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ORIGINAL RESEARCH

Omega-3 fatty acid supplementation and cognitive function: are smaller dosages more beneficial?

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Abstract: As longevity increases, so does the global prevalence of cognitive dysfunction. Numerous lifestyle and/or dietary interventions such as omega-3 fatty acids have been suggested to improve memory. Therefore, this study examined the consistency and strength of the impact of supplementation of omega-3 fatty acids on overall cognitive function using systematic reviews and meta-analytic methods. Of 905 studies retrieved from all searches, 12 randomized controlled trials were included in the meta-analysis. There were differences between studies reporting outcomes for single memory function parameters. Subgroup analysis of doses used (low versus high) indicated that subjects receiving low (<1.73 g/day) doses of omega-3 fatty acids had a significant reduction in cognitive decline rate (–0.07, 95% confidence interval –0.01, –0.02) but there was no evidence for beneficial effects at higher doses (+0.04, 95% confidence interval –0.06, +0.14) compared with the placebo group. This study suggests that omega-3 fatty acids may be beneficial in preventing memory decline at lower doses.

Keywords: cognitive impairment, Alzheimer's disease, dietary fatty acids, omega-3, docosahexaenoic acid

Introduction

The prevalence of dementia is increasing with increased life expectancy and longevity, and is estimated to reach over 34 million worldwide by 2025.[1,2] In the UK, there are over 800,000 people living with dementia, of whom approximately 17,000 are under the age of 65 years, and it is estimated to increase to nearly one million by 2021 and approximately 1.7 million by 2051.[2,3]

Although a number of hypotheses have been put forward to explain the etiology of cognitive decline, the exact etiology of dementia is not fully understood and it is not clear what can be done to prevent memory loss.[4–6] Nonetheless, the evidence indicates that a healthy diet and lifestyle may help to protect against dementia. There are a number of human studies reporting clear associations between lifestyle and late-life cognitive decline. In particular, exercising regularly, avoiding fatty foods, not smoking, drinking alcohol in moderation, and keeping mentally and socially active into old age may help to reduce the risk of developing vascular dementia and Alzheimer's disease.[7]

The role of healthy diet has been well established in a number of chronic illnesses, including obesity, diabetes, cardiovascular disease, and several cancers. Interestingly, nutrition has also been linked to delaying the onset of Alzheimer's disease or slowing its progression.[8–10] Amongst various nutritional elements, polyunsaturated fatty acids such as omega-3 are considered to exert positive effects on cognitive function. However, the outcome of published reports varies considerably between the studies

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depending on the cognitive parameters assessed, the study period, the selected population, and the omega-3 doses used. Apart from variations in sample and contextual characteristics, inconsistencies in the effect of interventions may also arise as a result of other factors, including lack of sufficient power (inadequate sample size) to detect a difference, especially where the effect of the intervention under consideration is small. Some of these problems (eg, variations in participant characteristics and inadequate sample size) can be addressed in part by carefully bringing together all existing evidence on the intervention, critically examining the assembled studies based on quality and comparability, and where appropriate, pooling the results of methodologically similar studies by statistical synthesis. Thus, this study examined the impact of omega-3 supplementation on composite cognitive function using systematic reviews and meta-analytic procedures.

Materials and methods

Search criteria

Electronic searches were conducted in PubMed, Web of Science (which included Medline and PsycINFO), and the Cochrane database of registered controlled trials. Reference lists of included articles were also searched. Appropriate search terms (key word and Medical Subject Headings) were used, and retrieved searches were combined using relevant Boolean operators (OR, AND). Where appropriate, search terms were truncated using relevant wild cards to retrieve alternative forms of the search terms, thereby increasing sensitivity. Search terms used included: "omega-3 fatty acid", "polyunsaturated fatty acid", "dietary fatty acid", "alpha linolenic acid" (ALA), "linolenic acid", "eicosapentaenoic acid" (EPA), "docosapentaenoic acid" (DPA), "docosahexaenoic acid" (DHA), "fish oil", "essential fatty acid", "cognitive function", "cognitive dysfunction", "cognitive impairment", "dementia", "Alzheimer's disease", "memory function", "memory impairment", "memory loss", "cognitive decline", and "cognitive performance".

Titles and abstracts of studies retrieved from searches were considered for inclusion independently by two reviewers. Full texts of articles that seemed to meet the inclusion criteria were obtained for further scrutiny. Also, full texts of articles which could not be excluded with certainty based on the title and the abstract were obtained and scrutinized further for inclusion or otherwise. Differences in opinion between the two reviewers were resolved by consensus. Electronic searches and study selection were conducted from June 2011 to September 2011.

Inclusion/exclusion criteria

We considered studies that reported the consumption or supplementation of any omega-3 fatty acids (ALA, EPA, DHA, DPA) or fish (or fish oil) and their relationship with cognitive function/decline. Studies included were randomized controlled trials (RCTs) reporting data on either healthy or clinical populations. Studies comparing omega-3 fatty acids versus control or placebo and reporting a measure of cognitive endpoints were included.

