Omega 3 fatty acids and cognitive health in older people

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Abstract

Oily fish and other sources of long-chain n-3 polyunsaturated fatty acids (n-3 LCPs) have been proposed as protective against dementia and age related cognitive impairment. The basic mechanisms underlying these proposed benefits have been postulated and experimental studies supporting the plausibility of the putative effects have been published. Observational epidemiological and case control studies also largely support a protective role of fish consumption on cognitive function with advancing age, albeit with important unexplained heterogeneity in findings. In this review we report the findings of the latest Cochrane review on the benefits of n-3 LCP supplementation on cognitive function among cognitively healthy older people and expand the review by including trials conducted with individuals with prevalent poor cognitive function or dementia. We identified seven relevant trials, four among cognitively healthy older people, and three among individuals with pre-existing cognitive decline or dementia, and overall conclude that there is no evidence to support the routine use of n-3 LCPs supplements for the prevention, or amelioration, of cognitive decline in later life. We identified several challenges in the design of intervention studies for the prevention of dementia and cognitive decline in older people that require careful consideration especially in recruitment and retention in long-term trials. Whether the lack of agreement in findings from mechanistic and observational data and from intervention studies reflects a real absence of benefit on cognitive function from n-3 LCP supplementation, or whether it reflects intrinsic limitations in the design of published studies remains open to question.

Key words: Older people: Cognitive health: Dementia: n-3 fatty acids

Numerous reviews of findings from animal research as well as biological, clinical and epidemiological data underscore a protective role of dietary intake of n-3 (or omega-3) long-chain polyunsaturated fatty acids (n-3 LCPs) on dementia, including Alzheimer's disease (AD). Various mechanisms of action have been proposed including improvement of cerebral blood flow, maintenance of the structural integrity of neuronal membranes, and reduction in amyloid-ß pathology[1–7]. The balance of evidence from prospective studies suggests that n-3 LCPs may have a greater role in slowing or delaying cognitive decline among healthy older people than in the treatment of individuals with dementia[2,3,6,7]. The brain is particularly rich in n-3 LCPs and several mechanisms have been postulated for their potential protective actions. First, docosahexaenoic acid (DHA) is a component of membrane phospholipids in the brain and adequate n-3 LCP status contributes to specific neural membrane structural properties and functions including ion transport, signal transduction, synapse formation, neurotransmitter release and reuptake. DHA also contributes to sequestering free radicals and preventing amplification of oxidative damage. Secondly, eicosanoids and docosanoids produced by cyclo- and lipo-oxygenase action on long-chain polyunsaturated fatty acids act as cellular mediators of inflammation, allergy and immunity, oxidative damage, vascular responses and thrombosis and may thereby influence risk especially of vascular dementia[8].

Evidence from cross-sectional analyses involving dietary fish and/or supplemental n-3 LCP intake, as well as findings based on plasma eicosapentaenoic acid (EPA) and DHA concentrations are equivocal. For example, some epidemiological studies document dose-response protective ass004sociations of n-3 LCPs on the cognitive performance of older individuals in different countries[9,10], with the associations applying to various cognitive domains[10], whereas other similarly designed studies report no associations in adjusted models[11,12]. Regarding plasma n-3 LCP concentrations, case-control[13] and prospective studies with older individuals free of dementia at baseline report significant inverse associations between

the concentrations of these nutrients and risk of cognitive decline or incident dementia[14,15]. However, other studies have documented elevated EPA concentrations among cognitively impaired older individuals, and elevated DHA, n-3 fatty acids, and total long-chain polyunsaturated fatty acids concentrations have been observed among individuals with dementia[16].

Population-based longitudinal analyses of data from older individuals who were cognitively healthy at baseline generally show an inverse association between fish consumption and incident dementia[17–19], albeit with some exceptions[12,20]. Somewhat less consistency exists among the research findings regarding the types of n-3 LCPs purporting the strongest benefit. Some prospective epidemiological studies show both EPA and DHA to be protective against cognitive decline[19], whereas others report associations either with DHA[18] or EPA[21].

