Original article

Dietary interventions in mild cognitive impairment and dementia

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Dietary intervention is an enticing approach in the fight against cognitive impairment. Nutritional supplements and dietetic counseling are relatively easy and benign interventions, but research has not yet yielded irrefutable evidence as to their clinical utility. Heterogeneity in the results of available clinical studies, as well as methodological and practical issues, does not allow replication and generalization of findings. The paper at hand reviews only randomized clinical trials of single nutrients, multi-nutrient formulations and dietary counseling in mild cognitive impairment and dementia of the Alzheimer's type focusing on both cognitive and functional outcomes. Thus far, folate, vitamin E, Ω-3 fatty acids, and certain multi-nutrient formulations have shown some preliminary promising results; larger, well-designed trials are needed to confirm these findings before nutritional elements can be incorporated in recommended clinical guidelines.

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Introduction

Dementia is almost always relentless, irreversible, and incapacitating for the patient, as well as having an equally burdensome impact on the patient's social surroundings. Dementia is projected to be a top public health, social, and fiscal concern in the decades to come, as the positive effect of enhanced preventive strategies and public awareness may be offset by global population growth – driven mainly by its increase in low-income countries – and by population aging in the "developed" world.

Evolution of pharmaceutical treatments is costly and requires extensive funding. Additionally, it has been proven to be an extremely challenging task. In contrast, prevention strategies are a lower-cost approach and can be implemented on a larger scale. Nutrition ranks very highly among such strategies and it has the added benefit of being acceptable by the majority of the public as more "benign" and potentially free of side effects.

Nutritional preventive measures range from supplementation of the everyday diet with specific nutrients, to changes of dietary habits (ie, enrichment with or avoidance of certain food groups/beverages) to compliance with whole dietary patterns. Evidence for the importance of nutrition in cognitive function as a lifelong modifiable factor arises from animal models, observational studies, and clinical trials. Longitudinal studies account for the bulk of available data on the relationship between nutrition and cognition, but they are commonly observational. Additionally, many of them focus mostly on cognitively normal elderly adults, examining nutrition as a *preventive* measure of future cognitive decline, with relatively

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fewer investigating potential associations with prognosis in already cognitively impaired populations.[1] Beyond observational studies, clinical trials of dietary interventions as a *treatment* for cognitive impairment are scarce. However, they are instrumental in shaping the clinicians' opinion on the potential of nutrition to be considered in the therapeutic armamentarium. The paper at hand is an attempt to review and summarize selected high-level scientific evidence on the topic of dietary interventions towards combating established cognitive dysfunction.

Method

Literature on dietary treatment for neurodegenerative disorders other than Alzheimer disease (AD) and its prodromal stage, mild cognitive impairment (MCI), is quite limited. There is some evidence on the role of dietary intervention in cognitive symptoms after stroke or coinciding with diseases increasing vascular risk (eg, diabetes mellitus), but the anticipated complex interplay between degenerative, inflammatory, and vascular mechanisms might prevent any attempt to coalesce data into meaningful conclusions. We therefore decided to focus on cognitive impairment due to clinically suspected underlying AD pathological changes.

A large part of published data in the field comes from observational and retrospective studies; we opted to restrict our search to controlled clinical trials reported in English, with an initial sample of at least 50 subjects with MCI or AD and an intervention spanning at least 24 weeks in duration, as neurodegenerative processes evolve slowly and nutritional treatment effects are expected to be low in magnitude. In order to collect evidence with as high practical value as possible, we encompassed only trials with clinical, neuropsychological, or functional end points and not biochemical or neuroimaging changes, as correlation of such changes with everyday outcomes is often indistinct. No limit was imposed on publication year.

We included in our search all types of intervention (eg, ingestion of a certain nutrient/food as well as dietary counseling/training and adherence to a certain diet). Nutritional intervention as both single and "add-on" treatment was accepted. Only therapeutic attempts related to chemical compounds found in food were included, eg, vitamins, minerals, antioxidants as well as whole foods/food groups. "herbal remedies," or other supplements that are not part of routine diet (eg, gingko biloba) were excluded.

Relevant literature was identified through the PubMed search engine in October 2018; the list of located papers is by no means exhaustive, even though every effort was made toward that end. When the results of a specific trial were reported in more than one paper, we focused on the seminal publication or the one discussing outcomes of a more clinical/neuropsychological nature.

Results

Scientific papers fulfilling the criteria outlined above are presented in *Tables Ia* and *Ib* in detail. The earliest identified papers date back as far as 1991, albeit in recent years larger and better designed studies have emerged.

Almost all identified randomized controlled trials (RCTs) were double-blind and compared an intervention against a placebo group; eighteen trials tested the therapeutic effect of nutrition on (usually mild-to-moderate) AD and ten on MCI. Diagnosis was established according to various sets of international criteria, although in some studies diagnostic methodology and baseline sample characteristics are not clearly presented. About half of the studies involved a single micronutrient and the rest a micronutrient combination. We did not detect any RCTs with the aforementioned characteristics on the effect of trace elements, vitamin D, coenzyme Q10, curcumin, caffeine, olive oil, whole foods, food groups, or whole diets on cognitive impairment.

A summary of the main findings of the studies by intervention category

B vitamins

B vitamins are usually studied as a complex related mainly to energy production in neurons and lowering of homocysteine levels. The B-complex has been studied in MCI in two RCTs. A study from the United Kingdom reported cognitive improvement mainly in those with high baseline homocysteine[2]; further analysis showed an interaction with baseline Ω-3 fatty acid plasma concentrations: only those with higher initial Ω-3 levels benefited from B vitamin supplementation.[3] A Dutch study examined a possible effect in quality of life (QoL) and reported essen-

tially no change.[4] In AD there is one study in subjects with mild-to-moderate AD (and normal baseline vitamin B12 and folate levels) that did not find any effect[5]; oddly, depression was more common in the active treatment group.

