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A systematic review and dose response meta analysis of Omega 3 supplementation on cognitive function

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The dose-dependent effects of omega-3 supplementation on cognitive function remain unclear. This study aimed to evaluate the relationship between omega-3 dosage and cognitive outcomes in adults. A systematic search was conducted in PubMed, Scopus, and ISI Web of Science up to December 2024. Only randomized controlled trials (RCTs) were included. For each trial, we estimated the change in cognitive function per 2000 mg/day increment in omega-3 supplementation. Standardized mean differences (SMDs) and 95% confidence intervals (CIs) were calculated using a random-effects model. Dose-dependent effects were assessed through a dose-response meta-analysis of mean differences. The certainty of the evidence was evaluated using the GRADE approach. In total, 58 studies met the inclusion criteria. Each 2000 mg/d omega-3 supplementation showed a significant improvement in attention (SMD: 0.98; 95%CI: 0.41,1.54; GRADE = low), perceptual speed (SMD: 0.50; 95%CI: 0.05,0.95; GRADE = moderate) language (SMD: 0.98; 95%CI: 0.41,1.54; GRADE = low), primary memory (SMD: 0.87; 95%CI: 0.17,1.56; GRADE = moderate), visuospatial functions (SMD: 0.86; 95%CI: 0.46,1.27; GRADE = moderate), global cognitive abilities (SMD: 1.08; 95%CI: 0.73,1.44; GRADE = low). Levels of episodic memory decreased with the increase in omega-3 dose and then appeared to increase with an upward curve (*P* for non-linearity = 0.01, *P* for dose-response = 0.005). Levels of global cognitive abilities increased with the increase in omega-3 dosage, and then appeared to decreased with a downward curve (*P* for non-linearity = 0.008, *P* for dose-response = 0.002). The existing evidence suggests that omega-3 supplementation may lead to a modest improvement in cognitive function among adults. However, well-designed randomized trials with long-term follow-up are necessary to confirm and strengthen these findings.

Keywords Cognition, Cognitive function, Omega-3, Dose-response, Long-chain fatty acids

Cognitive function refers to the continuous process of learning throughout one's life and encompasses various mental abilities, including working memory, attention, language comprehension and production, reasoning, problem-solving, and decision-making[1]. A decline in these abilities, known as cognitive decline, typically progresses with aging. Multiple etiological factors have been proposed for this decline, including inflammation, genetic abnormalities, and impaired neuronal and cerebrovascular functioning[2]. Cognitive impairment and neurocognitive disorders pose significant risks for older adults. Currently, over 55 million people live with dementia worldwide—a number projected to rise to 78 million by 2030. Globally, neurocognitive disorders, including dementias, are leading contributors to mortality, disability-adjusted life years (DALYs), and the burden on health and social care systems[3]. In 2020, the total medical and caregiving costs associated with Alzheimer's dementia in the United States alone were estimated to exceed $500 billion, with projections reaching $1.6 trillion by 2050[4].

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Aging is the primary risk factor for neurological diseases. However, modifiable lifestyle factors—such as poor diet, physical inactivity, smoking, and low cognitive engagement—have also been associated with increased dementia risk. Among these, diet has emerged as a particularly important modifiable factor. Prospective epidemiological studies have shown a reduced incidence of dementia associated with the consumption of foods rich in antioxidants, unsaturated fats, and especially fish and fish oil, which are high in omega-3 fatty acids, particularly docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA)[5–8].

Polyunsaturated fatty acids (PUFAs)—especially DHA—play a vital role in brain and nervous system function by supporting membrane integrity and neuronal activity. DHA may exert neuroprotective effects through anti-inflammatory mechanisms, in part by competing with pro-inflammatory omega-6 fatty acids. Based on these pathways, long-chain omega-3 fatty acids (LCn-3s) are hypothesized to offer protective effects against cognitive decline[9]. Epidemiological evidence supports a beneficial role of high concentrations of long-chain polyunsaturated fatty acids (LC-PUFAs) in preserving cognitive function[10–13]. Several clinical trials have further investigated the potential cognitive benefits of omega-3 supplementation in both cognitively healthy individuals and those with cognitive impairments[14,15]. While some meta-analyses have reported mixed or inconclusive findings regarding the effects of omega-3 on cognitive function[16,17]many of these studies either focused solely on healthy individuals or exclusively on those with cognitive impairments. Moreover, few have incorporated dose-response analyses, which are crucial for understanding the relationship between omega-3 intake levels and cognitive outcomes[18,19].

This study aimed to investigate the effect of omega-3 on cognitive function in healthy individuals, as well as those with dementia, mild cognitive impairment, or risk factors for cognitive decline. A key and distinguishing feature of our work is the incorporation of dose-response analysis, which allowed us to quantitatively assess the relationship between omega-3 intake and cognitive outcomes. This approach provides a more nuanced understanding than prior studies, which often lacked detailed exploration of dosage effects. Subgroup analyses further enriched the findings by examining variability across different populations.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) standards were followed in this study[20]and the protocol was registered on PROSPERO (registration number: CRD42024568781).

Search strategy

We systematically searched the literature from database inception until December 2024 using online databases such as PubMed, Scopus, and Web of Science to find published English studies. No publication time limitations were imposed. Supplementary Table 1 outlines the search strategy and keywords used from the MeSH database. We manually searched the reference lists of the retrieved publications and relevant reviews. To facilitate referencing, all publications were stored in an EndNote library (version X9 for Windows, Thomson Reuters, Philadelphia, PA, USA), and duplicate citations were removed. The literature search was conducted independently by ZY and NA, and any discrepancies were resolved through consultation with the lead researcher (SS-B).

Eligibility criteria

Original trials were considered if they met the following criteria: (1) Randomized controlled trials (RCTs) with a parallel or crossover design in adults (≥ 18 years) with dementia, mild to moderate cognitive impairments, Alzheimer's disease (AD) or healthy individuals; (2) Trials evaluating the effectiveness of omega-3 supplementation including docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), alone or in combination, to a control group; (3) Publications that provided means and standard deviation (SD) of changes in outcomes of interest (Supplementary Table 2), or reported sufficient information to estimate those values; (4) trials that administered doses of omega-3 supplements.

Studies were excluded if they (1) Were non-randomized controlled trials, animal studies, and other experimental designs; (2) Were performed in pregnant women, children, and adolescents; and (3) letters, commentaries, conference presentations, reviews, meta-analyses and ecological studies.

Data extraction

Data extraction was conducted independently by two reviewers (ZY and NA). The following information was extracted from each trial: the last name of the first author, year of publication, study design (parallel or crossover), sample size, mean age, baseline body mass index (BMI), intervention duration, description of the intervention and control arms, dose of omega-3 supplementation, types of outcome measurements, and the means and SDs of changes in outcomes from baseline for each group. When necessary, results were standardized to identical units for meta-analysis by incorporating mean and SDs changes in cognitive function throughout the trial for both intervention and control groups. Numerical estimates presented in graphical format were extracted using Plot Digitizer (http://plotdigitizer.sourceforge.net/). All discrepancies were resolved through consultation with the principal investigator (SS-B).

Risk of bias assessment

Two independent investigators (ZY and NA) conducted the quality assessment to evaluate the risk of bias in the included studies. The Risk of Bias 2 (RoB 2) tool, designed for randomized trials, was used to assess potential sources of bias[21].

Statistical analysis

Standardized mean difference (SMD) and its 95% confidence interval (CI) were used as the effect size in order to present the meta-analysis's findings. This approach was adopted due to the diverse outcome measures employed

by researchers in assessing cognitive function. The mean differences and their SDs in cognitive tests between the intervention and control groups were used to calculate the overall effect sizes. When mean changes were not available, they were calculated using changes in cognitive function during the intervention. Hozo et al. method was used for converting standard errors (SEs), 95% confidence intervals (CIs), and interquartile ranges (IQRs) to SDs[22]. We assessed the heterogeneity using I^2 values. We also conducted sensitivity analyses by eliminating one study at a time to examine the influence of each study on the results. Publication bias was assessed using Egger's test. Subgroup analyses were performed by using predetermined variables, such as types of outcome measurements, intervention duration, study's location, participant's age and sex, health status, baseline BMI, and co-intervention.

We used the method introduced by Crippa and Orsini[23] to calculate the SMD and its corresponding SD of change in cognitive function domains for every 2000 mg/d increments in omega3 supplementation in the intervention group relative to the control group in each trial. This method required the dose (mg/d) of omega-3 supplementation, the standardized mean, and its corresponding SD of change in cognitive function domains, and the number of participants in each study arm. For comparisons including ≤ 5 studies, trial-specific results were pooled using a fixed-effects model[24]. Finally, a dose-response meta-analysis provided further insight into the shape of the effect of omega-3 supplementation on cognitive function domains[24]. Statistical analyses were conducted using STATA software version 16.1. A two-tailed P value of less than 0.05 was considered significant.

Certainty of evidence

The certainty in the evaluations was assessed by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach[25]. According to GRADE recommendations, evidence obtained from RCTs is initially considered to have a high level of assurance. This tool rates studies as high, moderate, low, or very low quality, with options to downgrade or upgrade based on pre-specified criteria. Downgrade criteria include study limitations, inconsistency, indirectness, imprecision, and publication bias, while a significant effect size, a dose-response gradient, and attenuation by plausible confounding can upgrade the quality.

Results

A total of 4,520 records were identified through the systematic search, of which 1,240 were duplicates and excluded. After screening titles and abstracts of the remaining 3,280 records, 3,191 were excluded for not meeting the eligibility criteria. Following full-text review of 89 publications, 31 additional studies were excluded Supplementary Table 3. The final meta-analysis included 58 studies. Among the excluded studies, 23 lacked sufficient data, 2 investigated unrelated interventions, and 1 assessed an irrelevant outcome. One was a study protocol, and full texts or supplementary data could not be retrieved for three studies. The detailed selection process is presented in the PRISMA flow chart Fig. 1.

Study characteristics

Key characteristics of the included studies are summarized in Table 1. Trials were published between 2006 and 2023 and conducted in USA and Canada ($n = 14$)[12,26–38]Europe ($n = 20$)[15,39–57]and Asia /Oceania ($n = 24$)[7,14,58–79]. Thirty two studies enrolled cognitively healthy participants[15,26,28–36,41–44,46–48,50,51,53,54,57,60,62,64,65,70,71,73,76–78]while 16 investigations included those with cognitive impairments[7,12,14,27,37,40,55,58,61,63,66,68,69,72,79]. An additional three studies focused specifically on Alzheimer's disease (AD)[38,45,56]and three included participants with both AD and cognitive impairments[52,59,67]. Two trials involved participants with memory issues, and two assessed other mental disorders[39,49,74,75]. Nine studies used multi-component interventions combining omega-3 with compounds such as vitamins or antioxidants[28,39,40,44,50,53–55,74,78]. The daily dosage of omega-3 varied from 230 to 4950 mg/day, and the duration of the intervention ranged from 4 to 160 weeks. The most common cognitive assessment tools were the Mini-Mental State Examination (MMSE) for global cognition[12,14,28,30,32,39,45,46,52,55,56,59–63,67,68], Trail Making A and B and Stroop Tests for attention and executive function[15,26,28,30,33,35–37,39,44,47,49,50,55,69,76]Block Design for visuospatial functions[7,14,66,79]and a variety of recall assessment tools for memory[14,28,31,39,47].

