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B-Vitamins and Fatty Acids in the Prevention and Treatment of Alzheimer's Disease and Dementia: A Systematic Review

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Abstract. The increasing worldwide prevalence of dementia is a major public health concern. Findings from some epidemiological studies suggest that diet and nutrition may be important modifiable risk factors for development of dementia. In order to evaluate the strength of the available evidence of an association of dietary factors with dementia including Alzheimer's disease (AD), we systematically searched relevant publication databases and hand-searched bibliographies up to end July 2007. We included prospective cohort studies which evaluated the association of nutrient levels with the risk of developing dementia and randomized intervention studies examining the treatment effect of nutrient supplementation on cognitive function. One hundred and sixty studies, comprising ninety one prospective cohort studies and sixty nine intervention studies, met the pre-specified inclusion criteria. Of these, thirty-three studies (19 cohort and 14 randomized controlled trials) investigated the effects of folate, B-vitamins, and levels of homocysteine (a biomarker modifiable through B-vitamin supplementation) or fish/fatty acids and are the focus of the present report. Some observational cohort studies indicated that higher dietary intake or elevated serum levels of folate and fish/fatty acids and low serum levels of homocysteine were associated with a reduced risk of incident AD and dementia, while other studies reported no association. The results of intervention studies examining the effects of folic acid or fatty acid supplementation on cognitive function are inconsistent. In summary, the available evidence is insufficient to draw definitive conclusions on the association of B vitamins and fatty acids with cognitive decline or dementia, and further long-term trials are required.

Keywords: Alzheimer's disease, dementia, fatty acids, folate, nutrition, B-group vitamins

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INTRODUCTION

Alzheimer's disease (AD) is the leading cause of dementia in later life and manifests as a progressive, degenerative brain disorder resulting in cognitive and behavioral decline and functional and physical dependency. The prevalence of severe cognitive impairment is projected to quadruple from current levels to 81 million worldwide by 2040 [1], and treatment of dementia imposes a significant burden on patients, caregivers, and healthcare systems worldwide [2,3]. AD is a heterogeneous condition at the genetic, neurobiological and clinical levels and no specific marker has been identified that qualitatively distinguishes AD from "normal" aging processes.

At present, pharmacological therapies are not able to halt progression of dementia and only produce minimal symptomatic cognitive improvements for some patients [4–6]. Consequently, there is an increasing interest in efforts to identify modifiable risk factors that may delay or prevent the risk of cognitive decline or dementia. These efforts recognize that many factors can promote brain health including maintenance of cognitive and social activity as well as physical exercise and healthy dietary practices [7–9].

Nutritional intake can directly influence the availability of nutrients to the brain. Specific dietary nutrients may be used for membrane and synapse formation and neurotransmitter production [10]. There is increasing evidence that nutrients stimulate neural plasticity and ameliorate neurodegenerative processes in animal models [10]. Diet and nutrition may be important modifiable risk factors in the aetiology and prevention of cognitive decline and functional impairment [10–14]. The development of dementia may in part be a consequence of exposure to, or low intake of, particular nutrients over several decades, beginning in middle age or late adult life.

The aim of this systematic review was to determine the strength of the available evidence that serum nutrient levels, dietary consumption, or nutrient supplementation were associated with the primary prevention or treatment of dementia. Our systematic search included a large range of nutrients; in this review we report on folate (either as folate in food or serum or as folic acid dietary supplements) with or without other B-group vitamins, serum homocysteine concentration, polyunsaturated fatty acids [PUFA] and fish as these nutrient/food groups have been highlighted as potentially important in previous reviews on nutrition and cognitive function [12–16].

MATERIALS AND METHODS

Research design and methods

The present report forms part of the findings of a large systematic search that assessed the strength of evidence linking a large number of nutrients with the treatment and prevention of dementia and AD [17]. The review has been reported according to the recent Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [18].

Identification and retrieval of studies

Potentially relevant studies were identified by searching the following electronic databases: PubMed, Embase, and Cochrane Library, accessed July 2007. Search terms used included both Medical Subject Headings (MeSH) and free text terms. Neurocognitive search terms included "Alzheimer's disease", "dementia", "cognitive decline" and "cognitive impairment". Nutrient search terms included the common and chemical names for the dietary factors of interest. The neurocognitive and nutrient search terms were combined with a search strategy for identifying randomized controlled trials (RCTs), non-controlled intervention studies and prospective cohort studies (Supplemental Table 1, available online: http://www.j-alz.com/issues/22/vol22-1.html#supplementarydata03). Bibliographies of identified relevant publications and previously published systematic and Cochrane review articles were hand-searched for further references.

Study selection criteria, data extraction, and outcome measures

Studies were eligible for inclusion if they were reports of randomized or non-randomized clinical trials or prospective cohort studies, where cognitive function was measured at both baseline and follow up. Case-control studies, cross-sectional studies or studies that provided only cross-sectional correlation data were excluded from the present review due to the various sources of bias in these study designs. In addition to selection bias, case-control studies are susceptible to recall bias, which may occur when trying to ascertain past eating habits [19]. Cross sectional studies only measure association not causation [20]. Studies examining the effects of both single and multi-nutrient status or supplementation were included in the review. No other restrictions were placed on studies with re-

Table 1
Summary of cohort studies relating homocysteine, folate and other B-vitamins to risk of incident AD and dementia

First author, year	Study population	N (loss to follow-up)	Duration (mean follow-up)	Exposure	Cognitive measure	Statistical analysis	Outcomes/major results
Annerbo, 2006 [26]	Males and females Mean age: 65.4y Community-dwelling (hospital-recruited) Mild cognitive impairment (MCI) (defined by MMSE score 21–27 and clinical evaluation)	93 (retro-spective cohort, no loss to follow-up stated)	6 years	Routine hospital measures of serum homocysteine, folate and vitamin B-12 collected at admission	AD diagnosis based on criteria of the DSM-IV and ICD-10.	Independent t-test comparing risk factors (homocysteine, folate and vitamin B-12) between converters (to AD) and non-converters. Logistic regression used to assess impact of homocysteine on AD conversion adjusted for MMSE, thyroid-stimulating hormone and age.	32 cases of incident AD. Homocysteine levels higher for converters (18.4μmol/l) compared to non-converters (16.8μmol/l) (P: 0.034). No significant difference in folate (19.0 *vs* 16.4nmol/l) or vitamin B-12 (275 *vs* 305pmol/l) between groups. No main effect of homocysteine in adjusted model but interaction with age: higher homocysteine in lower age group (mean: 60y) associated with increased odds of AD (adjusted OR: 1.29; 95% CI: 1.03, 1.61) (OR at 65y: 1.09; 95%CI: 0.99, 1.37)
Corrada, 2005 [27][1]	Males and females > 60 y Community-dwelling Free of AD at baseline	579 (37%: variables associated with loss to follow-up not reported)	9.3y	Folate, vitamin B-6 and B-12 intake from foods and supplements assessed by 7-day record	Battery of neuro-psychological tests. AD diagnosis based on criteria from NINCDS-ADRDA, included participants with diagnosis 'consistent with AD'	Cox regression model, comparing risk of AD by nutrient intake above or below RDA (reference: below RDA). Adjusted for: age, gender, education, total caloric intake	57 cases of incident AD Higher intake of folate associated with decreased risk of AD ($\geqslant$ RDA (median 619.0 μg/d) *vs* $<$RDA (median 250.9μg/d); adjusted RR: 0.41; 95% CI: 0.22, 0.76) Higher intake of vitamin B-6 associated with decreased risk of AD ($\geqslant$ RDA (median 2.4mg/d) *vs* $<$RDA (median 1.1mg/d); adjusted RR: 0.41; 95% CI: 0.2, 0.84). No association between vitamin B-12 intake and risk of AD ($\geqslant$ RDA (median 7.2μg/d) *vs* $<$RDA (median 2.0μg/d); adjusted RR: 0.6; 95%CI: 0.26, 1.36)
Haan, 2007 [28][2]	Males and females $\geqslant 60$ y Community-dwelling Primarily Mexican American Free of dementia or CIND at baseline	1405 (21%: variables associated with loss to follow-up not reported)	4.5y	Plasma homocysteine and vitamin B-12, red blood cell (RBC) folate.	Battery of neuro-psychological tests. Dementia defined by criteria of DSM-III, NINCDS or ADRDA. CIND defined by failing ($<$10%) a cognition test but not diagnosed as having dementia	Proportional hazards models examining the association between exposures and combined incidence of all cause dementia and CIND (combined incidence termed 'cognitive impairment'). Adjusted for: age, education, gender and vitamin B-12 or homocysteine	62 cases of incident all cause dementia and 55 cases of incident CIND. Higher homocysteine (mean level: 10.78μmol/l) associated with increased risk of cognitive impairment (adjusted HR: 2.39; 95% CI: 1.11, 5.16). Higher vitamin B-12 (mean: 452.59pg/ml) associated with increased risk of cognitive impairment (adjusted HR: 1.07; 95% CI: 1.02, 1.11). No association between RBC folate (mean: 504.69 ng/ml) and cognitive impairment (unadjusted HR: 0.85; 95% CI: 0.57, 1.24).

