Omega 3 fatty acid for the prevention of cognitive decline and dementia (Review)

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[Intervention Review]

Omega 3 fatty acid for the prevention of cognitive decline and dementia

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ABSTRACT

Background

Evidence from observational studies suggests that diets high in omega-3 long-chain polyunsaturated fatty acids (PUFA) may protect people from cognitive decline and dementia. The strength of this potential protective effect has recently been tested in randomised controlled trials.

Objectives

To assess the effects of omega-3 PUFA supplementation for the prevention of dementia and cognitive decline in cognitively healthy older people.

Search methods

We searched ALOIS - the Cochrane Dementia and Cognitive Improvement Group's Specialized Register on 6 April 2012 using the terms: "omega 3", PUFA, "fatty acids", "fatty acid", fish, linseed, eicosapentaenoic, docosahexaenoic.

Selection criteria

Randomised controlled trials of an omega-3 PUFA intervention which was provided for a minimum of six months to participants aged 60 years and over who were free from dementia or cognitive impairment at the beginning of the study. Two review authors independently assessed all trials.

Data collection and analysis

The review authors sought and extracted data on incident dementia, cognitive function, safety and adherence, either from published reports or by contacting the investigators for original data. Data were extracted by two review authors. We calculated mean difference (MD) or standardised mean differences (SMD) and 95% confidence intervals (CI) on an intention-to-treat basis, and summarised narratively information on safety and adherence.

Main results

Information on cognitive function at the start of a study was available on 4080 participants randomised in three trials. Cognitive function data were available on 3536 participants at final follow-up.

In two studies participants received gel capsules containing either omega-3 PUFA (the intervention) or olive or sunflower oil (placebo) for six or 24 months. In one study, participants received margarine spread for 40 months; the margarine for the intervention group contained omega-3 PUFA. Two studies had cognitive health as their primary outcome; one study of cardiovascular disease included cognitive health as an additional outcome.

None of the studies examined the effect of omega-3 PUFA on incident dementia. In two studies involving 3221 participants there was no difference between the omega-3 and placebo group in mini-mental state examination score at final follow-up (following 24 or 40 months of intervention); MD -0.07 (95% CI -0.25 to 0.10). In two studies involving 1043 participants, other tests of cognitive function such as word learning, digit span and verbal fluency showed no beneficial effect of omega-3 PUFA supplementation. Participants in both the intervention and control groups experienced either small or no cognitive declines during the studies.

The main reported side-effect of omega-3 PUFA supplementation was mild gastrointestinal problems. Overall, minor adverse events were reported by fewer than 15% of participants, and reports were balanced between intervention groups. Adherence to the intervention was on average over 90% among people who completed the trials. All three studies included in this review are of high methodological quality.

Authors' conclusions

Direct evidence on the effect of omega-3 PUFA on incident dementia is lacking. The available trials showed no benefit of omega-3 PUFA supplementation on cognitive function in cognitively healthy older people. Omega-3 PUFA supplementation is generally well tolerated with the most commonly reported side-effect being mild gastrointestinal problems.

Further studies of longer duration are required. Longer-term studies may identify greater change in cognitive function in study participants which may enhance the ability to detect the possible effects of omega-3 PUFA supplementation in preventing cognitive decline in older people.

PLAIN LANGUAGE SUMMARY

Fish oils for the prevention of dementia in older people

Dementia is a progressive illness which mainly affects older people. Previous research from observational studies has suggested that increased consumption of fish oils rich in omega-3 long-chain polyunsaturated fatty acids (omega-3 PUFA) may reduce the chance of developing dementia, while other studies show no effect. Oily fish, such as salmon, mackerel, herring and sardines are a rich source of omega-3 PUFA which are essential for brain development.

The authors of this review included studies where healthy participants over the age of 60 years who were cognitively healthy at the start of the study were randomly assigned to receive extra omega-3 PUFA in their diet or a placebo (such as olive oil). The main outcomes of interest were new cases of dementia diagnosed during the study period, cognitive decline, side-effects, and adherence to the intervention.

The authors included three randomised controlled trials involving 3536 participants. In two studies participants were randomly assigned to receive gel capsules containing omega-3 PUFA or olive or sunflower oil for six or 24 months. In the third study, participants were randomly assigned to receive tubs of margarine spread for 40 months (regular margarine versus margarine fortified with omega-3 PUFA).

None of the studies examined the effect of omega-3 PUFA on new dementia cases over the study period. In two studies involving 3221 participants there was no difference between the omega-3 PUFA and placebo group in mini-mental state examination score at final follow-up. In two studies (1043 participants), other tests of cognitive function such as word learning, digit span and verbal fluency showed no beneficial effect of omega-3 PUFA supplementation. Participants in both the intervention and control groups experienced little or no cognitive decline during the studies.

The main reported side-effect of omega-3 PUFA supplementation was mild gastrointestinal problems, but overall minor symptoms were reported by fewer than 15% of participants, and people in the control group were just as likely to report symptoms as those

receiving an omega-3 PUFA supplement. Adherence to the supplementation protocol was high in all trials with on average over 90% of supplements being apparently consumed by trial participants. All three studies included in this review were of high methodological quality, and so the findings are unlikely to be due to chance or bias.

The results of the available studies show no benefit for cognitive function with omega-3 PUFA supplementation among cognitively healthy older people. Omega-3 PUFA supplements may have other health benefits, and the authors comment that consumption of fish is recommended as part of a healthy diet.

Longer studies are required, during which greater changes in cognitive function may occur, to enable researchers to identify possible benefits of omega-3 PUFA in preventing cognitive decline.

BACKGROUND

Description of the condition

Dementia is a progressive debilitating syndrome that manifests as loss of memory, language problems, difficulties in performing activities of daily living and psychological changes, and care for people with dementia imposes substantial burdens on caregivers and healthcare systems worldwide (Burns 2009b). Dementia mostly affects older people, but can sometimes begin in younger individuals. Alzheimer's disease (AD) is the most common cause of dementia (Burns 2009a). Global estimates suggest that by the year 2040 more than 80 million people will be affected with dementia, and more than 70% of these people will live in low-income countries (Ferri 2005). Pharmacological therapies appear to produce small symptomatic cognitive improvements for some patients but currently appear unable to halt progression of dementia (Raina 2008). There is significant interest in identifying modifiable risk factors (such as lifestyle) that may prevent dementia. Primary among these lifestyle factors is the potential role of dietary factors, and specifically the omega-3 long-chain polyunsaturated fatty acids (PUFA).

Description of the intervention

Omega-3 fatty acids are unsaturated fatty acids characterised by having a final carbon-carbon double bond as the third bond from the methyl end (the n-3 position). The omega-3 PUFA of nutritional importance include alpha linolenic acid (ALA, 18:3), and two longer chain fatty acids, eicosapentaenoic acid (EPA, 20:5), and docosahexaenoic acid (DHA, 22:6). Omega-3 fatty acids are essential fatty acids i.e. they cannot be synthesised afresh in humans, but there is a limited ability to form the long chain fatty acids EPA and DHA from the shorter chain ALA. Plants provide the primary dietary source of ALA with seeds (especially flaxseed) and nuts (especially walnuts) being significant sources. EPA and DHA are primarily provided in the diet by the consumption of oily fish such as salmon, mackerel, herring and sardines.

An increasing body of scientific literature has investigated the link between omega-3 PUFA dietary consumption or physiological status, and measures of cognitive function or dementia. A recent systematic review identified eight cohort studies that examined the effect of omega-3 PUFA intake or physiological status on dementia and AD incidence, two of which reported a reduction in the risk of dementia or AD with increased fish consumption (Dangour 2010a).

How the intervention might work

The brain is particularly rich in fatty acids and several mechanisms have been postulated for the possible protective role of omega-3 PUFAs in dementia. First, DHA is a key component of membrane phospholipids in the brain and adequate omega-3 PUFA status may help maintain membrane integrity and neuronal function. Secondly, the oxidative products of PUFAs act as key cellular mediators of inflammation, allergy and immunity, oxidative stress, bronchial constriction, vascular responses and thrombosis and may thereby influence risk especially of vascular dementia (Uauy 2006). Third, there is a suggestion that DHA may be directly involved in enhancing neuronal health in the aging brain through a range of potential mechanisms (Bazan 2006; Cole 2010). And finally, there is a growing body of evidence that DHA may modify the expression of genes that regulate a variety of biological functions potentially important for cognitive health, including neurogenesis and neuronal function (Rojas 2003).

Why it is important to do this review

Dementia is a significant global public health concern and there is a clear need to identify effective interventions to slow cognitive decline in later life and prevent dementia. Diet may prove to be

a major modifiable risk factor in the aetiology of dementia and of the numerous nutrients or group of nutrients that have been investigated, the omega-3 PUFA are frequently identified among those with the greatest evidence base to support their potential for clinical use (Gillette Guyonnet 2007; Luchsinger 2004). This Cochrane review update provides the latest evidence from randomised controlled trials of the effect of omega-3 PUFA supplementation for the primary prevention of dementia in cognitively healthy older people.

OBJECTIVES

To assess the effects of omega-3 PUFA supplementation in cognitively healthy older people for:

- preventing incident dementia;
- preventing or slowing cognitive decline.

METHODS

Criteria for considering studies for this review

Types of studies

- Randomised controlled trials (RCTs) were eligible for inclusion.

In addition, the studies had to include the following characteristics.

- Pre-screening of participants for dementia (dementia cases excluded).
- Pre-screening of participants for other cognitive impairment (cognitive impairment cases excluded).
- The trial report described the method of randomisation.
- The study must have involved 1) only participants who were over the age of 60 years, or 2) a subgroup of participants who were all over age 60 and whose data were analysed and reported separately.
- The study must have given an intervention of 1) omega-3 PUFA capsules or a placebo; or 2) a strictly enforced or provided dietary intervention (meals) including omega-3 PUFA supplemented foods in specific portions.
- The intervention must have been provided for 26 weeks or 180 days or longer.

Types of participants

- Participants must have been age 60 years or above, and without dementia or cognitive impairment at the beginning of the study.