Folate has been studied as a solitary intervention: cognitive improvement in general intelligence, attention span, and visuospatial metrics within 6 months has been reported in MCI[6]; two studies on patients with AD under acetyl-cholinesterase inhibitors (AChEI) reported either an increase in Mini-Mental State Examination (MMSE) with no change in Activities of Daily Living (ADL)[7] or the exact opposite result regarding MMSE and ADL.[8]

Antioxidants
Chemical compounds characterized as antioxidants are a diverse group. Vitamins C and E were studied in a simple study in subjects with MCI for 1 year[9]; no difference in MMSE was noted.

Vitamin E has been studied extensively. One study in AD concluded that vitamin E resulted in an MMSE increase in subjects who "responded" to it (ie, showed reduced glutathione oxidation – a marker of oxidative stress), but could even be detrimental in "non-responders."[10] Vitamin E has also been studied against active comparators: in a large study against donepezil for 3 years in subjects with amnestic MCI,[11] time to progression to AD was not different in either treatment group compared with placebo, even though vitamin E exerted a positive effect on language and overall cognition in the first half of the study period. Two other large studies examined the effect of vitamin E on progression rate in AD against placebo and memantine[12] or selegiline[13] for up to 4 years and showed slower functional decline with focus on the ADL, even though no effect was observed on cognitive measures.

Other potential antioxidants studied in AD include soy isoflavones[14] (patients that metabolize them effectively might show modest cognitive improvement), acetyl-L-carnitine[15,16] (contradictory results) and resveratrol[17] (no clinically meaningful benefit in secondary outcomes related to cognition).

Ω-3 fatty acids
Ω-3 fatty acids are credited with anti-inflammatory and neuroprotective properties. Three studies from China[18,19] and Australia[20] reported positive cognitive outcomes in subjects with MCI. Two studies were conducted in mild to moderate AD: one Swedish study showed a small benefit only in the population with very mild cognitive dysfunction (slower decline)[21]; less agitation was reported in *APOE-ε4* carriers and a lower depression score in non-*APOE-ε4* carriers in the same study.[22] Another study from the United States reported improved cognitive metrics only in non-*APOE-ε4* carriers[23] (*APOE:* apolipoprotein E).

Phosphatidylserine
Phosphatidylserine, a component of cell membranes, has been studied in two diverse populations: a somewhat poorly designed study in people with at least moderate cognitive decline[24] reported cognitive benefits, while another study in mild to moderate AD[25] that evaluated phosphatidylserine plus cognitive training as part of a multidomain intervention reported only transient cognitive amelioration.

Multi-nutrient formulations
Two distinct multi-nutrient formulations have failed to yield positive cognitive effects: one trial enrolled subjects that were normal or diagnosed with MCI[26] and another one patients with AD and normal baseline vitamin B12 and folate levels.[27]

Other relatively large studies examined the effect of a patented formulation called Fortasyn Connect. In subjects with MCI,[28] no change in a composite neuropsychological score was proven; nonetheless subjects with higher baseline MMSE showed some clinical benefit in the form of Clinical Dementia Rating (CDR) stabilization. One study in drug-naïve patients with mild AD showed improvement in a memory composite score[29] persisting during an open-label, 24-week extension,[30] while in patients with mild-to-moderate AD under standard treatment no cognitive effect was shown.[31] This formulation has also been shown to increase the body mass index (BMI) of patients with mild AD and improve everyday function in those with lower baseline BMI.[32] The safety profile was favorable.

Dietary counseling
One study aimed to identify functional and cognitive benefits of dietary counseling provided to AD patients' physicians and caregivers and failed to show any change; nonetheless the risk of malnutrition was reduced.[33]

PUBLICATION	POPULATION	INITIALLY RANDOMIZED SAMPLE SIZE	DIAGNOSIS (METHOD)	INTERVENTION (DAILY DOSAGE)	DURATION OF INTERVENTION	
Bo et al (2017)[18]	≥60 yr (mean: 71 yr), Chinese, community-dwelling	86	MCI according to the modified Petersen criteria (MMSE, CDR, ADL)	480 mg DHA & 720 mg EPA vs placebo (550 mg oleic acid)	6 mo	
Ma et al (2016)[6]	≥65 yr, Chinese, community-dwelling	180	MCI according to the modified Petersen criteria (MMSE & ADL)	Folic acid 400 μg vs conventional treatment	6 mo	
Zhang et al (2017)[19]	≥65 yr, Chinese, community-dwelling	240	MCI according to the modified Petersen criteria (MMSE, ADL)	DHA 2 g vs placebo	12 mo	
de Jager et al (VITACOG, 2011)[2]	≥70 yr, English	271	MCI (TICS-M & category fluency ± MMSE, subjective memory complaints & ADL)	Folic acid 0.8 mg, vitamin B6 20 mg & vitamin B12 0.5 mg vs placebo	2 yrs	
Sinn et al (2012)[20]	>65 yr, Australian, community-dwelling	50	MCI (MMSE, Verbal Paired Associates Task)	EPA 1.67 g & DHA 0.16 g vs DHA 1.55 g & EPA 0.40 g vs placebo	6 mo	
Soininen et al (LipiDiDiet, 2017)[28]	50-86 yr (mean: 71 yr), Finnish, German, Dutch & Swedish, outpatients	311	MCI (prodromal AD) according to the IWG-1 criteria	125 mL of Fortasyn Connect (DHA 1200 mg, EPA 300 mg, uridine monophosphate 625 mg, choline 400 mg, vitamins: B12 3 μg, B6 1 mg, C 80 mg & E 40 mg, folic acid 400 μg, phospholipids 106 mg, selenium 60 μg) vs placebo	24 mo (+12 mo optional double-blind extension)	
Baleztena et al (2018)[26]	≥75 yr (mean: 86.9 yr), Spanish, institutionalized	99	normal/MCI (MMSE & Global Deterioration Scale)	DHA 250 mg, EPA 40 mg, vitamin E 5 mg, phosphatidylserine 15 mg, tryptophan 95 mg, vitamin B12 5 μg, folate 250 μg & ginkgo biloba 60 mg vs placebo	1 yr	
Naeini et al (2014)[9]	60-75 yr, Iranian	256	MCI (MMSE)	Vitamin E 300 mg & vitamin C 400 mg vs placebo	1 yr	
Petersen et al (ADCS, 2005)[11]	55-90 yr (mean: 72.9 yr), US, outpatients	769	amnestic MCI (delayed recall score, CDR, MMSE)	Vitamin E 2000 IU vs donepezil 10 mg vs placebo; all groups additionally received vitamin E 15 IU	3 yrs	
van Uffelen et al (2007)[4]	70-80 yr (mean: 75 yr), Dutch, community-dwelling	179	MCI according to the Petersen criteria (MMSE, TICS, WLT, Groningen Activity Restriction Scale)	For the vitamin intervention: folic acid 5 mg, vitamin B12 0.4 mg, vitamin B6 50 mg vs placebo	1 yr	

