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Fish consumption, long-chain omega-3 fatty acids and risk of cognitive decline or Alzheimer disease: a complex association

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SUMMARY

Long-chain omega-3 fatty acids could have neuroprotective properties against dementia, which is becoming a major global public health issue. We conducted a systematic review of the literature to establish the association between eating fish (a source of long-chain omega-3 fatty acids) or taking long-chain omega-3 fatty acid supplements and the risk of cognitive decline or Alzheimer disease (AD). We identified eleven observational studies and four clinical trials. All three observational studies that used cognitive decline as an outcome reported significant benefits, whereas only four of eight observational studies that used incidence of AD or dementia as an outcome reported positive findings. None of four small clinical trials provided convincing evidence for the use of this approach in the prevention or treatment of any form of dementia. In summary, the existing data favor a role for long-chain omega-3 fatty acids in slowing cognitive decline in elderly individuals without dementia, but not for the prevention or treatment of dementia (including AD). This apparent dichotomy might reflect differences in study designs with regard to participants, dosages, the ratio of long-chain omega-3 to omega-6 fatty acids, or the choice of outcome measurements. Large clinical trials of extended duration should help to provide definitive answers.

KEYWORDS Alzheimer disease, cognitive decline, dementia, fish consumption, long-chain omega-3 fatty acids

REVIEW CRITERIA

We searched PubMed for articles published from January 1980 to September 2008 using the terms "omega-3 fatty acids OR docosahexaenoic (DHA) OR eicosapentaenoic acids (EPA)" AND "memory OR cognition OR dementia OR Alzheimer disease OR higher brain functions OR mild cognitive impairment" AND "treatment OR prevention". The abstracts of the 190 retrieved citations were reviewed, and the 15 studies that met our inclusion criteria were analyzed in detail. The reference sections of these articles were also checked for additional relevant studies.

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INTRODUCTION

Long-chain omega-3 fatty acids, such as docosahexaenoic acid (DHA), are essential polyunsaturated fatty acids (PUFAs) that are found in abundance in fish, as well as in some herbs, nuts and plants (Box 1). Long-chain omega-3 fatty acids can be also synthesized from smaller precursors, such as α-linolenic acid, but the rate of this conversion is very low in humans.[1] Long-chain omega-3 fatty acids are important building blocks for neuronal cell membranes, and they have key roles in brain development, neurotransmission and modulation of ion channels, as well as possessing neuroprotective properties.[2–5] Animal studies have shown that, long-chain omega-3 fatty acids are crucial for the growth of the brain in the fetal and early postnatal periods.[6–9] Consequently, DHA is routinely added to infant formula preparations in Western countries.

With aging, and especially among patients with Alzheimer disease (AD), DHA levels in the brain tend to decrease,[10–13] which suggests that a drop in DHA level could contribute to deterioration in memory and other cognitive functions. Consistent with this hypothesis, animals that are fed a diet low in DHA show marked deficits in cognitive function, and those that are subjected to chronic administration of DHA show improvements in their learning ability.[14,15]

Long-chain omega-3 fatty acids have multiple mechanisms of action in the brain and vascular system that could protect against cognitive decline and dementia (Figure 1). First, they seem to reduce cardiovascular risk factors, such as triglyceridemia, and improve cerebral blood flow in primate and rat models.[16,17] Despite some controversy over the clinical efficacy of a high intake of omega-3 fatty acids in preventing cardiovascular events,[18] they are thought to reduce the risk of coronary artery disease[19–22] and their increased intake is, therefore, recommended by the American Heart Association.[23] In a cross-sectional study, consumption of long-chain omega-3 fatty acids was associated

with a reduced incidence of white matter abnormalities,[24] and a meta-analysis of cohort studies revealed a reduced risk of stroke in association with substantial fish consumption.[25] As risk factors for cerebrovascular disease can accelerate cognitive impairment, the neuroprotective role of omega-3 fatty acids could be mediated through modification of these risk factors. Second, long-chain omega-3 fatty acids attenuate inflammation by inhibiting the conversion of arachidonic acid to proinflammatory factors; by inhibiting other proinflammatory cytokines such as interferon-γ, interleukin (IL)-2, IL-1, IL-1β and tumor necrosis factor; by decreasing T-cell proliferation; and by inhibiting leukocyte migration.[26–34] Given that inflammation is involved in the pathophysiology of dementia,[35] long-chain omega-3 fatty acids might exert protective effects through their anti-inflammatory properties.[36,37] Third, long-chain omega-3 fatty acids might directly limit AD pathology by reducing amyloid production, minimizing its aggregation into plaques, and increasing its clearance.[38]

We performed a systematic review of the literature to determine the strength of evidence for the use of long-chain omega-3 fatty acids in relation to cognitive impairment and dementia, including AD. Given the strong theoretical and biological background for the neuroprotective properties of these agents in dementia, numerous human studies have addressed their potential benefits in either prevention or treatment of AD.[39–45] However, these studies have produced conflicting results, and no randomized clinical trials have provided definitive answers to date. Satisfactory clinical trial data are also lacking for the role of long-chain omega-3 fatty acids in treating mild cognitive impairment (MCI), a syndrome defined by marked selective memory loss but preservation of functional abilities.

Box 1 Polyunsaturated fatty acids and their sources.

Polyunsaturated fatty acids (PUFAs) are fatty acids that contain more than two carbon–carbon double bonds. The omega number refers to the position of the double bond in relation to the methyl end of the fatty acid molecule. Most PUFAs have more than 18 carbon atoms and are consequently defined as long-chain PUFAs. Important long-chain omega-3 fatty acids include docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), both of which can be synthesized from short-chain omega-3 fatty acids such as α-linolenic acid via other intermediates. However, as the rate of conversion is low in humans, long-chain omega-3 fatty acids must be obtained primarily through the diet.