All forms of omega-3 fatty acid interventions were considered. Thus, interventions involving more than one component were included if the results for the omega-3 fatty acid component could be isolated. Interventions evaluating the effect of a single component of omega-3 fatty acid (eg, DHA, DPA, EPA, or ALA), combined omega-3 fatty acids (eg, DHA and EPA), or fish oil on cognitive function were also included. However, studies reporting omega-3 fatty acids or fish consumption plus another active compound where data for omega-3 fatty acids or fish intake could not be isolated from the other active compound were not included. Also, studies reporting any reasonable length of follow-up, dosage of supplementation, or type of sample population (healthy or clinical) were included.

The main outcome of interest was the mean change in global memory or cognitive function determined by an appropriate measure or scale, such as the Mini-Mental State Examination (MMSE). Where results for global cognitive function were not apparent, an appropriate specific scale of cognitive function (eg, word recall, verbal fluency) was used. No secondary outcomes were considered. Studies that did not report any measure of cognitive function were excluded. Also, studies that did not report sufficient data to permit the computation of effect size (mean difference) were not included. There was no restriction on age of participants.

Data extraction and quality assessment

A data extraction form was used to collect relevant information from individual studies. Information collected from studies included study methods and participant characteristics (eg, setting, population from which the sample was recruited, mean age), intervention/control characteristics, and study quality indicators such as randomization, blinding, treatment concealment, and dropouts (see Table 1). As shown in Table 2, relevant data on the outcome measures of interest (mean of cognitive outcome at baseline, mean of cognitive outcome at follow-up, and if reported, mean changes from baseline to follow-up and their respective standard deviations) were also

extracted. Although data on methodological quality indicators (eg, blinding, randomization, withdrawal/loss to follow-up) were extracted and are reported here, we did not actively rate the quality of studies included in this review.

Statistical analysis

In most of the studies, changes in cognitive function from baseline were not reported. These values were therefore computed from the relevant data (number of participants, mean, and standard deviation) reported at baseline and at follow-up. This is a conservative approach as it overestimates the standard deviation for the respective studies. As shown in Table 1, the studies used different scales/instruments to measure cognitive function/decline. Thus, the standardized mean difference (SMD) was used to compute the pooled treatment effect comparing intervention and control groups. The SMD is expressed as the absolute difference in means of the intervention and control groups divided by the pooled standard deviation.

For subanalysis of examining effects of dose differences, median dose of supplementation (1.7 g/day) was computed and used to divide studies into two groups of low-dose (≤1.7 g/day) or high-dose (>1.7 g/day).

Meta-analyses were conducted using the fixed effects model, as there was no evidence of heterogeneity in any of the pooled analyses conducted to justify the use of a random effects model. Pooled estimates were conducted for all studies combined as well as for study subgroups based on treatment dose (≤ median dose/> median dose), duration of intervention (short-term <6 months/long-term ≥6 months), and types of study participants (healthy/clinical population). The data were analyzed using the metan command in Stata version 9 (StataCorp LP, College Station, TX, USA).

Results

Description of included studies

As shown in Figure 1, 905 studies were retrieved from all the searches conducted and 12 RCTs were included in the meta-analysis. Table 1 shows details of the methodological and participant characteristics of the studies included in this review. Over half of the studies (n=7) were conducted in general or healthy populations.[11–16] The others were conducted in specific clinical or special populations including people with: schizophrenia,[17] various degrees of memory problems,[18–20] depression,[21] or pregnant women.[22] Included studies varied in sample size, ranging from 53 subjects[11] to 867 subjects.[16] Freund-Levi et al[19] used a randomized, double-blind, parallel-group study design for the first 6 months and then open treatment for all participants thereafter. All other studies were double-blind, parallel-group RCTs. Five of the studies involved young adult/middle-aged samples (mean age ≤40 years),[11,14,17,21,22] and all other studies involved older population samples (mean age ≥68 years).

Interventions were mostly presented as supplements in capsules as combinations of DHA and EPA,[12,16,19–21] DHA only,[11,13,15,18] EPA only,[18] ALA (the dietary precursor of DHA),[22] or fish oil.[14] Duration of intervention and follow-up ranged from 4 weeks to 24 months (median 23 weeks) and daily consumed doses of a single or combined components of omega-3 fatty acids ranged from 0.58 g of combined DHA and EPA[19] to 3.12 g of ALA.[22] Loss to follow-up was reported in ten of the included studies, and ranged from 3%[12] to 27%.[18]

Effect of omega-3 fatty acids on cognitive function/decline

Considering the results for individual studies included in this review, only Yurko-Mauro et al[15] reported significant changes in measures of cognitive function/decline for all participants randomized to omega-3 fatty acid intervention compared with placebo. Specifically, they found that participants randomized to DHA scored significantly fewer errors in the Cantab® paired associate learning (PAL) measure compared with those randomized to placebo (mean difference −1.63±0.76; P=0.032) after 24 weeks of supplementation. They also reported significant differences in other subscales of the Cantab measure but not MMSE scores between the intervention and placebo groups.