Table Ia. Randomized clinical trials on the therapeutic effect of dietary interventions on mild cognitive impairment (see abbreviations at end of Table).

	MAIN OUTCOME (MOSTLY PRIMARY)	TYPE OF MAIN OUTCOME	RESULT	POSITIVE/ NEGATIVE STUDY	OTHER FINDINGS/COMMENTS
	Differences in BCAT	Cognitive	Improvement in total BCAT scores, perceptual speed, space imagery efficiency & working memory	+	Olive oil as placebo. BCAT scores improved in both groups; working memory not changed in females
	Difference in IQ & WAIS-RC scores	Cognitive	Improvement in Full Scale IQ, Digit Span & Block Design	+	Unblinded RCT
	Difference in WAIS-RC	Cognitive	Greater increase in Full-Scale IQ, Information & Digit Span scores	+	Corn oil as placebo
	Changes in cognitive and clinical status	Cognitive & functional	No effect for MMSE, HVLT-DR, category fluency or CDR, IQCODE; stabilization of CLOX scores	±	In subjects with high baseline total homocysteine, improvement in all metrics
	Difference in GDS, QoL, cognition (focusing on memory & executive function)	Cognitive & QoL	Improvement in Initial Letter Fluency in the DHA group & in GDS in both active treatment groups	±	LA 2.2 g as placebo
	Difference in composite NTB score	Cognitive	NS	±	Reduced increase in CDR-SoB in the active treatment group; the effect was more pronounced in those with higher baseline MMSE. The control group had slower cognitive decline than anticipated in this study
	Difference in MMSE	Cognitive	NS	−	Improvement in memory subscale of MMSE in well-nourished subjects
	Difference in MMSE	Cognitive	NS	−	
	Time to conversion to AD (according to the NINCDS-ADRDA criteria)	Cognitive & functional	NS for all time intervals	−	Positive effect of vitamin E on the executive, language & overall cognitive scores for the first 18mo (The risk of progression to AD was lower in the donepezil group than in the placebo group in the first 12 mo; this effect was evident for the whole 3 yr in *APOE-ε4* carriers)
	Difference in D-QoL & SF-12 scores (overall & health-related QoL)	QoL	NS	−	The same subjects were randomized to a parallel exercise intervention. No cognitive outcomes. Baseline QoL scores above the general population average. Detrimental effect of vitamin supplementation on D-QoL-belonging

PUBLICATION	POPULATION	INITIALLY RANDOMIZED SAMPLE SIZE	DIAGNOSIS (METHOD)	INTERVENTION (DAILY DOSAGE)	DURATION OF INTER-VENTION	
Cenacchi et al (1993)[24]	65-93 yr, Italian, inpatients & institutionalized	494	Moderate to severe cognitive decline (MMSE, Global Deterioration Scale)	Brain cortex-derived phosphatidylserine 300 mg vs placebo	6 mo	
Dysken et al (TEAM-AD VA, 2014)[12]	53-96 yr (mean: 78.8 yr), >95% male, US, on AChEI	613	Mild to moderate AD (MMSE)	Vitamin E 2000 IU vs memantine 20 mg vs both vs placebo	6 mo-4 yrs (mean: 2.27 yr)	
Sano et al (ADCS, 1997)[13]	Mean age >72 yr, US, outpatients	341	Moderate AD (CDR of 2)	Selegiline 10 mg vs vitamin E 2000 IU vs both vs placebo	2 yrs	
Scheltens et al (Souvenir II, 2012)[29]	≥50 yr, Dutch, German, Belgian, Spanish, Italian & French, drug-naïve	259	Mild AD according to the NINCDS-ADRDA criteria (MMSE)	125 ml of Fortasyn Connect (as above) vs placebo	24 wks	
Spagnoli et al (1991)[15]	>40 yr (mean: >74 yr), Italian	130	AD according to DSM-III (Organic Brain Syndrome scale)	Acetyl-L-carnitine 2 g vs placebo	1 yr	
Chen et al (TFA-AD, 2016)[7]	>60 yr, Chinese, on donepezil 5-10 mg	162	AD (MMSE)	Folic acid 1.25 mg vs placebo	6 mo	
Connelly et al (2008)[8]	mean age 76.27 yr, Scottish, outpatients, on AChEI	57	AD according to the NINCDS-ADRDA criteria	Folic acid 1 mg vs placebo	6 mo	
Freund-Levi et al (OmegAD, 2006)[21]	mean age 74 yr, Swedish, outpatients, on AChEI	204	Mild to moderate AD according to DSM-IV (MMSE)	DHA 1.72 g & EPA 0.6 g vs placebo for 6 mo, open-label extension for 6 mo	6+6 mo	
Gleason et al (2015)[14]	>60 yr (mean: 76.3 yr), US, commu-nity-dwelling, on AChEI ± memantine	65	AD, mostly early	Purified soy isoflavone glycosides 100 mg vs placebo	6 mo	

Table 1b. Randomized clinical trials on the therapeutic effect of dietary interventions on Alzheimer disease (see abbreviations at end of Table).