As described in the protocol for this review (Lim 2005, p.3); "The chief consideration for the age cut-off is to ensure a characteristic representation of the neurodegenerative diseases that are typically seen in older persons (such as Alzheimer's disease), as the heterogeneous subset of young onset dementias are often due to underlying illnesses which are very different in aetiologies, presentation and rate of progression from those encountered in the elderly population. Subjects with a diagnosis of delirium and acute confusion at study onset will be excluded.
There should be demonstration of adequate screening to exclude pre-existing dementia or cognitive impairment via the use of cognitive instruments, dementia rating scales or psychometric tests that have been reported in peer-reviewed journals. Subjects with known cognitive impairment but which does not amount to dementia will be excluded from this review. These include (but are not are limited to) the following diagnostic categories: dementia prodrome, incipient dementia, cognitive impairment no dementia (CIND), mild cognitive impairment (MCI), vascular cognitive impairment (VCI), age-associated memory impairment (AAMI), and age associated cognitive decline (AACD). While some of these terms were conceptually meant to characterize memory changes reflecting a "normal" stage of aging, more recent data has cast some doubt on this premise (Ritchie 2000). In particular, MCI has been recognized as a diagnostically heterogeneous entity with a significant progression to dementia (Petersen 2001)."
Definitions of poor cognitive health at baseline could be selected by investigators, and could differ between research projects.

Types of interventions

- Any omega-3 PUFA intervention which involved dietary supplementation or provided meals, versus placebo or usual diet.

Studies were excluded if the intervention consisted solely of dietary advice, or if the intervention was based solely on self-report (without definitive provision of meals or dietary supplements).

Types of outcome measures

Primary outcomes

- Incident dementia of any cause as defined by accepted international diagnostic criteria.

Secondary outcomes

- Difference between study arms at final follow-up in recognised measures of memory and cognitive function.
- Safety of omega-3 PUFA supplementation in older people.
- Adherence to omega-3 PUFA supplementation in older people.

Search methods for identification of studies

There were no restrictions applied to the search.

Electronic searches

We searched ALOIS (www.medicine.ox.ac.uk/alois) - the Cochrane Dementia and Cognitive Improvement Group's Specialized Register on 6 April 2012. The search terms used were: "omega 3", PUFA, "fatty acids", "fatty acid", fish, linseed, eicosapentanoic, docosahexanoic.

ALOIS is maintained by the Trials Search Co-ordinator of the Cochrane Dementia and Cognitive Improvement Group and contains studies in the areas of dementia prevention, dementia treatment and cognitive enhancement in healthy people. The studies are identified from:

1. Monthly searches of a number of major healthcare databases: MEDLINE, EMBASE, CINAHL, PsycINFO and LILACS
2. Monthly searches of a number of trial registers: ISRCTN; UMIN (Japan's Trial Register); the WHO portal (which covers ClinicalTrials.gov; ISRCTN; the Chinese Clinical Trials Register; the German Clinical Trials Register; the Iranian Registry of Clinical Trials and the Netherlands National Trials Register, plus others)
3. Quarterly search of *The Cochrane Library*'s Central Register of Controlled Trials (CENTRAL)
4. Six-monthly searches of a number of grey literature sources: ISI Web of Knowledge Conference Proceedings; Index to Theses; Australasian Digital Theses

To view a list of all sources searched for ALOIS see About ALOIS on the ALOIS website (www.medicine.ox.ac.uk/alois).

Details of the search strategies used for the retrieval of reports of trials from the healthcare databases, CENTRAL and conference proceedings can be viewed in the 'methods used in reviews' section within the editorial information about the Dementia and Cognitive Improvement Group.

Additional searches were performed in many of the sources listed above to cover the timeframe from the last searches performed for ALOIS to ensure that the search for the review was as up-to-date and as comprehensive as possible. The search strategies used can be seen in Appendix 1.

Searching other resources

On 25 February 2011 one author (ES) contacted the following omega-3 PUFA supplement manufacturers to request unpublished data or information on any relevant research.

- Ocean Nutrition, Aalesund, Norway.
- Martek, Maryland, USA.
- Seven Seas, London, UK.
- Nordic Naturals, California, USA
- DSM, Basel, Switzerland.
- Pronova, Lysaker, Norway.

We received replies from DSM and Pronova which both provided published and unpublished information, none of which was relevant for inclusion in the review. Seven Seas reported that they have not conducted any research with their products on this topic (Seven Seas correspondence). Pronova reported that they have not conducted any research to examine the effects of their product Omacor on dementia (Pronova correspondence).

In March 2011 two review authors (AD and W-S L) contacted experts in nutrition research to obtain unpublished data and information about ongoing studies, and through this method we received information about the Geleijnse 2011 study.

Data collection and analysis

Selection of studies

Two review authors screened the search results: ES and W-S L through June 2010; AD and W-S L from June 2010 through June 2011; and ES and AD from June 2011 through April 2012. We then retrieved the full text of relevant records. For all potentially relevant studies, all three review authors independently compared the study design with the inclusion criteria for this review. AD and W-S L assessed the suitability of information provided from fish oil manufacturers for inclusion in the review; none was relevant. All authors agreed on the inclusion of the Geleijnse study. There were no disagreements related to the inclusion of studies. We then obtained the protocol for each included study.

Data extraction and management

One review author (ES) extracted the following information from each study.

- Report - author, year and source of publication.
- Study - study setting, sample characteristics.
- Patients - demographics, screening to exclude pre-existing cognitive impairment or dementia, absence of acute confusion or delirium at study onset, other concomitant medical conditions or medications that may affect cognition.
- Research design and features - sampling mechanism, treatment assignment mechanism, blinding, drop-out rates, length of follow-up, pertinent design features.

- Intervention - type, duration, dose, timing, mode of delivery.
- Outcome - number of patients randomised, outcome measure, estimate and standard error, adverse effects, adherence, measurement of omega-3 PUFA status.

This information was entered into Review Manager (RevMan) by ES; W-S L checked for accuracy. We contacted trial report authors for additional information or clarification. All report authors were helpful and provided unpublished data and answered our questions about the design of their study.

Assessment of risk of bias in included studies

We assessed the risk of bias in each included study according to the guidance of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011 Chapter 8.5-6). We assessed the following domains of trial quality.

- Sequence generation - adequate when the randomisation sequence protects against biased allocation to the comparison groups.
- Allocation concealment - adequate when measures are taken to ensure that recruitment according to the randomisation sequence is performed without knowledge of the participant's likely treatment group.
- Blinding (participants) - adequate when measures are taken to prevent the participants from knowing which intervention they received.
- Blinding (investigators) - adequate when the outcome assessor is unaware of the participant's allocation.
- Incomplete outcome data - adequate if study authors reported when and why participants left the study.
- Selective outcome reporting - adequate if a study protocol was available and all outcomes were reported in the study report.

On the basis of the above criteria, trials were given a quality rating of 'Low risk' (adequate), 'Unclear risk', or 'High risk' of bias for each domain. A description of the reason for our rating is given.

Measures of treatment effect

Where trials had comparable outcomes, mean differences (MDs) or standardised mean differences (SMDs), with 95% confidence intervals (CI), were calculated using a fixed-effect model. The difference between intervention groups at final follow-up was the effect measured (Higgins 2011 section 7.7.3.1). Safety and adherence were summarised narratively.

Unit of analysis issues

The participant was the unit of analysis.

Dealing with missing data

We contacted trial authors requesting missing information as needed and received replies to all our queries. The analyses were conducted on an intention-to-treat basis.

Assessment of heterogeneity

Clinical heterogeneity caused by differences in participant characteristics is likely to be minimal as included studies only randomised cognitively healthy older people. Heterogeneity would have been assessed separately within trials providing meals and trials providing nutritional supplements (we considered the margarine spread intervention in the Geleijnse study a nutritional supplement). Statistical heterogeneity was assessed using the Chi^2 and I^2 statistics according to the criteria in sections 9.5-6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Assessment of reporting biases

The study protocol was available for every trial, which enabled assessment of reporting bias.

Data synthesis

For outcomes presented in more than one trial, MDs or SMDs and 95% CIs were combined in a fixed-effect meta-analysis using the inverse variance method. The van de Rest study included two treatment groups (high dose and low dose) and for this study the shared group (placebo) was split into two to provide two reasonably independent comparisons (see *Cochrane Handbook for Systematic Reviews of Interventions* section 16.5.4). All analyses were conducted according to the principles of intention-to-treat.

Subgroup analysis and investigation of heterogeneity

No subgroups were explored due to inclusion of only three studies.

Sensitivity analysis

No sensitivity analysis was conducted as all included studies were of high methodological quality.

RESULTS

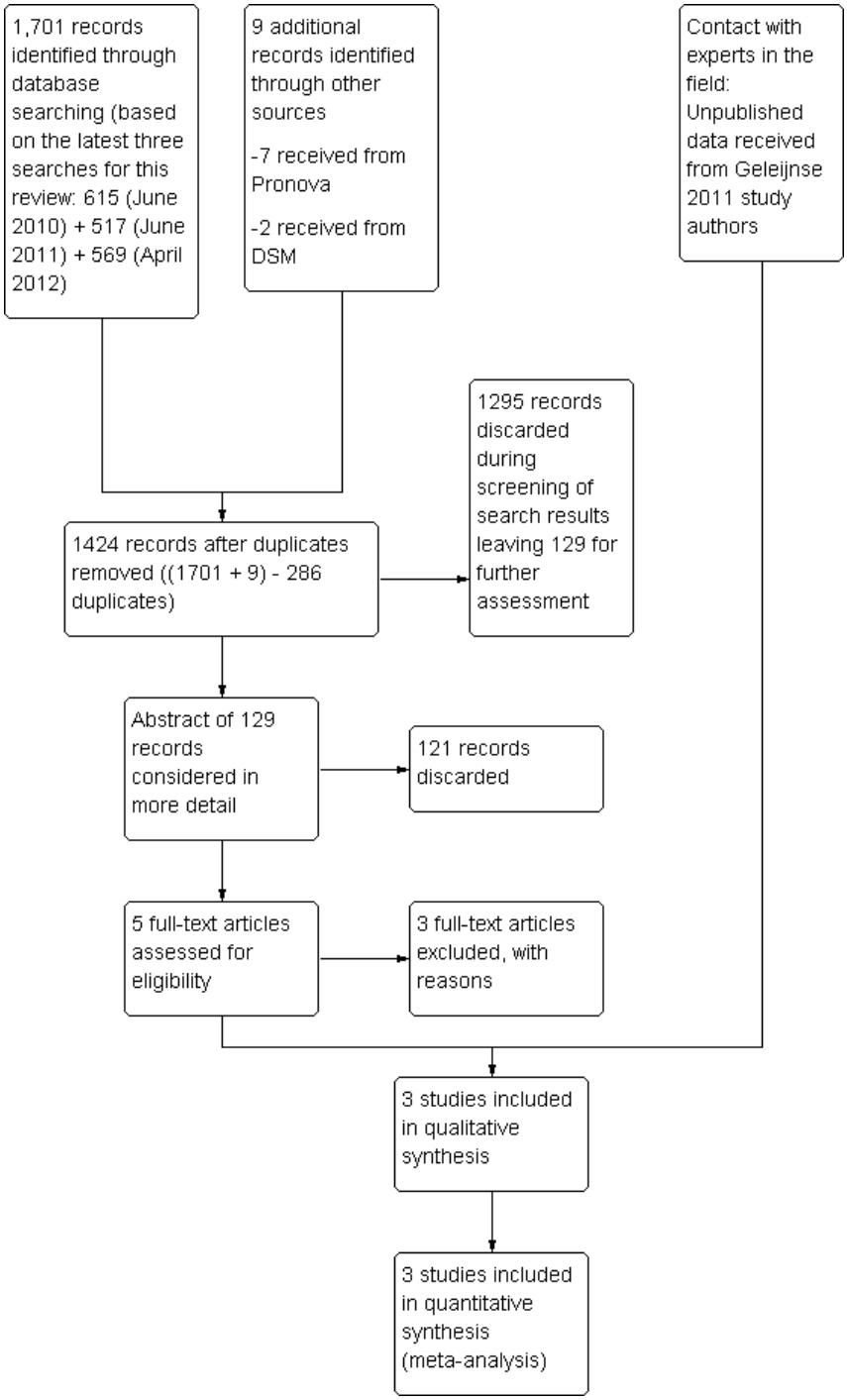
Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Results of the search