Table 1, continued

First author, year	Study population	N (loss to follow-up)	Duration (mean follow-up)	Exposure	Cognitive measure	Statistical analysis	Outcomes/major results
Luchsinger 2004 [29][3]	Males and females $\geqslant$ 65 y (mean: 76.2) Community-dwelling Free of AD and dementia at baseline	679 (25%: more likely to be white rather than Hispanic)	3206 person-years	Plasma homocysteine	Battery of neuropsychological tests. AD diagnosis based on criteria from NINCDS-ADRDA.	Cox proportional hazard model comparing risk of AD by quartile of plasma homocysteine (reference: lowest quartile). Adjusted for: age, gender, education, APOE- ε4 and stroke.	101 cases of incident AD In adjusted analysis, no association between plasma homocysteine (highest quartile (mean 27.4μmol/l) vs lowest quartile (mean 10.75μmol/l) and risk of AD (adjusted HR: 1.3; 95% CI: 0.8, 2.3).
Luchsinger 2007 [30][3]	Males and females $\geqslant$ 65 y (mean: 75.8) Community-dwelling Free of AD and dementia at baseline	965 (34%: more likely to be older)	6.1y (SD 3.3)	Folate, vitamin B-6 and vitamin B-12 intake (adjusted for energy intake) from foods and supplements assessed by semi-quantitative FFQ	Battery of neuropsychological tests. AD diagnosis based on criteria from NINCDS-ADRDA.	Cox proportional hazard model comparing risk of AD by quartile of nutrient intake (reference: lowest quartile). Adjusted for: age, gender, ethnic group, education, APOE-ε4, history of diabetes, hypertension, current smoking, heart disease and stroke, and levels of Vitamin B6 and B12.	192 cases of incident AD Higher intake of folate associated with decreased risk of AD (highest folate intake ($>$ 487.9μg/d) *vs* lowest folate intake ($\leqslant$ 292.9 μg/d); adjusted HR: 0.5; 95% CI: 0.3, 0.9) No association between vitamin B-6 intake and risk of AD (highest B-6 intake ($>$4.5mg/d) *vs* lowest B-6 intake ($<$2.3mg/d); adjusted HR: 1.3; 95%CI: 0.7, 2.3) No association between vitamin B-12 intake and risk of AD (highest B-12 intake ($>$13.5μg/d) *vs* lowest B-12 intake ($<$3.5μg/d); adjusted HR: 1.1; 95% CI: 0.7, 1.7).
Maxwell, 2002 [31][4]	Males and females $\geqslant$ 65 y (mean: 80.1) Community dwelling and institutionalized participants Free from AD and dementia at baseline but with 3MS score $<$ 78	226 (57%: more likely to be younger, less educated and community dwelling	5y	Serum folate	Screened using 3MS and clinical examination. Dementia diagnosis based on criteria from DSM-III. AD diagnosis based on criteria from NINCDS-ADRDA.	Logistic regression comparing odds of AD between quartiles of serum folate (reference: lowest quartile). Adjusted for age and gender	49 cases of incident AD. No association between baseline folate status and incident AD (lowest folate quartile (median 11.3nmol/l) *vs* highest folate quartile (median 25.0nmol/l); adjusted OR: 2.17; 95% CI: 0.85, 5.53)
Morris, 2006 [32][5]	Males and females $\geqslant$ 65 y Community dwelling Free of AD, with range of good to poor cognitive performance at baseline	1041 (83%: variables associated with loss to follow-up not reported)	median 3.9y	Folate, vitamin B-6 and vitamin B-12 intake from foods and vitamin supplements assessed by FFQ	Structured clinical evaluations. AD diagnosis based on criteria from NINCDS-ADRDA.	Logistic regression comparing the odds of incident AD for quintile of nutrient intake (reference: lowest quintile). Adjusted for: age, time period of observation, indicator variable for quintiles of nutrient intake gender, race, education, APOE-ε4, intake of vitamin E from food sources, frequency of participation in cognitive act-	161 cases of incident AD. No association between risk of developing AD and quintiles of total folate intake (highest folate intake (median 752.7 μg/d) *vs* lowest folate intake (median 202.8 μg/d); adjusted OR: 1.6; 95% CI: 0.5, 5.2). No association between risk of developing AD and quintiles of total vitamin B-6 intake (highest B-6 intake (median 5.5mg/d) *vs* lowest B-6 intake (median 1.2mg/d); adjusted OR: 0.7; 95% CI: 0.2, 2.4)