A comprehensive review of 27 prospective studies of fish or n-3 LCPs in diet or blood, and 9 cross-sectional studies of n-3 LCPs in plasma, erythrocytes, or in the diet suggested that the lack of consistency in the findings could be attributed to disparate study designs and populations, inadequate statistical adjustment, and differences in predictor/outcome assessment methodology[3]. Authors have also highlighted that fish intake is not equivalent to n-3 LCP intake and that the genetic heterogeneity among different populations with respect to both n-3 fatty acids metabolism and dementia susceptibility might weaken the benefits of these nutrients[2].

A Cochrane review of the evidence from randomised controlled trials found no trials published before October 2005 investigating the effects of n-3 polyunsaturated fatty acid supplementation on cognitive function among cognitively healthy older people[22]. We here present findings from the recently updated Cochrane review[23] of the effect of n-3 polyunsaturated fatty acid supplementation on the prevention of dementia and cognitive decline among cognitively healthy older people and expand the scope of the review to include randomised controlled trials conducted among individuals with prevalent poor cognitive function or dementia.

Methods

For a Cochrane review update[23], the major healthcare databases (Medline, Embase, Cinahl, Psycinfo and Lilacs) and trial registers (International Standard Randomised Controlled Trial Number, ClinicalTrials.gov and The Cochrane Library's Central Register of Controlled Trials) were systematically searched up to April 2012. Search terms included variants and combinations of: fatty acids, omega-3, polyunsaturated fatty acid, unsaturated fatty acid, essential fatty acid, eicosapentaenoic acid, docosahexaenoic acid, docosapentaenoic acid, alpha-linolenic acid, fish oil, n-3 fatty acid, long chain fatty acids, primrose oil, linseed oil, oily fish, flaxseed oil, randomized controlled trial, controlled clinical trial, healthy old or elderly or aged or senior, healthy persons, cognition, dementia.

For the Cochrane review update[23], randomised controlled trials involving individuals over 60 years of age were included if they also had the following characteristics. First, they pre-screened participants for dementia and excluded individuals

with pre-existing dementia. Second, they pre-screened participants for cognitive impairments and excluded individuals with pre-existing cognitive impairment. Third, the intervention period was a minimum duration of 26 weeks (180 days).

In this review we expand the inclusion criteria for studies and participants to include randomised controlled trials that did not screen or exclude individuals with possible cognitive decline or with existing cognitive impairment or dementia. We chose to include any n-3 polyunsaturated fatty acid intervention (including mixtures of n-3 fatty acids) that involved dietary supplementation or provided meals, versus placebo or usual diet. Our primary outcome of interest was incidence of dementia, our secondary outcome was cognitive decline defined as change in a relevant cognitive function over the intervention period.

Results

Our systematic search process identified 7 relevant studies for this review (Table 1). Three studies (included in the Cochrane review) enrolled only cognitively healthy older people[24–26], one study enrolled apparently cognitively normal older people but did not screen for cognitive function at baseline[27], one study enrolled participants with age-related cognitive decline[28] and two studies enrolled participants with mild to moderate AD[29,30]. All studies were conducted in high-income countries, sample sizes ranged from 204 to 4837 and study duration ranged from 24 weeks to 4 years. Of the identified trials, six provided interventions as daily capsules containing varying mixtures of EPA and DHA with overall doses up to 2 g per day. One trial provided fortified margarines containing EPA, DHA and alpha-linolenic acid (ALA)[25]. None of the identified trials provided information on the incidence of dementia. Change in cognitive outcome was assessed using a variety of measures (Table 2) and study findings are presented below in narrative format.

Trials in cognitively healthy older populations

In a study from the Netherlands, a total of 302 cognitively healthy older people aged ≥65 years were randomised into a low-dose treatment group (400 mg EPA + DHA daily), a high-dose treatment group (1800 mg EPA + DHA daily), or placebo (sunflower oil) for 26 weeks. Cognitive function was evaluated at baseline and follow-up with a large battery of cognitive tests assessing memory, executive function, attention and sensorimotor speed. An analysis of variance showed no significant differences between the groups in cognitive tests scores at the end of the study[26].