Some studies reported a significant effect of omega-3 fatty acid supplementation only after detailed investigations were conducted within subgroups of study participants. For example, compared with their omega-3 fatty acid intervention group, Freund-Levi et al[19] reported a significant decrease in MMSE scores (P=0.01) for their control group when subgroup analysis was conducted for participants with very mild Alzheimer's disease (MMSE >27 and Clinical Dementia Rating score 0.5–1). The change in MMSE scores for the omega-3 fatty acid group after 6 months of supplementation was −0.5 points (P>0.05) compared with −2.6 points (P<0.001) in the placebo group. Also, the placebo group experienced a significant worsening in cognitive function (as indicated by scores on the "delayed word recall" subscale of the Alzheimer's Disease Assessment Scale-Cognitive Subscale [ADAS-cog]; P=0.007) compared with no change in the intervention group. Chiu et al[20] also reported improvement

Table 1 Methodological, sample, and intervention characteristics of studies included in meta-analysis

Study characteristics				Sample characteristics	Intervention characteristics					Study quality
Reference	**a. Setting b. Sample recruited from**	**Sample size a. Total b. Intervention c. Control**	**Study design**	**a. Ratio of women to men b. Mean age ± SD (if not age range)**	**Description of intervention**	**Description of control**	**Measure/s of cognitive function**	**Duration of: a. Intervention b. Follow-up/s**	**Daily dose**	**a. Blinding (yes/no) b. Randomization (yes/no) c. Treatment concealment (yes/no) d. % loss to follow-up**
Hamazaki et al[11]	a. Two universities, Japan b. Second and fourth year university students (healthy student volunteers)	a. 53 b. 22# c. 19#	RCT Parallel design, two groups Double-blind	a. 34 F: 19 M b. 21–30	Intervention group asked to take 10–12 capsules of DHA for 3 months	Control group asked to take 10–12 capsules of control oil for 3 months	Stroop test: to measure accuracy and speed of instantaneous judgement Dementia-detecting test revised to assess higher function of brain	a. 3 months b. 3 months	1.5–1.8 g DHA	a. Yes (double-blind) b. Yes c. Yes d. NC
Fenton et al[17]	a. Not reported b. Outpatients aged 18–65 who met DSM-IV criteria for schizophrenia/ schizoaffective disorder	a. 87 b. 43 c. 44	RCT Parallel design, two groups Double-blind	a. 34 F: 53 M b. 40 ±10	Six 500 mg capsules of ethyl EPA (3 g)	Six capsules of mineral oil	Cognitive function measured by the RBANS	a. 16 weeks b. Follow-ups at several time points (data for week-16 used here)	3 g EPA	a. Yes b. Yes c. Yes d. 13.8%
de Groot et al[22]	a. Regions in the Netherlands b. Pregnant women attending midwives and obstetrics and Gynaecology departments in hospitals	a. 56 b. 30 c. 26	RCT Parallel design, two groups Double- blind	a. All female b. 29.45	Intervention group consumed 25 g per day of special margarine containing 2.82 g ALA + 9.02 g LA per day	Control group consumed 25 g per day of margarine containing 0.03 g ALA and 10.94 g LA per day	Cognitive function measured by several scales; only the WLTtot is reported here	a. Not clear b. Follow-ups at several time points, Data at baseline and at week-36 used here	2.82 g ALA	a. Yes b. Yes c. NR d. NC