Table 1, continued

First author, year	Study population	N (loss to follow-up)	Duration (mean follow-up)	Exposure	Cognitive measure	Statistical analysis	Outcomes/major results
						ivities, total intake of niacin	No association between risk of developing AD and quintiles of total vitamin B-12 intake (highest B-12 intake (median 20.6μg/d) *vs* lowest intake (median 3.1μg/d); adjusted OR: 0.6; 95%CI: 0.2, 1.6)
Ravaglia, 2005 [33][6]	Males and females $\geqslant$ 65 y (mean: 73.6) Community dwelling Free of dementia at baseline	816 (13%: variables associated with loss to follow-up not reported)	3.8y (SD: 0.8)	Plasma homocysteine, serum folate and vitamin B-12	Italian version of MMSE [90] and Mental Deterioration Battery [91]. Dementia diagnosis based on criteria from DSM-IV. AD diagnosis based on criteria from NINCDS-ADRDA.	Cox proportional hazard model comparing risk of dementia and AD for low (below median) compared to high serum folate and vitamin B-12 or for those with or without hyperhomocysteinemia Adjusted for: age, gender, education, APOE-ε4, stroke, serum creatinine, smoking status, diabetes, hypertension, cardiovascular disease and BMI. Additionally adjusted for homocysteine, folate or B-12 depending on outcome of interest.	112 cases of incident all cause dementia (70 of which were AD) Hyperhomocysteinemia (homocysteine $>$ 15μmol/l) associated with increased risk of dementia and AD (adjusted HR for all cause dementia: 2.18; 95%CI: 1.37, 3.48; adjusted HR for AD: 2.08; 95%CI: 1.15, 3.79) Low folate associated with increased risk of dementia and AD (low folate ($\leqslant$ 11.8nmol/l)); adjusted HR for all cause dementia: 1.87; 95% CI: 1.21, 2.89; adjusted HR for AD: 1.98; 95% CI: 1.15, 3.40). No association between serum B-12 and risk of dementia and AD (adjusted HR for all cause dementia: 0.83; 95% CI: 0.56, 1.24; adjusted HR for AD: 0.66; 95% CI: 0.40, 1.09)
Ravaglia, 2006 [34]	Males and females $>$ 60y Community dwelling Mild cognitive impairment (MCI) classified by Petersen's criteria [24] and the Italian version of MMSE [90]	165 (13%: more likely to be older, female, lower MMSE score at baseline)	2.8y (SD: 1.6)	Serum folate and vitamin B-12	Battery of neuropsychological tests. Dementia defined as $\geqslant$ 2 cognitive domains severe enough to affect functional abilities	Cox proportional hazards ratio for risk of conversion to all cause dementia from MCI for low (below 25th percentile) compared to high serum folate or vitamin B-12. Adjusted for: age, gender, education, high ($\geqslant$ 26) MMSE, MCI subtype, diastolic BP, atrial fibrillation and BMI categories	48 cases of incident dementia (of which 34 were AD). Low serum folate associated with increased risk of conversion to all cause dementia (low folate ($\leqslant$ 10.4nmol/l); adjusted HR: 3.11; 95% CI: 1.49, 6.47). Serum vitamin B-12 not associated with risk of conversion to all cause dementia (low B-12 ($\leqslant$ 217pmol/l); HR adjusted for age, gender and education only: 0.6; 95% CI: 0.26, 1.39).
Seshadri, 2002 [35][7]	Males and females Mean age: 76 (SD: 6) Free of dementia at baseline	1092 (58%: variables associated with loss to follow-up not reported)	Median: 8y	Plasma homocysteine, folate, vitamin B-12 and vitamin B-6	Dementia diagnosis based on criteria of DSM-IV as well as a duration of symptoms >6 months and a score of $\geqslant$ 1 of severity on the Clini-	Cox proportional hazards models to assess relationship between exposures and incidence of all cause dementia and AD. Adjusted for: age, gender, APOE genotype, history of stroke, smoking status, alcohol intake, diabetes mellitus, BMI,	111 cases of incident dementia (of which 83 were AD). Higher homocysteine (mean for men: 13.1μmol/l; for women: 13.0μmol/l) associated with increased risk of dementia and AD (adjusted RR for all cause dementia: 1.4; 95% CI: 1.1, 1.9; adjusted RR for AD: 1.8; 95% CI: 1.3, 2.5).

Table 1, continued

First author, year	Study population	N (loss to follow-up)	Duration (mean follow-up)	Exposure	Cognitive measure	Statistical analysis	Outcomes/major results
					cal Dementia Rating scale. AD defined based on criteria from NINCDS-ADRDA.	systolic BP. Additionally adjusted for homocysteine, folate, B-12 or B-6 depending on outcome of interest.	Folate, vitamin B-12 and vitamin B-6 not associated with risk of dementia or AD (data not shown)
Wang, 2001 [36][8]	Males and females > 75 y Community dwelling Free of dementia but cognitively impaired (MMSE score < 24)	370 (0%)	3y	Serum folate and vitamin B-12	Dementia diagnosis based on criteria from DSM-III, or from hospital records for those who had died (n: 86)	Cox proportional hazard model comparing risk of dementia and AD for low (deficient) compared to high serum folate or vitamin B-12. Adjusted for: age, gender and education	78 cases of incident dementia (of which 60 were AD). Low serum folate ($\leqslant$ 10nmol/l) was not associated with risk of dementia or AD. (adjusted RR for all cause dementia: 1.6; 95% CI: 0.9, 2.9; adjusted RR for AD: 1.7; 95% CI: 0.9, 3.2) Low serum B-12 ($\leqslant$ 150pmol/l) was not associated with risk of dementia or AD (adjusted RR for all cause dementia: 1.3; 95% CI: 0.7, 2.3; adjusted RR for AD: 1.6; 95% CI: 0.9, 2.8). Combined low serum folate or low serum B-12 was associated with increased risk of dementia and AD (adjusted RR for all cause dementia: 1.8; 95% CI: 1.1, 2.8; adjusted RR for AD: 2.1; 95% CI: 1.2, 3.5)

3MS = Modified Mini-Mental State (3MS) examination [92]; 95% CI = 95% Confidence Interval; AD = Alzheimer's Disease; BMI = Body Mass Index; BP = Blood Pressure; CIND = Cognitively Impaired but Not Demented; DSM-III/IV = Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition [93]/4th Edition [22]; FFQ = Food Frequency Questionnaire; HR = Hazard Ratio; ICD-10 = International Classification of Diseases, 10th Edition [21]; MMSE = Mini-Mental State Evaluation [94]; NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association [23]; OR = Odds Ratio; RDA = Reference Dietary Allowance according to US Institute of Medicine [95]; RR = Risk Ratio; SD = Standard Deviation.
[1]Baltimore Longitudinal Study of Aging (BLSA); [2]Sacramento Area Latino Study on Aging (SALSA); [3]Washington Heights-Inwood Columbia Aging Project (WHICAP); [4]Canadian Study of Health and Aging (CSHA); [5]Chicago Health and Aging Project (CHAP); [6]Conselice Study of Brain Aging (CSBA); [7]The Framingham Heart Study; [8]The Kungsholmen Project.

gard to year of publication or language of publication (providing an English abstract was available).

Study participants were healthy older people or people with cognitive impairment/decline or any type of dementia (including vascular dementia and AD), regardless of nutritional status. In these studies, dementia or AD diagnosis was generally confirmed using commonly accepted criteria such as those of the International Classification of Diseases (ICD-10) [21], the Diagnostic and Statistical Manual of Mental Disorders (DSM) [22] and the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association (NINCDS-ADRDA) [23]. Mild cognitive impairment (MCI) was generally diagnosed using clinical criteria [24]. Cognitive function was assessed using a large number of different psychometric tests.

This systematic review reports on the following nutrition-related exposures: single nutrients (folate/folic acid, other B-group vitamins, fatty acids), simple nutrient combinations (folic acid with other B-group vitamins), levels of homocysteine, and fish consumption (dietary source of the n-3 polyunsaturated fatty acids, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA)). These nutrient groups were specifically selected as they have been highlighted as potentially important in previous reviews [12–16]. The relevant outcome measures in this review were incident dementia or AD in cohort studies, and change in cognitive performance in intervention studies. Studies focusing on MCI exceeded the scope of the present review. It is of note that, while a relatively large number of reports on the prevention or treatment of dementia/AD with vitamin B12 were identified in the initial phase of the systematic review, the majority were excluded as they were case series/studies, and were not a relevant study type for inclusion in the present review.