The electronic search to April 2012 retrieved a total of 1701 results. After de-duplication and first-assessment by Anna Noel-Storr, Trials Search Coordinator of the Cochrane Dementia and Cognitive Improvement Group, the review authors were left with 129 references to assess further. Following assessment by two authors, 124 references were discarded, five trial reports were retrieved in full-text for further assessment, two were included and three were excluded. Nine records were received from fish oil manufacturers but none were relevant. Contact with researchers in the field resulted in the inclusion of a further study. The study selection process is outlined in Figure 1.

Figure 1.



Included studies

In total, we included three studies in this review. The studies are described in the Characteristics of included studies table. Van de Rest 2008 is included as two independent comparisons (Van de Rest 2008 (High); Van de Rest 2008 (Mod)) (see Data synthesis above).

Information on cognitive function at the start of the study was available on 4080 participants randomised in three studies; cognitive function data were available on 3536 participants at final follow-up.

Van de Rest 2008 was a three-arm randomised placebo-controlled trial involving 302 participants. Male and female potential participants aged 65 + were mainly recruited from an existing database of volunteers with interest in participating in studies at Wageningen University, the Netherlands. Potential participants with a Mini Mental State Examination (MMSE) score of less than 21 out of 30 or depression, or reporting the current or recent consumption of fish oil supplements, the consumption of more than 800 mg EPA+DHA from fish, the consumption of four or more glasses of alcohol per day or the current use of antidepressants or medication for dementia were excluded. The intervention period was six months and the intervention consisted of six 900 mg soft gelatin capsules per day containing a total of 1940 mg omega-3 LC-PUFAs (1093 mg EPA + 847 mg DHA) in the high-dose arm, 400 mg omega-3 LC-PUFAs (226 mg EPA + 176 mg DHA) in the low-dose arm or high-oleic sunflower oil in the placebo arm. Capsules were identical in appearance and packed in foil strips containing the daily dose. Three hundred and two participants were randomised into the study and completed a series of nurse-led paper-and-pencil cognitive tests at baseline, and cognitive function outcome data are available on 299 participants at six months. The primary outcome was cognitive function at six months.

Dangour 2010 was a two-arm randomised placebo-controlled trial involving 867 participants. Male and female potential participants aged 70-79 were drawn from patient lists of 20 General Practices in England and Wales and were pre-screened using General Practice recorded information for diabetes, dementia and significant illness (at physician's discretion). Potential participants underwent a cognitive function screen (MMSE) at the recruitment appointment and those with an MMSE score of less than 24 out of 30 were excluded. Potential participants reporting the current daily use of fish oil supplements (typically rich in omega-3 LC-PUFAs) were excluded. The intervention period was 24 months and the intervention consisted of two 650 mg soft gelatin capsules per day containing a total of 700 mg marine-source omega-3 LC-PUFAs (200 mg EPA + 500 mg DHA) in the active arm, or omega-9 rich olive oil in the placebo arm. Capsules in the two arms were identical in appearance and packed in pots. Eight hundred and sixty-seven participants were randomised into the study and completed a series of nurse-led paper-and-pencil cognitive tests at baseline, and cognitive function outcome data are available on 744 participants at 24 months. The primary outcome was change in cognitive function at 24 months.

Geleijnse 2011 was a four-arm randomised placebo-controlled trial (incorporating a 2x2 factorial design) involving 2911 participants. People age 60-80 who scored > 21 points on the MMSE were eligible to take part in the trial. Cognitive impairment at baseline was defined as a MMSE score of < 24 at baseline or use of antidementia drugs. Participants were provided with margarine containing either 400 mg of EPA-DHA (3:2 ratio), 2 g of ALA, the EPA-DHA and ALA combined, or placebo margarine for 40 months. (This was a study of people who had a clinically diagnosed myocardial infarction (heart attack) up to 10 years before the start of the study, and the primary outcome was mortality from a subsequent heart attack during the study period. Study recruitment was through cardiologists. 4,837 participants took part in the primary study and 2911 in the omega-3 sub-study; the unpublished data used in this review include 2493 participants who did not have cognitive impairment or use antidementia drugs at baseline, and who also had baseline and final MMSE scores.)

The randomisation and follow-up of participants were as follows:

Study	Dangour 2010	Geleijnse 2011	Van de Rest 2008 (High)
Total number of participants randomised	867	2911	302
Number of participants with cognitive function data at baseline	866	2493*	302
Randomisation group	I:433 C:433	I:1866 C:627	I-High:96 I-Mod:100 C:106

(*Continued*)

Number of participants with cognitive function data at final follow-up	744	2493	299
Randomisation group	I:375 C:369	I:1866 C:627	I-High:96 I-Mod:100 C:103

Intervention Group: I
Control Group: C
*the unpublished data provided by the authors in additional Table 1 below was for participants with cognitive function data at baseline and final follow-up.

Excluded studies

Three studies were excluded, and the reasons are given in the Characteristics of excluded studies table.

Risk of bias in included studies

Random sequence generation (selection bias)

There was adequate generation of the randomisation sequence in all three trials.

Allocation

Concealment of participant allocation according to the randomisation sequence was adequate in all three trials.

Blinding

All three trials adequately blinded participants and outcome assessors to treatment allocation.

Incomplete outcome data

Outcome reporting was adequate in all three trials and loss to follow-up rates were low.

Selective reporting

All the trials reported the outcomes stated in their protocols.

Other potential sources of bias

It is possible there was a healthy participant bias in the Van de Rest 2008 study as participants were primarily recruited from a register of people interested in taking part in research.
An overall assessment of the risk of bias can be found in Figure 2 and Figure 3.

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies. Please note there are three studies included in the review.

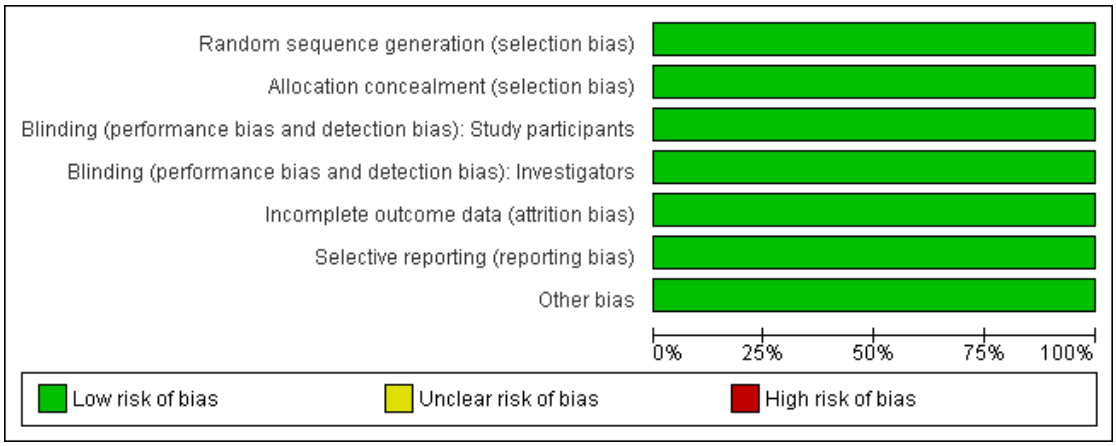
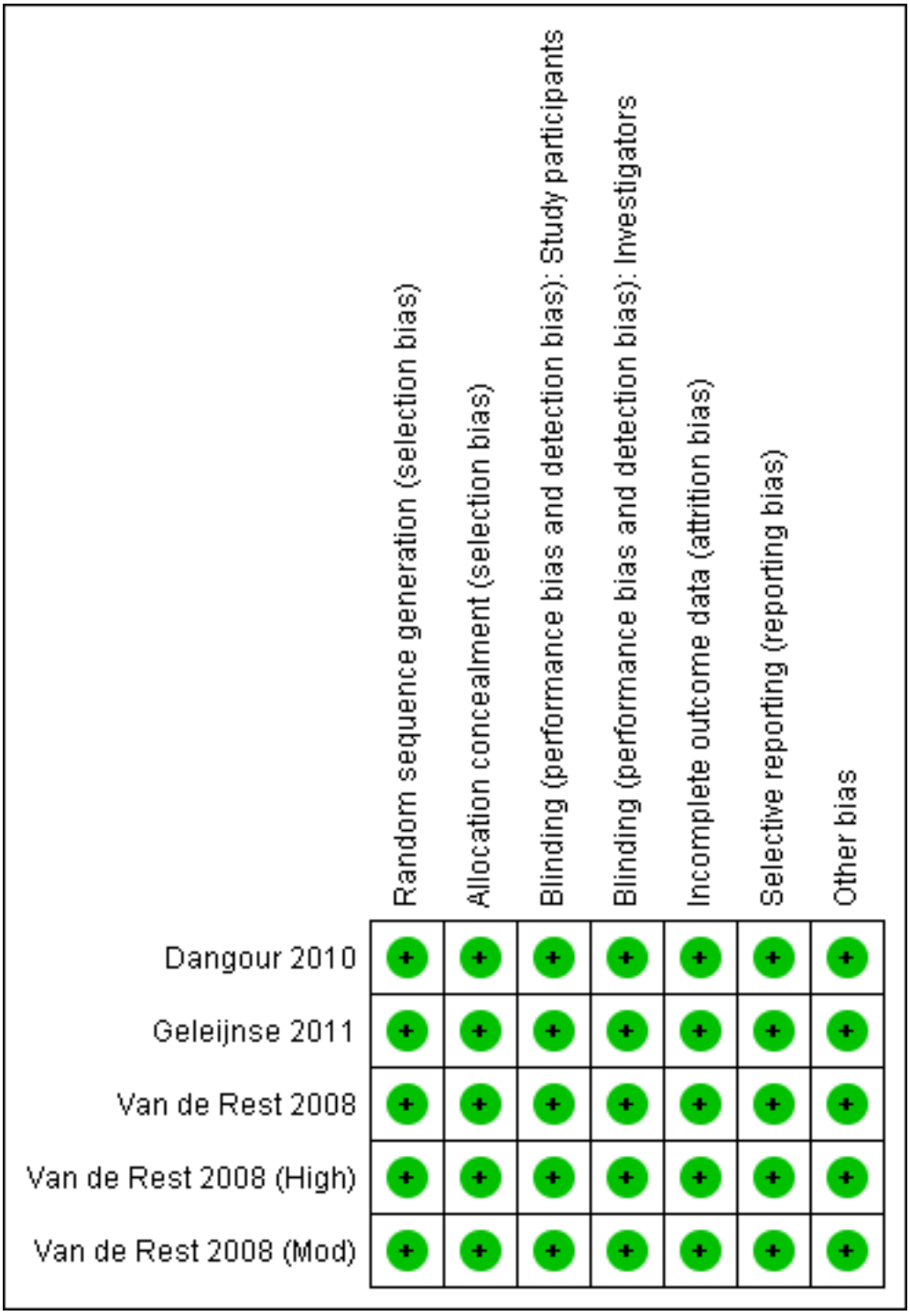