Freund-Levi et al[19]	a. Stockholm, Sweden b. AD patients attending specialist memory clinics with MMSE scores of 15–30	a. 204 b. 103 c. 101 (NB: 174 completed study; 91 for intervention, 87 for control)	RCT Parallel design, two groups for first 6 months then open treatment (cross-over) for another 6 months Double-blind	a. 110 F: 94 M b. 74±9	Intervention group received 4×1 g capsules containing 430 g DHA + 150 g EPA per day for 6 months	Control group received 4×1 g of placebo (containing 1 g of corn oil + 0.6 g of linolenic acid) per day for 6 months	Cognitive function measured by MMSE and ADAS-cog and global function by CDR	a. 6 and 12 months (6 months used due to crossover) b. 6 months used	430 mg DHA + 150 mg EPA (total n-3 LC-PUFA 580 mg)	a. Yes b. Yes c. Yes d. 12.75% in 6 months 14.7% in 12 months
Johnson et al[13]	a. Boston, MA, USA b. General/ healthy population (healthy nonsmoking women)	a. 57 b. 14* c. 10*	RCT Parallel design, four groups (only two, DHA/placebo compared) Double-blind	a. All female b. 68	Subjects consumed capsules of DHA supplements with a given nutritional drink	Controls consumed placebo capsules identical to intervention (content not clearly described)	Verbal fluency determined by number of items named from a category within a minute; Stroop test used to determine processing speed	a. 4 months b. 4 months	DHA 800 mg	a. Yes b. Yes c. Yes d. 14%
Chiu et al[20]	a. Taipei City hospital, Taiwan. b. AD and MCI patients as defined by MMSE 10–26 and CDR score of 1 or 2	a. 46 b. 24 c. 22	RCT Parallel design, two groups Double-blind	a. 20 F: 15 M b. 75.25	Six capsules containing 1080 mg EPA + 720 mg DHA per day	Six capsules containing olive oil esters per day	Cognitive function assessed using ADAS-cog and CIBIC-plus	a. 24 weeks b. Follow-ups at several time points baseline and week-24 data used	1,080mg EPA + 720 mg DHA (total n-3 PUFA 1,800 mg)	a. Yes b. Yes c. Yes d. 24% (31% in placebo and 23% in intervention)
Rogers et al[21]	a. Bristol, UK b. Mild to moderately depressed adults (determined using screening questionnaires) recruited mainly from general practice surgeries	a. 218 b. 109 c. 109 (NB: 190 completed the study)	RCT Parallel design, two groups Double-blind	a. 168 F: 50 M b. 38.1	Three capsules containing 630 mg EPA + 850 mg DHA per day	Three capsules containing 2360 mg olive oil per day	Cognitive function measured by several tasks. Scores for the simple reaction time is used in this review	a. 12 weeks b. Follow-ups at weeks 4 and 12 (12-week data used here)	1.5 g of n-3 PUFA (630 mg EPA + 850 mg DHA)	a. Yes b. Yes c. Yes e. 28 of 218 (12.8%)
van de Rest et al[12]	a. Wageningen University, the Netherlands b. Database of volunteers aged >65 years (healthy elderly)	a. 302 (202 relevant for this study) b. 96 c. 106	RCT Parallel design, three groups (two groups compared in this study) Double-blind	a. 135 F: 167 M b. 70	High dose group (six daily capsules containing a total of 1800 mg EPA-DHA)	Placebo group (six capsules containing oleic acid)	Cognitive function determined using five different instruments. Results for the WLT (immediate recall-75 words) are used here	a. 26 weeks b. Follow-ups at weeks 13 and 26 (26-week data used here)	1,800 mg of EPA-DHA	a. Yes b. Yes c. Yes d. 9 of 302 (3%)

(*Continued*)

Table 1 (*Continued*)

Study characteristics				Sample characteristics	Intervention characteristics					Study quality
Reference	**a. Setting b. Sample recruited from**	**Sample size a. Total b. Intervention c. Control**	**Study design**	**a. Ratio of women to men b. Mean age ± SD (if not age range)**	**Description of intervention**	**Description of control**	**Measure/s of cognitive function**	**Duration of: a. Intervention b. Follow-up/s**	**Daily dose**	**a. Blinding (yes/no) b. Randomization (yes/no) c. Treatment concealment (yes/no) d. % loss to follow-up**
Antypa et al[14]	a. The Netherlands (specific place not reported) b. Healthy volunteers with BMI 18–27	a. 54 b. 27 c. 27	RCT Parallel design, two groups Double-blind	a. 44 F: 10 M b. 22	Three capsules containing 3 g of fish oil per day	Three capsules containing olive oil	Cognitive function assessed using 15-word memory test	a. 4 weeks b. 4 weeks	3 g of fish oil (2.3 of n-3 PUFA (1.74 g EPA + 0.25 g DHA). Total n-3 PUFA 1.99 g	a. Yes b. Yes c. Yes d. 2 of 56 (3.6%)
Yurko-Mauro et al[15]	a. 19 clinical sites, USA b. Healthy subjects with ARCD with MMSE >26	a. 485 b. 242 c. 243	RCT Parallel design, two groups Double-blind	a. 116 F: 84 M b. 70	Three capsules containing a total of 900 mg/day of DHA	Three capsules containing 50% corn oil + 50% soy oil per day	Cognitive function determined by 24 week Cantab® PAL (number of Cantab pattern errors)	a. 24 weeks b. 24 weeks	900 g of DHA	a. Yes b. Yes c. Yes d. 10% (9.5% in DHA; 10.3% in placebo)
Quinn et al[18]	a. 51 clinical research sites, USA b. Volunteers with probable Alzheimer's disease (MMSE 14–26)	a. 402 b. 238 c. 164 Completers a. 295 b. 171 c. 124	RCT Parallel design, two groups Double-blind	a. 210 F: 192 M b. 76	Two capsules containing 2 g of DHA per day	Two capsules containing corn or soy oil per day	Change in cognitive function assessed using ADAS-cog	a. 18 months b. Follow ups at 6, 12, and 18 months (18 months data used)	2 g of DHA	a. Yes b. Yes c. Yes d. 107 of 402 (27%)
Dangour et al[16]	a. England and Wales b. Healthy adults from 20 general practices	a. 867 b. 434 c. 433	RCT Parallel design, two groups Double-blind	a. 390 F: 477 M b. 75	Two capsules containing 700 mg n-3 PUFAs (200 mg EPA + 500 mg DHA) per day	Two capsules containing olive oil per day	Cognitive function measured by CVLT	a. 24 months b. 24 months	700 mg n-3 PUFAs (200 mg EPA + 500 mg DHA)	a. Yes b. Yes c. Yes d. 14%

Notes: *Sample sizes for groups used in meta-analysis; #sample size reported for completers; †groups compared in meta-analysis.