	MAIN OUTCOME (MOSTLY PRIMARY)	TYPE OF MAIN OUTCOME	RESULT	POSITIVE/ NEGATIVE STUDY	OTHER FINDINGS/COMMENTS
	Differences in Plutchik Geriatric Rating Scale (behavior) and the Buschke Selective Reminding Test (cognition)	Cognitive & functional	Improved motivation, learning & retrieval	+	Corn oil as placebo. No adjustment for potential confounders. Very few AEs
	Difference in ADCS-ADL	Functional	Subjects receiving vitamin E had slower decline than those receiving placebo	+	Subjects receiving vitamin E showed a delay in ADL deterioration by 6.2 mo; caregiver time increased least in the vitamin E group compared to the memantine group. No effect on secondary cognitive measures
	Time to the occurrence of death, institutionalization, loss of the ability to perform basic ADL or CDR of 3	Cognitive & functional	Delayed progression in all three active treatment groups	+	Vitamin E delayed institutionalization; improvement in IADL. No effect on cognitive measures. Falls & syncope more frequent in the active treatment groups
	Difference in "trajectory of change" of the memory function domain z-score of the NTB	Cognitive	Increase of the score in the active treatment group	+	Patients in the active treatment group also received other vitamins, minerals, trace elements & macronutrients. Positive safety profile
	Difference in neuropsychological & clinical measures	Cognitive & functional	Slower rate of deterioration in the BDS	+	No major AEs
	Difference in MMSE & ADL	Cognitive & functional	Increase in MMSE, no difference in ADL	±	Single-blind RCT
	Number of good responders per NICE (difference in MMSE, behavioral & functional assessments)	Cognitive & functional	Improvement in IADL & social behavior, no difference in MMSE	±	Patients with a higher baseline DSST score responded better based on MMSE
	Difference in MMSE & ADAS-cog	Cognitive	NS	±	The active treatment & placebo included vitamin E 4 mg; placebo included LA 2.4 g. Reduction was shown in the MMSE decline rate in subjects with very mild cognitive dysfunction
	Differences in neuropsychological battery scores focusing on memory & executive function	Cognitive	NS	±	Treatment groups did not differ in *APOE-ε4* status or dietary intake of isoflavones. *APOE-ε4* genotype did not influence response. Only effective metabolizers showed improvement in verbal fluency & speed dexterity

PUBLICATION	POPULATION	INITIALLY RANDOMIZED SAMPLE SIZE	DIAGNOSIS (METHOD)	INTERVENTION (DAILY DOSAGE)	DURATION OF INTER-VENTION	
Lloret et al (2009)[10]	Spanish	57	AD according to the NINCDS-ADRDA criteria	Vitamin E 800 IU vs placebo	6 mo	
Aisen et al (ADCS, 2008)[5]	>50 yr (mean: 76.3 yr), US, outpatients	409	Mild to moderate AD (MMSE)	Folate 5 mg, vitamin B6 25 mg & vitamin B12 1 mg vs placebo	18 mo	
Heiss et al (1994)[25]	48-79 yr, German, outpatients	80	Mild to moderate AD according to the NINCDS-ADRDA criteria (MMSE)	Social support vs cognitive training vs cognitive training & pyritinol 1200 mg vs cognitive training & phosphatidylserine 400 mg	6 mo	
Quinn et al (ADCS, 2010)[23]	Mean age: 76 yr, US, outpatients	402	Mild to moderate AD (MMSE)	DHA 2 g vs placebo	18 mo	
Salva et al (NutriAlz, 2011)[33]	Mean age >78 yr, Spanish, outpatients	946	Mild to moderate dementia (AD) according to DSM-IV (MMSE)	Teaching and training of physician and caregiver on health and nutrition vs usual care	1 yr	
Shah et al (S-Connect, 2013)[31]	≥50 yr (mean: 76.7 yr), US, community-dwelling & outpatients, on stable doses of AChEI and/or memantine	527	Mild to moderate AD according to the NINCDS-ADRDA criteria (MMSE)	125 ml of Fortasyn Connect (as above) vs placebo	24 wks	
Sun et al (2007)[27]	>50 yr (mean: 75 yr), Taiwanese, outpatients, on AChEI, with normal serum levels of vitamin B12 & folic acid	89	Mild to moderate AD according to DSM-IV-TR (MMSE, CDR)	Vitamins: B12 0.503 mg, B6 5 mg, folic acid 1 mg, B3 10 mg, B2 2 mg, B1 3 mg, B5 1 mg, C 100 µg, A 4000 IU & D3 400 IU, iron ferrous 60 mg, calcium carbonate 250 mg, iodine 100 µg, copper 150 µg vs placebo	26 wks	

Table Ib. Randomized clinical trials on the therapeutic effect of dietary interventions on Alzheimer disease (see abbreviations at end of Table).

	MAIN OUTCOME (MOSTLY PRIMARY)	TYPE OF MAIN OUTCOME	RESULT	POSITIVE/ NEGATIVE STUDY	OTHER FINDINGS/COMMENTS
	Difference in MMSE, BDS, Clock Drawing Test	Cognitive & functional	Increased MMSE score in respondents vs non-respondents, reduced in non-respondents vs placebo	±	No difference in other scores
	Difference in ADAS-Cog	Cognitive	NS (incl. secondary outcomes measures)	−	Adverse events involving depression more common in the active treatment group
	Difference in MMSE & other neuropsychological tool scores	Cognitive	Transient positive effects at 8 wks, mainly in the phosphatidylserine group	−	Unblinded RCT
	Rate of change in ADAS-Cog & CDR-SoB	Cognitive & functional	NS	−	Corn or soy oil as placebo. *APOE-ε4* noncarriers showed benefit in ADAS-Cog & MMSE scores
	Difference in ADL-IADL scores	Functional	NS	−	Unblinded RCT. No difference in secondary cognitive outcomes
	Difference in ADAS-Cog	Cognitive	NS	−	Good safety & tolerability, high compliance to treatment
	Difference in ADAS-Cog	Cognitive	NS (incl. secondary outcomes measures)	−	

PUBLICATION	POPULATION	INITIALLY RANDOMIZED SAMPLE SIZE	DIAGNOSIS (METHOD)	INTERVENTION (DAILY DOSAGE)	DURATION OF INTERVENTION	
Thal et al (1996)[16]	≥50 yr, US, outpatients	431	Mild to moderate AD according to the NINCDS-ADRDA and DSM-III-R criteria (MMSE)	Acetyl-L-carnitine 3 g vs placebo	12 mo, open-label extension for 12 mo	
Turner et al (ADCS, 2015)[17]	>49 yr (mean: >69 yr), US	119	Mild to moderate AD according to the NINCDS-ADRDA criteria (MMSE)	Resveratrol 500 mg to 2000 mg vs placebo	52 wks	

Table Ib. Randomized clinical trials on the therapeutic effect of dietary interventions on Alzheimer disease.