Risk of bias assessment

Based on the RoB 2 tool, 16 trials were rated as good quality[7,14,15,30,34,35,38,41,43,49–51,54,55,59,79]19 as fair quality[12,27,36,40,47,48,52,53,58,60,64–70,73,77]and 23 trials were evaluated as poor quality[26,29,31–33,37,39,42,44–46,56,57,61–63,71,72,74–76,78] (Supplementary Table 4). Quality ratings reflected differences in randomization methods, blinding, outcome reporting, and attrition rates.

Meta-analysis

Effects of omega-3 supplementation on cognitive outcomes

In the following sections, the reported effect sizes reflect the impact of daily supplementation with 2,000 mg of omega-3 fatty acids. SMDs with 95% confidence intervals (CIs) were calculated for each cognitive domain. Subgroup analyses, dose–response trends, and assessments of heterogeneity and publication bias are also reported where applicable. Across outcomes, substantial statistical heterogeneity ($I^2 > 95\%$) was consistently observed. This was expected due to the wide variation in study populations, intervention dosages and durations, baseline cognitive status, and the cognitive assessment tools used. Summary of main results have shown in Fig. 2.

Effects of omega-3 supplements on attention

A total of 32 study arms examined the impact of omega-3 supplementation on attention. The outcomes were not significantly affected (SMD: 0.12; 95%CI: -0.96,1.19, Supplementary Fig. 1) and the GRADE assessment rated the certainty of this evidence as *low*, suggesting limited confidence in this finding. Marked heterogeneity was detected among these studies (I^2: 98.5%; $P < 0.0001$). Subgroup analyses (Table 2) were conducted based on

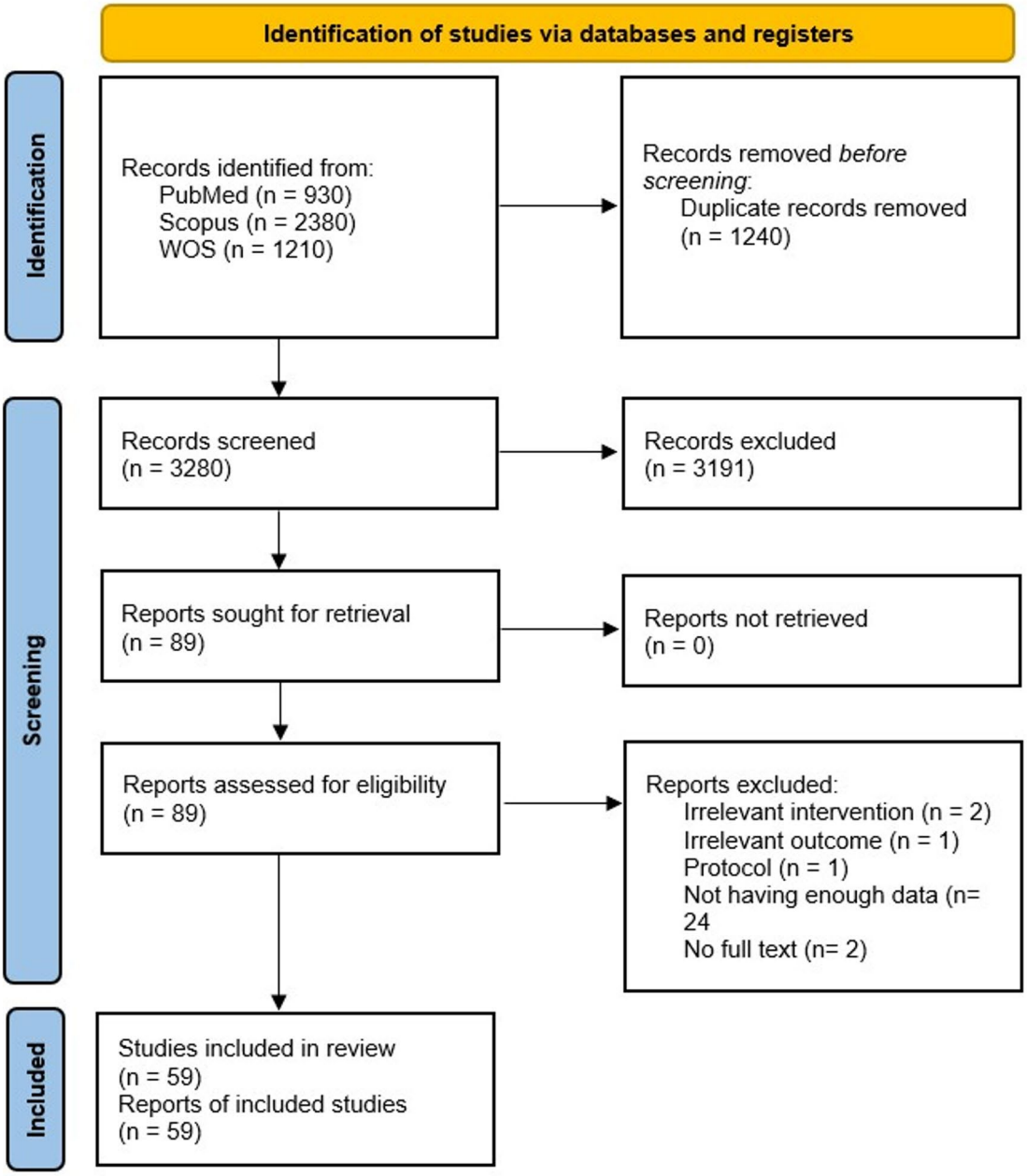

Fig. 1. Flow chart of the number of studies identified and selected into the meta-analysis.

participants' age, baseline BMI, health status, geographical location, intervention duration, and the cognitive test used to assess attention. Notably, omega-3 supplementation was associated with improved attention in trials lasting more than 26 weeks and in participants with a baseline BMI > 25 (SMD: 0.45; 95%CI: 0.24 ,0.66 and SMD: 0.39; 95%CI: 0.19 ,0.59 respectively). Positive effects were also evident in studies conducted in Asia and Oceania, and those using Stroop tasks for attention assessment (SMD: 0.98; 95%CI: 0.72 ,1.24 and SMD: 0.72; 95%CI: 0.43,1.01 respectively). Significant reverse effects were seen in RCTs that did not have co-intervention (SMD: -0.19; 95%CI: -0.37, -0.02) (Table 2). Visual inspection of the funnel plot and Egger's test did not suggest publication bias ($P = 0.85$) (Supplementary Fig. 2). The effect size remained non-significant after step-wise exclusion of each study from the main analysis (MD range: -1.16 to 1.41).

Dose-dependent effects of omega-3 on attention are indicated in Supplementary Fig. 3 and Table 3. Levels of attention increased proportionally with the increase in omega-3 dosage up to 1500 mg/d (SMD1500 mg/d: 0.58, 95%CI: -0.06, 1.22), followed by a modest decline at higher doses. However, the relationship was not statistically non-linear (P for non-linearity = 0.49), indicating that changes in effect were not significantly different across

Author, year	Location	Design	Participants, *n*	Health condition	Age (year)	Intervention		Duration (week)	Cognitive tools	Cognitive domains
						Treatment	Control group			
Michio Hashimoto et al.,2021	Japan	RA/parallel	M/F: 75 Int: 42, Con: 33	Healthy	Int: 71, Con: 71	7.0 ml/d Perilla seed oil (ω-3 PUFA rich oil)	7.0 ml/d Canola oil	48	MMSE FAB HDS-R	Global
Chizuru Konagai et al., 2013	Japan	RA/DB/parallel	M: 45 Int: 15, Con: 15 M: 45 Int:15 Con: 15	Healthy	Int: 67.0 ± 3.3 Con: 67.3 ± 3.4	1000 mg/d Krill oil (ω-3 PUFA rich oil) (285 mg ω-3) 1000 mg/d Sardine oil (742 mg ω-3)	1000 mg MCT	12	P300 latency	Perceptual speed
Isabella C. Arellanes et al., 2020	USA	RA/DB/parallel	M/F: 33 Int:18 Con: 15	Healthy	Int: 68.5 Con: 69	4000 mg/d soft-gel capsules (2152 mg DHA)	4000 mg/d corn/soy oil	24	MoCA Craft CVLT TMT A&B	Global Memory Attention Executive function
E.L. BOESPFLUG et al., 2015	USA	RA/DB/parallel	M/F: 21 Int: 11 Con: 10	subjective memory impairment	Int: 70.1 ± 6.12 Con: 66.4 ± 3.75	Fish oil capsule (2.4 g/d EPA + DHA)	Corn oil, 4 capsules/d	24	n-back task	Memory
Klára Daďová et al., 2022	Czech Republic	RA/DB/parallel	F: 52 Int: 27 Con: 25	Healthy	Int: 70.8 ± 3.6 Con: 71.2 ± 4.00	5 capsules/d of Calanus oil (230 mg/d EPA + DHA)	sunflower oil, 5 capsules/d	16	POBAV	Memory
Sandrine Andrieu et al., 2017	France	RA/parallel	M/F: 1525 Int: 374 Con: 390 Int: 381 Con: 380	memory complaints	Int: 75.4 ± 4.4 Con: 75.0 ± 4.1 Int: 75.6 ± 4.7 Con: 75.1 ± 4.3	multidomain intervention (cognitive stimulation, physical activity, and nutrition) + fish oil (1024 mg/d PUFA) fish oil (1024 mg/d PUFA)	multidomain intervention + flavored paraffin oil, 2 capsules/d flavored paraffin oil, 2 capsules/d	144	MMSE Free and Cued Selective Reminding Test memory functioning TMT A&B Verbal fluency DSST	Global Memory Attention Executive function Perceptual speed Language
Wei Tang et al., 2020	China	RA/DB/parallel	M/F: 80 Int: 40 Con: 40	schizophrenia	Int: 28.0 ± 3.10 Con: 28.75 ± 4.7	2400 mg fish oil as 2 soft-gels (1440 mg/d PUFA)	100 mg/d Vitamin E dissolved in glycerin and corn oil	12	RBANS	Global
Joaquin Baleztena et al., 2018	Spain	RA/DB/parallel	M/F: 78 Int: 44 Con:34	score between 1 to 3 on the Global Deterioration Scale (GDS)	Int: 85.8 ± 4.9 Con: 87.8 ± 6.5	3 capsule/d of the multinutrient supplement: DHA 250 mg, EPA 40 mg, vitamin E 5 mg, phosphatidylserine 15 mg, tryptophan 95 mg, vitamin B 12 5 µg, folate 250 µg and ginkgo biloba 60 mg. (1050 mg/d PUFA)	3 gelatin capsule/d	48	GDS SPMSQ MEC Verbal fluency	Global Language
Heike A. Bischoff-Ferrari et al., 2020	Switzerland	RA/DB/parallel	M/F: 2157 Int: 1073 Con: 1084	MMSE score of at least 24	Int: 74.7 ± 4.3 Con: 75.2 ± 4.6	2 gel capsules of omega-3s (1 g/d EPA + DHA)	2 gel capsules of placebo	144	MoCA	Global
Yacong Bo et al., 2017	China	RA/DB/parallel	M/F: 86 Int: 44 Con: 42	mild cognitive impairment	Int: 71.75 ± 5.68 Con: 70.45 ± 6.82	1 g soft gelatine capsules every nine days (1200 mg/d EPA + DHA)	Olive oil as placebo (each capsules contains 550 mg of oleic acid)	24	BCATs	Global
O.T. CARMICHAEL et al., 2018	USA	RA/DB/crossover	M/F: 10 Int: 5 Con: 5	Healthy	67.3 ± 2.01	a liquid emulsification containing fish oil, panax ginseng phospholipid complex, and green tea catechin phospholipid (1584 mg/d omega3)	Corn oil in water emulsion	4	MMSE Stroop Digit symbol Immediate recall Delayed recall	Global Executive function Perceptual speed Memory
Chih-Chiang Chiu et al., 2008	Taiwan	RA/DB/parallel	M/F: 35 Int: 20 Con: 15	AD and mild cognitive impairment	Int: 74 Con: 76.5	3 capsules of omega3 PUFAs twice a day (1800 mg/d EPA + DHA)	3 capsules of olive oil esters twice a day	24	MMSE ADAS-cog	Global