Abbreviations: ARCD, age-related cognitive decline; BMI, body mass index; F, female; M, male; NC, not clear; CDR, Clinical Dementia Rating score; AD, Alzheimer's disease; MCI, mild/moderate cognitive impairment; WLT, Word Learning Test; WLTtot, total Words Learning Test; SD, standard deviation; RCT, randomized controlled trial; MMSE, Mini-Mental State Examination; NR, not reported; NC, not clear from the data; ALA, alpha linolenic acid; LA, linolenic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; PUFA, polyunsaturated fatty acids; CIBIC-plus, Clinician Interview-Based Impression of Change, plus carer interview; ADAS-cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; CVLT, California Verbal Learning Test; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders Fourth Edition; PAL, paired associate learning; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status.

Table 2 Data analysis strategy, measures of cognitive function, and results from included studies

Study reference	Analysis strategy (ITT/PP)	Measures of cognitive function used in current study	Indicator of cognitive improvement (↑↓)	Outcome of interest (intervention group)	Outcome of interest (control group)
Hamazaki et al[11]	PP	Stroop test (100%)	↑ (+)	BL, 50.8±11.4 Final, 57.4±15.2	BL, 51.1±12.7 Final, 59.3±14.6
		Dementia-detecting test (DDT) (100%)	↓ (–)	BL, 46.6±8.0 Final, 55.5±9.1	BL, 49.1±9.9 Final, 57.9±8.7
Fenton et al[17]	ITT	RBANS	↑ (+)	BL, 75±15 Final, 76±18	BL, 77±40 Final, 74±14
de Groot et al[22]	NC	(WLTtot)	↑ (+)	BL, 9.9±1.3 Final, 10.9±1.5	BL, 10.5±1.8 Final, 11.4±1.4
Freund-Levi et al[19]	ITT/PP but results reported in PP	MMSE (0–30 points)	↑ (+)	BL, 23.6 (22.8–24.4) Final, 22.8 (21.9–23.7)	BL, 23.2 (22.4–24.0) Final, 22.4 (21.5–23.4)
		ADAS-cog (0–85 points)	↓ (–)	BL, 25.7 (23.6–27.8) Final, 27.7 (25.4–30.0)	BL, 27.2 (25.1–29.4) Final, 28.3 (26.0–30.6)
		CDR global score (0–3 points)	↓ (–)	BL, 1.0 (0.9–1.1) Final, 1.1 (1.0–1.2)	BL, 1.1 (1.0–1.2) Final, 1.1 (1.0–1.3)
Johnson et al[13]	PP	Verbal fluency	↑ (+)	BL, 15.0±4.9 Final, 17.8±3.1*	BL, 12.9±6.2 Final, 13.8±3.5
		Stroop test (total RT-interference)	↑ (+)	BL, 21.5±10.0 Final, 19.7±8.3	BL, 25.0±14.8 Final, 23.1±22.0
Chiu et al[20]	ITT/PP	ADAS-cog	↓ (–)	BL, 9.17±7.19 Final, 5.90±5.63	BL, 7.99±7.13* Final, 5.57±4.76
		MMSE	↑ (+)	BL, 25.06±3.99 Final, 25.47±3.81	BL, 25.27±3.34 Final, 25.09±3.67
Rogers et al[21]	ITT/PP PP used for cognitive function tests	Cognitive function measured using various tasks. Scores for simple reaction time is used	↓ (–)	BL, 370±75 Final, 391±85	BL, 381±56 Final, 398±71
van de Rest et al[12]	ITT	WLT (immediate recall-75 words)	↑ (+)	BL, 39.3±8.8 Final, 44.9±9.9	BL, 39.6±9.7 Final, 44.8±9.4
Antypa et al[14]	PP	15-word list memory test: Delayed recall	↑ (+)	BL, 9.55±2.48 Final, 9.36±3.24	BL, 9.04±2.54 Final, 9.92±3.22
		Immediate recall	↑ (+)	BL, 11.04±2.66 Final,11.0±2.83	BL, 10.72±2.56 Final, 11.04±2.61
Yurko-Mauro et al[15]	ITT	Cantab® PAL	↓ (–)	BL, 13.4±11.6 Final, 8.8±9.9	BL, 12.1±10.9 Final, 9.7±10.7
		MMSE	↑ (+)	BL, 28.3±1.3 Final, 28.0±1.9	BL, 28.2±1.3 Final, 27.9±1.9
Quinn et al[18]	ITT PP used in secondary analysis	ADAS-cog	↓ (–)	Mean change (95% CI)	Mean change (95% CI)
		CDR, sum of boxes	↓ (–)	7.98 (6.51–9.45) 2.87 (2.44–3.30)	8.27 (6.72–9.82) 2.93 (2.44–3.42)
		MMSE	↑ (+)	–3.70 (–4.44, –2.96);	–4.04 (–4.85, –3.23)
Dangour et al[16]	ITT	CVLT-total words recalled	↑ (+)	BL, 24.1±6.0 Final, 24.1±6.7	BL, 23.9±5.7 Final, 24.4±6.4
		Immediate story recall	↑ (+)	BL, 11.1±3.9 Final, 11.0±4.3	BL, 10.7±3.9 Final, 10.9±3.9
		Delayed story recall	↑ (+)	BL, 8.9±3.8 Final, 9.3±4.2	BL, 8.8±3.7 Final, 9.1±3.8
		Verbal fluency	↑ (+)	BL, 19.8±5.1 Final, 19.1±5.4	BL, 19.9±5.0 Final, 19.5±5.3