Each publication is identified by its first author and year of publication; if it was part of a broader clinical program or is known by an acronym they are also noted. The level of available information on the studied population differs; every effort was made to provide a short, but meaningful delineation. All presented studies are double-blind RCTs, unless stated otherwise. When reported, the set of criteria used to diagnose patients is presented, together with the main standardized neuropsychological tools that were used for diagnostic classification (in parentheses). When the primary outcome of a trial was not clinical, neuropsychological, or functional, it is omitted and clinical/neuropsychological/functional secondary outcomes are presented; the study is categorized as positive/indeterminate/negative (+/±/−) based on the main and secondary findings in the cognitive and functional domains.

AChEI: Acetyl-cholinEsterase inhibitor, **AD:** Alzheimer disease, **ADAS-Cog:** Alzheimer's Disease Assessment Scale-cognitive subscale, **ADCS:** Alzheimer's Disease Cooperative Study, **ADCS-ADL:** Alzheimer's Disease Cooperative Study-Activities of Daily Living, **ADL:** Activities of Daily Living, **AE:** Adverse Event, **APOE:** Apolipoprotein E, **BCAT:** Basic Cognitive Aptitude Tests, **BDS:** Blessed Dementia Scale, **CDR:** Clinical Dementia Rating, **CDR-SoB:** Clinical Dementia Rating-Sum of Boxes, **CLOX:** Clock Drawing Task, **DHA:** Docosohexanoic acid, **D-QoL:** Dementia Quality of Life, **DSM:** Diagnostic and Statistical Manual of Mental Disorders, **DSM-III-R:** Diagnostic and Statistical Manual of Mental Disorders, third edition-Revision, **DSM-IV-TR:** Diagnostic and Statistical Manual of Mental Disorders, fourth edition-Text Revision, **DSST:** Digit Symbol Substitution Test, **EPA:** Eicosapentaenoic acid, **GDS:** Geriatric Depression Scale, **HVLT-DR:** Hopkins Verbal Learning Test revised-Delayed Recall, **IADL:** Instrumental Activities of Daily Living, **IQ:** Intelligence quotient, **IQCODE:** Informant Questionnaire on Cognitive Decline in the Elderly, **LA:** Linoleic acid, **MCI:** Mild Cognitive Impairment, **MMSE:** Mini-Mental State Examination, **NICE:** National Institute of Clinical Excellence, **NINCDS-ADRDA:** National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association, **NPI:** NeuroPsychiatric Inventory, **NS:** Non-significant, **NTB:** Neuropsychological Test Battery, **QoL:** Quality of life, **RCT:** Randomized controlled trial, **SF-12:** 12-Item Short Form health survey, **TICS:** Telephone Interview for Cognitive Status, **TICS-M:** Telephone Interview for Cognitive Status-Modified, **US:** United States, **WAIS-RC:** Wechsler Adult Intelligence Scale-Revised Chinese, **WLT:** Word Learning Test.

Discussion

Given the body of evidence briefly delineated above, no firm guidance or even recommendation can be offered about any of the proposed dietary interventions for cognitive dysfunction. Indeed, several high-quality systematic reviews and meta-analyses found no or insufficient evidence of benefit.[34-44] Be that as it may, folate, vitamin E, Ω-3 fatty acids, and certain multi-nutrient formulations appear to be the best nutritional candidates for further investigation of potential efficacy in MCI or mild AD. The verdict is still open, as in many cases similar studies result in inconsistent results or a newer study does not replicate the findings of a previous one. The complex and –to a certain extent– unclear, still debatable pathophysiological mechanisms of cognitive dysfunction in AD may be among the main reasons for conflicting results. There are also multiple methodological and practical issues possibly

	MAIN OUTCOME (MOSTLY PRIMARY)	TYPE OF MAIN OUTCOME	RESULT	POSITIVE/ NEGATIVE STUDY	OTHER FINDINGS/COMMENTS
	Difference in ADAS-Cog & CDR-SoB	Cognitive & functional	NS	–	
	Difference in MMSE, ADAS-Cog, ADCS-ADL, NPI, CDR-SoB	Cognitive & functional	NS (except less decline in ADCS-ADL)	–	

preventing ascertainment of small treatment effects and generalization of findings.

A main observation involves the significant differences in diagnostic methodology, set or version of diagnostic criteria used, and dementia stage classification across studies. In virtually all cases, diagnosis and staging were mostly clinical, with limited use of objective AD neuroimaging/ neurochemical biomarkers. Heterogeneous (community-dwelling elderly, memory clinic outpatients, participants in day care programs, residents of institutions, etc) and ethnically diverse populations were studied. These issues hinder generalization of findings.

Regarding study design, we noted generally small sample sizes and perhaps not long enough duration of the interventions, sometimes accompanied by high dropout rates. Neurodegeneration evolves very slowly, so treatment effects can be expected to be modest at best; large samples and sufficient follow-up are needed to ascertain clinically and statistically important differences (to place findings from this literature in perspective, many novel drug trials in this population exceed a sample size of 2000 participants and, in several cases, last for as long as 2 years).[45] In some trials, biochemical, neurochemical, or neuroimaging parameters were selected as primary outcomes; such trials may not be adequately powered to reveal subtle differences that may exist in secondary cognitive and functional outcomes, which we consider more relevant in everyday clinical practice. To further complicate matters, some of the findings we report here were derived from post hoc analyses. Moreover, in some studies with relatively short follow-up periods and consequently frequent visits, apparent stabilization in neuropsychological scores might be the result of a learning effect that keeps differences under the statistical significance threshold. Various cognitive assessment tools and functional scales were used as outcome measures; some of them may have not been sensitive enough to detect small changes of mental/functional capacity or QoL in the population with mildly affected cognition. Daily variation of cognition is probably larger than nutritional treatment effects, thereby potentially rendering cognitive tests insensitive to them.