Dietary sources of PUFAs include dairy products, meat, vegetables, oils and fish. α-Linolenic acid can be obtained from flax, chia and hemp. Stearidonic acid, another omega-3 fatty acid, is present in blackcurrant oil. Sources of EPA and DHA include fish and krill, and DHA can also be derived from algae.

The omega-6 fatty acids include linoleic acid, γ-linolenic acid and arachidonic acid. Linoleic acid is present in sunflower, safflower and corn oils. γ-Linolenic acid occurs in borage, blackcurrant and evening primrose oils. Arachidonic acid can be obtained from meat, eggs and dairy products.

SEARCH STRATEGY

We sought to identify all studies on the association between omega-3 fatty acids (either in the diet or in the form of supplements) and cognition, dementia, MCI or AD. We undertook a systematic review of the literature in the English language and searched MEDLINE and the Cochrane database for relevant articles published from January 1980 to September 2008. We began with a general search using broad terms, namely "omega-3 fatty acids," "DHA," OR "EPA" AND "memory" OR "cognition" OR "dementia" OR "Alzheimer disease" OR "higher brain functions" OR "mild cognitive impairment". The 417 articles obtained were screened for human observational studies or trials that addressed the specific link between any form of omega-3 fatty acid and any measure of cognitive function in elderly individuals, using the terms "prevention" OR "treatment". This search identified 190 papers. To evaluate the effects of long-chain omega-3 fatty acids specifically in elderly individuals, we focused on studies with participants who were 65 years of age or older. To give us the best chance of elucidating the relationship between supplementation or dietary intake of long-chain omega-3 fatty acids and cognitive performance, we focused on prospective observational studies and clinical trials and excluded cross-sectional studies. In summary, we established the following inclusion criteria: participants aged 65 years or older, prospective observational studies or trials, and standard diagnosis of dementia or formal cognitive testing with validated tests.

Fifteen articles met the inclusion criteria. We also read related references cited in these papers to identify additional observational studies or clinical trials in this field. Each author read the papers separately and summarized his or her findings. For each study, we verified the design, the inclusion and exclusion criteria, duration of the analysis, and the outcome measures. We subdivided the studies into two groups: those that specifically examined the effects of long-chain omega-3 fatty acid consumption on the incidence or treatment of all-cause dementia or AD (Table 1, Figure 2), and those that specifically

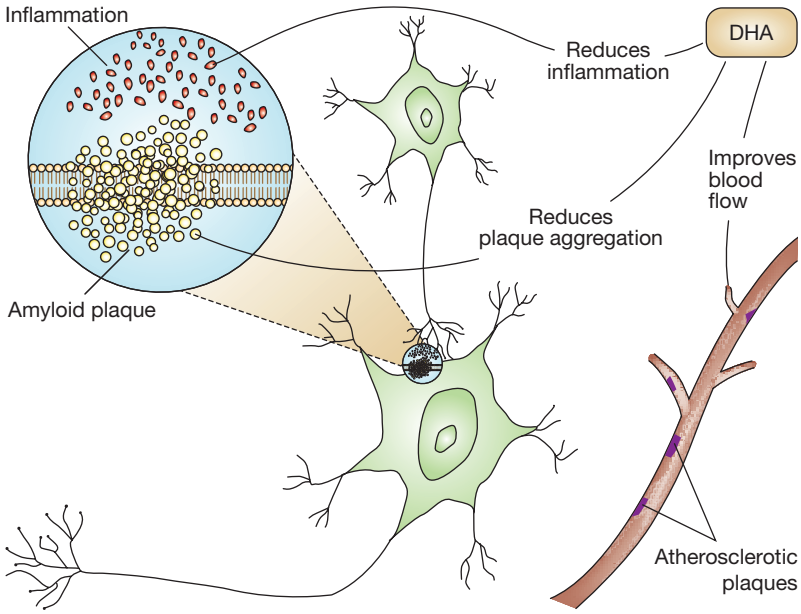

Figure 1 Proposed neuroprotective properties of DHA. DHA possesses three neuroprotective properties that could help to protect elderly individuals who are at risk of developing dementia. It improves cerebral blood flow, reduces inflammation, and mitigates amyloid plaque formation and aggregation. Abbreviation: DHA, docosahexaenoic acid.

examined the role of these agents in reducing overall cognitive decline (Table 2). In view of the fact that taking supplements or eating fish might reflect a healthy lifestyle and/or a high level of education, which could confound the outcomes of reduced cognitive decline or dementia, we paid particular attention to multivariate analysis. In fact, in several studies, positive results were no longer statistically significant after adjustments had been made for covariates such as education and income.

FINDINGS OF THE SYSTEMATIC REVIEW

Omega-3 fatty acids and risk of developing dementia or Alzheimer disease

The eight observational studies that investigated the association between long-chain omega-3 fatty acids and incidence of dementia produced conflicting results (Table 1, Figure 2). The Rotterdam study initially showed statistically significant benefits after 2.1 years of follow-up.[46] However, no statistically significant difference in the incidence of AD in relation to intake of fish or long-chain omega-3 fatty acids was noted after 6 years of follow-up, with a relative risk (RR) of 1.07 (95% CI 0.91–1.25) being recorded.[47] As in many other such observational studies, the investigators used semiquantitative food frequency questionnaires to monitor fish intake as a surrogate of omega-3 fatty acid intake and measured incidence of dementia or AD.

In the French PAQUID (Personnes Agées QUID) study, with 7 years of follow-up, consumption of at least one serving of fish or seafood per week decreased the risk of developing dementia by 44% (RR 0.56, 95% CI 0.47–0.93).[48] However, after adjustment for age, sex, and education level, the results proved to have only borderline statistical significance (RR 0.69, 95% CI 0.47–1.01).