Notes: [-]This study used a cross-over design, thus results for first 6 months are compared; *$P<0.05$. The upward arrows and (+) indicate cognitive improvement in cognitive outcome in intervention group compared to the control group. Similarly, downward arrow and (–) indicate decline in cognitive outcome in intervention group compared to control group.

Abbreviations: BL, baseline; CVLT, California Verbal Learning Test; ITT, intention-to-treat analysis; NC, not clear from data; PP, per protocol analysis; CDR, Clinical Dementia Rating score; WLT, Word Learning Test; WLTtot, total Words Learning Test; MMSE, Mini-Mental State Examination: ADAS-cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; CI, confidence interval; PAL, paired associate learning; RT, total interference from Stroop test for speed and accuracy of processing.

in cognitive function (indicated by reduced scores on ADAS-cog) in participants with mild cognitive impairment supplemented with omega-3 fatty acids compared with placebo (–3.23±3.82 versus –0.37±1.4; $P=0.03$). The study by van de Rest et al[12] also reported significant improvement in the cognitive domain of attention among apolipoprotein

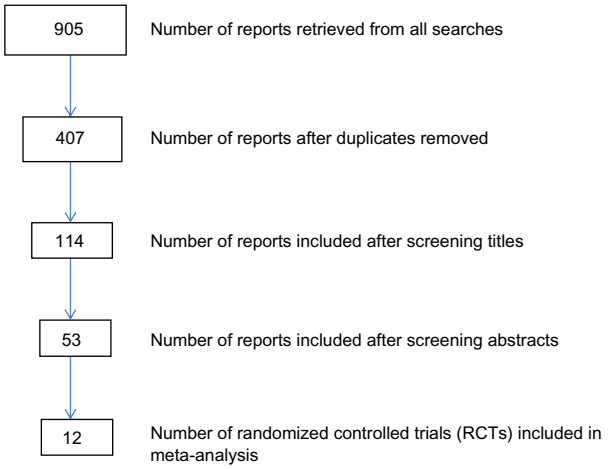

Figure 1 Search results and number of studies included at various stages.

E ε4 carriers and men supplemented with fish oil compared with controls. Another study[13] reported significant within-group change in cognitive function in the intervention group but not in the control group. Compared with baseline scores, participants in the intervention (DHA) group named significantly more items (2.8) from a category within a minute after 4 months of supplementation. However, there was no improvement in the number of items (0.9) named by participants in the control group within the same period.

Pooled analysis involved 2,510 participants, with 1,298 and 1,212 randomized to the intervention and control groups, respectively. The median duration of intervention was 23 (range 4–96) weeks. As shown in Figure 2, results for all the studies combined were consistent with the individual findings from most studies. The pooled results showed no significant change in memory function following supplementation with omega-3 fatty acids or the component elements (pooled SMD −0.04, 95% confidence interval [CI] −0.09, +0.01). As shown in the forest plot of the meta-analysis, only one study (Yurko-Mauro et al[15]) showed significant improvement in cognitive function (based on the Cantab PAL measure) following omega-3 fatty acid supplementation (SMD −0.21; 95% CI −0.3, −0.04). Heterogeneity between studies was not statistically significant (χ^2=11.99, *df* =23, *P*=0.97).