In the OPAL study a total of 867 cognitively healthy adults aged 70–79 years were randomised into an active group (200 mg EPA + 500 mg DHA daily) or placebo (olive oil) for 24 months. Cognitive function was evaluated at baseline and follow-up with a battery of cognitive tests, including the California Verbal Learning Test (CVLT) as the primary outcome. A total of 748 participants completed the study. Intention-to-treat analysis of covariance models showed no change over the course of the intervention in CVLT or any secondary cognitive

outcomes[24], secondary analysis revealed interaction between specific genetic polymorphisms in fatty-acid desaturase genes and lipid transport proteins and the response to the intervention (in preparation).

A secondary outcome paper from the Alpha Omega Trial[31], reported the impact of four margarine varieties (daily intake of margarine supplemented with 400 mg EPA + DHA in a 3:2 ratio, margarine supplemented with 2 g ALA, margarine supplemented with 400 mg EPA + DHA and 2 g ALA, or placebo margarine) for 40 months on 4837 older people aged 60–80 years with a history of myocardial infarction. Cognitive function data were collected on 2911 of the randomised individuals. Rates of change in cognitive function, assessed using the Mini-Mental State Examination (MMSE), did not differ between trial arms over the course of the study[25].

The SU.FOL.OM3 trial randomised 2501 individuals with a history of cardiovascular disease. Of the randomised individuals, 1748 had complete cognitive assessment data, 858 of whom were aged >60 years and are included in this review. There was no formal screening of participants for cognitive function at the start of the study. Participants were randomised in a 2 × 2 factorial design to one of four groups: 0·56 gm folate +3 mg vitamin B6 + 0·02 mg vitamin B12; or 600 mg EPA + DHA in a 2:1 ratio; or B vitamins and n-3 LCPs combined; or placebo (liquid paraffin + fish oil). Cognitive function after 4 years of supplementation was assessed with the French version of the modified Telephone Interview for Cognitive Status. Analysis of covariance and multiple logistic regression showed no significant effects of group assignment on cognitive function[27].

Trials among older populations with evidence of cognitive impairment

In a study from Sweden, 204 adults (mean age = 74 y) with mild to moderate AD were randomised to an active group (1700 mg DHA + 600 mg EPA daily) or placebo (corn oil including 0.6g linoleic acid) for 6 months. After 6 months, all participants received the n-3 LCP supplementation for an additional 6 months. Cognitive function was assessed with the MMSE, the cognitive subscale of the Alzheimer's Disease Assessment Scale and the Clinical Dementia Rating scale. A total of 174 participants completed the trial. At 6 months, repeated-measures analysis of variance showed that the decline in cognitive functions did not differ between the groups. However, in a subgroup (n = 32) with very mild cognitive dysfunction at baseline, statistically significant positive effects of the supplementation on MMSE scores were observed[29].

In the MIDAS trial, 485 individuals aged ≥55 years with defined age-related cognitive decline were randomised into an active group (900 mg DHA daily) or placebo (corn oil + soy oil) for 24 weeks. The primary outcome was the CANTAB Paired Associate Learning (PAL) and adjusted

Table 1. General characteristics of randomised controlled trials included in review

First author, study location	Study population	Interventions	Duration (months)
Andreeva, France[27]	Subsample of 858 adults aged >60 years	*Active* 600mg EPA + DHA daily *Placebo* liquid paraffin + fish oil + B vitamins	48
Dangour, England and Wales[24]	867 adults aged 70–79 years. Key exclusion: poor cognitive health (Mini-Mental State Examination [MMSE] <24)	*Active* 200mg EPA + 500mg DHA daily *Placebo* olive oil	24
Freund-Levi, Sweden[29]	204 adults with mean age 74 years and mild to moderate Alzheimer's Disease (MMSE ≥ 15)	*Active* 1·7g DHA + 0·6g EPA daily *Placebo* corn oil including 0.6g linoleic acid	6
Geleijnse, The Netherlands[25]	2911 adults aged 60–80 years with history of myocardial infarction. Key exclusion: poor cognitive health (MMSE < 21)	*Active* margarines containing a. 400mg EPA/DHA daily b. 2g ALA daily c. 400mg EPA/DHA + 2g ALA daily *Placebo* Margarine	40
Quinn, USA[30]	402 adults with mean age 76 years and mild to moderate Alzheimer's Disease (MMSE = 14–26)	*Active* 2g algal DHA daily *Placebo* corn or soy oil	18
Van de Rest, The Netherlands[26]	302 adults aged ≥65 years. Key exclusion: poor cognitive health (MMSE < 21)	*Active* a. 1800mg EPA + DHA daily b. 400mg EPA + DHA daily *Placebo* high-oleic sunflower oil	6
Yurko-Mauro, USA[28]	485 adults aged ≥55 years with age-related cognitive decline and ≤28 on logical memory immediate recall or ≤15 on delayed recall, and MMSE ≥ 26	*Active* 900mg DHA daily *Placebo* corn oil + soy oil	6