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study. Please note there are three studies included in the review.



Effects of interventions

Primary outcome

None of the three included trials assessed the primary outcome of this review i.e. omega-3 fatty acids for the primary prevention of dementia.

Secondary outcomes

All three trials investigated the effect of omega-3 fatty acid supplementation on measures of cognitive function and provided information on safety and adherence.

Cognitive function

In the Dangour 2010 and Van de Rest 2008 studies, participants were asked to complete a series of cognitive function tests at baseline and final follow-up that assessed different cognitive domains (i.e. memory, executive function, processing speed). In the Geleijnse 2011 study, participants completed the MMSE at baseline and final follow-up.

Participants in both the intervention and control groups experienced little or no cognitive decline during the studies. Van de Rest 2008 found no effect of low or high dose omega-3 PUFA supplementation on the primary cognitive function outcome (five listed: Word Learning Test (used to power study), Wechsler Digit Span Test (forward and backward), Trail Making Test, The Stroop Test, and Fluency). Dangour 2010 found no effect of omega-3 PUFA supplementation on the primary cognitive function outcome (California Verbal Learning Test - a test of memory) or any of the specified secondary cognitive function outcomes (z-scores of multiple tests combined by cognitive domain). Geleijnse 2011 found no effect of omega-3 PUFA supplementation on the MMSE.

There was sufficient similarity in the cognitive function tests used in the trials to allow the results of the following tests to be directly compared.

Mini-mental state examination

Participants in two studies (Dangour 2010 and Geleijnse 2011) completed the MMSE (Folstein 1975) at baseline and final follow-up. In the Dangour 2010 study, follow-up was after 24 months of intervention, and final follow-up in the Geleijnse 2011 study was after 40 months of intervention. Unpublished data (Table 1) for the Geleijnse 2011 study were provided by the authors to enable this analysis.

Two studies involving 3221 participants tested MMSE score; mean difference (MD) -0.07 (95% confidence interval (CI) -0.25 to 0.10) with evidence of moderate heterogeneity. Analysis 1.1

Word learning

Tests of memory assess the ability of participants to recall immediately (immediate recall) or after a short delay (delayed recall) a list of words read out to the participants, and to distinguish words from the list from various other words (word recognition). The word learning test used in the Van de Rest 2008 study was Van der Elst 2005, and the Dangour 2010 study used the California Verbal Learning Test (Delis 1987).

Two studies involving 1043 participants tested immediate recall of a list of words; standardised mean difference (SMD) 0.01 (95% CI -0.11 to 0.14) with no evidence of heterogeneity. Analysis 2.1

Two studies involving 1043 participants tested delayed recall of a list of words; SMD -0.04 (95% CI -0.16 to 0.09) with no evidence of heterogeneity. Analysis 2.2

Two studies involving 1042 participants tested word recognition of a list of words; SMD 0.04 (95% CI -0.08 to 0.16) with no evidence of heterogeneity. Analysis 2.3

Verbal fluency

Tests of executive function assess the ability of participants to call out as many animal names as possible. The Dangour 2010 study used the method described in Goodglass 1983 (name as many animals as possible in one minute), and the Van de Rest 2008 study used the method described in Van der Elst 2006 (name as many animals as possible which begin with the letter 'p' in two minutes).

Two studies involving 1042 participants tested verbal fluency; SMD 0.06 (95% CI -0.06 to 0.18) with no evidence of heterogeneity. Analysis 3.1

Digit spans

Tests of executive function assess the ability of participants to repeat either forwards or backwards chains of numbers of increasing length read out by the test administrator. Both the Van de Rest 2008 and Dangour 2010 studies used the digit span test from the Wechsler adult intelligence scale (Wechsler 1981).

Two studies involving 1018 participants tested digit span forwards; MD 0.03 (-0.25 to 0.31) with no evidence of heterogeneity. Analysis 4.1

Two studies involving 1015 participants tested digit span backwards; MD 0.12 (-0.12 to 0.36) with evidence of moderate heterogeneity. Analysis 4.2

Safety of omega-3 supplementation

Participants in the Van de Rest 2008 study recorded side-effects in their patient diary, and could report side-effects to the study nurse

at each three-monthly visit. Gastrointestinal problems were the most commonly reported side-effect; others included restlessness, weight gain, feeling lifeless, blurred vision, sore throat, muscle pain, skin irritation and poly-urination (p.433). The proportion of participants reporting side-effects was balanced between the intervention groups (14% in the high-dose fish oil group, 13% in the low-dose fish oil group, and 15% in the control group).

Participants in the Dangour 2010 study were given the opportunity to discuss any side-effects thought to be due to the intervention at their visit with the study nurse every three months (p.6 study protocol). There were no differences in reported side-effects between study groups; symptoms included flatulence, belching, abdominal discomfort, loose stools and 'other' (p.3 study report). About 9% of participants in the fish oil arm, and 10% in the placebo arm reported one or more side-effects.

Participants in the Geleijnse 2011 study recorded symptoms of side-effects in their patient diary, and reported symptoms during the annual nurse-led telephone interview and at the comprehensive examination at the end of the trial (p.46 of study protocol). About 1% of participants reported experiencing gastrointestinal problems, and there were no differences between the study groups. (Kromhout 2010; Table 3 of supplementary web appendix.)

Adherence to supplementation

Information on adherence to supplementation relates to 3536 participants who completed the studies.

Participants in the Van de Rest 2008 study received capsules every three months, and returned unconsumed capsules monthly. Participants also recorded missed capsules in their study diary. Average adherence was 99% based on the number of returned capsules, and only three participants consumed fewer than 80% of their capsules (p.432). All participants provided blood samples at baseline and six months, and analysis demonstrated an increase in plasma EPA-DHA in participants in the intervention arms.

Every three months participants in the Dangour 2010 study met with a study nurse, and were asked to bring their study capsule container with them. New capsules were provided to participants at each visit, and the study nurse later counted the number of returned capsules as a measure of compliance. There was no difference between study groups in the number of capsules returned (p.3), and adherence was high as approximately 95% of the capsules given to participants over the course of the study were not returned. A sub-sample of 235 participants provided blood samples at 24 months (study final follow-up), and analysis demonstrated an increase in EPA and DHA in participants in the intervention arm, and higher concentrations of constituents of olive oil (n-9 oleic acid) in the placebo arm.

Adherence in the Geleijnse 2011 study was measured by collecting any unused trial margarine during delivery of the next fresh batch, self-report during the annual nurse-led telephone interview, self-report in the participant's study diary (p.45-6 of study protocol). Overall, 91% of participants consumed the trial margarine more than 80% of the time during the 40-month study period. A random sample of 800 participants provided blood samples at baseline, 1.5 and three years of follow-up, and analysis demonstrated increases in alpha-linolenic acid and in EPA and DHA in the corresponding study arms.

DISCUSSION

Summary of main results

Three studies involving a total of 3536 participants are included in this review. None of the studies examined the effect of omega-3 PUFA on incident dementia. Omega-3 PUFAs were shown to provide no benefit to cognitive function among cognitively healthy older people who took a variety of cognitive tests at baseline and final follow-up, including the Mini-Mental State Examination and tests of memory and executive function.

Overall completeness and applicability of evidence

There is no evidence from randomised controlled trials on the effect of omega-3 PUFA on incident dementia. All of the analyses of the effect of omega-3 PUFA supplementation on cognitive function showed no benefit. Participants in both the intervention and control groups experienced little or no cognitive decline during the studies. The main side-effect of omega-3 PUFA supplementation was mild gastrointestinal problems, but symptoms were reported by a minority of participants in all three studies. Adherence to the intervention was high in all three studies.

Further studies of longer duration are required. Longer-term studies may identify greater change in cognitive function in study participants which may enhance the ability to detect the possible effects of omega-3 PUFA supplementation in preventing cognitive decline in older people.