There were no significant differences in cognitive function between the intervention and control groups when pooled analyses were stratified by duration of follow-up ([short-term <6 months SMD −0.08, 95% CI −0.16, +0.01]; [long-term ≥6 months SMD −0.03, 95% CI −0.09, +0.03]); type of participants included ([general/healthy population SMD −0.04, 95% CI −0.10, +0.01]; [diseased/clinical population SMD 0.00, 95% CI −0.10, +0.09]). However, there was a statistically significant effect when analysis was stratified by

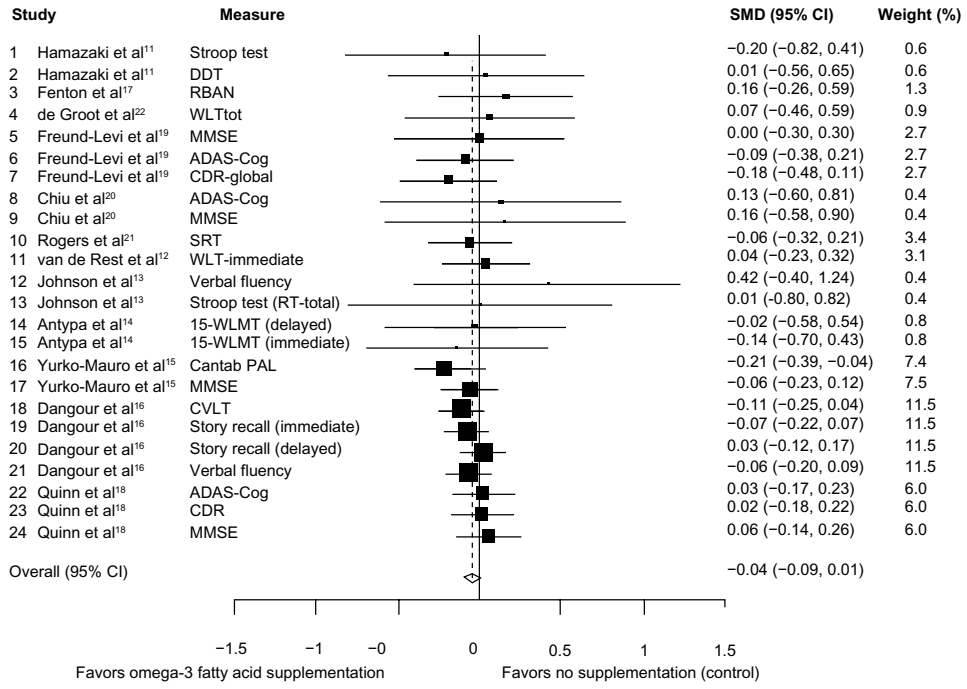

Figure 2 Forest plot for omega-3 fatty acid supplementation and cognitive decline.

Abbreviations: ADAS-cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; CI, confidence interval; CVLT, California Verbal Learning Test; DDT, dementia detecting test; WLTtot, total Words Learning Test; 15-WLMT, Word List (memory) Test; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; MMSE, Mini-Mental State Examination; WLT, Word Learning Test; PAL, paired associate learning; CDR, Clinical Dementia Rating; SMD, standardized mean difference; SRT, simple reaction time.