Table 2. Primary cognitive test results from randomised controlled trials included in review

First author	Intention to treat sample	Primary cognitive outcome measure	Baseline score[a]	Final score[a]
Andreeva et al.[27]	*Active* 420 *Placebo* 438	Telephone Interview for Cognitive Status, modified French version	Not collected	*Active* 27·2 (4·9) *Placebo* 27·3 (5·1)
Dangour et al.[24]	*Active* 375 *Placebo* 369	California Verbal Learning Test immediate recall (sum of 3 trials)	*Active* 24·1 (6·0) *Placebo* 23·9 (5·7)	*Active* 24·1 (6·7) *Placebo* 24·4 (6·4)
Freund-Levi et al.[29]	*Active* 103 *Placebo* 101	Mini-Mental State Examination (MMSE) Alzheimer's Disease Assessment Scale (ADAS-Cog)	*Active* MMSE: 23·6 (22·8, 24·4)[b] ADAS-Cog: 25·7 (23·6, 27·8)[b] *Placebo* MMSE: 23·2 (22·4, 24·0)[b] ADAS-Cog: 27·2 (25·1, 29·4)[b]	*Active* MMSE: 22·1 (21·1, 23·1)[b] ADAS-Cog: 31·2 (28·3, 34·2)[b] *Placebo* MMSE: 21·9 (20·8, 22·9)[b] ADAS-Cog: 32·8 (29·8, 35·9)[b]
Geleijnse et al.[25]	*Active* 1,240 *Placebo* 1,282	MMSE	*Active and placebo* 28·3 (1·6)	*Active* a. Change: −0·78 (2·32) b. Change: −0·67 (2·24) c. Change: −0·53 (2·07) *Placebo* Change: −0·71 (2·36)
Quinn et al.[30]	*Active* 238 *Placebo* 164	ADAS-Cog Clinical Dementia Rating (CDR) sum of boxes	*Active* ADAS-Cog: 23·77 (8·9) CDR: 5·61 (2·62) *Placebo* ADAS-Cog: 23·96 (9·2) CDR: 5·77 (2·61)	*Active* ADAS-Cog change: 7·98 CDR change: 2·87 *Placebo* ADAS-Cog change: 8·27 CDR change: 2·93
Van de Rest et al.[26]	*Active high dose* 96 *Active low dose* 100 *Placebo* 106	Word Learning Test (WLT) immediate recall (sum of 5 trials)	*Active high dose* 39·3 (8·8) *Active low dose* 40·8 (8·6) *Placebo* 39·6 (9·7)	*Active high dose* 44·9 (9·9) *Active low dose* 46·1 (10·1) *Placebo* 44·8 (9·4)
Yurko-Mauro et al.[28]	*Active* 242 *Placebo* 243	CANTAB Paired Associate Learning (PAL) test	*Active* 13·4 (11·6) *Placebo* 12·1 (10·9)	*Active* 8·8 (9·9) *Placebo* 9·7 (10·4)

a Values are mean (SD) unless stated.
b Mean (95 % confidence interval).

ANCOVA showed that treatment was associated with significantly fewer PAL 6 pattern stage errors[28].

Finally, the Alzheimer's Disease Cooperative Study randomised 402 individuals (mean age = 76 y) with mild to moderate AD into an active group (2000 mg DHA daily) or placebo (corn or soy oil) for 18 months. Cognitive function was assessed with the cognitive subscale of the Alzheimer's Disease Assessment Scale and the Clinical Dementia Rating sum of boxes. A total of 295 participants completed the trial and analysis did not identify any evidence that compared to the placebo, DHA slowed the rate of cognitive decline in these participants[30].