Quality of the evidence

All three studies included in this review were of high methodological quality. The studies involved 3536 participants and the duration of the intervention period had to be over six months long (duration was six, 24 and 40 months respectively). Where the same or similar cognitive tests were used to assess outcomes across the studies, no benefit for omega-3 PUFA was observed.

Potential biases in the review process

Every effort was made to conduct this review to the highest standards recommended in the *Cochrane Handbook for Systematic Reviews of Interventions*, and The Cochrane Collaboration's Methodological Expectations of Cochrane Intervention Reviews criteria.

Agreements and disagreements with other studies or reviews

A comprehensive systematic review by MacLean 2005 identified no randomised controlled trials of cognitively healthy participants at baseline.

AUTHORS' CONCLUSIONS

Implications for practice

The findings of three high-quality randomised controlled trials involving 3536 participants show that there is no benefit to cognitive function from omega-3 PUFA supplementation in cognitively healthy people over 60 years of age. Omega-3 PUFA may have other health benefits. Consumption of two portions of fish per week (of which, one should be oily) is recommended as part of a healthy diet (SACN 2004).

Implications for research

There may be benefit in conducting future long-term trials among populations with low dietary intakes of omega-3 PUFA.

Studies of longer duration are required to determine whether omega-3 PUFA supplementation delays cognitive decline in older people.

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See See Van de Rest 2008.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Dangour 2010

Methods	Double-blind, placebo-controlled, randomised controlled trial
Participants	Cognitively healthy people age 70-79.
Interventions	• Intervention: 500 mg DHA + 200 mg EPA in two soft gel capsules. • Control: olive oil in two soft gel capsules. The duration of the intervention was 24 months.
Outcomes	• Primary: 'Change in cognitive function at 24 months; determined by the California Verbal Learning Test.' p.4 of protocol (consistent in study report, p.2). • Secondary: 'Cognitive performance as measured by immediate and delayed recall of a short story, tests of prospective memory, timed letter search/cancellation task, verbal fluency, digit span forwards and backwards, symbol digit modalities test, simple and choice reaction time, and spatial memory.' p.4 of protocol (consistent in study report, p.2).
Notes	The study also measured retinal function, the results of which are to be reported elsewhere Study registration number on www.clinicaltrials.com: ISRCTN 72331636 The DHA and EPA used was of marine origin.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	'Randomization was minimized by age group (70-74 and 75-79 y) and general practice to ensure a balance across trial arms.' p.2 'Research nurses telephoned a central computerized randomization service to obtain treatment-allocation codes previously generated by the trial statistician.' p.2
Allocation concealment (selection bias)	Low risk	'Research nurses telephoned a central computerized randomization service to obtain treatment-allocation codes previously generated by the trial statistician.' p.2
Blinding (performance bias and detection bias) Study participants	Low risk	'Supplements were packaged into identical pots, each containing 180 capsules, and labelled by staff who were not involved in the study.' p.2

Dangour 2010 (*Continued*)

Blinding (performance bias and detection bias) Investigators	Low risk	'Supplements were packaged into identical pots, each containing 180 capsules, and labelled by staff who were not involved in the study.' p.2 'All project staff were unaware of group assignments until the completion of the trial and after data analysis.' p.2
Incomplete outcome data (attrition bias) All outcomes	Low risk	'There were no preset criteria for participant withdrawal during the trial. Participants who wished only to discontinue supplementation were invited to an interview at 24 months.' p.3 The reasons people withdrew from the study are presented in Figure 1, and are balanced between arms. Outcome data was available for 375/276 participants in the intervention arm, and 369/372 in the placebo arm
Selective reporting (reporting bias)	Low risk	The study protocol is available. The primary and secondary outcomes are reported in full
Other bias	Low risk	No major sources of bias in the study design.

Geleijnse 2011

Methods	Double-blind, placebo-controlled, randomised controlled trial
Participants	Cognitively healthy people age 60-80 years.
Interventions	Using a 2 x 2 factorial design, participants were randomised to a dietary intervention of margarine containing: • 400 mg/d EPA-DHA; • 2 g/d ALA; • both EPA and ALA; • placebo. The duration of the intervention was 40 months.
Outcomes	• Global cognitive function assessed through the mini-mental state examination • Incident dementia • Others such as: mortality from coronary heart disease (primary outcome of study)
Notes	Study website: www.alphaomegatrial.com (Accessed 29 October 2011) Study registration number on www.clinicaltrials.gov: NCT00127452 The DHA and EPA used was of marine origin.

Geleijnse 2011 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	'Patients were randomly assigned to daily intake of approximately 20g of trial margarines ...' p.3 Study protocol: Section D7, page 49: 'Simple randomisation is applied, using a randomization table (with a randomization ratio of 1:1:1:1). The table was produced on the computer by a random-number generator before the start of the trial, with numbers running from 1001 through 9999.'
Allocation concealment (selection bias)	Low risk	Study protocol: Section D7, page 49: 'Treatment codes (A,B,C,D) are assigned by Unilever to four types of trial margarine and are not known to others involved in the trial. A table linking randomization numbers to treatment codes is stored in a safe, which is only accessible by a third person who is not involved in the Alpha Omega Trial.'
Blinding (performance bias and detection bias) Study participants	Low risk	'The four different types of trial margarine were identical in taste, odor, texture, and color.' p.3 'Blinding was successful, as 75% of the patients could not tell which margarine they had used and the remaining patients were unable to perform better than chance.' p.6
Blinding (performance bias and detection bias) Investigators	Low risk	'Data were analyzed before deblinding of treatment codes by an independent statistician who used a predefined data analysis plan.' p.5
Incomplete outcome data (attrition bias) All outcomes	Low risk	'Blinding was maintained throughout the study and compliance was excellent, as reflected in substantial increases in plasma EPA, DHA, and ALA in active treatment arms. No patients were lost to follow-up, and treatment with n-3 fatty acids had no significant side effects.' p.8
Selective reporting (reporting bias)	Low risk	The study protocol is available on the study website: www.alphaomegatrial.com

Geleijnse 2011 (*Continued*)

		(Accessed 29 October 2011), and there is no indication of selective outcome reporting. This review uses data which were neither primary nor secondary outcomes of the study but were published (Geleijnse 2011). The authors provided additional data to us upon request in October 2011 to enable a meta-analysis
Other bias	Low risk	No major sources of bias in the study design.

Van de Rest 2008

Methods	Double-blind, placebo-controlled, randomised controlled trial
Participants	People age 65 and over.
Interventions	• Intervention 1: 400 mg EPA/DHA in soft gel capsules (Van de Rest 2008 (Mod). • Intervention 2: 1800 mg EPA/DHA in soft gel capsules (Van de Rest 2008 (High). • Placebo: sunflower oil in soft gel capsules. The duration of the intervention was 26 weeks.
Outcomes	• Primary: ○ Cognitive function (measured at baseline and at 3 and 6 months through the Word Learning Test, the Wechsler Digit Span Task (forward and backward), the Trail Making Test (version A and B), the Stroop Test, and Fluency (recall of animals in 2 minutes)). ○ Depression (measured at baseline and at 3 and 6 months through the Center for Epidemiologic Studies Depression Scale, the Montgomery-Asberg Depression Rating Scale, the Geriatric Depression Scale, and the Hospital Anxiety and Depression Scale (subscale version A)). • Secondary: ○ Quality of life (measured at baseline and at 6 months through the WHOQOL-BREF questionnaire). ○ Blood samples were taken to assess: APOE-ϵ4, CRP, cholesterol, triglycerides, haematology.
Notes	The outcomes are reported in three publications. Study registration number on www.clinicaltrials.gov: NCT00124852. The DHA and EPA used was of marine origin.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Van de Rest 2008 (*Continued*)

Random sequence generation (selection bias)	Low risk	'An independent person randomized subjects by means of computer-generated random numbers in stratified permuted blocks of six. Stratification factors included age (< and ≥69 y), sex, MMSE (< and ≥ 28), and CES-D screening test score (< and ≥ 5). Individuals were randomly allocated to receive a daily dose of fish oil containing either approximately 400 mg or approximately 1800 mg of EPA-DHA, or a placebo oil (high-oleic sunflower oil) for 26 weeks. ' p.431
Allocation concealment (selection bias)	Low risk	'An independent person randomized subjects by means of computer-generated random numbers in stratified permuted blocks of six. ...Staff members and participants were blinded toward treatment allocation until completion of blind data analysis.' p. 431
Blinding (performance bias and detection bias) Study participants	Low risk	'Capsules with fish oil or placebo oil were indistinguishable in appearance.' p.431
Blinding (performance bias and detection bias) Investigators	Low risk	'Staff members and participants were blinded toward treatment allocation until completion of blind data analysis.' p.431
Incomplete outcome data (attrition bias) All outcomes	Low risk	The reasons some participants withdrew from the study are described (p.432 and p.436). There was minimal loss to follow-up; 299/302 participants provided outcome data. p.432
Selective reporting (reporting bias)	Low risk	The study protocol is available. The outcomes are reported in full, but in three separate publications
Other bias	Low risk	'Subjects age > 65 years were mainly recruited through an existing database of volunteers with interest in participating in studies at Wageningen University.' p.431 It is possible there was a 'healthy participant' bias among people included in the study, see page 9 of the protocol for further details on recruitment There were no other major sources of bias

		in the study design

Van de Rest 2008 (High)

Methods	See Van de Rest 2008
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	See Van de Rest 2008.
Allocation concealment (selection bias)	Low risk	-
Blinding (performance bias and detection bias) Study participants	Low risk	-
Blinding (performance bias and detection bias) Investigators	Low risk	-
Incomplete outcome data (attrition bias) All outcomes	Low risk	-
Selective reporting (reporting bias)	Low risk	-
Other bias	Low risk	-

Van de Rest 2008 (Mod)

Methods	See Van de Rest 2008.
Participants	
Interventions	
Outcomes	

Van de Rest 2008 (Mod) (*Continued*)

Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	See Van de Rest 2008.
Allocation concealment (selection bias)	Low risk	-
Blinding (performance bias and detection bias) Study participants	Low risk	-
Blinding (performance bias and detection bias) Investigators	Low risk	-
Incomplete outcome data (attrition bias) All outcomes	Low risk	-
Selective reporting (reporting bias)	Low risk	-
Other bias	Low risk	-

ALA: alpha linolenic acid
APOE-ϵ4: apolipoprotein E
CRP: C-reactive protein
DHA: docosahexaenoic acid
EPA: eicosapentaenoic acid