Following the identification of potentially relevant studies based on their title and abstract, full articles were obtained and evaluated by one researcher. A second independent assessor verified inclusion/exclusion decisions. Disputes as to eligibility were referred to the author panel. Study data were extracted by one member of the study team (SAM) and checked by a second member (SH).

Quality assessment

The methodological quality of RCTs was assessed using Cochrane Collaboration guidelines on randomization (method of generation and concealment of allocation), masking of treatment allocation and loss to follow-up [25].

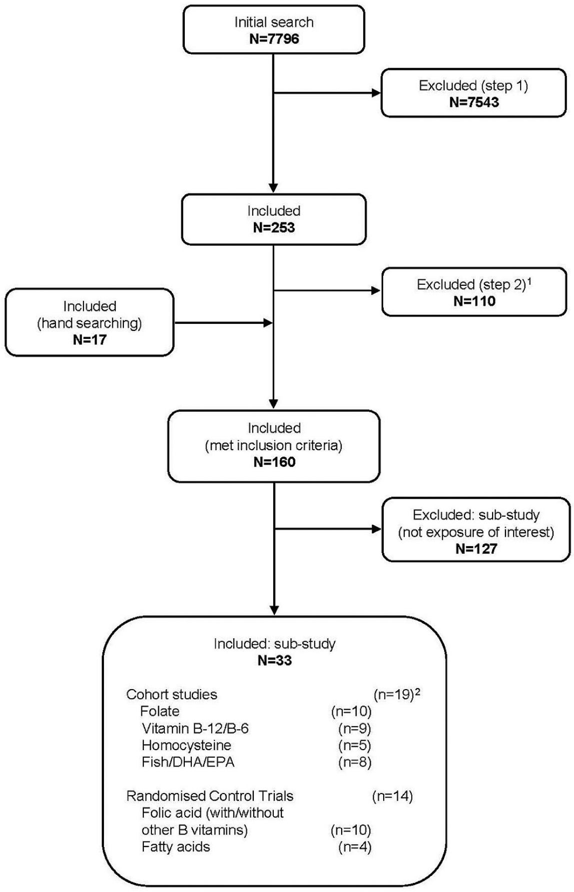

Fig. 1. Flow chart of included and excluded papers in the literature search. [1] Details of excluded studies from step 2 are in Supplemental Table 2; [2] A number of cohort studies included relevant data on folate, other B-vitamins and homocysteine.

RESULTS

Overall search findings

In total, 7,796 references were identified by the systematic literature search of which 7,543 were excluded on examination of their titles and abstracts. The full reports of 253 publications were assessed and of these 110 papers were excluded (Supplemental Table 2). Hand searching indentified a further 17 references and in total 160 papers met the inclusion criteria (Fig. 1).

The present review is restricted to thirty-three studies that reported on folate, B-vitamins, homocysteine levels, or fish/fatty acids. Results for other nutrients studied (antioxidants, dietary patterns, multivitamins) are not presented here. Of the 33 included papers, 19 were cohort studies including 11 on folate, other B-group vitamins and/or homocysteine [26–36] and eight on fish, DHA or EPA [37–44]. The remaining 14 were randomized controlled trials (RCTs) including ten on folic acid with or without other B-group vitamins [45–54], and four on mixed fatty acids [55–58].

Folate and other B-vitamins

Ten cohort studies (Table 1) evaluated the association of folate and other B-vitamins in cognitively intact or impaired aging participants with incident AD or dementia over a 3–9 year follow-up period [26–28,30–36]. Only one study considered folate only [31], nine included vitamin B-12 [26–28,30,32–36] and four included vitamin B-6 [27,30,32,35] in their assessment. Sample sizes ranged from 93 to 1405 participants. Three of the studies reported dietary intake (including supplement use) [27,30,32] and seven examined nutrient concentrations in blood samples [26,28,31,33–36]. The incidence rates of AD or dementia were compared between individuals based on their folate and B-vitamin intake or their blood concentrations at enrollment into the study. Two out of the three studies which considered dietary intake reported a significantly decreased risk of developing incident AD with increased folate consumption [27,30], one of which also observed the same association with vitamin B-6 consumption [27]. There was no association between dietary vitamin B12 consumption and incident AD or dementia [27,30,32].

One study reporting serum folate found that low folate concentrations increased the risk of developing dementia and AD [33], whilst a second reported an increased risk of conversion from mild cognitive impairment to dementia for individuals with low serum folate [34]. The remaining five studies reported no association between blood folate levels at enrollment and the risk of developing AD or dementia [26,28,31,35,36]. One study reported an increased risk of cognitive impairment (including dementia and cognitively impaired but not demented individuals) with increased levels of plasma vitamin B-12 [28]; the remaining five studies found no association between vitamin B-12 and risk of dementia or AD [26,33–36], although one of these did report a combined effect of low serum vitamin B-12 together with low folate and increased risk of AD and dementia [36].

Four RCTs (Table 2) investigated the effect of folic acid supplementation alone, on cognitive function [45,46,48,52]. The method used for randomization of participants was adequately reported in two studies [46,52] and unclear in the remaining studies [45,48]. Study groups were comparable at baseline and masking was adequately addressed in all studies. Three of the studies reported that folic acid supplementation resulted in a significant improvement in memory and cognitive function for some of the outcomes studied [45,46,48], although one also reported a decline in one cognitive domain [45].

A further six RCTs (Table 2) examined the effect of supplementation of folic acid in combination with other B-vitamins on cognitive function [47,49–51,53,54]. The method used for randomization was adequate in four studies [49,50,53,54], unclear in one study [51] and inadequate in the remaining study [47]. The method used for masking was adequate in three [50,53,54] and unclear in three studies [47,49,51]. Study groups were comparable at baseline in five of six studies [47,49,50,53,54] and not reported in the remaining study [51]. None of the trials reported increased cognitive performance following supplementation with folic acid in combination with other B-vitamins and three trials reported a trend for increased performance or slower decline in the placebo compared to vitamin groups [47,49,50].

Homocysteine

Five cohort studies (Table 1) reported data on the relationship between levels of serum homocysteine and development of incident dementia and/or AD [26,28,29,33,35]. Four studies found a positive association between blood concentrations of homocysteine and incidence of cognitive impairment [26,28,33,35], although in one the association was only apparent in the younger age group (mean age 60y) [26].

Fish and fatty acids

Eight cohort studies (Table 3) examined the effects of n-3 fatty acids on the incidence of dementia and AD [37,38,49,40–44], seven of which assessed dietary intake of fish and/or general PUFAs [37,39–44], one study also assessed serum concentrations of DHA [41] and a final study reported only serum DHA, EPA, and n-3 PUFA [38]. One study reported a marginal reduced risk of dementia and AD with increased fish consumption [42], and a second study reported a reduced risk of AD with increased total n-3 fatty acids, DHA and fish consumption [40]. The remaining dietary studies reported no association between n-3 fatty acid intake and risk of dementia and/or AD with the exception of a reduced risk of dementia associated with moderate PUFA intake from spreads reported by one study [44].