Studying patients with overt dementia may prevent unveiling of the beneficial effect of a nutrient, as the neuropathologic process may already have been so advanced that all available intervention may be futile. Despite that, positive results were not more common in studies on MCI than on AD, highlighting perhaps the utility of applying our intervention at an even more prodromal stage of neurodegeneration, if possible.

Great variability was noted in supplement dosage and duration of administration; different chemical compounds were often used for a certain vitamin. Furthermore, results may have been confounded by previous dietary habits or concurrent intake of the studied nutrient in food. In some studies, olive/corn oil were used as placebo, although they contain unsaturated fatty acids that may exert positive effects on cognition.[46] In certain Western countries, folic acid fortification programs may complicate detection of a

relationship between folate status and cognitive impairment. Also, most studies do not report baseline vitamin levels, which may influence the effect of supplemented vitamins on cognition, ie, deficient individuals might show greater benefit. Moreover, in many studies, data on concomitant use of drugs commonly prescribed for AD were not provided. These issues, in addition to the omnipresent risk of publication bias (which is commonly more of a concern for studies of relatively smaller size and power), make interpretation of the results much harder.

It seems reasonable to expect that multi-nutrient formulations may be more potent; conversely, multi-nutrient or whole-diet interventions do not allow identification of the specific action of each component with a possibility of unidentified synergistic, neutral, or even antagonistic effects between them. Theoretically, such interventions might be easier and less expensive, as they do not entail any manufacturing costs, but only advice/counseling and close follow-up of the subjects' compliance. It should be noted, though, that RCTs (with the characteristics we specified in "Methods") studying whole foods or diets as treatment for cognitive impairment have not been identified; perhaps the scientific community opts for simpler, straightforward experimental designs or the practical difficulties of implementing such a trial in the elderly population with cognitive dysfunction are hard to overcome. Nonetheless, the existing body of evidence for the potential preventive benefits of the Mediterranean diet, in particular, against cognitive impairment in normal cohorts is substantial; data originating from both RCTs [PREDIMED (on subjects at high cardiovascular risk)][47] and observational studies[48-50] show reduction in the rate and risk of cognitive decline. More data are certainly needed in MCI and AD, but until then patients and caregivers can be encouraged to follow the Mediterranean diet.

Evidence shows that the BMI decreases prior to AD onset and remains stable or increases afterwards.[51] Reasons for weight loss in the preclinical stage of AD comprise pathological changes in brain areas that regulate weight, disruption in hormone and neuropeptide levels, apathy, reduced olfaction, eating difficulty, and inadequate nutrition due to cognitive impairment itself. Conversely, it is possible that weight loss might also be a potential risk factor for developing AD, via, for example, a deficiency of biologically important micronutrients and antioxidative compounds. Body weight changes before and after dementia diagnosis highlight the importance of acknowledging the full interplay between nutrition and cognitive function; in fact, nutrition is just one of many potentially modifiable determinants of future cognitive decline.

As single nutrients may not be potent enough to produce clinically significant benefits, perhaps future research should steer toward multi-nutrient, whole-diet and multidomain interventions

Indeed, recently, interest in more holistic approaches has increased; multidomain interventions attempt to impact many lifestyle aspects that have been hypothesized to benefit cognition. Such interventions encompass not only nutritional guidance for a healthy diet, but also coaching on modification of other important factors (eg, physical activity), cognitive training, and control of cardiovascular risk. Some of the large multidomain interventions (preDIVA,[52] MAPT,[53] and FINGER[54]) may have included some subjects who could be categorized into MCI; nevertheless, they mostly focused on prevention, which is out of scope for this manuscript. In the future such approaches in patients with MCI or dementia may yield significant results.

As single nutrients may not be potent enough to produce statistically and–more importantly–clinically significant benefits, perhaps future research should steer toward multi-nutrient, whole-diet, and multidomain interventions in even larger, homogeneous, community-dwelling samples with as early disease stages as possible; strict diagnostic criteria, sufficient follow-up, and consensus on the use of specific functional outcomes could enhance comparison of different trials and improve our understanding on the role of diet as a treatment option for cognitive impairment. Recent technological breakthroughs might become invaluable aids to such research, as sensors on portable hand-held/wearable devices and social media-embedded applications could assist in recording dietary habits and even collection of biomarkers. Innovative techniques, such as metabolomics and cerebrospinal fluid neurobiology, or investigation of novel aspects of

nutrition (including hydration status and chronobiology of food intake) may further unravel hidden associations between nutrition and cognitive dysfunction.

Conclusions

Nutrition is an important lifestyle factor related to cognitive impairment. Clinical studies of the potential utility of dietary intervention in ameliorating mild cognitive impairment and dementia are certainly warranted. Thus far, folate, vitamin E, Ω-3 fatty acids, and certain multi-nutrient formulations have shown some initial promise; larger, well-designed trials with robust methodology may hopefully corroborate some of these findings. ■