In the Canadian Study of Health and Aging, 79 participants without dementia who had undergone blood tests for PUFAs at the beginning of the study were monitored for 5 years. Most of the participants remained cognitively normal, although some developed cognitive impairment, no dementia (CIND), and others developed AD or other types of dementia. Compared with cognitively normal individuals, participants who developed dementia had 21% higher mean relative concentrations of omega-3 PUFAs ($P=0.04$) and 6% higher mean relative concentrations of total PUFA ($P=0.03$), after adjustment for age, sex, education level and the *APOE* ε4 allele.[49] Similarly, participants who developed CIND had a 31% higher mean relative concentration of eicosapentaenoic acid (EPA; $P=0.01$). This study was the only one that showed a link between higher PUFA levels and worse cognitive outcome.

In the Chicago Health and Aging Project, a large prospective cohort study with 4 years of follow-up, consumption of at least one serving of fish per week decreased the risk of developing AD by 60% (RR 0.40, 95% CI 0.20–0.90).[50] After adjustment for covariates, those in the highest quintiles of DHA intake continued to show a statistically significant reduction in the risk of AD (RR 0.30, 95% CI 0.10–0.90). The results were not statistically significant for total omega-3 fatty acid, EPA or linolenic acid.

In the Cardiovascular Health and Cognition study, consumption of two or more servings of fatty fish per week decreased the incidence of dementia by 28% (hazard ratio [HR] 0.72, 95% CI 0.51–1.02) and reduced the risk of AD by 41% (HR 0.59, 95% CI 0.36–0.95).[51] However, after adjustment for age, sex, education and income, the results were no longer significant (HR 0.73, 95% CI 0.44–1.17).

In the Framingham Heart Study, in which the participants were followed for 9.1 years, increased

Table 1 Observational studies of the association between intake of fish or long-chain omega-3 fatty acids and risk of developing all-cause dementia or AD.

Study	Design	Inclusion criteria	Omega-3 fatty acid intake and measurement	Outcome measures criteria	Results
Rotterdam Study[47] (Netherlands)	6-year prospective cohort; *n* = 5,395; mean age 68 (SD: 7.8)	Normal cognition and living independently	Intake of total fat, saturated fat, trans fat, cholesterol, MUFAs and PUFAs in diet (FFQ)	Incidence of dementia (DSM-III), AD (NINCDS–ADRDA) and VaD (NINDCS–AIREN)	No statistically significant difference in incidence of total or subtypes of dementia (adjusted for age, vitamin E, education, and consumption of fruits and vegetables); RR for AD 1.07 (95% CI 0.91–1.25)
Personnes Agees QUID[48] (France)	7-year prospective cohort; *n* = 1,416; age ≥68	Normal cognition and living at home	Consumption of fish or seafood at least once a week (FFQ)	Incidence of dementia (DSM-III-R), neurological evaluation	RR for dementia 0.66 (95% CI 0.47–0.93), or 0.73 (95% CI 0.52–1.03) after adjustment for age, sex and education; RR for AD 0.69 (95% CI 0.47–1.01)
Canadian Study of Health and Aging[49] (Canada)	5-year prospective cohort; *n* = 79; age ≥65	Normal cognition	Measurement of serum levels of PUFAs	Incidence of dementia (DSM-IV), AD (NINCDS–ADRDA), and CIND (Zaudig's)	Participants who developed dementia had higher concentrations of omega-3 PUFAs by 21% ($P = 0.04$) and total PUFAs by 6% ($P = 0.03$), after adjustment for age, sex, education and *APOE* ε4 allele
Chicago Health and Aging Project[50] (USA)	3.9-year prospective cohort; *n* = 815; mean age 73 (65–94)	Normal cognition	Fish intake (per week or month) and intake of total omega-3 fatty acids, DHA, EPA and LA (FFQ), divided into quintiles	AD (CERAD and NINCDS–ADRDA)	RR for AD 0.4 (95% CI 0.2–0.9) adjusted for age, sex, and education; participants who consumed fish once or more per week had 60% reduced risk of AD
Cardiovascular Health and Cognition Study[51] (USA)	Prospective cohort; *n* = 2,233; mean age 71 (≥65); mean follow-up to onset of dementia 5.4 years	Volunteers without dementia from Medicare eligibility lists	Fish intake (serving/week; FFQ), divided into two groups: fatty fish and lean fried fish	Incidence of dementia (DSM-IV), AD (NINCDS–ADRDA) and VaD (ADDTC)	Reduced risk of all-cause dementia by 28% and of AD by 41%; no statistically significant benefit after adjustment for age, sex, education and income
Framingham Heart Study[52] (USA)	9.1-year prospective cohort; *n* = 899; median age 76 (55–88)	Normal cognition, no dementia	Fish intake (FFQ) and levels of plasma DHA, divided in quartiles	Dementia diagnosis (DSM-IV) or AD (NINCDS–ADRDA)	For all-cause dementia (highest quartile compared with lowest three quartiles, adjusted for age, sex, and education), RR 0.53 (95% CI 0.29–0.97, $P = 0.04$); for AD, RR 0.61 (95% CI 0.31–1.18, $P = 0.14$)
Three-City cohort study[53] (France)	4-year prospective cohort; *n* = 8,085; age ≥65	Normal cognition, no dementia	Consumption of fish and other nutritional factors (FFQ)	Dementia (DSM-IV) or AD (NINCDS–ADRDA)	Reduced risk of AD in relation to fish consumption two to three times per week (after adjustment for age, sex, *APOE* ε4, education and income), HR 0.59 (95% CI 0.37–0.94); reduced risk of all-cause dementia noted only in *APOE* ε4 noncarriers: HR 0.54 (95% CI 0.35–0.85)
Subset of Three-City cohort study from Bordeaux[54] (France)	4-year prospective cohort; *n* = 1,214; age ≥65	No dementia, community living	Measurement of plasma levels of PUFAs	Dementia (DSM-IV) and/or depression (CES-D)	Plasma EPA concentration inversely associated with incidence of dementia, HR 0.69 (95% CI 0.48–0.98) after adjustment for age, sex and education

