heterogeneity ($P < .00001$) that may be explained by the variability in trials' duration (Figure 2F).[65,66] Antioxidants, including vitamin E, were divided into single and composite antioxidants (for treatments using more than 1 antioxidant). The effect of single[36-38,41,42,44,65] and composite antioxidants[37,44,53] with a moderate ($I^2 = 46\%$, $P = .08$) and a considerable heterogeneity ($I^2 = 81\%$, $P = .005$), respectively, showed no effect on cognition (Figure 2A, 2B). This heterogeneity may be attributed to the variability in trials' duration, dosage, and type of compound, regardless of their antioxidant function. Results did not change after a sensitivity analysis using only vitamin E ($P = .73$). Supplementation with omega 3 fatty acid had a null response (Figure 2D).[48,52–54] Polymeric formula revealed a nonsignificant trend toward treatment intervention (Figure 2E).[56,61] A ketogenic agent, a medium-chain triglyceride (MCT) of glycerin and caprylic acid,[56] inositol,[47] and Vitamin D[35] were unable to show a significant effect on cognition evaluated by the MMSE, CAMCOG (Cambridge Cognitive Examination) scale, and the Alzheimer Disease Assessment Scale—Cognitive subscale, respectively (Supplementary Figure 3).

Effect of Nutrition interventions on Functional Outcomes

In terms of functional, single antioxidants, with a moderate heterogeneity ($I^2 = 52\%$, $P = .10$) (Figure 3A)[36,41,42,44] and polymeric formula were not able to demonstrate any effect on this outcome (Figure 3B).[56,62,64] One study using omega 3 displayed no treatment effect on functional capacity[52]; nor vitamin D by using the Disability Assessment for Dementia scale (Supplementary Figure 4).[35]

Effect of Nutrition interventions on Behavioral Outcomes

Supplementation with single antioxidants did not show significant change (Figure 4A).[36,41] Studies using omega-3, with a moderate heterogeneity ($I^2 = 56\%$, $P = .13$) probably attributed to substances of

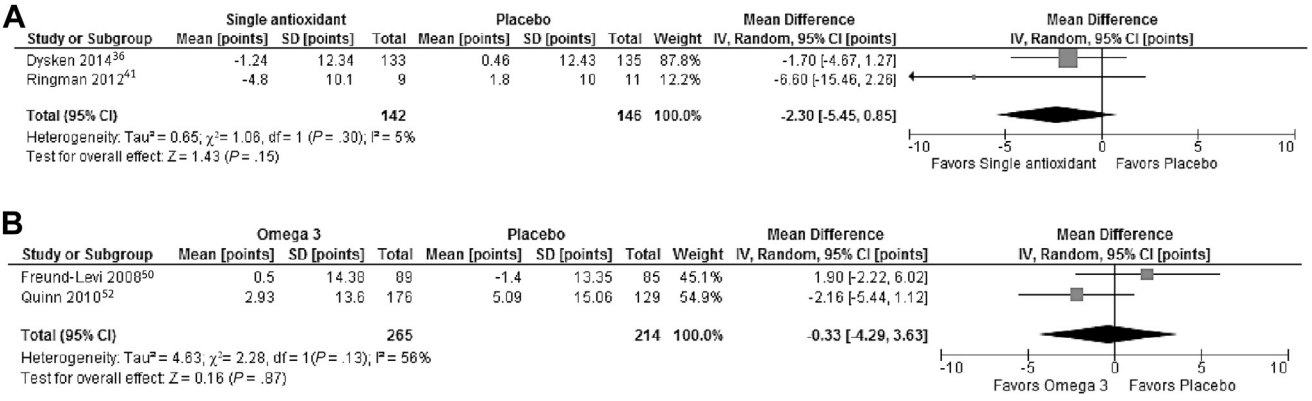


Fig. 4. Random-effects meta-analysis of the data on the effects of different nutrition interventions on behavioral outcomes.