Discussion

Several mechanisms have been postulated for the possible protective role of n-3 LCPs in cognitive decline and dementia. Experimental animal studies using a mouse model of AD have shown that dietary DHA deficiency induces a decline in DHA content of the frontal cortex which is significantly associated with loss of dendritic spine formation, increases oxidative damage and affects the hippocampus impairing memory acquisition, while supplementation with DHA increases n-3 LCP content of the brain, protects against adverse biochemical effects of deficiency, and results in improved cognitive performance[32]. DHA also modulates expression of genes related to neurogenesis[33] and is directly involved in protection of the ageing brain from hypoxic injury through docosanoid-related mechanisms[34,35].

The recent United Nations Food and Agriculture Organisation consultation on fats and fatty acids in human nutrition recommended an n-3 LCP (EPA + DHA) intake for adults of 250 mg per day and stated that this may contribute to the prevention of cardiovascular disease[36]. The significant role of n-3 LCPs for brain health was acknowledged but no recommendations were established for older people based on this role because the data on specific functional outcomes were considered insufficient. The average dietary intake of preformed DHA in European adults consuming omnivorous diets is about 150–200 mg per day although intake levels in much of the rest of the world are far lower[37].

For this review we identified seven trials that investigated the effect of n-3 LCP supplementation on cognitive function in older people. Four of these trials were among cognitively healthy (or presumptively cognitive healthy) older people[24–27], and none of these trials identified any benefit from n-3 LCP supplementation. A further three trials enrolled older people with cognitive function impairments ranging from defined age-related cognitive decline to moderate AD. One of these three trials identified some evidence of a benefit from DHA supplementation[28], the other two trials did not support this finding[29,30]. Overall, the evidence from trials of n-3 LCP supplementation among cognitively healthy and cognitively impaired older people does not support the use of n-3 LCPs for the prevention of cognitive decline.

The strength of the epidemiologic associations and the proposed mechanisms underlying the effects of n-3 LCPs on brain function are increasing, and yet of seven trials included in our review, only one identified any potential benefits from n-3 LCP supplementation on cognitive function. This discrepancy between epidemiological associations and trial evidence is not unique to n-3 LCPs[38] although there may also be some unique challenges in the design of long-term intervention studies for the prevention of dementia and cognitive decline in older people.

From the standpoint of determining the primary health effectiveness of interventions, a key concern relates to the recruitment of samples of older people that match the health and demographic characteristics of the target population[39]. Recruitment procedures (including the use of extensive exclusion criteria) favour the selection of healthier participants, and participants who are more motivated and adherent to instructions tend to be healthier, consume a better diet and are more active. Physical activity and food consumption patterns may have an effect on disease progression that is separate from the effect of the intervention under investigation.

Retention of participants in long-term studies of cognitive function is also a concern since individuals who drop out of trials frequently have different demographic and health characteristics from those who remain active until the end of the trial. In the four trials that recruited cognitive healthy (or presumptively cognitive healthy) adults, the percentage of participants with data available for the final trial analyses varied from between 62 % in a trial of 40 month duration[25] to 99 % in a trial of 6 month duration[26]. In the OPAL trial (24 month duration), retention was 86 %, and those individuals who withdrew had poorer cognitive function at the start of the study than those who remained in the study[24]. Similarly, in the SU.FOL.OM3 trial (48 month duration), retention was 75 % and individuals who completed the trial had higher EPA and DHA concentrations and had slightly higher verbal fluency at baseline[27]. As expected, longer trials had lower overall retention and the evidence also suggests that those participants who drop out of trials are potentially exactly those who might benefit most from n-3 LCP supplementation.

From the perspective of identifying a suitable intervention to maintain cognitive function into later life, the current evidence base is disappointing. Whether this lack of evidence results from insufficient thought into designing studies of appropriate size and duration, or whether it relates to the selection of study populations who may benefit most from n-3 supplementation, such as those with low n-3 LCP status at study entry, or finally whether it suggests that despite the epidemiological and mechanistic evidence n-3 LCP supplementation does not affect cognitive function, remains open to question.

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