Abbreviations: AD, Alzheimer disease; ADDTC, State of California Alzheimer's Disease Diagnostic and Treatment Centers; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; CES-D, Center for Epidemiologic Studies-Depression; CIND, cognitive impairment, no dementia; DHA, docosahexaenoic acid; DSM, Diagnostic and Statistical Manual of Mental Disorders; EPA, eicosapentaenoic acid; FFQ, Food Frequency Questionnaire; HR, hazard ratio; LA, linoleic acid; MUFAs, monounsaturated fatty acids; NINCDS–ADRDA, National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders; NINCDS–ARIEN, National Institute of Neurological and Communicative Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neuroscience; PUFAs, polyunsaturated fatty acids; RR, relative risk; VaD, vascular dementia.

plasma levels of DHA-containing phospholipids were associated with a 47% reduction in the risk of developing all-cause dementia, after adjustments were made for age, sex, the *APOE* ε4 allele, plasma homocysteine concentration, and education (RR 0.53, 95% CI 0.29–0.97).[52] However, the adjusted risk reduction was not significant for incident AD (RR 0.61, 95% CI 0.31–1.18).

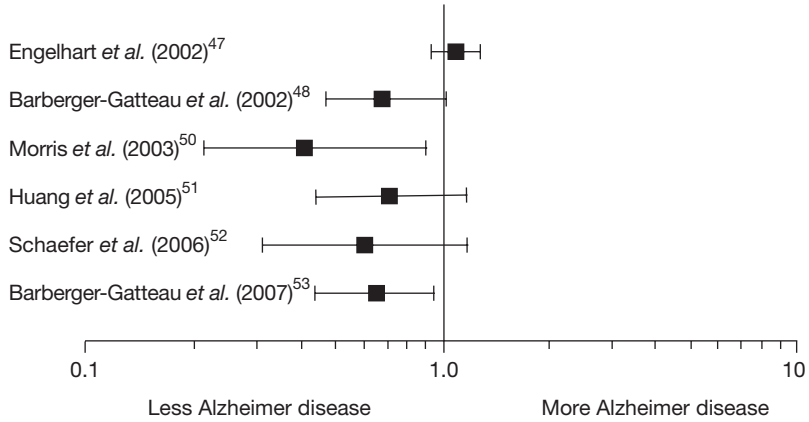

Figure 2 Summary of observational studies of the effects of long-chain omega-3 fatty acids on the risk of developing Alzheimer disease. The results are presented after multivariate adjustments (see Table 1). Half of the studies revealed significant protective effects of consumption of either fish or long-chain omega-3 fatty acid supplements. In combination with other studies reviewed (Tables 2 and 3), these findings favor a modest role for omega-3 fatty acids in the prevention of cognitive decline, but not in the prevention or treatment of Alzheimer disease or other dementias.

In the Three-City cohort study in France, after adjustment for covariates, individuals who consumed fish two to three times per week showed a significantly reduced risk of AD compared with controls who never consumed fish or consumed fewer than one serving per week (HR 0.59, 95% CI 0.37–0.99). However, consumption of more than four servings of fish per week did not produce a statistically significant benefit (HR 0.58, 95% CI 0.25–1.34). A reduction in all-cause dementia with fish consumption two to three times per week was noted among *APOE* ε4 noncarriers (HR 0.54, 95% CI 0.35–0.85) but not among carriers (HR 1.24, 95% CI 0.53–2.90).[53] When the serum levels of long-chain omega-3 fatty acids were measured in a subset of participants, plasma EPA concentration was inversely associated with the incidence of dementia (HR 0.69, 95% CI 0.48–0.98) after adjustment for age, sex, education level, and *APOE* ε4 allele status.[54]

In summary (Table 1, Figure 2), in the Canadian Study of Health and Aging,[49] participants who developed dementia had significantly higher concentrations of long-chain omega-3 fatty acids than those who did not develop dementia, whereas in the Rotterdam study[47] no statistically significant results were noted. The initial borderline positive findings of the Cardiovascular Health and Cognition study[51] and the Framingham Heart Study[52] were no longer statistically significant once they had been adjusted for sex, age, education level and/or income. By contrast, positive results in the PAQUID,[48] the Chicago Health and Aging Project[50] and the Three-City Cohort Study,[53] remained statistically or borderline significant after these adjustments.

Omega-3 fatty acids and cognitive function

We identified three prospective cohort studies in which the rate of cognitive decline was the primary outcome (Table 2). The EVA (Etude du Vieillissement Artériel) study used erythrocyte membrane lipid composition as a measure of omega-3 fatty acid intake.[55] The participants were 246 healthy men and women whose cognitive function was assessed by use of the Mini-Mental State Examination (MMSE). Cognitive decline was defined as a drop of 2 or more points in the MMSE score during the 4-year follow-up period. In this study, the proportion of total omega-3 fatty acids in the erythrocyte membrane was inversely associated with the risk of cognitive decline, with an odds ratio (OR) of 0.59 (95% CI 0.38–0.93).[55]

A 6-year follow-up of the Chicago Health and Aging Project also showed that fish intake was associated with a reduced rate of cognitive decline ($P = 0.04$ for trend).[56] Cognition in this study was measured as a standardized score from four tests, including the East Boston tests of immediate and delayed recall, the MMSE, and the symbol digit modalities test.