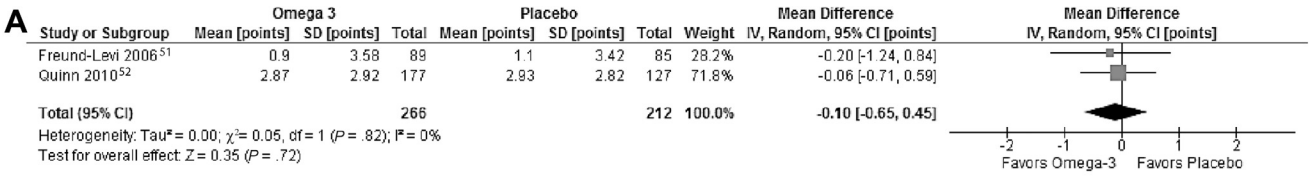


Fig. 5. Random-effects meta-analysis of the data on the effects of different nutrition interventions on global outcomes.

intervention, time point, and dosage, also failed to demonstrate an effect (Figure 4B).[50,52] One study assessing the effect of vitamin E and selegiline in behavioral outcome measured with the Behavioral Rating Scale of Dementia revealed a statistically significant effect ($P < .00001$).[44] One study using B-vitamins and 1 study with polymeric formula that analyzed this outcome were unsuccessful in obtaining significant results (Supplementary Figure 5).[34,64]

Effects of Nutrition interventions on Global Outcomes

Two studies using omega-3 were insufficient to observe a significant influence on global performance (Figure 5A).[51,52] One study with polymeric formula did not support significant results for this outcome (Supplementary Figure 6).[62]

Effects of Nutrition interventions on Biomarkers

Two trials assessing CSF levels of Aβ-42, T-tau, P-tau, and F2-isoprostanes did not found any difference between single antioxidant and placebo.[41,44] Another study did not find significant differences between omega-3 and placebo in Aβ1-42, T-tau, and P-tau, neither on inflammatory biomarkers high sensitive C-reactive protein, IL-6, or TNF-α.[49]

Network Meta-Analysis

The indirect comparison among nutrient interventions on the cognitive outcome (by the MMSE), polypeptide (proline-rich) appears to show a higher significant efficacy in improving mental status when compared with remaining interventions (Table 3). Nutrients were ranked for the probability of having the best treatment effect (Figure 6A, 6B). Proline-rich polypeptide showed the highest probability of being the most effective treatment of improvement in cognitive status (100%). However, this data is controversial because of the reduced number of studies (Figure 6C) and different treatment duration. Polymeric formula was ranked as the second probable best treatment (25%) followed by B-vitamins (24%), and single antioxidant as (24%) the third effective treatment intervention; omega-3 was ranked as the probable worst treatment (42%). These results are relatively consistent with pairwise meta-analysis; a prevalent treatment effect was observed with proline-rich polypeptide. However, the effect of B-vitamins, single antioxidants and omega-3 on cognitive outcomes were inconclusive (Table 4). Results of the NMA exhibit the same heterogeneity found in pairwise meta-analyses. Because of the inconsistency in these findings, we cannot use this model to draw conclusions about the relative effect of treatments.

Quality of the Evidence

The quality of evidence and strength of recommendation for the use of nutrient interventions to support the management of AD was classified as very low for trials using polymeric formula, proline-rich polypeptide, single, and composite antioxidants; low for trials with omega-3 and moderate for B-vitamins complex. Details are described in Supplementary Table 5.

Discussion

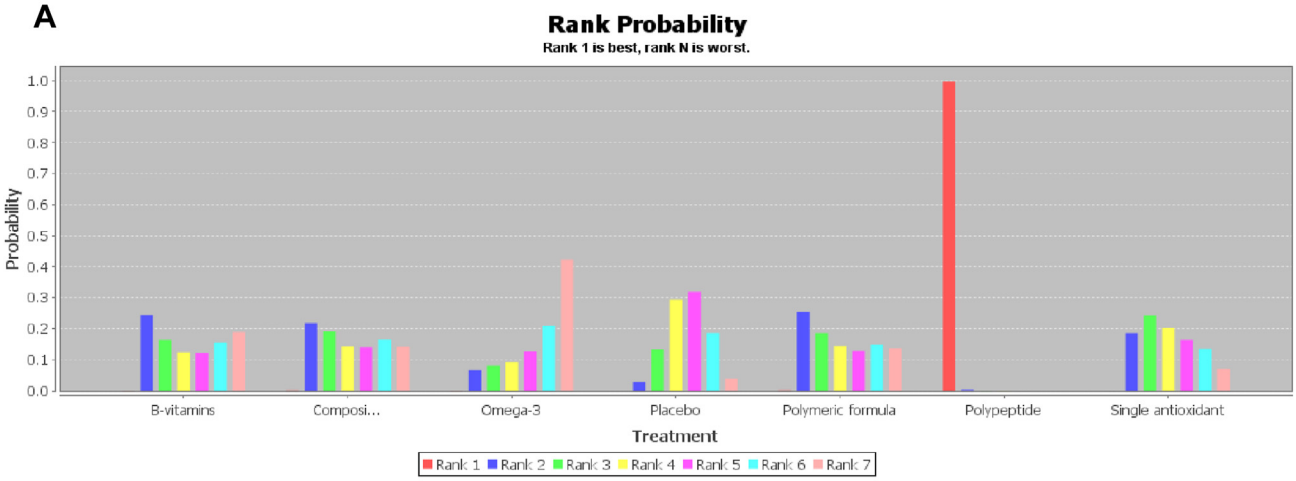
This work synthesized data from published trials performed to evaluate the effects of different nutrient interventions on neuropsychological and neuropathologic outcomes in AD at different stages. The insufficient evidence found was unable to prove clinical or statistical significance of the efficacy of isolated and/or mixed nutrients supplementation on the related outcomes. In general, considering the small number of studies, the small sample sizes and short duration of these studies, notably the attempt for achieving significant impact on clinical indicators was abortive. We must highlight that most AD outcomes in the evidence included in this research were mainly restricted to cognitive state and functional abilities; outcomes concerning neuropsychiatric behavior, global clinical state, biomarkers and neuroimaging were limited. The limited evidence suggests a subtle trend associating nutrient and reduced risk of dementia,