Continued

Author, year	Location	Design	Participants, *n*	Health condition	Age (year)	Intervention		Duration (week)	Cognitive tools	Cognitive domains
						Treatment	Control group			
Alan D Dangour et al., 2010	UK	RA/DB/parallel	M/F: 867 Int: 434 Con:433	Healthy	Int: 74.7 ± 2.5 Con: 74.6 ± 2.7	2 soft-gel capsules/d (700 mg/d EPA + DHA)	2 soft-gel capsules of olive oil/d	96	Reaction time Letter search Symbol letter modality spatial memory story recall Digit span F&B Verbal fluency	Perceptual speed Memory Language
Vanessa Danthiir et al.,2018	Australia	RA/DB/parallel	M/F: 391 Int: 195 Con: 196	Healthy	Int: 73.1 ± 5.4 Con: 73.1 ± 5.7	Fish oil, 4 capsules/d (2320 mg/d EPA + DHA)	4 capsules/d containing 990 mg of low polyphenol olive oil and 10 mg of fish oil	72	MMSE	Global
Paul Fairbairn et al., 2020	UK	RA/SB/parallel	F: 51 Int: 13 Con:12 Int: 14 Con:12	Healthy	Int: 69 ± 4 Con: 67 ± 4 Int: 68 ± 5 Con: 67 ± 4	4 capsules/d of multi nutrient supplement (1160 mg/d EPA + DHA) MS + exercise	4 capsules/d of an isocaloric oil with a small amount of fish oil placebo + exercise	24	spatial memory verbal memory Executive function Interference control (Stroop)	Memory Executive function
Yvonne Freund-Levi et al., 2006	Sweden	RA/DB/parallel	M/F: 174 Int: 89 Con: 85	AD	Int: 72.6 ± 9.0 Con: 72.9 ± 8.6	four 1-g capsules daily (2320 mg/d EPA + DHA)	four 1-g capsules of corn oil daily	24	MMSE ADAS-cog CDR	Global
Johanna M. Geleijnse et al., 2012	Netherlands	RA/DB/parallel	M/F: 1265 Int: 627 Con: 638	Healthy	Int: 69.2 ± 5.4 Con: 68.9 ± 5.4	20 g of trial margarines contain fish oil (400 mg/d EPA + DHA)	20 g of trial margarines placebo	160	MMSE	Global
Grace E. Giles et al., 2015	USA	RA/DB/parallel	M/F: 72 Int: 36 Con: 36	Healthy	Int: 20.80 ± 2.38 Con: 20.49 ± 1.70	Fish oil, 7 capsules/d (2800 mg/d EPA + DHA)	Olive oil, 7 capsules/d	5	STICSA	Global
James C Jackson et al., 2018	USA	RA/DB/parallel	M/F: 320 Int: 159 Con: 161	Healthy	Int: 62 Con: 61	1-g n–3 PUFA capsules (840 mg/d DHA + EPA)	Olive oil, 1 g/d capsules	4	MMSE RBANS TMT A&B	Global Attention Executive function
Michael J Patan et al., 2021	UK	RA/DB/parallel	M/F: 310 Int:105 Con: 101 Int: 104 Con: 101	Healthy	Int: 35.15 ± 8.01 Con: 36.63 ± 7.33 Int: 35.14 ± 7.88 Con: 36.63 ± 7.33	3 capsules/d of ~1 g fish oil (900 mg/d DHA & 270 mg/d EPA) 3 capsules/d of ~1 g fish oil (900 mg/d EPA & 360 mg/d DHA)	Olive oil, 1000 mg/each capsule	26	Global accuracy Global speed Word Recognition (RT) Accuracy of memory	Global Memory
Philippa A. Jackson et al., 2011	UK	RA/DB/parallel	M/F: 140 Int: 46 Con: 48 Int: 46 Con: 48	Healthy	Int: 21.96 Con: 21.94 Int: 22.74 Con: 21.94	1 g fish oil, 2 capsules/d (450 mg/d DHA + 90 mg/d EPA) 1 g fish oil, 2 capsules/d (300 mg/d EPA + 200 mg/d DHA)	Olive oil, 1 g/d	12	Stroop RT (simple, choice) Verbal fluency Working memory Word & picture recognition Corsi Blocks Span Word recall N-Back Task	Executive function Perceptual speed Language Memory

Continued

Author, year	Location	Design	Participants, *n*	Health condition	Age (year)	Intervention		Duration (week)	Cognitive tools	Cognitive domains
						Treatment	Control group			
Elizabeth J. Johnson et al., 2008	USA	RA/DB/parallel	F: 24 Int: 14 Con: 10	Healthy	Int: 68.5 Con: 68.0	Fish oil capsules (800 mg/d DHA)	Placebo capsules	16	Stroop Verbal fluency Pattern recognition test Digit span forward & backward Memory recall tests	Executive function Language Visuospatial functions Memory
Jae H. Kang et al., 2022	USA	RA/DB/parallel	M/F: 3424 Int: 1699 Con: 1725	Healthy	Int: 71.9 ± 5.6 Con: 71.8 ± 5.3	1 g/d fish oil capsules (840 mg/d EPA + DHA) + 2000 IU/d vit D3	Olive oil capsules	48	MMSE Global composite score TICS Executive function/attention composite score Verbal composite score	Global Executive function Memory
Justin E. Karr et al., 2012	Canada	RA/DB/parallel	M/F: 41 Int: 20 Con: 21	Healthy	Int: 19.90 ± 1.83 Con: 20.43 ± 1.63	2 capsules/d of fish oil (1200 mg/d n-3 PUFA)	2 capsules/d of coconut oil	4	TMT A&B Stroop word & color RAVLT	Executive function Attention Memory
Nadine Kulzow et al., 2016	Germany	RA/DB/parallel	M/F: 44 Int: 22 Con: 22	Healthy	Int: 63 ± 6 Con: 61 ± 6	4 × 1000 mg fish oil capsules/d (2200 mg/d n-3 PUFA)	4 × 1015 mg sunflower oil capsules/d	26	Learning (accuracy) Cued recall	Memory
Julia C Kuszewski et al., 2020	Australia	RA/DB/parallel	M/F: 64 Int:32 Con: 32	Healthy	Int: 65.8 ± 1.4 Con: 65.8 ± 1.4	4 capsules/d of fish oil (2400 mg/d EPA + DHA)	Placebo capsules (mix of corn and olive oil with 20 mg fish oil)	16	Fluid cognition Overall cognitive performance Cognitive flexibility Processing speed Language Episodic memory Working memory Verbal memory	Global Executive function Perceptual speed Language Memory
Regina L. Leckie et al., 2019	USA	RA/DB/parallel	M/F: 271 Int: 134 Con: 137	Healthy	Int: 43.1 ± 7.5 Con: 42.4 ± 7	2 × 1000 mg fish oil capsules/d (1400 mg/d EPA + DHA)	2 × 1000 mg soybean oil capsules	18	Fluid intelligence Executive function Psychomotor speed Learning/memory	Global Executive function Perceptual speed Memory
Lai Kuan Lee et al., 2012	Malaysia	RA/DB/parallel	M/F: 35 Int: 17 Con:18	mild cognitive impairment	Int: 66.4 ± 5.1 Con: 63.5 ± 3	3 × 1 g soft gelatine capsules (1750 mg EPA + DHA)	3 × 1 g soft gelatine capsules of corn oil	48	MMSE GDS Clock test Digit symbol Matrix reasoning VR 1 and 2 RAVLT Digit span Block design	Global Executive function Perceptual speed Language Memory Visuospatial functions