Table 2

Summary of RCTs examining folic acid intervention (with or without B vitamins) on cognitive function

First author, year	Study population	N	Intervention[1]	Duration	Cognitive measure	Outcome/main results
Bryan, 2002 [45]	Women only Three age bands: 20–30y; 45–55y and 65–92y Community-dwelling Non-smoking, not pregnant or lactating, no oral contraceptives or hormone replacement and no medication likely to affect mental performance or mood.	211	4. trial arms: a. folate (750μg/d); b. vitamin B-12 (15μg/d); c. vitamin B-6 (75mg/d) d. placebo	35 days	Cognitive performance assessed at baseline and after treatment. Cognitive performance tests: speed of processing (boxes test, digit symbol-coding and symbol search); working memory (digit span-backwards and letter-number sequencing); memory (Rey auditory-verbal learning test, recall of digit-symbol-coding and activity recall); executive function (neuro-psychological test); verbal ability (vocabulary and spot-the-word). Statistical analysis of the intervention effect focused on the interaction between treatment x age x time of testing (pre and post intervention)	Supplementation reduced verbal fluency performance (P: $<$0.05). When stratifying by age, supplementation improved Rey auditory-verbal learning test in older (65–92y) participants (P: $<$0.05).
Durga, 2007 [46]	Males and females 50–70y (mean: 60) Community-dwelling Excluded individuals with low ($<$ 13μmol/l) or raised ($>$ 26μmol/l) homocysteine No B-vitamin supplements	818	800μg/ day folic acid *vs* placebo	3 years	Cognitive function assessed at baseline and after treatment. Cognitive tests from Maastricht Aging Study [96], characterizing following domains: memory; sensorimotor speed; complex speed; information processing speed and word fluency. Test components: word learning test, concept shifting test, Stroop color-word test, verbal fluency test and letter digit substitution test	Folic acid improved global cognitive function (average of 5 domains) (mean difference in cognitive change Z-score: 0.05; 95% CI: 0.004, 0.096; P: 0.033). Domain-specific analysis: information processing speed declined in both groups but less in folic acid group (mean difference: 0.087; 95% CI: 0.016, 0.158; P: 0.016). Memory improved in both groups with a bigger improvement in folic acid group (mean difference: 0.132; 95%CI: 0.032, 0.233; P: 0.01). Sensorymotor speed declined in both groups but less in folic acid group (mean difference: 0.064; 95% CI: $-$0.001, 0.129; P: 0.055)
Eussen, 2006 [47]	Males and females $\geqslant$ 70 y (mean: 82) Community and Institutional-dwelling Mild vitamin B-12 deficiency (serum B-12 100–200pmol/l or 200–300pmol/l plus methylmalonic acid $\geqslant$ 0.32 μmol/l and creatinine $\leqslant$ 120μmol/l) No vitamin B-12 or folic acid supplementation MMSE score $\geqslant$ 19	162	3 trial arms: a. vitamin B-12 (1mg/d); b. B-12 (1mg/d) + folic acid (400μg/d); c. placebo	24 weeks	Cognitive function assessed at baseline and after treatment. Battery of neuopsychologic tests assessed sensorymotor speed, construction memory, executive function, attention and memory. MMSE also conducted	No effect of vitamin B-12 alone or in combination with folic acid on cognitive function. Only memory domain showed significant difference between trial groups (time x treatment interaction: P: 0.014), although each group improved, the greatest improvement was in the placebo group.

Table 2, continued

First author, year	Study population	N	Intervention[1]	Duration	Cognitive measure	Outcome/main results
Fioravanti, 1997 [48]	Males and females 70–90y (mean: 80.2) Community-dwelling Mild to moderate severity of cognitive decline (GDS) MMSE score 16–24 Serum folate $<$3ng/ml	30	15mg folic acid/d *vs* placebo	60 days	Cognitive status assessed at baseline and after treatment. Cognitive function assessed by Randt Memory Test (RMT) [97]. Test components: acquisition and recall; delayed recall; memory index; encoding factor; cognitive efficiency; attention efficiency	Folic acid improved attention efficiency score ($P <0.05$). When taking into account baseline folate status, folic acid improved acquisition and recall ($P < 0.007$); delayed recall ($P < 0.007$), memory index ($P < 0.002$) and encoding ($P < 0.005$)
Lewerin, 2005 [49]	Males and females Mean age: 76y Community-dwelling	179	Vitamin tablet (0.5mg vitamin B-12, 0.8mg folic acid and 3mg vitamin B-6)/d *vs* placebo (Vitamin tablet provided to 64% of participants)	4 months	Cognitive testing at baseline and after treatment. Tests included: digit span forward, digit span backward, identical forms, visual reproduction, synonyms, block design, digit symbol 90s, Thurstone's Picture Memory test and figure classification	Cognitive test scores improved for both arms and were only different between placebo and vitamin arms for identical forms (P: 0.039) and synonyms (P: 0.017) tests, both of which had greater improvement in the placebo arm.
McMahon, 2006 [50]	Males and females $\geqslant$ 65 y (mean: 74) Community-dwelling No suspected dementia No medications that interfere with folate metabolism No B-vitamin supplementation Fasting homocysteine $\geqslant$ 13 μmol/l Normal plasma creatinine ($\leqslant$ 133μmol/l in men; $\leqslant$ 115 μmol/l in women)	253	Vitamin tablet (1mg folate, 0.5mg vitamin B-12 and 10mg of vitamin B-6)/d *vs* placebo	2 years	Cognitive function assessed at baseline, 1 year and 2 years. Global cognitive function assessed by MMSE. Other tests included: memory and learning capacity, paragraph-recall, learning and recall ability, verbal fluency, semantic fluency, information-processing speed and reasoning ability.	Combined treatment score for all 8 tests was poorer in vitamin compared to placebo group ($-$0.11 SD scores poorer; 95% CI: $-$0.22, 0.00; P: 0.05). Significant difference between trial arms only observed for paragraph recall test (mean difference: $-$1.19; 95%CI: $-$2.30, $-$0.04; P: 0.03, but no longer significant if adjusted for gender and education) and retain trail marking test, part B (mean difference: $-$7%; 95% CI: $-$13, $-$2; P: 0.009) with both poorer in vitamin group.
Obeid, 2005 [51]	Males and females Mean age: 81y Glomerular filtration rate $>$30ml/min MMSE score $>$15	69	Daily subcutaneous injection: vitamin (1mg vitamin B-12, 5mg vitamin B-6 and 1.1mg folate)/d *vs* placebo for 3 weeks followed by daily tablet ingestion (same composition) for 3 weeks.	45 days	Cognitive function assessed at baseline and after treatment. Function assessed by MMSE and Structured Interview for Diagnosis of Dementia of Alzheimer Type, Multi-infarct Dementia and Dementia	No treatment effects reported, only within-group difference in performance