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Johnson 2008	The study was only for 4 months, without longer follow-up. Cognitive testing was done at the beginning of the study, but people with mild/any cognitive impairment (if there were any cases) were not excluded
Svetkey 1999	Follow-up was for less than 26 weeks. Participants were older than 22 years, but we are not able to extract data on those over 60 years from the report

(*Continued*)

Yurko-Mauro 2010	The participants were aged 55 or over. Although the authors report the participants were stratified into two groups, ≥55 to 69 and over 70, data on the over 70 group are not presented separately in the report. No useable information is provided in this report. The participants had diagnosed age-related cognitive decline, so are ineligible for inclusion in this review

Characteristics of ongoing studies *[ordered by study ID]*

Aiken 2010

Trial name or title	In older adults (60+ years) at risk for depression, can sertraline and/or omega-3 fatty acids compared with a placebo, reduce or prevent depressive symptoms, incidence of new cases of depression and/or cognitive decline
Methods	Double-blind, placebo-controlled, randomised controlled trial
Participants	Participants must have participated in the first phase of the 'Beyond Ageing Project' run by the Centre for Mental Health Research at the Australian National University and have completed the 24-month follow-up/ baseline survey; and have had a score greater than 15 on the K10 depression questionnaire. Participants must be age 60 or over
Interventions	One daily oral dose of: Intervention: Four omega-3 fatty acid capsules (2g in total: Eicosapentaenoic acid (EPA) 1200 mg + Docosahexaenoic acid (DHA) 800 mg). Placebo A: One placebo tablet (cellulose - microcrystalline). Placebo B: One sertraline 25 mg tablet and four placebo capsules (paraffin oil)
Outcomes	Primary: • Prevention of depressive symptoms over 12 months, measured by total Kessler-10 (K10), Primary Care Evaluation of Mental Disorders Patient Health Questionnaire-9 item (PHQ-9) and Mini International Neuropsychiatric Interview (MINI). Secondary: • Cognitive decline as measured by performance on the Telephone Interview Cognitive Status - Modified (TICS-M). • Neuropsychological performance on processing speed (CANTAB reaction time, Trailmaking Test, Part A), memory (CANTAB paired associate learning, Wheschler Memory Scale - Third Edition (WMS-III) Logical Memory) and Executive Functioning (Trailmaking Part B, Verbal Fluency). • Premorbid Intelligence Quotient (IQ) estimates (Wechsler Test of Adult Reading). • Scores on the Mini-Mental State Examination (MMSE). • various others.
Starting date	1/03/10
Contact information	Alexandra Aiken Beyond Ageing Project Brain & Mind Research Institute Room 312, Building F 94 Mallet Street Camperdown, NSW 2050 Australia

Aiken 2010 (*Continued*)

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Notes	http://www.anzctr.org.au/ACTRN12610000032055.aspx

Danthiir 2007

Trial name or title	Older People, Omega-3, and Cognitive Health (EPOCH). (An 18 month study investigating the effects of long chain omega-3 polyunsaturated fatty acids supplementation on cognition and wellbeing in older people.)
Methods	Double-blind, placebo-controlled, randomised controlled trial
Participants	People between 65 and 90 years of age.
Interventions	Participants will consume two capsules in the morning and two in the evening, for 18 months, of either: • Intervention: Long chain omega-3 polyunsaturated fatty acids (450 mg DHA; 135 mg EPA). • Placebo: Olive oil capsules.
Outcomes	Primary: • Rate of cognitive decline • Change in well being measures Secondary: • Plasma fatty acid changes • Blood pressure • Oxidative stress • Inflammation
Starting date	1/08/2007
Contact information	Dr. Vanessa Danthiir CSIRO Human Nutrition PO Box 10041 (Gate 13 Kintore Avenue) Adelaide BC SA 5000 Australia +61 8 8305 0605 +61 8 83038899 vanessa.danthiir@csiro.au
Notes	Published protocol: Danthiir 2007. http://www.anzctr.org.au/ACTRN12607000278437.aspx

Vellas 2008

Trial name or title	Omega-3 Fatty Acids and/or Multi-domain Intervention in the Prevention of Age-related Cognitive Decline (MAPT)
Methods	Double-blind, placebo-controlled, randomised controlled trial

Vellas 2008 (*Continued*)

Participants	People age 70 and over.
Interventions	Participants are randomised to one of three interventions or the placebo. Interventions: 1. Omega-3 group: 800 mg/day of docosahexaenoic acid (V0137CA nutritional supplement). 2. Omega-3 + multi-domain intervention group: 800 mg/day of docosahexaenoic acid (V0137CA) + multi-domain intervention. 3. Placebo + multi-domain intervention group: omega-3 placebo not described + multi-domain intervention. Placebo: 1. Placebo omega-3 only: omega-3 placebo not described. Note: The multi-domain intervention includes training/information sessions in the following areas: nutrition, physical activity, cognitive training and social activities, and preventive consultations
Outcomes	Primary: • Changes in memory function scores at 36 months determined by Gröber & Buscke test. (Time Frame: Baseline, 6, 12, 24, 36 months.) Secondary: • Changes in other cognitive functions, and in functional capacities. To study the long-term safety and tolerability of V0137 CA treatment. To study compliance and adhesion to the "multi-domain" intervention program. (Time Frame: Baseline, 6, 12, 24, 36 months.)
Starting date	May 2008
Contact information	Dr. Bruno Vellas +33 5 61 77 76 49 ext 33 vellas.b@chu-toulouse.fr Dr. Sandrine Andrieu +33 5 51 14 59 32 ext 33 andrieu.s@chu-toulouse.fr
Notes	http://clinicaltrials.gov/ct2/show/NCT00672685

DHA: docosahexaenoic acid
EPA: eicosapentaenoic acid

DATA AND ANALYSES

Comparison 1. Mini-Mental State Examination Score

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 MMSE score	2	3221	Mean Difference (IV, Fixed, 95% CI)	-0.07 [-0.25, 0.10]

Comparison 2. Memory - Word learning test

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Immediate recall	3	1043	Std. Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.11, 0.14]
2 Delayed Recall	3	1043	Std. Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.16, 0.09]
3 Word Recognition	3	1042	Std. Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.08, 0.16]

Comparison 3. Verbal fluency test

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of animals named	3	1042	Std. Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.06, 0.18]

Comparison 4. Executive Function

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Digit Span Forward	3	1018	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.25, 0.31]
2 Digit Span Backward	3	1015	Mean Difference (IV, Fixed, 95% CI)	0.12 [-0.12, 0.36]

Analysis 1.1. Comparison 1 Mini-Mental State Examination Score, Outcome 1 MMSE score.

Review: Omega 3 fatty acid for the prevention of cognitive decline and dementia

Comparison: 1 Mini-Mental State Examination Score

Outcome: 1 MMSE score

Study or subgroup	Control N	Mean(SD)	Omega-3 N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Dangour 2010	363	28.3 (2.2)	365	28.2 (1.8)		35.3 %	0.10 [-0.19, 0.39]
Geleijnse 2011	627	27.56 (2.45)	1866	27.73 (2.17)		64.7 %	-0.17 [-0.39, 0.05]
Total (95% CI)	**990**		**2231**			**100.0 %**	**-0.07 [-0.25, 0.10]**

Heterogeneity: $Chi^2 = 2.12$, df = 1 (P = 0.14); I^2 =53%

Test for overall effect: Z = 0.85 (P = 0.40)

Test for subgroup differences: Not applicable

Analysis 2.1. Comparison 2 Memory - Word learning test, Outcome 1 Immediate recall.

Review: Omega 3 fatty acid for the prevention of cognitive decline and dementia

Comparison: 2 Memory - Word learning test

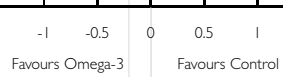
Outcome: 1 Immediate recall

Study or subgroup	Control N	Mean(SD)	Omega-3 N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
Dangour 2010	369	24.4 (6.4)	375	24.1 (6.7)		73.4 %	0.05 [-0.10, 0.19]
Van de Rest 2008 (High)	51	44.8 (9.4)	96	44.9 (9.9)		13.1 %	-0.01 [-0.35, 0.33]
Van de Rest 2008 (Mod)	52	44.8 (9.4)	100	46.1 (10.1)		13.5 %	-0.13 [-0.47, 0.20]
Total (95% CI)	**472**		**571**			**100.0 %**	**0.01 [-0.11, 0.14]**

Heterogeneity: $Chi^2 = 0.93$, df = 2 (P = 0.63); I^2 =0.0%

Test for overall effect: Z = 0.23 (P = 0.82)

Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2 Memory - Word learning test, Outcome 2 Delayed Recall.

Review: Omega 3 fatty acid for the prevention of cognitive decline and dementia

Comparison: 2 Memory - Word learning test

Outcome: 2 Delayed Recall

Study or subgroup	Control N	Mean(SD)	Omega-3 N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
Dangour 2010	369	7.5 (3)	375	7.6 (3.2)		73.4 %	-0.03 [-0.18, 0.11]
Van de Rest 2008 (High)	51	9 (3.2)	96	9.1 (3.2)		13.1 %	-0.03 [-0.37, 0.31]
Van de Rest 2008 (Mod)	52	9 (3.2)	100	9.2 (3)		13.5 %	-0.06 [-0.40, 0.27]
Total (95% CI)	**472**		**571**			**100.0 %**	**-0.04 [-0.16, 0.09]**

Heterogeneity: Chi² = 0.03, df = 2 (P = 0.98); I² =0.0%

Test for overall effect: Z = 0.58 (P = 0.56)

Test for subgroup differences: Not applicable

Analysis 2.3. Comparison 2 Memory - Word learning test, Outcome 3 Word Recognition.