Continued

Author, year	Location	Design	Participants, *n*	Health condition	Age (year)	Intervention		Duration (week)	Cognitive tools	Cognitive domains
						Treatment	Control group			
Mengyue Li et al., 2020	China	RA/DB/parallel	M/F: 120 Int: 60 Con: 60	mild cognitive impairment	Int: 71.55 ± 6.62 Con: 70.38 ± 6.73	2 DHA capsules (800 mg/d DHA) and 1 placebo tablet (corn starch/day	2 placebo capsules (soybean oil) and 1 placebo tablet (corn starch)/d	24	Full scale IQ Arithmetic Information Digit span Block design Picture arrangement Picture completion	Global Executive function Perceptual speed Memory Visuospatial functions
Mohammad Jafar Mahmoudi et al., 2014	Iran	RA/DB/parallel	M/F: 199 Int: 100 Con: 99	mild to moderate cognitive impairment	Int: 74.13 ± 9.96 Con: 75.17 ± 8.70	1 capsule/d of Cod liver oil (300 mg/d EPA + DHA)	1 capsule/d MCTs (coconut oil + glycerol)	26	MMSE AMT	Global
Mathieu Maltais et al., 2022	Canada	RA/DB/parallel	M/F: 193 Int: 96 Con: 97	Healthy	Int: 49.4 ± 16.4 Con: 50.5 ± 16.6	Fish oil, 4 × 1 g capsules/d (2500 mg/d n-3 PUFA)	4 capsules/d of high–oleic acid soybean/corn oil (50/50)	24	TMT B Working memory Delayed Cued Recall score Cued letter	Executive function Memory Visuospatial functions
Bernadette P. Marriott et al., 2021	USA	RA/DB/parallel	M/F: 555 Int: 276 Con: 279	Healthy	Int: 23.4 ± 2.8 Con: 23.4 ± 2.8	Krill oil, 8 capsules/d (2300 mg/d n-3 PUFA)	Macadamia nut oil, 8 capsules/d	20	Stroop Four choice reaction time Digit symbol Grammatical reasoning Spatial working memory	Executive function Perceptual speed Language Memory
Robert K. McNamara et al., 2017	USA	RA/DB/parallel	M/F: 37 Int: 17 Con: 20	subjective cognitive impairment	Int: 69 ± 5.2 Con: 67 ± 4.9	Fish oil, 4 capsules/d (2400 mg/d EPA + DHA)	Corn oil, 4 capsules/d	24	DEX TMT A&B Phonological access Semantic access HVLT	Global Attention Executive function Language Memory
Alexia Mengelberg et al., 2022	New Zealand	RA/DB/parallel	M/F: 60 Int: 30 Con: 30	mild cognitive impairment	Int: 72.33 ± 6.16 Con: 73.40 ± 6.96	3 capsules/d (1842 mg/d DHA + EPA) + 1.15 mg vit E/capsules	3 capsules/d (1857 mg/d linoleic acid) + 1.15 mg vit E/capsules	48	RBANS TMT B COAST (Stroop) Coin Rotation Task Digit span	Global Executive function Perceptual speed Memory
C. Moran et al., 2018	Ireland	RA/DB/parallel	M/F: 37 Int: 20 Con: 17	Healthy	Int: 75.45 ± 3.56 Con: 74.76 ± 3.80	liquid nutrient support, 200 ml/d (3000 mg/d PUFA + 10mcg vit D + 150 mg resveratrol + 8 g whey protein)	200 ml/d juice	24	TMT A&B Stroop color-word Subjective Awareness TUG real and imagined Category Phoneme AVLT Digit span MI accuracy	Executive function Attention Perceptual speed Language Memory Visuospatial functions

Continued

Author, year	Location	Design	Participants, *n*	Health condition	Age (year)	Intervention		Duration (week)	Cognitive tools	Cognitive domains
						Treatment	Control group			
Matthew P. Pase et al., 2015	Australia	RA/DB/parallel	M/F: 78 Int: 41 Con: 37	Healthy	Int: 59.51 ± 5.89 Con: 59.19 ± 5.96	6 fish oil capsules/d (960 mg/d EPA + DHA)	6 placebo capsules/d (sunola oil)	16	Reaction time Cognitive processing speed Short term memory Visual memory	Perceptual speed Memory
Michelle A. Phillips et al., 2015	UK	RA/DB/parallel	M/F: 76 Int: 37 Con: 39	cognitive impairment and AD	Int: 71.1 ± 8.6 Con: 71.1 ± 9.5	2 capsules/d (1225 mg/d EPA + DHA)	2 capsules/d, olive oil	16	MMSE Clock test Verbal reasoning Verbal memory Visual memory Word finding test	Global Executive function Language Memory
Rebecca Power et al., 2021	Ireland	RA/DB/parallel	M/F: 50 Int: 28 Con: 22	Healthy	Int: 69.03 ± 4.41 Con: 69.77 ± 3.74	2 capsules/d containing 1 g fish oil, 22 mg xanthophyll carotenoids and 15 mg vitamin E (520 mg/d EPA + DHA)	Sunflower oil, 2 capsules/d	96	RBANS language Spatial working memory RBANS immediate	Language Memory
Joseph F. Quinn et al., 2010	USA	RA/DB/parallel	M/F: 295 Int: 171 Con: 124	AD	Int: 76 ± 9.3 Con: 76 ± 7.8	2 × 1 g DHA capsules/d (2000 mg/d DHA)	Corn or soy oil, 2 capsules/d	72	ADAS-cog CDR ADCS-ADL NPI	Global
Peter J. Rogers et al., 2007	UK	RA/DB/parallel	M/F: 190 Int: 96 Con: 94	Healthy	Int: 38 ± 13.5 Con: 38.2 ± 13.7	3 capsules/d (1480 mg EPA + DHA, 870 mg olive oil, 7·5 mg mixed tocopherols and 12 mg orange oil daily)	3 capsules/d (2360 mg olive oil, 7·5 mg mixed tocopherols and 12 mg orange oil daily)	12	Visual probe task Reaction time Digit symbol Impulsivity N-back test Lexical decision	Attention Perceptual speed Memory Language
Natalie Sinn et al., 2011	Australia	RA/DB/parallel	M/F: 40 Int: 16 Con: 11 Int: 13 Con: 11	mild cognitive impairment	Int: 74.22 ± 7 Con: 73 ± 3.96 Int: 74.88 ± 5.06 Con: 73 ± 3.96	4 capsules/d of DHA (1950 mg/d DHA + EPA) 4 capsules/d of EPA (1830 mg/d EPA + DHA)	4 capsules/d of safflower oil (2200 mg/d LA)	24	Letter fluency	Language
Pinelopi S. Stavrinou et al., 2020	Cyprus	RA/DB/parallel	M/F: 36 Int: 18 Con: 18	mild cognitive impairment	Int: 77.4 ± 9.2 Con: 81.2 ± 5.3	20 mL/d cocktail formula (4950 mg/d n-3 + 4950 mg/d n-6 + 0.6 mg/d vit A + 782 mg/d vit E + citrus-aroma)	20 mL/d of placebo, pure virgin olive oil	24	MMSE ACE-R TMT A&B Stroop color-word Symbol cancellation	Global Executive function Attention Perceptual speed
Welma Stonehouse et al., 2013	New Zealand	RA/DB/parallel	M/F: 176 Int: 85 Con: 91	Healthy	Int: 33.4 ± 7.76 Con: 33.2 ± 7.90	3 × 750 mg capsules/d (1330 mg/d DHA + EPA)	3 capsules/d, sunflower oil	24	Attention Processing speed Episodic memory Working memory	Attention Perceptual speed Memory
Continued										

Author, year	Location	Design	Participants, *n*	Health condition	Age (year)	Intervention		Duration (week)	Cognitive tools	Cognitive domains
						Treatment	Control group			
HisanoriTokuda et al., 2020	Japan	RA/parallel	M/F: 48 Int: 21 Con: 27	Healthy	Int: 67.1 ± 1.1 Con: 67.8 ± 0.8	6 capsules/d of LCPUFA (400 mg/d DHA + EPA)	6 capsules/d of purified olive oil	24	TMT A&B Stroop color-word KWCST CA Verbal memory Visual memory Digit span Verbal fluency	Attention Executive function Memory Language
Hisanori Tokuda et al., 2015	Japan	RA/DB/parallel	M: 69 Int: 30 Con: 39	Healthy	Int: 59.8 Con: 59.5	6 soft-gel capsules/d of LCPUFA (1033 mg/d PUFA)	6 soft-gel capsules of purified olive oil	4	P300 Latency	Perceptual speed
O. van de Rest et al., 2008	Netherlands	RA/DB/parallel	M/F: 299 Int: 96 Con: 103 Int: 100 Con: 103	Healthy	Int: 69.9 ± 3.4 Con: 70.1 ± 3.7 Int: 69.5 ± 3.2 Con: 70.1 ± 3.7	High dose fish oil capsules (1800 mg/d DHA + EPA) Low dose fish oil capsules (400 mg/d DHA + EPA)	Placebo capsules (oleic acid)	26	TMT A&B Stroop color-word Word fluency Word learning Digit span forward and backward	Attention Executive function Memory
A. Veronica Witte et al., 2013	Germany	RA/DB/parallel	M/F: 65 Int: 32 Con: 33	Healthy	Int: 65 ± 6.3 Con: 62.9 ± 6.8	4 fish oil capsules/d (2200 mg/d LCPUFA + 15 mg/d vit E)	4 sunflower oil capsules/d	26	Executive function	Executive function
Fumihiko Yasuno et al., 2012	Japan	CT/parallel	M/F: 663 Int: 41 Con: 622	Healthy	Int: 72.7 ± 4.8 Con: 73 ± 5.4	Capsules of purified fish oil + lycopene, and Ginkgo biloba leaf dry extracts daily (493 mg/d DHA + EPA)	No supplement	144	Composite score Attention Language ability Reasoning Memory	Global Attention Language Memory
Karin Yurko-Mauro et al., 2010	USA	RA/DB/parallel	M/F: 485 Int: 242 Con: 243	age-related cognitive decline	Int: 70 ± 9.3 Con: 70 ± 8.7	3 soft-gel capsules of algal triglyceride oil (900 mg/d DHA)	3 soft-gel capsules of corn and soy oil	24	MMSE SOC PAL PRM Spatial working memory Recognition verbal memory	Global Executive function Memory
Yan-Ping Zhang et al., 2017	China	RA/DB/parallel	M/F: 240 Int: 120 Con: 120	mild cognitive impairment	Int: 73.71 ± 2.24 Con: 73.58 ± 2.65	2 g/d algal-derived DHA capsules (2000 mg/d DHA)	Corn oil capsules	96	Full scale IQ Verbal IQ Performance IQ Arithmetic Digit symbol Information Comprehension Similarities Vocabulary Digit span Block design Picture arrangement Picture completion Object assembly	Global Executive function Perceptual speed Language Memory Visuospatial functions