Table 2, continued

First author, year	Study population	N	Intervention[1]	Duration	Cognitive measure	Outcome/main results
Sommer, 2003 [52]	Males and females $\geqslant$ 65 y (mean: 76.7) Community-dwelling With dementia (diagnosed by DSM-III) Serum folate 2–5μg/l Red blood cell folic acid 127–452μg/l Normal vitamin B-12 ($>$ 200ng/l)	7	Folic acid (10mg) *vs* placebo twice daily	10 weeks	Cognitive function assessed at baseline and after treatment. Tests included: MMSE and a test battery assessing: intellectual function, confrontation naming, verbal fluency, verbal memory, visuospatial memory, visual scanning, conceptual flexibility and motor speed.	No difference in change in test scores between folic acid and placebo groups. Trend for folic acid to reduce performance on the associate learning subtests (P: 0.08) (a measure of short-term verbal memory) and Trail B marking test (P: 0.08) (a measure of speed and concentration).
Stott, 2005 [53]	Males and females $\geqslant$ 65 y (mean: 75) Hospital-based with ischemic vascular disease[2] MMSE score $\geqslant$ 19 No B-vitamin treatment Normal folate (red blood cell folate $\geqslant$ 280ng/ml) Normal vitamin B-12 ($\geqslant$ 250pg/ml)	167	2 $\times$ 2 $\times$ 2 factorial design: a. folic acid (2.5mg) + vitamin B-12 (0.5mg) *vs* placebo b. vitamin B-6 (25mg) *vs* placebo c. riboflavin (25mg) *vs* placebo.	12 weeks	Cognitive function assessed at baseline, and 12 months after randomization. General cognitive function assessed by TICSm. Face-to-face interviews also assessed attention and speed of information processing	No effect on change in cognitive function
VITAL, 2003 [54]	Males and females Community-dwelling Dementia (diagnosed by DSM-IV) and MMSE score 12–26 or TICSm score $<$ 27	128	2 $\times$ 2 $\times$ 2 factorial design: a. aspirin (81mg) *vs* placebo b. folic acid (2mg) + vitamin B-12 (1mg) *vs* placebo c. vitamin-E (500mg) + vitamin-C (200mg) *vs* placebo	12 weeks	Cognitive function assessed at randomization and after treatment. Cognitive function assessed by MMSE and ADAS-Cog	No effect of treatment on cognitive function

ADAS-Cog = cognitive part of Alzheimer's Disease Assessment Scale [98]; DSM-III/IV = Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition [93]/ 4th Edition [22]; MMSE = Mini-Mental State Examination [94]; TICSm = Telephone Interview for Cognitive Status;

[1]All are randomized double-blind, placebo-controlled trials;

[2]Ischemic vascular disease defined as one or more of: history of angina pectoris, previous acute myocardial infarction, evidence of major ischemia or previous acute myocardial infarction on the basis of a 12-lead electrocardiogram, ischemic stroke, transient ischemic attack, intermittent claudication or surgery for peripheral arterial disease.

Table 3
Summary of cohort studies included in analysis relating fish, DHA, EPA, n-3 PUFAs intake to risk of incident AD and dementia

First author, year	Study population	N (loss to follow-up)	Duration (mean follow-up)	Exposure	Cognitive measure	Statistical analysis	Outcomes/major results
Barberger-Gateau, 2002 [42][1]	Males and females $\geqslant$ 68 Community-dwelling Free from dementia at baseline	1674(15.4%: variables associated with loss to follow-up not reported)	7 years	Fish or seafood consumption assessed by FFQ	MMSE score and diagnosis of dementia based on criteria from DSM-III (AD diagnosis criteria not-specified)	Cox proportional hazards model comparing risk of dementia according to fish or seafood consumption group (once a day /at least once a week (but not every day)/from time to time (but not weekly)/never (reference group)) Adjusted for age, gender and education	170 cases of incident dementia (of which 135 were AD). Marginal association between consumption of fish or seafood at least once a week and a reduced risk of dementia and AD (adjusted HR for all cause dementia: 0.73; 95% CI: 0.52, 1.03; adjusted HR for AD: 0.69; 95% CI: 0.47, 1.01).
Engelhart, 2002 [39][1]	Males and females $\geqslant$ 55 y (mean: 68) Community-dwelling Free from dementia at baseline	5395 (16%: more likely to be older, males and to have less education)	6y (SD: 1.3)	Intake of n-3 PUFAs assessed by semi-quantitative FFQ	Screened using MMSE and clinical examination Dementia diagnosis based on criteria from DSM-III. AD diagnosis based on criteria from NINCDS-ADRDA.	Cox proportional hazards model comparing risk of dementia or AD in relation to standard deviation of fat intake (linear variable) Energy-adjusted intake Adjusted for age, gender, education, intake of vitamin E and total energy intake	197 cases of incident dementia (of which 146 were AD). No association between n-3 PUFA intake and dementia or AD (adjusted HR for all cause dementia: 1.07; 95% CI: 0.94, 1.22; adjusted HR for AD: 1.07; 95% CI: 0.91, 1.25)
Huang, 2005 [43][3]	Males and females $\geqslant$ 65 y Community-dwelling Free from dementia or MCI at baseline	2233 (23.4%: variables associated with loss to follow-up not reported)	5.4y	Fish intake assessed by semi-quantitative FFQ	Dementia diagnosed according to criteria of DSM-IV. AD diagnosis based on criteria from NINCDS-ADRDA	Cox proportional hazards model comparing risk of dementia for group of fish (fried fish or tuna and other fish) intake. Fried fish intake grouped into three categories ($<$0.25 servings/wk: reference), tuna and other fish grouped into four categories ($<$0.25 servings/wk: reference) Adjusted for age, minority status, gender, APOE-ε4, total energy intake, BMI, region, education and income.	378 cases of incident dementia (of which 190 were AD). No association between fried fish consumption and risk of dementia or AD (highest intake ($\geqslant$ 2 servings/wk) adjusted HR for all cause dementia: 0.97; 95% CI: 0.69, 1.35; adjusted HR for AD: 0.95; 95% CI: 0.60, 1.52). Despite a univariate association, in fully-adjusted models there was no association between tuna and other fish consumption and risk of dementia or AD (highest intake ($\geqslant$ 4 servings/wk) adjusted HR for all cause dementia: 0.79; 95% CI: 0.53, 1.20; adjusted HR for AD: 0.69; 95% CI: 0.91, 1.22)

Table 3, continued

First author, year	Study population	N (loss to follow-up)	Duration (mean follow-up)	Exposure	Cognitive measure	Statistical analysis	Outcomes/major results
Laitinen, 2006 [44][4]	Males and females Mean age at baseline: 50.4y (SD: 6.0) Community-dwelling Free from dementia at baseline	1449 (27.5: variables associated with loss to follow-up not reported)	21y (SD: 4.9)	PUFA intake from spreads derived from self-administered questionnaire with short quantitative section on spreads used on bread	Screening via MMSE and dementia diagnosis with criteria of DSM-IV. AD diagnosis based on criteria from NINCDS-ADRDA.	Logistic regression models comparing odds of dementia and AD for quartiles of PUFA intake (lowest quartile: reference). Adjusted for: age, gender, education, follow-up time, APOE-ε4, other fat intake, baseline systolic BP, BMI, cholesterol, smoking, history of myocardial infarction, stroke and diabetes.	117 incident cases of dementia (of which 76 were AD). Moderate PUFA intake was associated with decreased risk of dementia but not AD (second quartile (0.5–0.8g) *vs* first quartile ($<$ 0.5g) adjusted OR for all cause dementia: 0.4; 95% CI: 0.17, 0.94; adjusted OR for AD: 0.53; 95% CI: 0.21, 1.37). No association between higher intakes and risk of dementia or AD.
Laurin, 2003 [38][5]	Males and females $\geqslant$ 65 y (mean: 76.9) Community and institutional-dwelling Free from dementia at baseline Participants chosen from large national cohort of which only 4% provided blood sample	79 (81.4%: variables associated with loss to follow-up from the 425 individuals with blood samples not reported)	5 years	Serum concentrations of EPA, DHA and n-3 PUFA	Screening via MMSE, CIND according to modified Zaudig's criteria [99] and dementia diagnosis with criteria of DSM-IV.	t-test comparing fatty acid concentration between individuals developing CIND or dementia and those without. Adjusted for: age, gender, education, smoking, alcohol intake, BMI, history of cardiovascular disease and APOE-ε4.	16 cases of incident CIND and 11 cases of dementia. Individuals with CIND had 31% higher mean relative concentration of EPA (P: 0.01) compared to unimpaired individuals. Individuals with all cause dementia had 30% higher mean relative concentrations of DHA (P: 0.07), and 21% higher n-3 PUFAs (P: 0.04) than unimpaired individuals There were no other differences relating to EPA, DHA or n-3 PUFAs.
Morris, 2003 [40][6]	Males and females $\geqslant$ 65 y Community-dwelling Free from dementia or with mild cognitive impairment at baseline	815 (35%: variables associated with loss to follow-up not reported)	3.9y	Fish, total n-3 fatty acid, DHA and EPA intake assessed by self-administered FFQ	AD diagnosis based on criteria of NINCDS-ADRDA (demented cases without AD were analyzed as non-cases)	Logistic regression models comparing odds of AD with quintiles of energy-adjusted n-3 fatty acid intake (first quintile: reference). Logistic regression models comparing frequency of fish consumption with risk of AD (never: reference). Adjusted for: age, gender, education, APOE-ε4, race x APOE-ε4 interaction, period of observation.	131 cases of incident AD. Higher intake of total n-3 fatty acids was associated with reduced risk of AD (highest quintile (median: 1.75g/d) *vs* lowest quintile (0.9g/d) adjusted RR: 0.4; 95% CI: 0.1, 0.9). Higher intake of DHA associated with reduced risk of AD (highest quintile (median: 0.1g/d) *vs* lowest quintile (median: 0.03g/d) adjusted RR: 0.3; 95% CI: 0.1, 0.9). No association between EPA intake and risk of AD (highest quintile (median: 0.03g/d) *vs* lowest quintile (0.0g/d) adjusted RR: 0.9; 95% CI: 0.4, 2.3). Frequent fish consumption associated with reduced risk of AD (highest frequency ($\geqslant$ 2/wk) *vs* never adjusted RR: 0.4; 95% CI: 0.2, 0.9)