Review: Omega 3 fatty acid for the prevention of cognitive decline and dementia

Comparison: 2 Memory - Word learning test

Outcome: 3 Word Recognition

Study or subgroup	Control N	Mean(SD)	Omega-3 N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
Dangour 2010	369	37.8 (4)	374	37.6 (4.3)		73.4 %	0.05 [-0.10, 0.19]
Van de Rest 2008 (High)	51	28.6 (1.7)	96	28.4 (2.1)		13.1 %	0.10 [-0.24, 0.44]
Van de Rest 2008 (Mod)	52	28.6 (1.7)	100	28.7 (1.5)		13.5 %	-0.06 [-0.40, 0.27]
Total (95% CI)	**472**		**570**			**100.0 %**	**0.04 [-0.08, 0.16]**

Heterogeneity: Chi² = 0.50, df = 2 (P = 0.78); I² =0.0%

Test for overall effect: Z = 0.64 (P = 0.52)

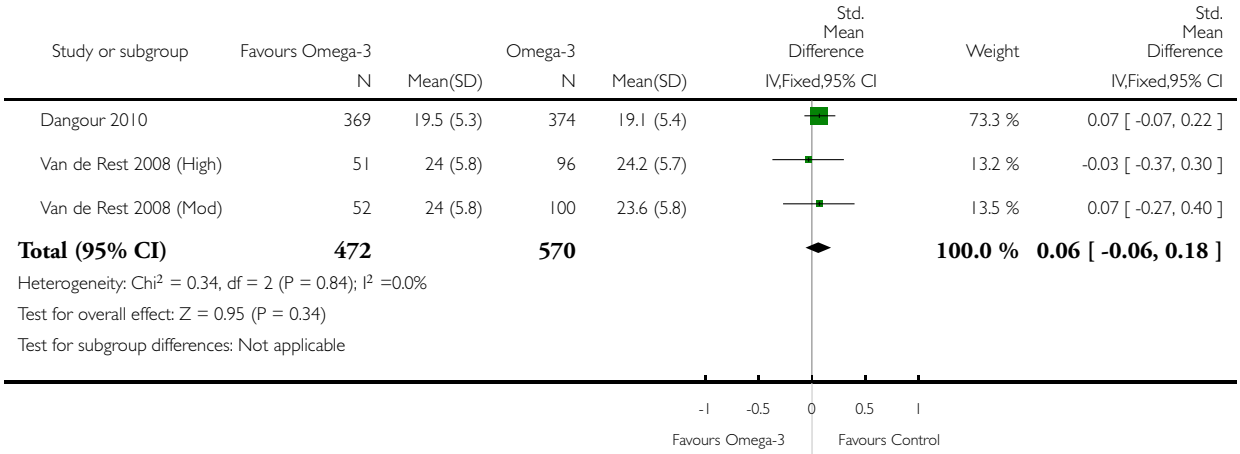
Test for subgroup differences: Not applicable

Analysis 3.1. Comparison 3 Verbal fluency test, Outcome 1 Number of animals named.

Review: Omega 3 fatty acid for the prevention of cognitive decline and dementia

Comparison: 3 Verbal fluency test

Outcome: 1 Number of animals named

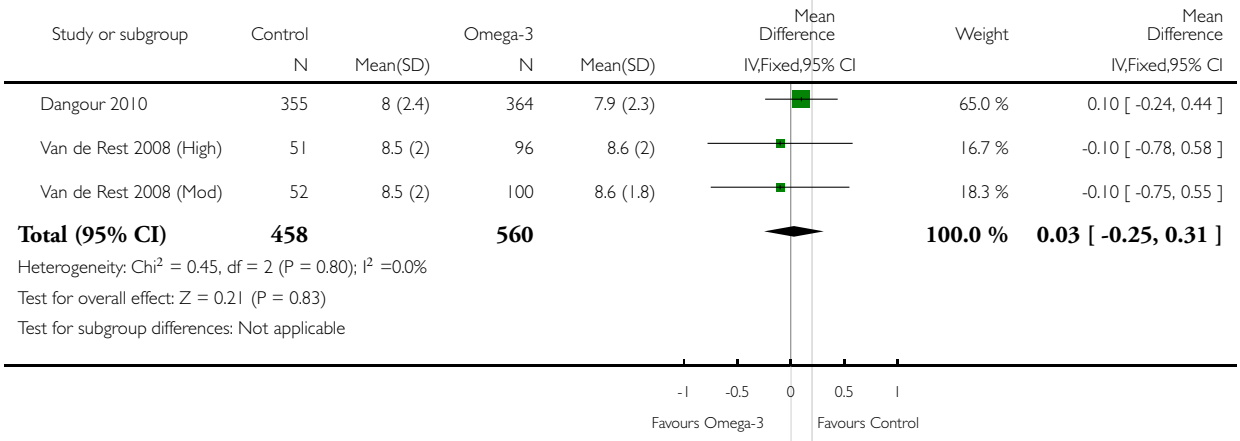


Analysis 4.1. Comparison 4 Executive Function, Outcome 1 Digit Span Forward.

Review: Omega 3 fatty acid for the prevention of cognitive decline and dementia

Comparison: 4 Executive Function

Outcome: 1 Digit Span Forward

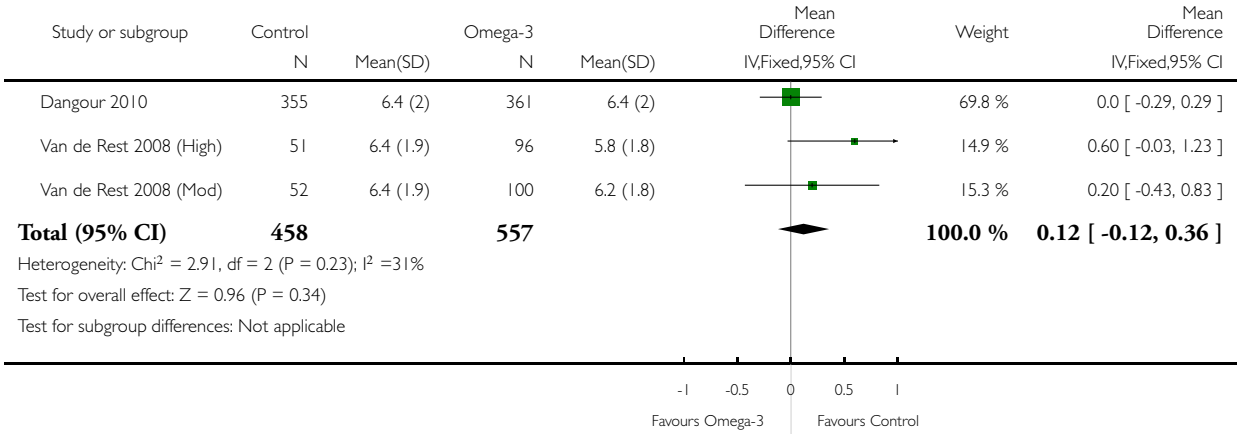


Analysis 4.2. Comparison 4 Executive Function, Outcome 2 Digit Span Backward.

Review: Omega 3 fatty acid for the prevention of cognitive decline and dementia

Comparison: 4 Executive Function

Outcome: 2 Digit Span Backward



ADDITIONAL TABLES

Table 1. Unpublished data from Geleijnse 2011 study

Baseline (only those with follow-up MMSE)			**Final follow-up (180.2 ± 5.3 weeks)**		
Control Group (N = 627)			Control Group (N = 627)		
Mean	SD	Range	Mean	SD	Range
28.32	1.54	24-30	27.56	2.45	12-30
EPA-DHA Group (N = 620)			EPA-DHA Group (N = 620)		
Mean	SD	Range	Mean	SD	Range
28.37	1.48	24-30	27.61	2.28	18-30
ALA Group (N = 638)			ALA Group (N = 638)		
Mean	SD	Range	Mean	SD	Range
28.42	1.37	24-30	27.72	2.20	14-30
EPA-DHA + ALA Group (N = 608)			EPA-DHA + ALA Group (N = 608)		

Table 1. Unpublished data from Geleijnse 2011 study (*Continued*)

Mean	SD	Range	Mean	SD	Range
28.42	1.39	24-30	28.42	1.39	24-30
Combined intervention groups (N = 1866)			Combined intervention groups (N= 1866)		
Mean	SD		Mean	SD	
28.40	1.41		27.73	2.17	

Participants with baseline and final follow-up MMSE scores, who did not have dementia, cognitive impairment or use anti-dementia drugs at baseline.

ALA: alpha linolenic acid
DHA: docosahexaenoic acid
EPA: eicosapentaenoic acid
MMSE: Mini Mental State Examination
SD: standard deviation

APPENDICES

Appendix 1. Search: June 2011

Source	Search strategy	Hits
ALOIS (www.medicine.ox.ac.uk/alois)	Keyword search: "omega 3" OR PUFA OR "fatty acids" OR "fatty acid" OR fish OR linseed OR eicosapentanoic OR docosa-hexanoic	June 2010:39 June 2011: 41
MEDLINE In-process and other non-indexed citations and MEDLINE 1950-present (Ovid SP)	1. exp *Fatty Acids, Omega-3/ 2. (omega-3 or "omega 3").mp. 3. "Polyunsaturated fatty acid*".mp. 4. PUFA.mp. 5. ("unsaturated fatty acid*" or "essential fatty acid*").mp 6. EFA.ti,ab. 7. Eicosapentaenoic Acid/	June 2010:73 June 2011: 36 April 2012: 24

(*Continued*)

	8. "eicosapentanoic acid".ti,ab. 9. (EPA or "ethyl-eicosapentanoic acid" or E-EPA).mp. 10. Docosahexaenoic Acids/ 11. "docosahexanoic acid*".ti,ab. 12. DHA.ti,ab. 13. ("docosapentanoic acid*" or DPA).ti,ab. 14. ("alpha-linolenic acid*" or ALA).ti,ab. 15. ("fish oil" or "n-3 fatty acid*" or "long chain fatty acids").mp 16. ("primrose oil" or "linseed oil" or "oily fish" or "flaxseed oil").mp 17. or/1-16 18. randomized controlled trial.pt. 19. controlled clinical trial.pt. 20. randomized.ab. 21. placebo.ab. 22. randomly.ab. 23. trial.ab. 24. groups.ab. 25. or/18-24 26. (animals not (humans and animals)).sh. 27. 25 not 26 28. 17 and 27 29. (2008* or 2009* or 2010* or 2011*).ed. 30. 28 and 29 31. (participant* adj2 (healthy or old* or elderly or aged or senior)).ti,ab 32. (adult adj2 (old* or elderly or aged or senior)).ti,ab. 33. "healthy persons".ti,ab. 34. (cognit* or "prevent* dementia*").mp. 35. or/31-34 36. 30 and 35	
EMBASE 1980-2010 week 25 (Ovid SP)	1. exp *omega 3 fatty acid/ 2. (omega-3 or "omega 3").mp. 3. "Polyunsaturated fatty acid*".mp. 4. PUFA.mp. 5. ("unsaturated fatty acid*" or "essential fatty acid*").mp 6. EFA.ti,ab. 7. icosapentaenoic acid/ 8. "eicosapentanoic acid".ti,ab. 9. (EPA or "ethyl-eicosapentanoic acid" or E-EPA).mp.	June 2010:98 June 2011: 127 April 2012: 133