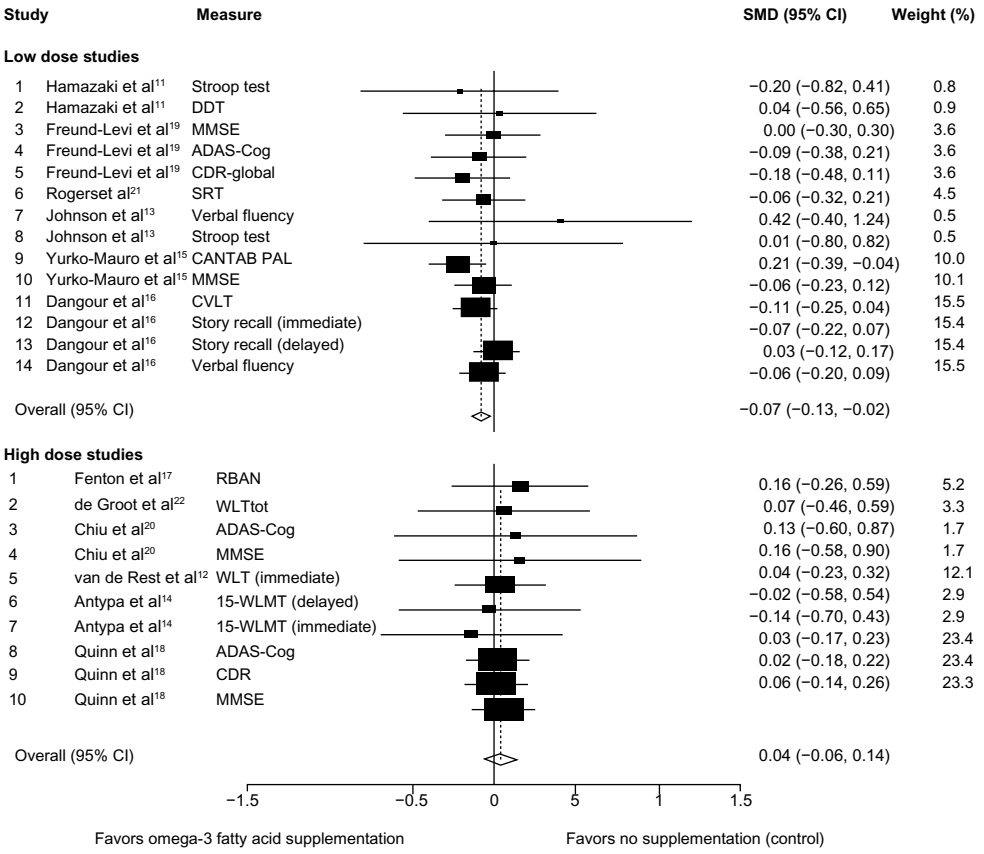

Figure 3 Forest plot of omega-3 fatty acid for low and high dose compared with no supplementation (control).
Abbreviations: ADAS-cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; CVLT, California Verbal Learning Test; DDT, dementia detecting test; WLTtot, total Words Learning Test; 15-WLMT, Word List (memory) Test; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; MMSE, Mini-Mental State Examination; WLT, Word Learning Test; PAL, paired associate learning; CDR, Clinical Dementia Rating; SMD, standardized mean difference; SRT, simple reaction time; CI, confidence interval.

dose of supplementation, as shown in Figure 3. Compared with controls, there was a significant reduction in the rate of cognitive decline in groups supplemented with low doses (≤1.73 g/day) of omega-3 fatty acids (SMD –0.07, 95% CI –0.13, –0.02). There was no evidence of cognitive benefit for supplementation with higher doses of omega-3 fatty acids (SMD +0.04, 95% CI –0.06, +0.14). Further, no statistically significant heterogeneity was observed in any of the stratified analyses.

Discussion

There are a number of clinical forms of memory loss, with Alzheimer's disease being the main contributor to the number of patients with dementia. The pathological signs of Alzheimer's disease appears to be susceptible to the effects of DHA, an omega-3 polyunsaturated fatty acid that is essential for the development and maintenance of the prenatal brain and maintenance of vision in adults.[23,24] Indeed, patients with established Alzheimer's disease have decreased levels of DHA in their brain membrane.[25,26] Therefore, it is plausible to assume that replenishment of DHA would have a positive impact on memory function. Nonetheless, the clinical trials published thus far have failed to provide a clear consensus on the impact of omega-3 supplementation on cognitive function. The information on the effects of omega-3 on memory function provided in the published literature varies according to the parameter tested, study duration, and the baseline memory function of the subjects participating in the study. These variations ultimately exacerbate ambiguity with regard to the effects of omega-3 supplementation on memory function. Needless to say, memory health/cognition should be considered as the sum of the ability of an individual's memory to respond to various cognitive parameters. Therefore, this study included a pooled analysis on data from 12 relevant published RCTs to determine whether or not omega-3 has any beneficial effects on memory function.

Of the 12 RCTs included in this study, four measured MMSE, three measured ADAS-cog, two measured the Stroop test, four measured various forms of the Word Learning Test, two measured the Clinical Dementia Rating, two measured verbal fluency, one measured Cantab PAL, one measured

the California Verbal Learning Test, one measured various tasks of simple reaction time, one measured the Repeatable Battery for the Assessment of Neuropsychological Status, and one measured dementia detecting test, giving a total of 24 measurements of different parameters. Where a parameter was reported to be measured in more than one study (eg, MMSE, ADAS-cog, Stroop test, Word Learning Test, or Clinical Dementia Rating) the data were not similar and variation did exist (Figure 2); however, pooling the data indicated a significant positive effect of omega-3 on overall cognitive function, at least for the six low dose studies (see top forest plot of Figure 3). This clearly indicates that clinical trials investigating the impact of an agent on cognition cannot solely rely on testing specific parameters of cognition, but rather a comprehensive assessment of cognition should be included in any clinical trials examining memory function.

The published data examining the impact of omega-3 supplementation has shown contrasting outcomes[19,27] with no clear explanation. Therefore, in this study, we performed a subanalysis of 12 RCTs for two groups of low-dose (14 parameters assessed) and high-dose (10 parameters assessed) omega-3 usage. Interestingly, clear differences became apparent between the effects of low-dose and high-dose omega-3 use on memory function. The subanalysis suggests that low-dose but not higher-dose omega-3 supplementation has positive effects on cognitive function. This variation may in part explain the contrasting reports observed with clinical trials of omega-3 and cognitive function. However, what is important to note is the positive impact of low-dose omega-3 on memory. The mechanism(s) of effect remains to be elucidated, but may include reducing the production of amyloid beta-protein,[28,29] thus reducing the plaque burden on neuronal cells and ultimately preventing neuronal cell death. This in turn would prevent memory loss and/or reduce the speed of cognitive deterioration.

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Disclosure

The authors report no conflicts of interest in this work.

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