Table 3, continued

First author, year	Study population	N (loss to follow-up)	Duration (mean follow-up)	Exposure	Cognitive measure	Statistical analysis	Outcomes/major results
Schaefer, 2006 [41][7]	Males and females $\geqslant$ 55 y Community-dwelling Free from dementia at baseline	488 (75%: more likely to be older; other variables associated with loss to follow-up not reported)	9.1y	Plasma DHA and EPA. Dietary fish and DHA intake also assessed by self-administered semi-quantitative FFQ.	Dementia diagnosis based on criteria of DSM-IV as well as a duration of symptoms >6 months and a score of $\geqslant$ 1 of severity on the Clinical Dementia Rating scale. AD defined based on criteria from NINCDS-ADRDA.	Cox proportional hazards models comparing risk of dementia with quartiles of plasma DHA (quartiles 1–3: reference). Similar analysis was conducted for baseline DHA and fish intakes. Adjusted for: age, gender, APOE-ε4, homocysteine concentration, education	99 cases of incident dementia (of which 71 were AD). Highest DHA concentration associated with reduced risk of all cause dementia (highest quartile (> 4.2%) *vs* quartiles 1–3 combined adjusted RR: 0.53; 95% CI: 0.29, 0.97). No association between DHA concentration and risk of AD (adjusted RR: 0.61; 95% CI: 0.31, 1.18). No association between plasma levels of EPA and risk of dementia or AD (data not shown). No association between dietary DHA or fish consumption with dementia or AD.
Solfrizzi, 2006 [37][8]	Males and females $\geqslant$ 65 y (mean: 73) Community and institutional-dwelling	278 (61%: more likely to be older and with less education)	622 person-years	Dietary intake of PUFA assessed by semi-quantitative FFQ	MCI assessed by MMSE score, memory status (BSRT) and functional capacity (ADL). MCI defined as MMSE adjusted score < 1.5SD from the mean age- and education adjusted MMSE score for non-demented individuals. Total BRST score in lowest 10th percentile and disabilities compromising ADL	Proportional hazard models comparing risk of MCI by quartile of PUFA intake. Adjusted for: age, education and total energy intake	18 cases of incident MCI. No association between PUFA intake and risk of MCI in adjusted analysis, (highest quartile ($\geqslant$ 9g/d) *vs* lowest quartile ($\leqslant$ 5g/d) adjusted HR: 0.62; 95% CI: 0.34, 1.13).

95% CI = 95% Confidence Interval; AD = Alzheimer's Disease; ADL = Activities of Daily Living scale [100]; BMI = Body Mass Index; BP = Blood Pressure; BSRT = Babcock Story Recall Test [101]; CIND = Cognitively Impaired but Not Demented; DHA = Docosahexaenoic Acid; DSM-III/IV = Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition [93]/ 4th Edition [22]; EPA = Eicosapentaenoic Acid; FFQ = Food Frequency Questionnaire; HR = Hazard Ratio; MCI = Mild Cognitive Impairment; MMSE = Mini-Mental State Evaluation [94]; NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association [23]; PUFA = Polyunsaturated Fatty Acids; SD = Standard Deviation;

[1]Personnes Agees QUID study (PAQUID); [2]The Rotterdam Study; [3]Cardiovascular Health Cognition Study (CHCS); [4]Cardiovascular risk factors, Aging and Incidence of Dementia study (CAIDE); [5]Canadian Study of Health and Aging (CSHA); [6]Chicago Health and Aging Project (CHAP); [7]The Framingham Heart Study; [8]The Italian Longitudinal Study on Aging (ILSA).

Of the two studies investigating plasma fatty acids, one reported a reduced risk of dementia, but not AD, with higher compared to lower plasma DHA [41], while the second reported that individuals with dementia had higher concentrations of DHA and other n-3 PUFAs than individuals who did not develop the condition [38].

Four RCTs (Table 4) examined the effect of mixed fatty acid supplementation on cognitive functioning [55–58]. The method of randomization employed was adequate in all studies and masking was either adequate [55,58] or not clearly reported [56,57]. These studies are characterized by a high level of inter-study variation in the nature of the intervention and study duration (4 weeks to 1 year). Only one study [56], which enrolled a small number of participants ($n = 20$) and was not placebo-controlled, reported an improvement in cognitive measures while a second study reported improvements in quality of life following treatment [58]. It should be noted however that in neither of these trials was the statistical analysis of the treatment effect clearly reported. There was no effect of fatty acid supplementation on cognitive function tests in the two remaining trials [55,57].

DISCUSSION

The potential effect of dietary factors in both the prevention and treatment of dementia has become a topic of increasing interest. Reviews conducted to date have not identified good evidence for specific recommendation of particular dietary interventions [12–16,59]. Despite this lack of evidence some health providers continue to recommend dietary supplements which may not confer additional benefits to an adequate diet [60], and individuals who perceive themselves to be at increased risk of dementia frequently seek nutritional therapy [61].

This systematic review identified some evidence from cohort studies that lower dietary intakes of folate or low levels of serum folate were associated with an increased risk of developing AD. Trials of folic acid supplementation, either alone or in combination with other B-vitamins, had limited or no effect on measures of cognitive function. Older adults are likely to be at risk of low serum folate levels only in cases of low total energy intake [62], and over 50 countries currently implement mandatory fortification of flour with folic acid [63]. It should be noted that the relationship between dietary folate intake and serum folate levels is complex [64] and even where body stores of folate remain relatively constant, serum concentrations vary in line with changes in dietary folate intake and other physiological and health characteristics of study participants. The evidence from RCTs that provided folic acid supplementation in combination with other B vitamins is less supportive of a beneficial effect on cognitive function. The lack of any consistent beneficial effect on cognitive function of folic acid with or without vitamin B12 in healthy or cognitively impaired older participants has been confirmed in previous systematic reviews [16].