The Zutphen Elderly Study in the Netherlands, in which the participants were followed for 5 years, showed that DHA and EPA (as estimated by fish intake) significantly decreased cognitive decline, as assessed by the MMSE, after multivariate adjustments for sex, age and education level.[57] A linear trend was noted between increased intake of EPA plus DHA and improved cognitive performance ($P = 0.01$).

Randomized clinical trials

To investigate the protective properties of DHA and other PUFAs with respect to cognitive performance and dementia, four clinical trials have now been completed, and five additional trials are in progress (Tables 3 and 4). A small trial, in which 20 elderly patients with vascular dementia were assigned at random to DHA treatment or placebo, did not find any between-group differences in the change in MMSE after 12 months.[58] A statistically significant benefit at

Table 2 Observational studies of the association between consumption of fish or long-chain omega-3 fatty acids and cognitive performance.

Study	Design	Inclusion criteria	Omega-3 fatty acid intake and measurement	Outcome measures	Results	Comments
Etude du Vieillissement Arteriel[55] (France)	4-year prospective cohort study; $n=246$; mean age 68 (63–74)	Normal volunteers	Measurement of erythrocyte membrane fatty acid content (total omega-3 PUFA, omega-3:omega-6 fatty acid ratio and DHA:AA ratio)	Cognitive decline measured as ≥2-point drop in MMSE score (decliners compared with nondecliners)	Omega-3 PUFA:OR 0.59 (95% CI 0.38–0.93, $P=0.05$); omega-3: omega-6 fatty acid ratio: OR 0.55 (95% CI 0.33–0.91, $P=0.043$); DHA:AA ratio: OR 0.57 (95% CI 0.35–0.92, $P=0.047$	High proportions of omega-3 fatty acid levels in blood were associated with 41% less cognitive decline; results were statistically significant for DHA level and DHA:AA ratio, but not for EPA levels
Chicago Health and Aging Project[56] (USA)	6-year prospective cohort study; $n=3,718$; mean age 73 (65–94)	Normal cognition	Fish meals per week (zero, one or two)	Change in rate of global cognitive decline estimated from mixed models	Rate of cognitive decline per year decreased by 10–13% among individuals who consumed one or more fish meals per week	The benefits of eating fish meals could not be accounted for by the amount of dietary DHA or EPA
Zutphen Elderly Study[57] (The Netherlands)	5-year prospective cohort study; $n=210$; mean age 75 (70–89)	Men with no dementia (MMSE score >24)	Fish consumption based on food frequency questionnaire; levels of DHA and EPA from both fish and other sources	Cognitive decline measured by MMSE	A linear trend was seen between high intake of EPA plus DHA and reduced 5-year cognitive decline ($P=0.01$)	400 mg of DHA plus EPA per day was associated with a 1.1-point reduction in cognitive decline over 5 years

Abbreviations: AA, arachidonic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; MMSE, Mini-Mental State Examination; OR, odds ratio; PUFA, polyunsaturated fatty acid.

6 months was observed among those assigned to DHA treatment, but this effect did not persist to 12 months.

Another small, double-blind trial evaluated the potential treatment role for PUFAs in 21 patients with MCI, 8 patients with AD, and 10 patients with organic brain lesions (e.g. stroke or trauma sustained at least 5 years previously).[59] After 90 days of treatment with DHA and arachidonic acid, patients with MCI had improved attention and immediate memory ($P<0.01$). Patients with organic brain lesions showed improvement in their immediate ($P<0.01$) and delayed ($P<0.001$) memory, but patients with AD demonstrated no significant benefit with respect to any form of memory or attention. Thus, the subgroup of patients with MCI, but not those with AD, seemed to derive a marginal benefit from the treatment.[59]

A randomized, controlled trial of DHA supplementation in 174 elderly individuals with AD in Sweden (OmegAD)[60] showed no differences in the rate of cognitive decline over 6 months between those who received DHA supplementation and those who received placebo, as measured by the MMSE or the cognitive portion of the Alzheimer disease assessment scale. Participants in this double-blind trial had baseline MMSE scores ranging from 15 to 30, and their dietary adherence was monitored with serum DHA level measurements. A subgroup ($n=32$) of patients with very mild AD and MMSE scores above 27 (typical of patients with MCI) who received DHA had better MMSE scores (by a statistically significant increment of 2.1 points) than had those taking the placebo ($P=0.01$). This result suggests that DHA might have favorable effects only in patients with very mild AD and not in those with moderate-to-severe AD.

A recent, randomized, controlled trial of omega-3 fatty acid supplementation, conducted as part of the MEMO (Mental Health in Elderly Maintained with Omega-3) study in The Netherlands,[61] failed to show any statistically significant differences between placebo and treatment groups with regard to cognitive function. The participants were 302 cognitively healthy elderly individuals (MMSE score range 23–30) who were randomly assigned to placebo, low-dose (400 mg per day) DHA–EPA, or high-dose (1,800 mg per day) DHA–EPA, and their dietary adherence was monitored by measuring serum levels of DHA–EPA. No significant benefit from supplementation was detected with regard to cognitive tests such as verbal fluency, Trail Making or Wechsler Digit Span.

In summary, the limited, randomized, clinical trials completed to date do not show clear

Table 3 Clinical trials of the effects of long-chain omega-3 fatty acids and either onset of dementia or AD or changes in cognitive performance.