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References

1. Scarmeas N, Anastasiou CA, Yannakoulia M. Nutrition and prevention of cognitive impairment. *Lancet Neurol.* 2018;17(11):1006-1015.
2. de Jager CA, Oulhaj A, Jacoby R, Refsum H, Smith AD. Cognitive and clinical outcomes of homocysteine-lowering B-vitamin treatment in mild cognitive impairment: a randomized controlled trial. *Int J Geriatr Psychiatry.* 2012;27(6):592-600.
3. Oulhaj A, Jerneren F, Refsum H, Smith AD, de Jager CA. Omega-3 fatty acid status enhances the prevention of cognitive decline by B vitamins in mild cognitive impairment. *J Alzheimers Dis.* 2016;50(2):547-557.
4. van Uffelen JG, Chin APMJ, Hopman-Rock M, van Mechelen W. The effect of walking and vitamin B supplementation on quality of life in community-dwelling adults with mild cognitive impairment: a randomized, controlled trial. *Qual Life Res.* 2007;16(7):1137-1146.
5. Aisen PS, Schneider LS, Sano M, et al. High-dose B vitamin supplementation and cognitive decline in Alzheimer disease: a randomized controlled trial. *JAMA.* 2008;300(15):1774-1783.
6. Ma F, Wu T, Zhao J, et al. Effects of 6-month folic acid supplementation on cognitive function and blood biomarkers in mild cognitive impairment: a randomized controlled trial in China. *J Gerontol A Biol Sci Med Sci.* 2016;71(10):1376-1383.
7. Chen H, Liu S, Ji L, et al. Folic acid supplementation mitigates Alzheimer's Disease by reducing inflammation: a randomized controlled trial. *Mediators Inflamm.* 2016;2016:5912146.
8. Connelly PJ, Prentice NP, Cousland G, Bonham J. A randomised double-blind placebo-controlled trial of folic acid supplementation of cholinesterase inhibitors in Alzheimer's disease. *Int J Geriatr Psychiatry.* 2008;23(2):155-160.
9. Naeini AM, Elmadfa I, Djazayery A, et al. The effect of antioxidant vitamins E and C on cognitive performance of the elderly with mild cognitive impairment in Isfahan, Iran: a double-blind, randomized, placebo-controlled trial. *Eur J Nutr.* 2014;53(5):1255-1262.
10. Lloret A, Badia MC, Mora NJ, Pallardo FV, Alonso MD, Vina J. Vitamin E paradox in Alzheimer's disease: it does not prevent loss of cognition and may even be detrimental. *J Alzheimers Dis.* 2009;17(1):143-149.
11. Petersen RC, Thomas RG, Grundman M, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. *N Engl J Med.* 2005;352(23):2379-2388.
12. Dysken MW, Sano M, Asthana S, et al. Effect of vitamin E and memantine on functional decline in Alzheimer disease: the TEAM-AD VA cooperative randomized trial. *JAMA.* 2014;311(1):33-44.
13. Sano M, Ernesto C, Thomas RG, et al. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. The Alzheimer's Disease Cooperative Study. *N Engl J Med.* A1997;336(17):1216-1222.
14. Gleason CE, Fischer BL, Dowling NM, et al. Cognitive effects of soy isoflavones in patients with Alzheimer's Disease. *J Alzheimers Dis.* 2015;47(4):1009-1019.
15. Spagnoli A, Lucca U, Menasce G, et al. Long-term acetyl-L-carnitine treatment in Alzheimer's disease. *Neurology.* 1991;41(11):1726-1732.
16. Thal LJ, Carta A, Clarke WR, et al. A 1-year multicenter placebo-controlled study of acetyl-L-carnitine in patients with Alzheimer's disease. *Neurology.* 1996;47(3):705-711.
17. Turner RS, Thomas RG, Craft S, et al. A randomized, double-blind, placebo-controlled trial of resveratrol for Alzheimer disease. *Neurology.* 2015;85(16):1383-1391.
18. Bo Y, Zhang X, Wang Y, et al. The n-3 polyunsaturated fatty acids supplementation improved the cognitive function in the Chinese elderly with mild cognitive impairment: a double-blind randomized controlled trial. *Nutrients.* 2017;9(1).
19. Zhang YP, Miao R, Li Q, Wu T, Ma F. Effects of DHA supplementation on hippocampal volume and cognitive function in older adults with mild cognitive impairment: a 12-month randomized, double-blind, placebo-controlled trial. *J Alzheimers Dis.* 2017;55(2):497-507.
20. Sinn N, Milte CM, Street SJ, et al. Effects of n-3 fatty acids, EPA v. DHA, on depressive symptoms, quality of life, memory and executive function in older adults with mild cognitive impairment: a 6-month randomised controlled trial. *Br J Nutr.* 2012;107(11):1682-1693.
21. Freund-Levi Y, Eriksdotter-Jonhagen M, Cederholm T, et al. Omega-3 fatty acid treatment in 174 patients with mild to moderate Alzheimer disease: OmegAD study: a randomized double-blind trial. *Arch Neurol.* 2006;63(10):1402-1408.
22. Freund-Levi Y, Basun H, Cederholm T, et al. Omega-3 supplementation in mild to moderate Alzheimer's disease: effects on neuropsychiatric symptoms. *Int J Geriatr Psychiatry.* 2008;23(2):161-169.
23. Quinn JF, Raman R, Thomas RG, et al. Docosahexaenoic acid supplementation and cognitive decline in Alzheimer disease: a randomized trial. *JAMA.* 2010;304(17):1903-1911.
24. Cenacchi T, Bertoldin T, Farina C, Fiori MG, Crepaldi G. Cognitive decline in the elderly: a double-blind, placebo-controlled multicenter study on efficacy of phosphatidylserine administration. *Aging (Milano).* 1993;5(2):123-133.
25. Heiss WD, Kessler J, Mielke R, Szelies B, Herholz K. Long-term effects of phosphatidylserine, pyritinol, and cognitive training in Alzheimer's disease. A neuropsychological, EEG, and PET investigation. *Dementia.* 1994;5(2):88-98.
26. Baleztena J, Ruiz-Canela M, Sayon-Orea C. Association between cognitive function and supplementation with omega-3 PUFAs and other nutrients in >/= 75 years old patients: A randomized multicenter study. *PLoS One.* 2018;13(3):e0193568.
27. Sun Y, Lu CJ, Chien KL, Chen ST, Chen RC. Efficacy of multivitamin supplementation containing vitamins B6 and B12 and folic acid as adjunctive treatment with a cholinesterase