Three RCTs published subsequent to the searches performed for the present review do not provide support for the use of folic acid either individually or in combination with other B vitamins for the prevention of cognitive decline in older participants with or without diagnosed dementia [65–67]. This review identified some evidence that raised levels of homocysteine were associated with an increased incidence of AD and dementia. A recent review of case-control and cohort studies also reported that raised homocysteine levels were associated with an increase risk of AD but only included three of the five cohort studies in the current review [68].

Several recent reviews consider the role of fish consumption or fatty acids in the prevention of dementia or AD and come to the conclusion that the current evidence is in support of a protective effect of fish and n-3 fatty acid consumption [69–71]. Fish oils, especially DHA, may have neuroprotective actions [72], and some recent in vitro experiments [73] also suggest that DHA may play an important role in preventing late-onset AD. In the current review, only two out of eight cohort studies that examined the effect of fish or DHA consumption reported reduced AD and dementia incidence in those participants with the highest intake levels. These findings have been confirmed in three recently published cohort studies [74–76], only one of which reported that higher plasma n-3 PUFA proportions predicted less decline in speed-related cognitive domains over three years follow-up [76]. In addition, two recently published RCTs provide no evidence of a benefit to cognitive function from supplementation with combinations of EPA and DHA among cognitively healthy older people [77,78].

This systematic review has several strengths. The use of a comprehensive search strategy (electronic databases in addition to selected conference proceedings) maximized the likelihood of identifying all potentially relevant publications. In addition, it is the most up-to-date systematic review of the published literature

Table 4

Summary of RCTs examining fatty acid intervention on cognitive function

First author, year	Study population	N	Intervention[1]	Duration	Cognitive measure	Outcome/main results
Freund-Levi, 2006 [55]	Males and females Mean age: 74y With AD according to DSM-IV criteria MMSE score 15–30 Living in own home Receiving treatment with acetylcholine esterase inhibitors	174	4 tablets daily containing: 430mg DHA + 150mg EPA *vs* placebo Intervention for 6 months followed by open treatment with n-3 supplements for all participants for further 6 months	12 months	Cognitive function assessed at baseline, 6 and 12 months by MMSE and ADAS-COG	MMSE declined and ADAS-COG increased from baseline to 6 and 12 months in both groups but with no significant difference between treatment groups (values not reported).
Jorissen, 2001 [57]	Males and females > 57y Community-dwelling With mild to moderate cognitive deterioration as assessed by AAMI MMSE score > 24	120	Three trial arms: a. 300mg Soya bean Phosphatidyl-serine (S-PS) b. 600mg S-PS c. Placebo (S-PS contains 28% PUFA)	12 weeks	Cognitive function assessed by battery of neuropsychological tests at baseline, 6 weeks and 12 weeks. Tests included: visual verbal learning, memory scanning, verbal fluency, Stroop color word, signal detection, motor choice reaction time, concept shifting and tower of London test.	No effect of treatment on primary outcome of long-term memory performance (assessed by visual verbal learning test). No treatment effects on secondary cognitive outcomes.
Terano, 1999 [56][2]	Males and females Mean age: 83y Institutional-dwelling MMSE score 15–22 HDS-R score 15–22	20	Intervention group: 0.72g DHA/d Control group: nothing	1 year	Cognitive function assessed at baseline, 3, 6 and 12 months. Cognitive function assessed by MMSE, HDS-R and clinical evaluation	HDS-R and MMSE scores improved in the supplementation group whereas the control group remained unchanged. However, treatment effect statistics not reported.
Yehuda, 1996 [58]	Males and females 50–73y Community-dwelling Complaints of disorientation and cognitive deficit Low score on MMSE (mean sample score: 7.8) No multi-infarction dementia, post-depressive dementia or post-traumatic dementia	100	Fatty acid preparation (n-3: n-6 ratio of 1:4) known as SR-3 provided as 2ml/d *vs* placebo	4 weeks	Cognitive function assessed by a 12 item questionnaire completed by patient's guardian or care-giver and rating (5-point scale) various aspects of quality of life. Questionnaire assessed at baseline and after treatment. Components: space orientation, cooperation, mood, appetite, organization, short-term memory, long-term memory, sleep problems, daytime alertness, hallucinations, self-expression and bladder control	Greater improvement in intervention arm compared to placebo for all of the components of quality of life questionnaire with the exception of bladder control (statistical analysis of treatment effect not reported).

AAMI = Age-Associated Memory Impairment; AD = Alzheimer's Disease; ADAS-COG = Alzheimer Disease Assessment Scale [98]; DHA = Docosahexaenoic Acid; DSM-III/IV = Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition [93]/4th Edition [22]; EPA = Eicosapentaenoic Acid; HDS-R = Hasegawa's Dementia rating scale; MMSE = Mini-Mental State Evaluation [94]; PUFA = Polyunsaturated Fatty Acids;

[1] All studies are randomized double-blind, placebo-controlled trials unless stated otherwise; [2] This trial was not double-blind and the control group did not receive a placebo.

in this field and has a broad scope, focusing on both single and multiple nutrients and including both cohort and RCT studies.

There are a number of factors which complicate interpretation of the results reported in studies included in this review. First, included studies used a wide variety of cognitive function tests to measure different or overlapping domains of cognitive function [79]. Second, the degree to which cohort studies controlled for confounding or modifying factors differed. Third, the presence of subclinical dementia in the population at baseline may have differed between studies which could affect the dietary habits or participant response during the course of the study. Fourth the robustness of the dietary data is dependent on the use of a validated dietary assessment instrument to collect data during the study. Fifth, the time from exposure to a dietary factor to outcome measurement is invariably short, contrasting with the fact that the degenerative process often takes several years before a diagnosis is/can be made. Finally, the number of incident cases of AD or dementia reported at follow up was small in some studies which may limit the power to detect any associations. We were unable to conduct meta-analyses of the included studies due to marked heterogeneity in study designs, an issue that has similarly hampered other systematic reviews in this field [80]. Results from the prospective cohort studies frequently conflicted with findings from intervention trials. This is not a novel finding [81,82], but suggests that future cohort studies and RCTs would benefit from better standardization of protocols.

Multi-nutrient approaches have been proposed [10] and are supported by some [83] but not all available trial data [84]. Trials are underway among participants with early [85] and late-stage AD [86]. In addition, multi-domain interventions encompassing nutritional, physical and cognitive training may offer a potential synergistic effect in preventing cognitive decline in susceptible populations [87]. High-quality trials with clearly defined, well validated outcomes of interest are required to allow firm conclusions regarding the effects of either single nutrients or combinations of nutrients on neurodegenerative disorders. In addition, there is now increasing evidence to support the collection of genetic information from study participants to investigate potentially important nutrient gene interactions. Finally, future trials should be conducted in people with the earliest stages of cognitive impairment, since the window of opportunity for effective intervention from the onset of symptoms may be limited [88]. In conclusion, the available evidence base is currently insufficient to draw firm conclusions about the effects of individual dietary factors on the development or treatment of AD and dementia, and further large, well-designed RCTs of long duration need to be undertaken [89].

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