Continued

Author, year	Location	Design	Participants, *n*	Health condition	Age (year)	Intervention		Duration (week)	Cognitive tools	Cognitive domains
						Treatment	Control group			
Yan-Ping Zhang et al., 2016	China	RA/DB/parallel	M/F: 240 Int: 120 Con:120	mild cognitive impairment	Int: 74.49 ± 2.65 Con: 74.57 ± 3.31	algal-derived DHA, 2 g/d capsules (2000 mg/d DHA)	Corn oil capsules	48	Full scale IQ Arithmetic Digit symbol Information Comprehension Similarities Vocabulary Digit span Block design Picture arrangement Picture completion Object assembly	Global Executive function Perceptual speed Language Memory Visuospatial functions
Avin Tofiq et al., 2021	Sweden	RA/DB/parallel	M/F: 33 Int: 18 Con: 15	AD	Int: 72 ± 8 Con: 68 ± 7	4 × 1 g capsules/d (2300 mg/d n-3 PUFA)	4 × 1 g capsules/d, corn oil	24	MMSE	Global
Ruihua Dong et al., 2022	China	RA/DB/parallel	M/F: 68 Int: 35 Con: 33	Neurocognitive impairment	Int: 54.6 ± 9.7 Con: 55.3 ± 9.3	algal oil DHA capsules (3150 mg/d DHA)	Soy oil capsules	24	MMSE GDS	Global
Chuntida Kamalashiran et al., 2018	Thailand	RA/DB/parallel	M/F: 182 Int: 94 Con: 88	Mild to Moderate Dementia	Int: 76.9 Con: 75	500 mg of perilla oil, 6 capsules/d (1700 mg/d n-3 PUFA)	500 mg of olive oil, 6 capsules/d	24	TMSE MoCA	Global
Havva Banu Salman et al., 2022	Turkey	RA/parallel	M/F: 40 Int: 20 Con: 20	Healthy	Int: 41.8 ± 8.8 Con: 43.4 ± 8.4	1020 mg/d omega-3 PUFA + weight loss diet	No supplement + weight loss diet	12	MoCA	Global
Pan-Yen Lin et al., 2021	Taiwan	RA/DB/parallel	M/F: 163 Int: 123 Con: 40	AD and mild cognitive impairment	Int (EPA): 77.80 ± 8.49 Int (DHA): 78.95 ± 7.89 Int(EPA + DHA): 76.73 ± 9.15 Con: 78.10 ± 8.59	4 × 0.5 g capsules/d (EPA group: 1600 mg/d, DHA group: 700 mg/d, EPA + DHA group: 1150 mg/d)	4 × 0.5 g capsules/d, soybean oil	96	MMSE GDS ADAS-cog	Global
Bjørn Lundbergh et al., 2022	Denmark	RA/DB/crossover	M/F: 22 Int: 11 Con: 11	ASD (autism)	Int: 28 ± 7 Con: 28 ± 7	5.2 g/d n-3 PUFA from fish oil, 4 capsules/d (4000 mg EPA + DHA)	2·8 g/d of linoleic acid from the Safflower oil, 4 capsules/d	8	Corsi Blocks tests Stroop color-word Relative Stroop effect d2 test	Memory Attention
Toshiaki Sueyasu et al., 2023	Japan	RA/DB/parallel	(trial 1) M/F: 71 Int: 35 Con: 36 (trial 2) M/F: 180 Int: 92 Con: 88	memory complaints but no dementia	(trail 1) Int: 65.7 Con: 65 (trial 2) Int: 65.1 Con: 65.1	6 soft-gel capsules containing LCPUFAs + lutein and zeaxanthin (400 mg/d EPA + DHA)	6 soft-gel capsules containing safflower and olive oil	12	Composite memory Verbal memory Visual memory	Memory

Table 1. Characteristics of trials included in the dose-response meta-analysis of omega-3 supplementation on cognitive function. Int, Intervention; Con, Control.

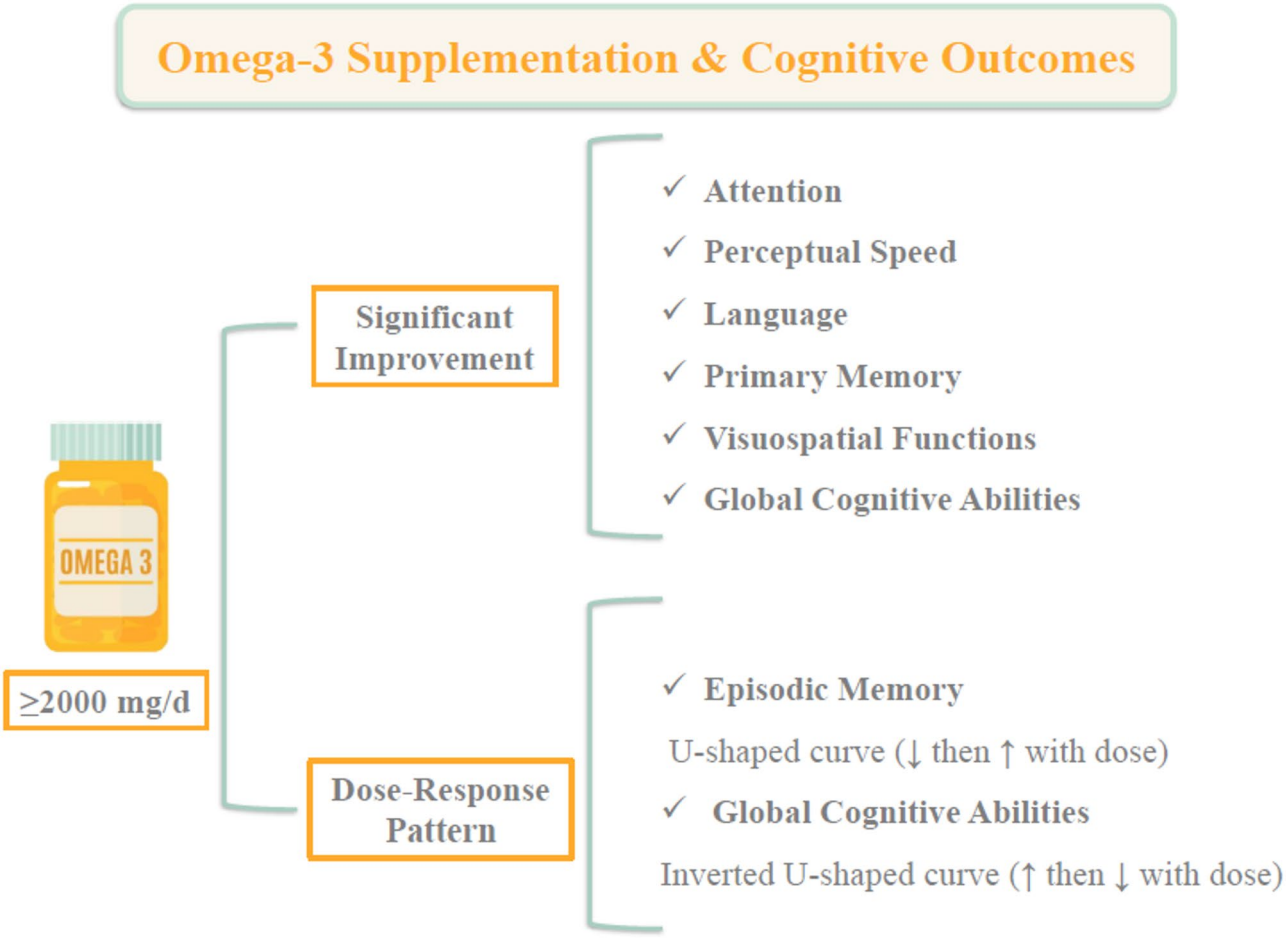

Fig. 2. Summary of main results.

increasing doses. The overall dose-response trend did not reach statistical significance either (*P* for dose-response = 0.14).

Effects of omega-3 supplements on executive functions

Thirty-nine study arms assessed the effect of omega-3 supplementation on executive function. No statistically significant effect was observed (SMD: 0.53; 95% CI: -0.16, 1.21), and the low certainty of evidence suggests that future studies may alter this estimate. Considerable heterogeneity was detected across studies ($I^2 = 98.6\%$; $P < 0.0001$) Supplementary Fig. 4. Subgroup analyses (Table 2) revealed notable differences in effect based on study location and participant characteristics. A remarkable improvement in executive functions was found in trials conducted in European and Asian countries, as well as among participants with a baseline BMI greater than 25 (SMD: 0.28; 95%CI: 0.16,0.41 and SMD: 1.074; 95%CI: 0.87,1.26 and SMD: 0.39; 95%CI: 0.31,0.48 respectively). Conversely, a significant decline in executive function was observed in studies that included only women (SMD: -0.48; 95%CI: -0.91, -0.04), which highlights potential sex-specific differences in response. Significant positive effects were demonstrated in RCTs with having no co-intervention (SMD: 0.56; 95%CI: 0.46, 0.66) (Table 2). Funnel plot analysis and Egger's test indicated no evidence of publication bias ($P = 0.718$) Supplementary Fig. 5. Sensitivity analyses demonstrated that the overall findings remained stable after the stepwise exclusion of individual studies (MD range: -0.35 to 1.31).

Dose-response modeling (Supplementary Fig. 6; Table 3) suggested no meaningful trend between omega-3 dosage and executive function outcomes. The effect size decreased slightly with increasing doses, but no statistically significant linear or non-linear relationship was observed (*P* for non-linearity = 0.92; *P* for dose-response = 0.97). This suggests that increasing omega-3 intake was not associated with a dose-dependent change in executive function performance.

Effects of omega-3 supplements on perceptual speed

A statistically significant improvement in perceptual speed was not observed (SMD: 0.44; 95%CI: -0.01,0.90), which was supported by *moderate-certainty* evidence, indicating a reasonably robust finding. Supplementary Fig. 7. However, substantial heterogeneity was detected among the studies ($I^2 = 96.4\%$, $p < 0.0001$). Based on subgroup analysis, studies conducted on both men and women revealed a significant enhancement in perceptual speed (SMD: 0.42; 95%CI: 0.34,0.49). Significant positive effects were illustrated in RCTs that did not have co-

	Effect size, *n*	SMD (95% CI)[1]	*P*-within[2]	I^2 (%)[3]	*P*-heterogeneity[4]	*P*-between[5]
Attention outcome						
Overall	32	0.117 (-0.958, 1.193)	0.831	98.5	< 0.001	
Intervention duration (weeks)						0.001
< 26	25	-0.054 (-0.211, 0.102)	0.498	92.5	< 0.001	
26≤	7	0.456 (0.248, 0.665)	0.001	99.6	< 0.001	
Age (years)						0.684
< 60	13	0.093 (-0.125, 0.310)	0.403	74.1	< 0.001	
60≤	19	0.148 (-0.005, 0.301)	0.058	99.1	< 0.001	
Location						0.001
America	15	-0.098 (-0.301, 0.105)	0.344	94.5	< 0.001	
Europe	10	-0.153 (-0.353, 0.047)	0.135	99.4	< 0.001	
Asia and Oceania	7	0.981 (0.720, 1.241)	0.001	95.5	< 0.001	
Health status						0.141
Healthy	20	0.029 (-0.153, 0.212)	0.752	94.9	< 0.001	
Cognitive disorders	12	0.218 (0.046, 0.389)	0.013	99.3	< 0.001	
BMI						0.001
Normal	27	-0.028 (-0.186, 0.130)	0.726	93.4	< 0.001	
Over weight	5	0.394 (0.190, 0.599)	0.001	99.8	< 0.001	
Assessment tool						0.001
TMT A	10	-0.081 (-0.259, 0.096)	0.370	99.5	< 0.001	
Stroop	14	0.725 (0.439, 1.011)	0.001	93.8	< 0.001	
Other tools	8	0.099 (-0.126, 0.323)	0.388	61.9	0.010	
Co-intervention						0.001
Yes	10	0.469 (0.291, 0.648)	0.001	92.3	0.010	
No	22	-0.199 (-0.375, -0.024)	0.026	99.5	< 0.001	
Executive function outcome						
Overall	39	0.520 (-0.159, 1.212)	0.132	98.6	< 0.001	
Intervention duration (weeks)						0.003
< 48	29	0.384 (0.286, 0.482)	0.001	97.2	< 0.001	
48≤	10	0.162 (0.043, 0.282)	0.008	99.5	< 0.001	
Age (years)						0.405
< 49	4	0.235 (0.062, 0.409)	0.008	76.6	0.005	
49≤	35	0.309 (0.225, 0.393)	0.001	98.7	< 0.001	
Location						0.001
America	12	0.062 (-0.046, 0.171)	0.259	97.8	< 0.001	
Europe	15	0.287 (0.160, 0.413)	0.001	99.3	< 0.001	
Asia and Oceania	12	1.074 (0.878, 1.269)	0.001	95.3	< 0.001	
Health status						0.001
Healthy	25	0.213 (0.125, 0.301)	0.001	97.6	< 0.001	
Cognitive disorders	14	0.530 (0.381, 0.679)	0.001	99.2	< 0.001	
BMI						0.001
Normal	14	-0.371 (-0.583, -0.158)	0.001	95.7	< 0.001	
Over weight	25	0.399 (0.318, 0.480)	0.001	99.0	< 0.001	
Sex						0.001
Males and females	34	0.319 (0.242, 0.396)	0.001	98.7	< 0.001	
Females	5	-0.482 (-0.917, -0.048)	0.03	48.4	0.10	
Assessment tool						0.001
TMT B	12	0.531 (0.384, 0.679)	0.001	99.5	< 0.001	
Stroop	6	0.332 (0.132, 0.533)	0.001	93.6	< 0.001	
Other tools	21	0.192 (0.090, 0.290)	0.001	93.8	< 0.001	
Co-intervention						0.001
Yes	14	-0.038 (-0.153, 0.077)	0.515	99.2	< 0.001	
No	26	0.560 (0.460, 0.661)	0.001	97.6	< 0.001	
Perceptual speed outcome						
Overall	34	0.444 (-0.014, 0.901)	0.057	96.4	< 0.001	
Intervention duration (weeks)						0.075
Continued						