Reference	Study design	Inclusion criteria	Omega-3 fatty acid intake and measurement	Outcome measures	Results	Comments
Terano *et al.* (1999)[58]	12-month RCT; *n* = 20; location: Japan	Elderly individuals with mild-to-moderate vascular dementia (MMSE score 15–22) living in a home for the elderly	Placebo: no supplementation; treatment: 12 months of 4.32 g per day DHA	Cognitive decline measured by MMSE and HDS-R	DHA supplementation significantly reduced the rate of cognitive decline over 3 months and 6 months of follow-up ($P < 0.05$), but not over 12 months	None
Kotani *et al.* (2006)[59]	90-day RCT; *n* = 39; location: Japan	Subjects with amnesia owing to mild cognitive impairment, AD or organic brain lesions	Placebo: 90 days of 240 mg per day olive oil; treatment: 240 mg per day of DHA and arachidonic acid and 6.4 mg per day asthaxanthine	Cognitive dysfunction measured by repeatable battery for the assessment of neuropsychological status	No significant benefit for patients with AD; patients with organic brain lesion showed improvement in both immediate and delayed memory	Patients with mild cognitive impairment assigned to treatment improved their attention and immediate memory ($P < 0.01$), but no change was noted in their delayed memory
Freund-Levi *et al.* (2006)[60] (OmegAD study)	12-month RCT; *n* = 174; location: Sweden	AD according to DSM-IV; MMSE score 15–30; living in own home	Placebo: 6 months of placebo followed by 6 months of DHA and EPA; treatment: 12 months of DHA and EPA	Cognitive decline measured by MMSE and cognitive subscale of the AD assessment scale	No statistically significant difference in MMSE score between two groups at 6-month and 12-month time points	Statistically significant benefit in subgroup of patients with very mild AD; that is, MMSE score >27 ($P = 0.01$)
van de Rest *et al.* (2008)[61] (MEMO study)	26-week RCT; *n* = 302; location: The Netherlands	≥65 years old with MMSE score >21; not on dementia or depression medications	DHA–EPA 400 mg or DHA–EPA 1800 mg versus placebo (oil capsule); serum DHA and EPA measurement	Cognitive function and mental well-being assessed by word learning test, forward and backward test of the Wechsler digit span, trail making test versions A and B, Stroop color–word test and verbal fluency test	No statistically significant change was noted in any of the cognitive domains for either low-dose or high-dose fish oil supplementation compared with placebo	None

Abbreviations: AD, Alzheimer disease; DHA, docosahexaenoic acid; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; EPA, eicosapentaenoic acid; HDS-R, Hasegawa Dementia Rating Scale; MMSE, Mini-Mental State Examination; RCT, randomized, controlled trial.

benefits of DHA or other forms of long-chain omega-3 fatty acid for slowing the rate of cognitive decline, treating AD, or slowing progression in any forms of dementia. Some marginal benefit was noted in small subgroups of patients with MCI or mild AD, which suggested that patients with mild cognitive deficits could benefit from this approach.

Ongoing clinical trials

OPAL (Older people and n-3 long-chain polyunsaturated fatty acids),[62] DHA in Slowing the Progression of Alzheimer Disease,[63] and several other multicenter trials (Table 4) are now in progress or nearing completion. The durations of follow-up in these trials range from 30 weeks to 36 months, and the results are likely to become available between 2009 and 2014. These trials should finally ascertain the efficacy of long-chain omega-3 fatty acid supplementation in the primary or secondary prevention of dementia.

DISCUSSION OF REVIEW FINDINGS

After adjustment for covariates, including age, sex, education level and income, four of the eight observational studies in our systematic review of the literature reported a significant or trend-level benefit of a high intake of fish or long-chain omega-3 fatty acid supplements with

Table 4 Ongoing clinical trials studying the effects of long-chain omega-3 fatty acids and either onset of dementia or AD or changes in cognitive performance.

Trial, sponsor and start year	Study design	Main inclusion and exclusion criteria	Omega-3 fatty acid intake and measurement	Primary outcome measures	Secondary outcome measures	Comments
OPAL; Medical Research Council (UK); 2004	24-month RCT; *n* = 800; location: UK (20 clinical practices)	Healthy, age 70–79 years, with no dementia or diabetes and MMSE score >24	DHA 500 mg per day plus EPA 200 mg per day versus placebo	Changes in cognitive function, as determined by California verbal learning test; changes in vision	Other measures of cognitive performance, such as recall of a short story, verbal fluency and spatial memory; changes in blood pressure, depression, BMI, color vision and eye health	Study recruitment was completed in 2007
DHA in Slowing the Progression of AD; National Institute on Aging; 2007	18-month RCT; *n* = 400; location: USA (51 centers from AD Cooperative Study)	≥50 years old with MMSE score 14–26, living in the community with no clinical history of stroke	DHA 1020 mg per day versus placebo	Changes in rate of cognitive and functional decline, measured by ADAS-Cog and CDR-SOB	Changes in brain MRI and cerebrospinal fluid in subsets of participants	Study recruitment was completed in 2008
MIDAS; Martek Biosciences Corporation; 2005	24-week RCT; *n* = 465; location: USA (14 locations in 9 states)	≥55 years old with subjective memory complaint but otherwise healthy, MMSE score >26	DHA 900 mg per day	Changes in cognitive function	Changes in visual acuity and levels of plasma phospholipids	Study recruitment was completed in 2008
Omega-3 Fatty Acids and/or MAPT; Toulouse University Hospital; 2008	36-month RCT; *n* = 1,200; location: France (4 cities)	Frail, ≥70 years old with no dementia and MMSE score >24	DHA 800 mg per day	Changes in memory function as determined by Gröber & Buscke test	A parallel group of participants will receive behavioral multi-domain intervention plus or minus DHA, and their compliance and adherence to this program will be evaluated	Study recruitment will be completed in 2013
The Efficacy of Phosphatidylserine–Omega-3 in Elderly with Age-Associated Memory Impairment; Enzymotec; 2007	30-week RCT (double-blind for first 15 weeks); *n* = 157; location: Israel	50–90 years old, MMSE score >27 for individuals with college education and >26 for all others	Phosphatidylserine–omega-3 300 mg/day for 15 weeks; then open-label phase with 100 mg/day for 15 weeks	Changes on neuropsychological computerized tests, Trail Making Test, Rey Auditory–Verbal Learning Test, and Osterrieth Complex Figure Test	Blood tests	Study recruitment was completed in 2008