Table 3
Network Meta-Analysis of Cognitive Effect of Nutrient Interventions*

Consistency Model of Nutrient Interventions [MD (95% CrI)]						
B-vitamins	0.03 (−3.42, 3.62)	0.81 (−4.28, 2.65)	0.14 (−2.81, 2.41)	0.12 (−3.42, 3.62)	6.48 (2.44, 10.54)	0.16 (−2.94, 3.22)
−0.03 (−3.62, 3.42)	Composite antioxidants	0.85 (−3.93, 2.18)	0.19 (−2.60, 2.20)	0.09 (−3.27, 3.41)	6.49 (2.59, 10.23)	0.10 (−2.51, 2.65)
0.81 (−2.65, 4.28)	0.85 (−2.18, 3.93)	Omega-3	0.66 (−1.64, 2.93)	0.92 (−2.31, 4.25)	7.31 (3.42, 11.09)	0.93 (−1.82, 3.76)
0.14 (−2.41, 2.81)	0.19 (−2.20, 2.60)	0.66 (−2.93, 1.64)	Placebo	0.26 (−1.95, 2.61)	6.65 (3.55, 9.75)	0.29 (−1.37, 1.98)
−0.12 (−3.62, 3.42)	−0.09 (−3.41, 3.27)	0.92 (−4.25, 2.31)	0.26 (−2.61, 1.95)	Polymeric formula	6.37 (2.52, 10.21)	0.02 (−2.90, 2.88)
−6.48 (−10.54, −2.44)	−6.49 (−10.23, −2.59)	7.31 (−11.09, −3.42)	6.65 (−9.75, −3.55)	6.37 (−10.21, −2.52)	Polypeptide	6.35 (−9.56, −3.04)
−0.16 (−3.22, 2.94)	−0.10 (−2.65, 2.51)	0.93 (−3.76, 1.82)	0.29 (−1.98, 1.37)	0.02 (−2.88, 2.90)	6.35 (3.04, 9.56)	Single antioxidant
Inconsistency model of nutrient interventions						
B-vitamins	0.02 (−3.56, 3.83)	1.16 (−5.67, 3.10)	0.16 (−2.76, 2.56)	0.17 (−3.32, 3.79)	6.28 (1.53, 11.17)	0.30 (−3.10, 3.87)
−0.02 (−3.83, 3.56)	Composite antioxidants	1.19 (−5.27, 2.56)	0.16 (−2.78, 2.36)	0.13 (−3.32, 3.55)	6.24 (1.69, 10.64)	0.29 (−2.51, 3.15)
1.16 (−3.10, 5.67)	1.19 (−2.56, 5.27)	Omega-3	0.57 (−1.86, 3.09)	1.33 (−2.63, 5.72)	7.45 (2.29, 12.86)	1.45 (−2.37, 5.91)
0.16 (−2.56, 2.76)	0.16 (−2.36, 2.78)	0.57 (−3.09, 1.86)	Placebo	0.31 (−1.97, 2.73)	6.78 (3.42, 10.04)	0.04 (−2.05, 2.04)
−0.17 (−3.79, 3.32)	0.13 (−3.55, 3.32)	1.33 (−5.72, 2.63)	0.31 (−2.73, 1.97)	Polymeric formula	6.10 (1.51, 10.72)	0.13 (−3.12, 3.47)
−6.28 (−11.17, −1.53)	6.24 (−10.64, −1.69)	7.45 (−12.86, −2.29)	6.78 (−10.04, −3.42)	6.10 (−10.72, −1.51)	Polypeptide	5.95 (−9.71, −2.07)

MD, mean difference; CrI, credible interval.
*Organization is given alphabetically.