	Effect size, *n*	SMD (95% CI)[1]	*P*-within[2]	I^2 (%)[3]	*P*-heterogeneity[4]	*P*-between[5]
< 48	20	0.478 (0.367, 0.590)	0.001	96.9	< 0.001	
48≤	14	0.350 (0.241, 0.460)	0.001	95.6	< 0.001	
Age (years)						0.001
< 60	12	0.619 (0.492, 0.747)	0.001	98.0	< 0.001	
60≤	22	0.290 (0.191, 0.388)	0.001	93.9	< 0.001	
Location						0.006
Asia and Oceania	17	0.570 (0.425, 0.716)	0.001	95.8	< 0.001	
Europe and America	17	0.350 (0.257, 0.442)	0.001	97.0	< 0.001	
Health status						0.020
Healthy	22	0.491 (0.393, 0.590)	0.001	96.3	< 0.001	
Cognition disorders	12	0.279 (0.150, 0.408)	0.001	96.7	< 0.001	
BMI						0.676
Normal	16	0.413 (0.206, 0.619)	0.001	97.0	< 0.001	
Over weight	18	0.413 (0.329, 0.498)	0.001	95.8	< 0.001	
Sex						0.001
Males and females	31	0.421 (0.343, 0.499)	0.001	98.3	< 0.001	
Males	3	-3.871 (-5.694, -2.049)	0.001	96.1	< 0.001	
Co-intervention						0.001
Yes	9	-0.131 (-0.286, 0.024)	0.099	98.0	< 0.001	
No	25	0.598 (0.507, 0.688)	0.001	94.7	< 0.001	
Language outcome						
Overall	26	0.976 (0.413, 1.539)	0.001	96.8	< 0.001	
Intervention duration (weeks)						0.001
< 48	12	0.784 (0.654, 0.914)	0.001	97.9	< 0.001	
48≤	14	-0.161 (-0.282, -0.039)	0.010	91.6	< 0.001	
Age (years)		0.001				
< 60	3	0.838 (0.688, 0.989)	0.001	99.5	< 0.001	
60≤	23	-0.018 (-0.129, 0.092)	0.744	92.3	< 0.001	
Location						0.001
Europe and America	16	0.401 (0.293, 0.508)	0.001	97.8	< 0.001	
Asia and Oceania	10	0.022 (-0.136, 0.180)	0.785	87.2	< 0.001	
Health status						0.001
Healthy	12	0.540 (0.414, 0.667)	0.001	98.2	< 0.001	
Cognitive disorders	14	0.030 (-0.095, 0.155)	0.638	91.0	< 0.001	
BMI						0.001
Normal	12	1.073 (0.762, 1.383)	0.001	97.8	< 0.001	
Over weight	14	0.210 (0.117, 0.303)	0.001	94.8	< 0.001	
Assessment tool						0.001
Verbal fluency	6	-0.476 (-0.778, -0.175)	0.002	95.9	< 0.001	
Other tools	20	0.353 (0.260, 0.446)	0.001	97.0	< 0.001	
Co-intervention						0.001
Yes	10	0.043 (-0.135, 0.222)	0.001	97.9	< 0.001	
No	16	0.359 (0.257, 0.462)	0.001	95.5	< 0.001	
Episodic memory outcome						
Overall	103	0.265 (-0.058, 0.588)	0.108	92.9	< 0.001	
Intervention duration (weeks)						0.001
< 48	86	0.423 (0.337, 0.508)	0.001	83.9	< 0.001	
48≤	17	-0.286 (-0.405, -0.167)	0.001	98.1	< 0.001	
Age (years)						0.001
< 60	31	0.532 (0.430, 0.634)	0.001	82.8	< 0.001	
60≤	72	-0.119 (-0.213, -0.024)	0.014	94.0	< 0.001	
Location						0.001
America	40	0.373 (0.283, 0.463)	0.001	82.6	< 0.001	
Europe	42	-0.255 (-0.375, -0.136)	0.001	95.5	< 0.001	
Asia and Oceania	21	0.659 (0.392, 0.927)	0.001	90.8	< 0.001	
Health status						0.001
Continued						

	Effect size, *n*	SMD (95% CI)[1]	*P*-within[2]	I^2 (%)[3]	*P*-heterogeneity[4]	*P*-between[5]
Healthy	69	0.280 (0.202, 0.357)	0.001	90.3	< 0.001	
Cognitive disorders	34	-0.211 (-0.366, -0.055)	0.008	95.4	< 0.001	
BMI						0.451
Normal	63	0.231 (0.086, 0.375)	0.002	85.1	< 0.001	
Over weight	40	0.167 (0.088, 0.246)	0.001	96.2	< 0.001	
Sex 0.153						
Males and females	90	0.187 (0.118, 0.257)	0.001	93.5	< 0.001	
Females	13	-0.282 (-0.922, 0.358)	0.387	82.4	< 0.001	
Co-intervention						0.001
Yes	23	-0.258 (-0.373, -0.143)	0.001	96.8	< 0.001	
No	80	0.434 (0.347, 0.521)	0.001	88.1	< 0.001	
Primary memory outcome						
Overall	20	0.768 (0.059, 1.477)	0.034	96.2	< 0.001	
Intervention duration (weeks)						0.001
< 48	13	0.189 (-0.028, 0.407)	0.021	63.0	< 0.001	
48≤	7	1.144 (0.984, 1.304)	0.001	98.6	< 0.001	
Location						0.001
America	2	0.610 (0.018, 1.201)	0.043	0.0	0.829	
Europe	10	-0.054 (-0.213, 0.106)	0.509	60.6	0.007	
Asia and Oceania	8	2.718 (2.483, 2.953)	0.001	94.0	< 0.001	
Health status						0.001
Healthy	15	0.004 (-0.149, 0.158)	0.955	55.2	0.005	
Cognitive disorders	5	2.741 (2.503, 2.978)	0.001	96.5	< 0.000	
BMI						0.405
Normal	6	1.054 (0.466, 1.642)	0.001	8.3	0.363	
Over weight	14	0.797 (0.665, 0.929)	0.001	97.4	< 0.001	
Assessment tool						0.001
Digit span	15	0.972 (0.822, 1.120)	0.001	97.0	< 0.001	
Other tools (recall)	5	0.372 (0.112, 0.631)	0.005	0.0	0.848	
Co-intervention						0.001
Yes	5	-0.126 (-0.461, 0.209)	0.460	55.5	0.061	
No	15	0.972 (0.833, 1.112)	0.001	97.0	0.001	
Visuospatial functions outcome						
Overall	15	0.893 (0.452, 1.333)	0.001	97.4	< 0.001	
Intervention duration (weeks)						0.001
< 48	6	2.038 (1.739, 2.338)	0.001	98.0	< 0.001	
48≤	9	0.364 (0.295, 0.433)	0.001	95.1	< 0.001	
Location						0.001
America and Europe	3	4.236 (3.768, 4.703)	0.001	98.1	< 0.001	
Asia	12	0.368 (0.300, 0.436)	0.001	93.4	< 0.001	
Health status						0.001
Healthy	3	4.236 (3.768, 4.703)	0.001	98.1	< 0.001	
Cognitive disorders	12	0.368 (0.300, 0.436)	0.001	93.4	< 0.001	
BMI						0.001
Normal	6	2.038 (1.739, 2.338)	0.001	98.0	< 0.001	
Over weight	9	0.364 (0.295, 0.433)	0.001	95.1	< 0.001	
Assessment tool						0.001
Block design	4	0.041 (-0.080, 0.171)	0.482	37.5	0.171	
Picture arrangement	3	0.122 (-0.002, 0.253)	0.059	87.8	< 0.001	
Picture completion	3	0.881 (0.747, 1.032)	0.001	81.7	0.001	
Other tools	5	0.852 (0.712, 0.980)	0.001	98.9	< 0.001	
Co-intervention						0.001
Yes	1	2.735 (2.033, 3.437)	0.001	-	-	
No	14	0.427 (0.360, 0.495)	0.001	97.3	< 0.001	
Global cognitive ability outcome						
Continued						

	Effect size, *n*	SMD (95% CI)[1]	*P*-within[2]	I^2 (%)[3]	*P*-heterogeneity[4]	*P*-between[5]
Overall	60	1.001 (0.650, 1.353)	0.001	97.1	< 0.001	
Intervention duration (weeks)						0.001
< 48	33	0.276 (0.168, 0.383)	0.001	93.4	< 0.001	
48≤	27	-0.137 (-0.203, -0.071)	0.001	98.3	< 0.001	
Age (years)						0.014
< 60	10	0.173 (0.012, 0.335)	0.036	62.7	0.004	
60≤	50	-0.041 (-0.101, 0.012)	0.161	97.4	< 0.001	
Location						0.001
America	17	-0.469 (-0.555, -0.384)	0.001	96.1	< 0.001	
Europe	17	0.214 (0.112, 0.315)	0.001	73.1	< 0.001	
Asia and Oceania	26	0.463 (0.341, 0.565)	0.001	98.2	< 0.001	
Health status						0.011
Healthy	19	0.071 (-0.021, 0.163)	0.131	96.3	< 0.001	
Cognitive disorders	41	-0.079 (-0.151, -0.008)	0.029	97.4	< 0.001	
BMI						0.001
Normal	30	0.322 (0.207, 0.437)	0.001	96.4	< 0.001	
Over weight	30	-0.131 (-0.196, -0.067)	0.001	97.5	< 0.001	
Co-intervention						0.002
Yes	15	0.141 (0.026, 0.255)	0.016	96.8	< 0.001	
No	45	-0.075 (-0.140, -0.011)	0.022	97.2	< 0.001	

Table 2. Subgroup analyses for the effects of omega-3 supplementation on cognitive function. CI: confidence interval, PP analysis: per protocol analysis, SMD: standardized mean difference. [1]Obtained from the random effects model. [2]Refers to the mean (95% CI). [3]Inconsistency, percentage of variation across studies due to heterogeneity. [4]Obtained from the Q-test.