Abbreviations: AD, Alzheimer disease; ADAS-Cog, cognitive subscale of the AD Assessment Scale; CDR-SOB, Clinical Dementia Rating-Sum of Boxes; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; MAPT, Multi-Domain Intervention in the Prevention of Age-related Cognitive Decline; MIDAS, Memory Improvement with Docosahexaenoic Acid Study; MMSE, Mini-Mental State Examination; OPAL, Older People And n-3 Long-chain polyunsaturated fatty acids); RCT, randomized, controlled trial.

regard to reducing the risk of AD or other forms of dementia. Moreover, none of the four clinical trials conducted to date has provided convincing evidence for the use of omega-3 fatty acids to treat any form of dementia or to prevent cognitive decline. However, post hoc analyses of data from some of these studies have shown a possible benefit in patients with MCI. By contrast, all three observational studies that targeted elderly individuals with no dementia at baseline and used cognitive change as an outcome reported positive results with consumption of either fish or DHA–EPA supplements.

A Cochrane review of studies conducted before 2006 also noted conflicting results and could not find strong evidence to support the use of dietary or supplemental omega-3 PUFAs for the prevention or treatment of dementia.[64] The seemingly heterogeneous results in our analysis, as well as in those of the Cochrane review, might be attributable to several issues that make analysis of the data from observational and clinical trials in this field

challenging. These issues, which are summarized below, could serve as lessons to be considered in the ongoing and future clinical trials.

Subtypes, dosage, and duration of consumption of omega-3 fatty acids or fish

The specific type, dosage, and duration of use of any of the components of fish or PUFAs could have influenced the outcomes of the studies described above. For example, analogous to the ratio of LDL (harmful) to HDL (protective) cholesterol with regard to the development of cardiovascular disease, a specific ratio of long-chain omega-3 to omega-6 PUFAs might be particularly beneficial. The importance of the omega-3:omega-6 ratio has already been supported by findings in some cardiovascular studies.[65–68]

Most of the studies that we have reviewed only focused on long-chain omega-3 fatty acids in general or on DHA in particular, and not on long-chain omega-6 fatty acids. In fact, Barberger-Gateau and colleagues reported an increased risk of dementia with regular consumption of omega-6 PUFA if not compensated for by regular consumption of omega-3 fatty acids (HR 2.12, 95% CI 1.30–3.46).[53] Heude and colleagues also reported an increased risk of cognitive decline in individuals with a high consumption of omega-6 fatty acids (OR 1.59, 95% CI 1.04–2.44).[55] Moreover, as observed in studies in the cardiovascular system, the quantities and ratios of different forms of omega-3 fatty acids, such as DHA and EPA, could be important. Morris *et al.*, for example, reported a statistically significant reduction in dementia risk for intakes of total omega-3 fatty acids and DHA, but their findings were not statistically significant for EPA intake.[50]

The type of fish consumed could also affect the results. Huang and colleagues reported that consumption of fatty fish reduced the risk of dementia by 28%, whereas consumption of lean fried fish had no protective effect.[51] The average dose of each of the sources of fatty acids (ranging from 180 mg in the Framingham Heart Study[52] to 4,320 mg in the clinical trial by Terano *et al.*[58]) might also affect the outcome. Interestingly, higher doses do not always seem to be better. Participants in the Three-City cohort study showed statistically significant benefits of PUFAs if they ate fish two to three times per week (HR 0.59, CI 0.37–0.94) but not if they ate fish four times, or more, per week (HR 0.58, CI 0.25–1.34).

Duration of use could also be a key factor. For example, the results from a follow-up of 2.1 years in the Rotterdam study formed a significant reduction in risk of developing AD in participants who consumed fish (RR 0.3, CI 0.1–0.9);[46] however, after an additional 4 years of follow-up, the positive results lost their statistical significance. The reason for this finding is not clear, but it could have been related to changes in the diets of participants during the extended study period. Similarly, the randomized, clinical trial of Terano *et al.* showed a beneficial reduction in progression of dementia with DHA after 6 months of treatment but not after 12 months.

Another issue that is relevant to the duration of clinical trials and observational studies in the fields of cognitive health and dementia onset is that the optimal time for primary prevention of AD could be in the early mid-life period. However, clinical trials to examine this possibility are not feasible owing to high attrition rates (many participants stop such programs early, for example because they move to a different city, become tired of attending research centers, or have transportation problems), the large sample sizes required to perform such studies, and the challenges involved in long-term follow-up over 3–4 decades.

Future clinical trials must carefully monitor the dietary sources and dosages of both omega-3 and omega-6 fatty acids (Box 1), as well as the type and duration of fish consumption.

Genetic and environmental heterogeneity

Heterogeneity among different populations with regard to genetic susceptibility to dementia might dilute the benefits of long-chain omega-3 fatty acids. For example, a few studies found protective effects only among participants who were not carriers of the *APOE* ε4 allele.[51,53,69] Conversely, the MEMO trial found a protective effect in the cognitive domain of attention in carriers of *APOE* ε4.[61] The selection criteria for observational studies or clinical trials might particularly attract individuals who have a genetically increased risk of dementia (e.g. *APOE* ε4 carriers), which would confound the reported findings. In fact, some of the participants might already have subclinical cognitive impairment at baseline. Such participants are likely to experience rapid cognitive decline, regardless of whether they receive active treatment or placebo during a clinical trial. Their cognitive impairment might

also be associated with impaired and imbalanced food intake, which would further contaminate the findings of the study.