inhibitor in Alzheimer's disease: a 26-week, randomized, double-blind, placebo-controlled study in Taiwanese patients. *Clin Ther.* 2007;29(10): 2204-2214.
28. Soininen H, Solomon A, Visser PJ, et al. 24-month intervention with a specific multinutrient in people with prodromal Alzheimer's disease (LipiDiDiet): a randomised, double-blind, controlled trial. *Lancet Neurol.* 2017;16(12):965-975.
29. Scheltens P, Twisk JW, Blesa R, et al. Efficacy of Souvenaid in mild Alzheimer's disease: results from a randomized, controlled trial. *J Alzheimers Dis.* 2012;31(1):225-236.
30. Olde Rikkert MG, Verhey FR, Blesa R, et al. Tolerability and safety of Souvenaid in patients with mild Alzheimer's disease: results of multi-center, 24-week, open-label extension study. *J Alzheimers Dis.* 2015;44(2):471-480.
31. Shah RC, Kamphuis PJ, Leurgans S, et al. The S-Connect study: results from a randomized, controlled trial of Souvenaid in mild-to-moderate Alzheimer's disease. *Alzheimers Res Ther.* 2013;5(6):59.
32. Kamphuis PJ, Verhey FR, Olde Rikkert MG, Twisk JW, Swinkels SH, Scheltens P. Effect of a medical food on body mass index and activities of daily living in patients with Alzheimer's disease: secondary analyses from a randomized, controlled trial. *J Nutr Health Aging.* 2011;15(8):672-676.
33. Salva A, Andrieu S, Fernandez E, et al. Health and nutrition promotion program for patients with dementia (NutriAlz): cluster randomized trial. *J Nutr Health Aging.* 2011;15(10): 822-830.
34. Canhada S, Castro K, Perry IS, Luft VC. Omega-3 fatty acids' supplementation in Alzheimer's disease: A systematic review. *Nutr Neurosci.* 2018;21(8):529-538.
35. Farina N, Llewellyn D, Isaac MG, Tabet N. Vitamin E for Alzheimer's dementia and mild cognitive impairment. *Cochrane Database Syst Rev.* 2017;1:Cd002854.
36. Li MM, Yu JT, Wang HF, et al. Efficacy of vitamins B supplementation on mild cognitive impairment and Alzheimer's disease: a systematic review and meta-analysis. *Curr Alzheimer Res.* 2014;11(9):844-852.
37. Malouf R, Areosa Sastre A. Vitamin B12 for cognition. *Cochrane Database Syst Rev.* 2003(3):Cd004326.
38. Malouf R, Grimley Evans J. The effect of vitamin B6 on cognition. *Cochrane Database Syst Rev.* 2003(4):Cd004393.
39. Malouf R, Grimley Evans J. Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people. *Cochrane Database Syst Rev.* 2008(4):Cd004514.
40. Munoz Fernandez SS, Ivanauskas T, Lima Ribeiro SM. Nutritional strategies in the management of Alzheimer Disease: systematic review with network meta-analysis. *J Am Med Dir Assoc.* 2017;18(10):897.e813-897.e830.
41. Onakpoya IJ, Heneghan CJ. The efficacy of supplementation with the novel medical food, Souvenaid, in patients with Alzheimer's disease: A systematic review and meta-analysis of randomized clinical trials. *Nutr Neurosci.* 2017; 20(4):219-227.
42**.** Ooi CP, Loke SC, Yassin Z, Hamid TA. Carbohydrates for improving the cognitive performance of independent-living older adults with normal cognition or mild cognitive impairment. *Cochrane Database Syst Rev.* 2011(4): Cd007220.
43. Rijpma A, Meulenbroek O, Olde Rikkert MG. Cholinesterase inhibitors and add-on nutritional supplements in Alzheimer's disease: a systematic review of randomized controlled trials. *Ageing Res Rev.* 2014;16:105-112.
44. Rodriguez-Martin JL, Qizilbash N, Lopez-Arrieta JM. Thiamine for Alzheimer's disease. *Cochrane Database Syst Rev.* 2001(2):Cd001498.
45. Schneider LS, Mangialasche F, Andreasen N, et al. Clinical trials and late-stage drug development for Alzheimer's disease: an appraisal from 1984 to 2014. *J Intern Med.* 2014;275(3):251-283.
46. Martinez-Lapiscina EH, Clavero P, Toledo E, et al. Virgin olive oil supplementation and long-term cognition: the PREDIMED-NAVARRA randomized, trial. *J Nutr Health Aging.* 2013;17(6):544-552.
47. Valls-Pedret C, Sala-Vila A, Serra-Mir M, et al. Mediterranean diet and age-related cognitive decline: a randomized clinical trial. *JAMA Intern Med.* 2015;175(7):1094-1103.
48. Lourida I, Soni M, Thompson-Coon J, et al. Mediterranean diet, cognitive function, and dementia: a systematic review. *Epidemiology.* 2013;24(4):479-489.
49. Psaltopoulou T, Sergentanis TN, Panagiotakos DB, Sergentanis IN, Kosti R, Scarmeas N. Mediterranean diet, stroke, cognitive impairment, and depression: a meta-analysis. *Ann Neurol.* 2013;74(4):580-591.
50. Singh B, Parsaik AK, Mielke MM, et al. Association of mediterranean diet with mild cognitive impairment and Alzheimer's disease: a systematic review and meta-analysis. *J Alzheimers Dis.* 2014;39(2):271-282.
51. Gu Y, Scarmeas N, Cosentino S, et al. Change in body mass index before and after Alzheimer's disease onset. *Curr Alzheimer Res.* 2014; 11(4):349-356.
52. Moll van Charante EP, Richard E, Eurelings LS, et al. Effectiveness of a 6-year multidomain vascular care intervention to prevent dementia (preDIVA): a cluster-randomised controlled trial. *Lancet.* 2016;388(10046):797-805.
53. Andrieu S, Guyonnet S, Coley N, et al. Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): a randomised, placebo-controlled trial. *Lancet Neurol.* 2017;16(5):377-389.
54. Ngandu T, Lehtisalo J, Solomon A, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. *Lancet.* 2015;385(9984): 2255-2263.