A



B

Drug	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5	Rank 6	Rank 7
B-vitamins	0.00	0.24	0.16	0.12	0.12	0.16	0.19
Composite antioxidants	0.00	0.22	0.19	0.14	0.14	0.17	0.14
Omega-3	0.00	0.07	0.08	0.09	0.13	0.21	0.42
Placebo	0.00	0.03	0.13	0.29	0.32	0.19	0.04
Polymeric formula	0.00	0.25	0.19	0.14	0.13	0.15	0.14
Polypeptide	1.00	0.00	0.00	0.00	0.00	0.00	0.00
Single antioxidant	0.00	0.19	0.24	0.20	0.16	0.13	0.07

C

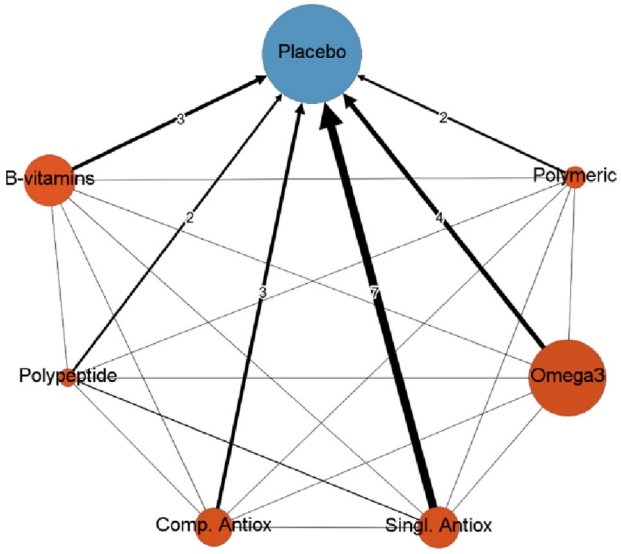


Fig. 6. Rank probability of cognitive effect and network of nutrient interventions.

especially for studies with proline-rich polypeptide and B-vitamin complex.

The mechanism of action of proline-rich peptides has been investigated particularly from nonhuman models and includes the inhibition of nitric oxide production[67] or protection against Aβ-induced neurodegeneration.[68] Results found in our meta-analysis showed somewhat positive effects on cognition[65,66]; however, this result may be biased because of the small number of studies included and different treatment duration producing a possible spurious effect. A relatively positive treatment effect of B-vitamin on cognition was observed, albeit it shows a faint lower decline in mental status compared with control group, rather than the improvement of symptoms.[32–34] Compared with these findings, earlier reviews of different types of studies looking at the efficacy of folate,[69] vitamin B6,[70] vitamin B1,[71] vitamin B12[72] did not provide support for a positive effect on cognition or risk of dementia in healthy elderly or demented

Table 4
Summary Effects Estimates on Cognition From Pairwise and Network Meta-Analysis

Nutrient Intervention	Number of Studies/Arms	Sample Size	Pairwise (MD)	Network (MD)	Weight	Rank (probability)
Polypeptide	2	136	6.93 (−3.04, 16.89)	6.65 (3.55, 9.75)	5.84%	1 (100%)
Polymeric formula	2	237	0.33 (−0.53, 1.19)	0.26 (−1.95, 2.61)	10.18%	2 (25%)
B-vitamins	3	521	0.52 (−0.05, 1.09)	0.14 (−2.41, 2.81)	22.37%	2 (24%)
Composite antioxidants	3	234	0.10 (−2.34, 2.54)	0.19 (−2.20, 2.60)	10.05%	2 (22%)
Single antioxidants	7	574	−0.00 (−0.85, 0.84)	0.29 (−1.37, 1.98)	24.65%	3 (24%)
Omega 3	4	627	−0.00 (−0.62, 0.62)	−0.66 (−2.93, 1.64)	26.92%	7 (42%)

MD, mean difference.