Omega-3 supplementation (mg/d)	0 (Ref)	500	1000	1500	2000	2500	3000	3500	4000	4500	5000
Attention (SD)	0	0.36 (-0.19, 0.92)	0.55 (-0.16, 1.26)	0.58 (-0.06, 1.22)	0.47 (-0.49, 1.43)	0.25 (-1.60, 2.09)	-0.06 (-3.10, 2.98)	-0.42 (-4.83, 3.99)	-0.80 (-6.67, 5.06)	-1.20 (-8.54, 6.15)	-1.59 (-10.4, 7.23)
Executive functions (SD)	0	-0.07 (-0.55, 0.40)	-0.16 (-0.99, 0.66)	-0.27 (-2.09, 1.56)	-0.37 (-3.64, 2.89)	-0.48 (-5.32, 4.35)	-0.59 (-7.02, 5.83)	-0.70 (-8.73, 7.32)	-0.81 (-10.4, 8.81)	-0.92 (-12.1, 10.3)	-1.03 (-13.8, 11.8)
Perceptual speed (SD)	0	-0.41 (-1.42, 0.60)	1.16 (-0.30, 2.62)	4.44 (-2.29, 11.1)	8.56 (-4.92, 22.0)	12.8 (-7.65, 33.3)	17.10 (-10.3, 44.5)	21.36 (-13.1, 55.8)	25.6 (-15.8, 67.1)	29.9 (-18.5, 78.3)	34.1 (-21.3, 89.6)
Language (SD)	0	0.54 (-1.00, 2.08)	0.85 (-1.11, 2.81)	0.96 (-0.55, 2.47)	0.95 (-0.23, 2.12)	0.88 (-1.29, 3.04)	0.81 (-2.80, 4.41)	0.73 (-4.41, 5.87)	0.66 (-6.03, 7.35)	0.69 (-6.01, 8.01)	0.65 (-5.51, 4.21)
Episodic memory (SD)	0	-0.54 (-1.49, 0.41)	-0.24 (-0.98, 0.49)	0.73 (0.13, 1.33)	2.09 (-0.21, 4.40)	3.56 (-0.64, 7.76)	5.03 (-1.08, 11.1)	6.50 (-1.52, 14.5)	7.97 (-1.96, 17.8)	9.44 (-2.40, 21.2)	10.9 (-2.84, 24.6)
Primary memory (SD)	0	0.18 (-0.02, 0.38)	-0.24 (-0.98, 0.49)	0.73 (0.13, 1.33)	2.09 (-0.21, 4.40)	3.56 (-0.64, 7.76)	5.03 (-1.08, 11.1)	6.50 (-1.52, 14.5)	7.97 (-1.96, 17.8)	9.44 (-2.40, 21.2)	10.9 (-2.84, 24.6)
Visuospatial functions (SD)	0	-0.03 (-0.35, 0.28)	0.41 (0.01, 0.81)	1.21 (-0.15, 2.58)	2.21 (-0.50, 4.91)	3.23 (-0.87, 7.34)	4.26 (-1.26, 9.77)	5.28 (-1.64, 12.2)	6.30 (-2.02, 14.6)	6.61 (-2.22, 12.6)	7.21 (-3.12, 11.2)
Global cognitive (SD)	0	0.56 (0.13, 0.98)	0.89 (0.26, 1.52)	1.00 (0.31, 1.68)	0.96 (0.16, 1.76)	0.87 (-0.20, 1.94)	0.77 (-0.66, 2.20)	0.67 (-1.16, 2.49)	0.57 (-1.67, 2.81)	0.47 (-2.19, 3.13)	0.37 (-2.71, 3.46)

Table 3. The effects of different doses of omega-3 supplementation on cognitive function form the nonlinear dose-response meta-analysis (standardized mean difference and 95% confidence interval). mg/d, milligram per day; Ref, reference; SD, standard deviation.

intervention (SMD: 0.59; 95%CI: 0.50, 0.68) (Table 2). No evidence of publication bias was detected according to funnel plot and Egger's test ($P = 0.51$) Supplementary Fig. 8. Sensitivity analysis revealed that studies conducted by Philippa A. Jackson et al. (SMD: 0.58, 95%CI: 0.14, 1.03), Matthew P. Pase et al. (SMD: 0.47, 95%CI: 0.01, 0.93), Hisanori Tokuda et al. (SMD: 0.64, 95%CI: 0.21,1.07), Sandrine Andrieu et al. (SMD: 0.50, 95%CI: 0.04, 0.96), and Pinelopi S. Stavrinou et al. (SMD: 0.50, 95%CI: 0.03, 0.96) had a notable influence on the overall results.

Dose-response analysis illustrated in Supplementary Fig. 9 and Table 3 showed that perceptual speed declined with increasing omega-3 dosage up to 500 mg/d (SMD500mg/d: -0.41, 95%CI: -1.42, 0.60), and then appeared to increase with an upward curve (P for non-linearity = 0.18), and the overall dose-response relationship did not reach significance ($P = 0.09$).

Effects of omega-3 supplements on Language

Twenty-six arms of studies evaluated the effect of omega-3 supplementation on language abilities. While a substantial improvement in language was observed (SMD: 0.98; 95%CI: 0.41,1.54) Supplementary Fig. 10, the GRADE rating of *low certainty* limits the strength of this conclusion. Marked heterogeneity was detected across studies ($I^2 = 96.8\%$; $P < 0.0001$), likely reflecting variation in populations, intervention durations, and assessment methods prompting subgroup analysis which revealed statistically significant increase in language abilities after omega-3 supplementation when the duration was less than 48 weeks, the participants were younger than 60 years old, without any cognitive disorders, and when trials were carried out in American and European countries (SMD: 0.78; 95%CI: 0.65, 0.91 and SMD: 0.83; 95%CI: 0.68, 0.98 and SMD: 0.54; 95%CI: 0.41, 0.66 and SMD: 0.40; 95%CI: 0.29, 0.50 respectively) (Table 2). Additionally, the use of assessment tools other than verbal fluency exams significantly greater improvement language abilities (SMD: 0.35; 95%CI: 0.26,0.44) (Table 2). Significant positive effects were showed in RCTs with having no co-intervention (SMD: 0.359; 95%CI: 0.25, 0.46) (Table 2). Visual inspection of funnel plot and the results of Egger's tests did not suggest any publication bias ($P = 0.375$) Supplementary Fig. 11. According to the sensitivity analysis, a study by Peter J. Rogers et al.[54] had a notable impact on the overall findings (SMD: 0.34; 95%CI: -0.08,0.78).

Dose-dependent effects of omega-3 on language abilities are demonstrated in Supplementary Fig. 12 and Table 3. Language abilities increased with the increase in omega-3 dosage up to 1500 mg/d (SMD1500mg/d: 0.96, 95%CI: -0.55, 2.47), and then appeared to plateau. However, the non-significant P for non-linearity (*P* for non-linearity = 0.69) and overall dose-response trend (*P* for dose-response = 0.26) suggest that the relationship was approximately linear and not statistically dependent on dosage within the range studied.

Effects of omega-3 supplements on episodic memory

No statistically significant effect of omega-3 supplementation on episodic memory was observed (SMD: 0.27; 95%CI: -0.06, 0.59) (Supplementary Fig. 13), but the evidence was rated as *low certainty*, reflecting concerns about the consistency and precision of the results. Substantial heterogeneity was present across studies (I^2: 92.9%; $P < 0.0001$). Subgroup analysis revealed a significant improvement in episodic memory among cognitively healthy individuals and in studies with intervention durations less than 48 weeks (SMD: 0.28; 95%CI: 0.20, 0.35 and SMD: 0.42; 95%CI: 0.33, 0.50 respectively). Significant positive effects were also demonstrated in RCTs that did not have co-intervention (SMD: 0.43; 95%CI: 0.34, 0.52) (Table 2). No evidence of publication bias was detected, based on funnel plot inspection and Egger's test ($P = 0.912$) (Supplementary Fig. 14). Sensitivity analysis identified that individual studies by Karin Yurko-Mauro et al.[12] (SMD: 0.32; 95%CI: 0.007, 0.64), Sandrine Andrieu et al.[39] (SMD: 0.32; 95%CI: 0.03,0.61) and Rebecca Power et al.[53] (SMD: 0.32; 95%CI: 0.005,0.64) had an influence on the overall results, each producing modest positive effects.

Dose-response analysis is presented in Supplementary Fig. 15 and Table 3. Levels of episodic memory decreased with the increase in omega-3 dose up to 1000 mg/d (SMD1000mg/d: -0.24, 95%CI: -0.98, 0.49), then appeared to increase with an upward curve. The test for non-linearity was statistically significant (*P* for non-linearity = 0.01), and the overall dose-response association reached significance (*P* for dose-response = 0.005), suggesting that benefits on episodic memory may only emerge at higher intake levels.

Effects of omega-3 supplements on primary memory

Our meta-analysis showed that omega-3 supplementation has a positive effect on primary memory (SMD: 0.77; 95% CI: 0.06, 1.48), and the high-certainty evidence strongly supports the reliability of this finding. (Supplementary Fig. 16). However, marked heterogeneity was detected across the included studies ($I^2 = 96.2\%$; $P < 0.0001$). We could explain the heterogeneity by doing subgroup analyses depending on the study's location and memory assessment tools. Notably, significant improvements in primary memory were observed in studies conducted in America and those utilizing recall-based tests (SMD: 0.37; 95%CI: 0.11,0.63 and SMD: 0.61; 95%CI: 0.01,1.20 respectively) (Table 2). Significant positive effects were also demonstrated in RCTs that did not have co-intervention (SMD: 0.991; 95%CI: 0.852, 1.130) (Table 2). Funnel plot symmetry and Egger's test results provided no indication of publication bias ($P = 0.995$) (Supplementary Fig. 17). Sensitivity analysis showed that individual studies by Lai Kuan Lee et al. (SMD: 0.67; 95%CI: -0.04, 1.40), Yan-Ping Zhang et al. (SMD: 0.55; 95%CI: -0.02, 1.14), Mengyue Li et al. (SMD: 0.71; 95%CI: -0.01, 1.45) had an influence on the overall results.

Dose-dependent effects of omega-3 on primary memory are revealed in Supplementary Fig. 18 and Table 3. Dose-response analysis (Supplementary Fig. 18 and Table 3) revealed a linear relationship between omega-3 dosage and primary memory performance, with greater benefits emerging at doses above 1000 mg/d. The absence of a significant non-linear trend (*P* for non-linearity = 0.48) alongside a significant dose-response association (*P* for dose-response = 0.02) supports a gradual, dose-related enhancement of primary memory.