Several other issues might complicate the findings of observational studies and clinical trials. First, people vary with regard to their metabolism of fish and omega-3 fatty acids. Second, different types of fish and different preparations of commercially available PUFA have varying proportions of omega-3 and omega-6 subtypes. Third, not all individuals who eat two to three servings of fish every week (or take daily supplements) would be expected to have similar levels of omega-3 or omega-6 fatty acids, owing to differences in genes, age, and consumption of nuts or seafood other than fish (Box 1). Fourth, food frequency questionnaires might not necessarily reflect the actual amounts of omega-3 fatty acid intake. Finally, eating fish or taking supplements might be a proxy for individuals who are fitter and lead healthier lifestyles than those who do not have this dietary pattern, so any effects on cognitive decline or dementia might have little or nothing to do with the foods or supplements. Clinical trials must, therefore, attempt to enlist participants with homogenous backgrounds and to monitor their serum levels of omega-3 and omega-6 fatty acids throughout the study, as was done in the Canadian Study of Health and Aging, a subset of the Three-City cohort study, EVA, and the Framingham Heart Study.[49,52,54,55]

Variations in outcome measures and diagnostic evaluation

Individual studies can vary with regard to the diagnostic criteria used for MCI, AD or other forms of dementia. For example, investigators in the OmegAD study found protective effects for omega-3 fatty acids among participants who had mild AD, which was defined in this study as an MMSE score of 27 and above.[60] Investigators in other studies, however, might categorize individuals with such a high MMSE score as having MCI rather than AD. Similarly, participants in the MEMO study had MMSE scores ranging from 23 to 30 and were considered to be cognitively healthy.[61] Investigators in other studies might consider participants with a MMSE score of 23 to have MCI or mild AD.

Participants included in the OmegAD study had MMSE scores ranging from 15 to 30, whereas those in the MEMO study had scores ranging from 23 to 30. The wide range of cognitive performance reflected in these MMSE scores probably represents a broad spectrum of underlying pathology. Studies that included patients with a heterogeneous combination of vascular dementia, 'pure' AD and other pathologies could dilute the reliability of their results, as omega-3 fatty acids might work only in a subgroup of patients with a specific type of brain pathology. This phenomenon is particularly interesting, as evidence is growing that dementia in elderly individuals is associated with mixed pathologies;[70–72] not all patients diagnosed with AD necessarily carry the same load of AD-associated plaques and tangles. In addition, a patient's clinical presentation would be heavily influenced by his or her degree of superimposed brain vascular pathology.[72] Theoretically, if DHA exerts its neuroprotective effects largely through vascular factors, researchers might obtain positive results only among elderly individuals with multiple vascular risk factors, and might fail to observe a benefit if most of their participants have pure AD pathology. Careful selection and characterization of participants' cognitive level (normal, MCI or AD) at baseline can be essential to avoid dilution of data through the inclusion of individuals with varying degrees of pathology and varying levels of severity. This selectivity is particularly important in the wake of recent PET imaging studies, which revealed that a substantial proportion of elderly individuals can have large loads of amyloid deposition with no apparent signs of cognitive impairment or AD.[73]

Given the strong theoretical and biological evidence for a neuroprotective role of omega-3 fatty acids against cognitive decline and dementia—for example, by improving cerebral blood flow, mitigating inflammation and reducing amyloid aggregation (Figure 1)—one possibility is that the lack of uniformly positive associations reflects inherent complexities in the designs of the studies that we reviewed. Careful and detailed clinical trials that take these complexities into account are needed to establish the effectiveness of long-chain omega-3 fatty acids for primary or secondary prevention of cognitive decline or dementia. Tolerability and adverse effects must also be closely monitored, as high doses of antioxidants in nutritional supplements might be associated with increased lipid peroxidation and deleterious health effects.[74]

CONCLUSIONS

Our systematic review of observational studies in the literature suggests that long-chain omega-3

fatty acids provide a modest benefit with regard to slowing cognitive decline among elderly individuals without dementia. By contrast, clinical trials have failed to detect any beneficial role for the use of DHA, EPA or other forms of omega-3 fatty acids for secondary prevention or treatment of AD. Given the superiority of clinical trials over observational studies, we conclude that omega-3 fatty acids, administered in the diet or through supplements, cannot be recommended for patients who have already developed dementia. However, our review favors the recommendation of fish consumption two to three times per week and/or the use of long-chain omega-3 fatty acid supplements such as DHA–EPA in elderly individuals who are looking for ways to maintain their cognitive function as they age. Such recommendations must be balanced with warnings about the potential adverse effects of high-dose vitamins and supplements,[74] and with the promotion of healthy lifestyle choices that consist of a balanced diet, regular exercise, brain-stimulation activities, and avoidance of stress.[71,75–77] Definitive guidelines for the use of long-chain omega-3 fatty acid supplements in the prevention or treatment of MCI or AD should be possible to compile in the next 2–3 years, once the results of ongoing clinical trials have become available.

KEY POINTS

- Long-chain omega-3 fatty acids are essential for normal brain development
- Levels of omega-3 fatty acids are decreased in the brains of patients with Alzheimer disease (AD)
- Biological studies and animal models suggest that omega-3 fatty acids have a role in primary prevention of cognitive decline by improving blood flow, decreasing inflammation and/or reducing amyloid-β pathology
- Evidence from observational studies in humans favors consumption of long-chain omega-3 fatty acids to reduce cognitive decline with aging
- The clinical trials conducted to date have shown no benefits of omega-3 fatty acids for secondary prevention or treatment of AD
- Larger, ongoing, randomized trials should provide more-definitive answers regarding the use of long-chain omega-3 fatty acids for the prevention and/or treatment of AD

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