persons. The controversial findings of our meta-analysis evaluating the efficacy of B-vitamin complex "as a whole" (that is, including the different B vitamins in the same analysis) in contrast with the existent similar works evaluating these vitamins independently, lead us to consider that these vitamins have close interrelated roles and may work together, in cooperation. B-vitamins are well known by their mutual main role in the CNS and should not be evaluated distinctly in the management or prevention of neurodegenerative conditions.[73] These interventions are considered relatively stronger when compared with other nutrients investigated in the present study (as shown in our ranking of NMA). For instance, for their possible role associated with oxidative stress in the pathogenesis and progress of AD, antioxidants are expected to ameliorate oxidative status, contributing to delay neurodegeneration. Studies included in our analysis using single antioxidant nutrient[36–38,41,42,44,65] presented a large heterogeneity that might prevent the examination from bringing about a result different from a null effect. The exploratory analysis using only vitamin E also was futile, certainly attributed to the inconsistent results of individual trials.[36–38] Parallel to our findings, other studies found no evidence of the efficacy of vitamin E in the prevention or progression of AD.[74] Despite the evidence indicating the role of inositol,[75] vitamin D,[76] omega-3 fatty,[77–80] and MCT[81] in the functions of the CNS, studies using these compounds[35,47,52–54,56] in patients with AD at different stages did not show any significant enhancement in cognition or the other AD outcomes. Our results with omega-3 are consistent with other reviews that did not find enough evidence of this supplementation in the prevention of cognitive impairment or dementia in nondemented older individuals.[82–84] Treatments with multinutrient supplements intervention, denominated as "polymeric formula," showed some fair benefits on cognition, but not for other AD outcomes.[56,61] Few reports examining the effects of different multi-nutrient in AD showed a nonsignificant beneficial effect in any outcome.[85,86]

Across studies, there was observed inconclusive treatment effect of nutrients on clinical and neuropathological outcomes in patients diagnosed with AD at different stages, which may be attributed to the use of isolated nutrient supplementation overlooking the role of their counterpart to exert an appropriate physiological function in every metabolic pathway. The slight tendency favoring toward nutrients intervention suggests that an approach joining nutrients altogether may offer strengthened benefits. Single nutrient intervention is a narrowed approach putting aside the concept of food and nutrients synergy. Despite the importance of studies with isolated nutrients, to understand their function in the physiopathology of diseases, treatment strategies probably should be focused in the major embodiment of this concept; nutrients are comprised in a unit, food. The interrelation between constituents in foods is a remarkable fundament demonstrating that they act synergistically to influence the risk of several chronic diseases; single nutrients cannot exert functions independently, which is the basis for promoting consumption of food variety and selecting nutrient-rich foods.[87–90] Our findings suggest that a nutrient-based perspective is limited and does not reach significant effects. Studies related to Mediterranean diet,[91,92] DASH (Dietary Approaches to Stop Hypertension),[93] or combinations of dietary patterns such as the MIND diet[94] have proved these statements since they have been associated with a better cognitive function, lower rates of cognitive decline, and developing mild cognitive impairment and AD.

It is noteworthy that most studies regarding nutrient interventions in dementia were conducted in healthy elderly or with mild cognitive impairment. The extent of our results is also limited owing to the noninclusion of the gray literature, language restriction, and key search terms limited to the group of nutrients; which may have led to overlooked relevant records. The principal limitation in the analysis of results was the variety of scales used to assess neuropsychological outcomes and incomplete reporting of results, generating difficulties in pooling the results of trials. Several studies assessing single nutrients have small sample sizes that may introduce bias in the statistical analysis; indeed, few studies match the type of compound, dosage and time point measurement leading to heterogeneity in results. Some of the trial duration may be too short for the intervention to bring about noteworthy differences in cognitive domains and functions that comprise acquiring knowledge and skills that might not be affected following the nutritional supplementation on the shorter term. Among other limitations, not enough data for adjustment of possible important confounding variables was found, for example, education level or dietary nutrients intake.

Conclusions

Our findings did not provide consistent evidence to establish conclusive statements whether nutrients can slow down or decrease neuropathologic and clinical manifestations of AD. Future studies with single nutrients may focus on their role or behavior in the pathologic process of this disease and possibly in other body systems affected by the altered brain neurologic functions, as well as their interaction with other nutrients, or medications; rather than their isolated supplementation as a treatment. In such cases, we encourage monitoring also dietary nutrients ingestion and related factors.

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Supplementary Data

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