(*Continued*)

	10. docosahexaenoic acid/ 11. "docosahexanoic acid*".ti,ab. 12. DHA.ti,ab. 13. ("docosapentanoic acid*" or DPA).ti, ab. 14. ("alpha-linolenic acid*" or ALA).ti,ab. 15. ("fish oil" or "n-3 fatty acid*" or "long chain fatty acids").mp 16. ("primrose oil" or "linseed oil" or "oily fish" or "flaxseed oil").mp 17. or/1-16 18. (adult adj2 (old* or elderly or aged or senior)).ti,ab. 19. (participant* adj2 (healthy or old* or elderly or aged or senior)).ti,ab 20. "healthy persons".ti,ab. 21. (cognit* or "prevent* dementia*").mp. 22. (cognit* or "prevent* dementia*" or "reduc* risk*").mp. 23. *primary prevention/ 24. or/18-23 25. 17 and 24 26. randomized controlled trial/ 27. controlled clinical trial/ 28. randomi?ed.ab. 29. placebo.ab. 30. randomly.ab. 31. trial.ab. 32. groups.ab. 33. ("double-blind*" or "single-blind*").ti, ab. 34. or/26-33 35. 25 and 34 36. (2009* or 2010* or 2011*).em. 37. 35 and 36	
PSYCINFO 1806-June week 4 2010 (Ovid SP)	1. exp Fatty Acids/ 2. (omega-3 or "omega 3").mp. 3. "Polyunsaturated fatty acid*".mp. 4. PUFA.mp. 5. ("unsaturated fatty acid*" or "essential fatty acid*").mp 6. EFA.ti,ab. 7. "eicosapentaenoic acid*".mp. 8. (EPA or "ethyl-eicosapentanoic acid" or E-EPA).mp. 9. "docosahexaenoic acid*".mp. 10. DHA.ti,ab. 11. ("docosapentanoic acid*" or DPA).ti,	June 2010: 31 June 2011: 36 April 2012: 28

(*Continued*)

	ab. 12. ("alpha-linolenic acid*" or ALA).ti,ab. 13. ("fish oil" or "n-3 fatty acid*" or "long chain fatty acids").mp 14. ("primrose oil" or "linseed oil" or "oily fish" or "flaxseed oil").mp 15. or/1-14 16. (adult adj2 (old* or elderly or aged or senior)).ti,ab. 17. (participant* adj2 (healthy or old* or elderly or aged or senior)).ti,ab 18. "healthy persons".ti,ab. 19. (cognit* or "prevent* dementia*").mp. 20. (cognit* or "prevent* dementia*" or "reduc* risk*").mp. 21. *Prevention/ 22. or/16-21 23. 15 and 22 24. random*.ti,ab. 25. placebo*.ti,ab. 26. trial*.mp. 27. ("double-blind*" or "single-blind*").ti,ab. 28. or/24-27 29. 23 and 28 30. (2009* or 2010* or 2011*).up. 31. 29 and 30	
CINAHL (EbscoHOST)	S1 (MH "Fatty Acids+") or (MH "Fatty Acids, Omega 3+") S2 TX "fatty acid*" or fats or omega-3 or "omega 3" or PUFA or EPA or E-EPA or DHA or DPA or ALA S3 TX n-3-fatty-acid* or "n-3 fatty acid*" or "linseed oil" or "flaxseed oil" or "fish oil" or "salmon oil" or "cod liver oil" S4 TX "eicosapentanoic acid*" or "docosahexanoic acid*" or "dosapentanoic acid*" or "alpha-linolenic acid*" or "ethyl-eicosapentanoic acid*" S5 S1 or S2 or S3 or S4 S6 (MH "Preventive Trials") S7 TX prevent* OR avoid* or "reduc* ADJ2 risk*" S8 S6 or S7 S9 S5 and S8 S10 TX healthy OR normal OR elderly OR older S11 S9 and S10	June 2010: 6 June 2011: 3 April 2012: 1

(*Continued*)

	S12 TX random* OR placebo* OR double-blind* S13 S11 and S12 S14 TX cognit* S15 S13 and S14 S16 em 2009 S17 EM 2010 OR EM 2011 S18 S16 or S17 S19 S15 and S18	
Web of Science with Conference Proceedings (1945 to present) (ISI Web of Knowledge)	#1 Topic=("fatty acid*" OR "omega 3" OR PUFA OR EFA OR EPA OR DHA OR eicosapentanoic OR docosahexanoic OR "alpha-linolenic acid" OR "fish oil*" OR "primrose oil" OR "linseed oil") #2 Topic=("prevent* dement*" OR "prevent* alzheimer*" OR cognition OR cognitive OR brain OR mental) #3 Topic=(random* OR placebo OR "double-blind*" OR trial OR "control group*" OR "single-blind*") #4 #3 AND #2 AND #1 #5 Topic=(#4) *Databases=SCI-EXPANDED, SSCI, CPCI-S Timespan=2009-2011*	June 2010: 206 June 2011: 174 April 2012: 251
LILACS (BIREME)	"omega 3" OR PUFA OR "fatty acid$" OR eicosapentanoic OR docosahexanoic OR "linseed" OR "fish oil$" [Words] and brain OR cognition OR cognitive OR mental [Words] and random$ OR trial$ OR group$ OR placebo$ [Words]	June 2010: 6 June 2011: 6 April 2012: 11
CENTRAL (*The Cochrane Library*)	#1 MeSH descriptor Fatty Acids, Omega-3 explode all trees #2 omega-3 OR "omega 3" #3 "polyunsaturated fatty acid*" #4 PUFA #5 "unsaturated fatty acid*" OR "essential fatty acid*" #6 EFA OR "eicosapentanoic acid" #7 MeSH descriptor Eicosapentaenoic Acid explode all trees #8 EPA OR "ethyl-eicosapentanoic acid" OR E-EPA #9 "docosahexanoic acid*" #10 DHA #11 "docosapentanoic acid*" OR DPA #12 "alpha-linolenic acid*" OR ALA	June 2010: 53 June 2011: 54 April 2012: 48

(*Continued*)

	#13 "fish oil" OR "n-3 fatty acid*" OR "long chain fatty acids" #14 "primrose oil" OR "linseed oil" OR "oily fish" OR "flaxseed oil" #15 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14) #16 participant* NEAR/2 (healthy or old* or elderly or aged or senior) #17 adult NEAR/2 (old* or elderly or aged or senior) #18 "healthy persons" #19 cognit* or "prevent* dementia*" #20 (#16 OR #17 OR #18 OR #19) #21 (#15 AND #20) #22 (#21), from 2009 to 2011	
ClinicalTrials.gov	cognition OR cognitive OR brain OR mental OR dementia | Interventional Studies | omega OR fish OR linseed OR fatty acid OR fatty acids OR PUFA OR eicosapentanoic OR docosahexanoic OR DHA | updated from 01/01/2009 to 06/17/2011	June 2010: 76 June 2011: 20 April 2012: 14
ICTRP (WHO portal)	cognition OR cognitive OR brain OR mental OR dementia | Interventional Studies | omega OR fish OR linseed OR fatty acid OR fatty acids OR PUFA OR eicosapentanoic OR docosahexanoic OR DHA | updated from 01/01/2009 to 17/06/2011	June 2010: 27 June 2011: 20 April 2012: 17
Total		June 2010: 615 June 2011: 517 April 2012: 569
Total after de-duplication and first-assess		June 2010: 36 June 2011: 76 April 2012: 17

WHAT'S NEW

Last assessed as up-to-date: 6 April 2012.

Date	Event	Description
30 April 2012	New citation required and conclusions have changed	The search for studies is updated to 6 April 2012. Three studies are included; the results and conclusions have changed. The authors of the review have changed
6 April 2012	New search has been performed	The search is updated to 6 April 2012.

HISTORY

Protocol first published: Issue 3, 2005

Review first published: Issue 1, 2006

Date	Event	Description
6 November 2008	Amended	Converted to new review format.
12 November 2005	New citation required and conclusions have changed	Substantive amendment.

CONTRIBUTIONS OF AUTHORS

Contribution to the first published version (2006):

Wee-Shiong Lim led the review team, screened the search for studies, and took the lead in drafting the manuscript. Julie Gammack and Jan Van Niekerk assisted in searching for studies and sought to identify studies for inclusion by screening the search results. All authors provided intellectual input into the final version of the review.

Contribution to the 2012 update:

Emma Sydenham (ES), Wee-Shiong Lim (W-S L), and Alan Dangour (AD) screened the search results and selected studies for inclusion. AD contacted experts in the field, sought additional data from included study investigators, and re-wrote the Background section. ES contacted omega-3 manufacturers for additional data; the data were reviewed by AD and W-S L. ES extracted data from the study reports, entered the data into RevMan, assessed the risk of bias in included studies, undertook the analysis, and updated the text of the review; W-S L checked for accuracy. All authors contributed to the final version of the manuscript. No sources of support are listed as all authors contributed to this review in their own time.

DECLARATIONS OF INTEREST

Alan Dangour is the principal investigator of Dangour 2010 (the Older People And n-3 Long-chain polyunsaturated fatty acids (OPAL) study).

ES and W-S L: None known.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The methods of the review were updated to comply with the most recent version of the *Cochrane Handbook for Systematic Reviews of Interventions* (Version 5.1 March 2011) and the Cochrane Collaboration's Methodological Expectations of Cochrane Intervention Reviews criteria (November 2011).

The analysis of secondary outcomes was changed from mean change from baseline to difference between intervention groups at final follow-up (Handbook section 7.7.3.1).

The secondary outcomes health-related quality of life, depression, and anxiety which are listed in the protocol have been removed from this review. These outcomes have been assessed elsewhere (Appleton 2010).

NOTES

Future updates of this review will include participants age 50 years and over.

INDEX TERMS

Medical Subject Headings (MeSH)

Cognition Disorders [*prevention & control]; Dementia [*prevention & control]; Fatty Acids, Omega-3 [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Aged; Humans