Effects of omega-3 supplements on visuospatial functions

Omega-3 supplementation was linked to a significant improvement in visuospatial function (SMD: 0.89; 95% CI: 0.45, 1.33), with the GRADE assessment assigning a high certainty to this evidence, thereby reinforcing the strength of this result (Supplementary Fig. 19. Considerable heterogeneity was anticipated, and indeed, substantial variability was observed ($I^2 = 97.4\%$; $P < 0.0001$). To explore potential sources, subgroup analysis was performed based on intervention duration, location of the study, participants' health status and baseline BMI, outcome assessment tools and co-intervention. However, none of them were able to explain the cause of heterogeneity except assessment tools (Table 2). No publication bias was found based on funnel plot and Egger's test ($P = 0.169$) (Supplementary Fig. 20). Sensitivity analysis confirmed the stability of the findings, as no study influenced the overall results after individual study effects were removed (MD range: 0.20 to 1.44).

Dose-dependent effects of omega-3 on visuospatial functions are revealed in Supplementary Fig. 21 and Table 3. Visuospatial functions increased linearly, indicating a consistent effect across increasing doses of omega-3, particularly at doses above 500 mg (P for non-linearity = 0.37, P for dose-response = 0.004).

Effects of omega-3 supplements on global cognitive ability

Global cognitive abilities markedly improved by omega-3 supplementation (SMD: 1.00; 95%CI: 0.65,1.35), although the *low certainty* rating from GRADE suggests caution in interpreting the robustness of this finding. (Supplementary Fig. 22). To discover the potential source of the considerable heterogeneity ($I^2 = 97.1\%$; $P < 0.0001$), subgroup analysis was conducted. Studies with intervention duration less than 48 weeks, participants younger than 60 years old, cognitively healthy individuals, and participants with normal BMI accounted for the observed heterogeneity (Table 2). Significant reverse effects were seen in RCTs that did not have co-intervention (SMD: -0.07; 95%CI: -0.14, -0.01) (Table 2). Funnel plot asymmetry and Egger's test indicated significant publication bias ($P < 0.0001$) (Supplementary Fig. 23). Despite this, sensitivity analysis confirmed the robustness of the overall effect estimate, as no single study significantly influenced the results (MD range: 0.50 to 1.41). Dose-dependent effects of omega-3 on language abilities are demonstrated in Supplementary Fig. 24 and Table 3. Enhancement of global cognitive abilities was observed with increasing omega-3 dosage up to 1500 mg/day. (SMD1500mg/d: 1.00, 95%CI: 0.31, 1.68), followed by downward trend at higher doses. The significant non-linearity (P for non-linearity = 0.008) suggests that the relationship between dose and cognitive effect was not consistent across the full dosage range, despite an overall significant dose-response trend (P for dose-response = 0.002).

GRADE assessment

The GRADE evidence profile and the certainty of omega-3 supplementation's effects on cognitive function are shown in Supplementary Table 5. The certainty of evidence was low for attention, executive functioning, language, episodic memory, and global cognitive ability; moderate for perceptual speed, and high for primary memory and visuospatial functions.

Discussion

Globally, the role of omega-3 fatty acids in preserving and enhancing cognitive function has attracted increasing attention, particularly as populations age and the burden of cognitive decline grows. However, evidence remains inconclusive regarding the optimal dosage and the specific cognitive domains that benefit most. To the best of our knowledge, this is the first GRADE-assessed meta-analysis to evaluate the dose-response effects of omega-3 supplementation on adult cognitive function, including both cognitively healthy individuals and those with cognitive impairments. It represents a key methodological advancement over previous reviews, offering more detailed insights into the effects of different omega-3 dose levels which highlighting the novelty of our research.

Our primary analysis revealed that omega-3 supplementation is associated with a notable improvement in in perceptual speed, language, primary memory, visuospatial function, and global cognitive ability. The subgroup analysis indicates that greater cognitive benefits in the most of the cognitive domains are observed in participants who are cognitively healthy and in trials with intervention durations shorter than 48 weeks.

The dose-response analysis revealed valuable findings regarding omega-3 dosage and improvements in primary and episodic memory, visuospatial functions, and global cognitive ability. According to our analysis, the optimal dose of omega-3 supplementation—associated with the most consistent and pronounced effects—is between 1000 and 2500 mg per day. Moreover, no adverse effects were reported among participants consuming omega-3 supplements within this dosage range. This apparent optimal range may reflect both a biological plateauing of benefits at higher doses and the limited number of trials that evaluated doses beyond 2500 mg/day.

Sensitivity analysis indicated that several studies exerted a notable influence on the overall results. Their impacts might be linked to their methodological and population characteristics. For instance, studies conducted by Zhang was conducted on Chinese older adults with mild cognitive impairments, and assessed all cognitive domains comprehensively. Additionally, they prescribed high-dose DHA supplements (up to 2000 mg) which may have caused greater positive effect. In contrast, Marriott et al. included younger adults and used much more sensitive test, such as Stroop and reaction time task, which efficiently detect subtle changes. Rogers et al. conducted a 12-week study including healthy mid-age adult, which might be the reason of capturing early effects of omega-3 supplementation. Similarly, studies by Yurko-Mauro et al., Andrieu et al., and Power et al. targeted older adults (~69–75 years), but varied in terms of health conditions (e.g., subjective memory complaints vs. healthy aging) and intervention types, influencing effect sizes accordingly.

While these findings are promising, those should be interpreted with caution due to considerable heterogeneity and the low certainty of evidence, primarily driven by variability in study population, dosage and duration, outcome measures, baseline cognitive status, and the cognitive assessment tools used.

These findings seem to be in line with the results of A. Alex et al.[80]who showed a slight improvement in memory function. Although Mazereeuw et al.[18] reported consistent findings for attention, immediate recall and processing speed, the effects of n-3 FAs were limited to CIND (cognitive impairment no dementia) populations. In contrast to our findings, several previous meta-analyses have reported divergent results. Ruth E Cooper et al.[81] discovered no evidence of an effect of n-3 PUFA supplementation on cognitive performance in the general population, and Balachandar et al.[2] found that DHA supplementation has an insignificant or no beneficial role in slowing or improving age-related decline in memory, executive functions, working memory, and attention. The differing results between our meta-analysis and those of Balachandar et al. (2020) and Cooper et al. (2015) likely stem from variations in study populations, cognitive domains assessed, and methodological approaches. While Balachandar et al. focused mainly on older adults with age-related cognitive decline and Cooper et al. included general populations without detailed subgroup analyses, our study encompassed both cognitively healthy and impaired individuals and examined multiple specific cognitive domains. Additionally, unlike the

previous reviews, we conducted a dose-response analysis identifying an optimal omega-3 dose range (1000–2500 mg/day), which may clarify inconsistencies in prior findings due to heterogeneous dosing. Differences in intervention duration and updated inclusion criteria further contribute to the contrasting results observed.

In terms of underlying mechanisms, omega-3 poly-unsaturated fatty acids, particularly DHA and EPA, play crucial roles in brain structure and function. These fatty acids offer protective effects notably mitigating cognitive decline in aging population.

Perceptual speed declines have been closely associated with reduced white matter integrity, which disrupts neural connectivity and negatively impacts cognitive processing speed[82]. Notably, long-chain omega-3 fatty acids may help preserve white matter structure and support neural integrity, thereby enhancing perceptual speed[83]. Additionally, the hippocampus plays a central role in primary memory functions[84]and its atrophy has been strongly linked to memory impairments[85]. Omega-3 supplementation has demonstrated potential in attenuating hippocampal volume loss among older adults, offering a protective effect against age-related memory decline[86]. Furthermore, the parietal lobe is critically involved in visual-spatial processing, underscoring its importance in maintaining visuospatial cognitive functions[87]. Evidence indicates that long-chain omega-3 supplementation preserves brain structure—including the parietal lobe—by exerting beneficial effects on white matter integrity and gray matter volume[57]. Ultimately, omega-3 fatty acids serve as precursors for synthesis of neuroprotectin D1 (NPD1) and resolvins. These lipid mediators actively attenuate neuroinflammation, a major contributor to neurodegeneration and cognitive ability decline[88,89].

The current meta-analysis has several strengths, including a large sample size that enabled a comprehensive investigation of the dose-response relationship between omega-3 supplementation and various cognitive domains. This dose-response analysis represents a key methodological advancement over previous reviews, offering more detailed insights into the effects of different omega-3 intake levels. Our meta-analysis is novel in combining dose-response modeling with a formal GRADE assessment of the certainty of evidence in the context of omega-3 supplementation and cognitive function. This integrated approach provides a more nuanced understanding of how different omega-3 doses relate to cognitive outcomes, while transparently evaluating the quality and strength of the evidence. Additionally, we performed subgroup analyses to explore variability across different populations, further enhancing the clinical relevance and interpretability of our findings.

This study also has a few limitations. First, several cognitive tests were used to reflect a single cognitive domain. Nonetheless, by giving the most popular cognitive test for analysis priority, an attempt was made to lessen this heterogeneity. Additionally, it was discovered that some cognitive tests lacked specificity for the assigned cognitive domain. Second, we couldn't perform subgroup analysis based on cognitive assessment methods for all of the domains due to this variety of cognitive tests. Third, the majority of the studies were low quality based on risk of bias assessment. Finally, sensitivity analysis demonstrated that by removing five studies in perceptual speed[7,36,54,79]one study in language[54]and three studies in episodic memory[12,39,53]the overall effect size was significantly changed; therefore, the results for these outcomes should be interpreted with caution. To reduce heterogeneity and improve comparability, we recommend standardizing cognitive assessment tools across future studies. Moreover, higher-quality randomized controlled trials with rigorous methodology are needed to strengthen the certainty of evidence. Lastly, longer-term studies exploring optimal dosing strategies and their sustained impact on diverse cognitive domains are warranted to better inform clinical recommendations.

Conclusion

In conclusion, our meta-analyses indicate that omega-3 fatty acid supplementation may confer beneficial effects on several cognitive domains, including perceptual speed, language ability, primary memory, visuospatial functions, and overall cognitive performance. Furthermore, dose-response analysis suggests that memory, visuospatial functions, and global cognition may improve at specific dosage levels of omega-3 intake. However, based on the GRADE assessment, high certainty of evidence supports only the outcomes related to primary memory and visuospatial functions. The findings for other cognitive domains should be interpreted with caution.

Data availability

The data are available from the corresponding author on reasonable request.

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HSH and ZY were involved in the systematic search, screening, and extraction of data. HSH and KT contributed to the statistical analysis and interpreting the data. ZY and NA took part in drafting the manuscript. SS-B contributed to the interpretation of the results and critically revised the manuscript. All authors gave their approval for the final manuscript to be submitted. SS-B is the guarantor.

Declarations

Competing interests
The authors declare no competing interests.

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