Cognitive efficacy of omega-3 fatty acids in Alzheimer's disease: A systematic review and meta-analysis

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Abstract. Alzheimer's disease (AD), the most prevalent form of dementia, is a progressive neurodegenerative disorder characterized by a gradual decline in several domains of higher cortical function. Both preclinical and clinical research has suggested that the supplementation omega-3 fatty acids (FAs) may have potential benefits for individuals with AD. The present study aimed to identify all randomized controlled trials (RCTs) examining the association between omega-3 FA supplementation and cognitive function in patients with AD, using the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) Subscale test as the primary outcome measure. A comprehensive search of the PubMed and Cochrane Library databases was conducted for all published RCTs up to December, 2023 that assessed cognition following omega-3 FA supplementation compared to placebo. A total of five studies met the eligibility criteria and were included in the qualitative synthesis, with four of these studies being incorporated into the meta-analysis. From these studies, data were collected from a total of 702 patients with AD, with 376 participants receiving omega-3 FA supplementation and 326 participants receiving a placebo. The primary outcome measure was the ADAS-Cog score. The meta-analysis revealed that omega-3 FA supplementation had a non-significant impact on the ADAS-Cog score compared to placebo, with a mean difference of 1.37 [95% confidence interval (CI) 0.00-2.73]. The heterogeneity among the included studies was moderate (I^2=35%, P=0.17). The test for overall effect (z=1.96, P=0.05) indicated no statistical significance. Therefore, it was concluded that omega-3 FA supplementation does not significantly affect the cognitive function of adults with AD.

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Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder and the most common type of dementia, accounting for 60 to 80% of cases. Dementia encompasses a group of neurodegenerative disorders characterized by chronic and progressive cognitive deterioration in various higher cortical functions, including memory, thinking and decision-making abilities, which significantly impair independent living. The global prevalence of AD has substantial public health implications. In 2018, it was estimated that ~50 million individuals worldwide suffered from dementia, rendering AD a critical global public health concern. According to recent data, the prevalence of dementia in Europe is projected to double by the year 2050 (1).

Aging is a key risk factor for the development of AD. Of note, <5% of AD cases occur prior to the age of 65 years and are classified as early-onset AD, while the majority of cases occur after 65 years of age and are characterized as sporadic or late-onset AD (2). In line with the hypothesis that AD is age-related, normal aging is associated with a decline in cognitive abilities. However, in AD, these pathophysiological changes are exacerbated by neuroinflammation, cellular biological alterations and injuries (3).

The Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) Subscale test is widely used in research and clinical trials to measure cognitive function, primarily assessing language, memory and praxis. This score is considered the gold standard for evaluating treatments against dementia (4).

Recently, there has been growing interest in the role of omega-3 fatty acids (FAs) in promoting health and reducing morbidity. Omega-3 FAs are polyunsaturated FAs with long hydrocarbon chains, including α-linolenic acid (ALA, 18:3 ω-3), stearidonic acid (SDA, 18:4 ω-3), eicosapentaenoic acid (EPA, 20:5 ω-3), docosapentaenoic acid (22:5 ω-3) and docosahexaenoic acid (DHA, 22:6 ω-3). EPA and DHA are synthesized from the essential omega-3 FA ALA through

elongation and desaturation, catalyzed by delta-15 desaturase. ALA is found in plants, particularly in vegetable oils, seeds and nuts. These FAs play a critical role in the healthy development and functioning of the human body. Various potential health benefits have been investigated (5).

Dietary supplementation with omega-3 FAs may influence brain function by altering membrane fluidity, the activity of membrane-bound enzymes, ion channel function, receptor affinity and number, and signal transduction pathways that regulate neurotransmitter and neuronal growth factor activity (6). Epidemiological research has suggested an association between a low omega-3 FA intake and an increased risk of cognitive decline or dementia, particularly AD (7). In 2004, MacLean *et al* (8) provided clinical evidence linking omega-3 FAs to the prevention of AD. Omega-3 FAs are essential for the assembly, maturation and physiological function of neuronal structures. Additionally, omega-3 FAs are crucial for higher cognitive functions, such as cognition and memory (9).

The association between omega-3 FAs and cognition remains under investigation, with accumulating evidence and inconsistent results regarding the efficacy of dietary supplementation on the cognitive functions of patients with AD. While recent clinical and epidemiological research has indicated that specific dietary components may influence the risk of developing AD, the cognitive health benefits of fish and omega-3 FAs in older healthy individuals appear to be more consistent than in patients diagnosed with AD (5).

The critical question of whether dietary supplementation with omega-3 FAs, such as DHA, can alter the risk of developing AD or the progression of the condition remains unanswered. Randomized controlled trials (RCTs) are essential for evaluating the efficacy of various treatment options. Therefore, the present study aimed to identify all RCTs examining the association between omega-3 FA supplementation and cognitive function in patients with AD, as measured by the ADAS-Cog test, and to conduct a meta-analysis and determine whether these nutrients improve cognition.

Data and methods

Search strategy. A comprehensive literature search was conducted in two electronic databases, PubMed and Cochrane Library, for all eligible published RCTs assessing cognition following omega-3 FA supplementation compared to a placebo, from inception up to December 31, 2023. Key words, synonyms and Boolean operators were utilized to create the search strategy. The search query on the Medline database was as follows: (Alzheimer Disease) AND [(Omega3 Fatty) OR (Omega-3) OR (Fatty acids) OR (Omega-3 fatty acids) OR (Omega 3 fatty acids)] AND [(RCT) OR (randomized controlled trial) OR (clinical trial)]. Similar queries were employed for controlled vocabulary searches. Filters applied included article type (Clinical trial, RCT) and species (humans). There were no restrictions on language and time. Unpublished manuscripts were not considered.

Study selection. Studies were included based on the following Population, Intervention, Comparator, Outcome, Study type (PICOS) criteria: i) Participants: Adults with AD; ii) intervention: Omega-3 FA supplementation; iii) comparator: Placebo; outcome: Cognition, assessed using the ADAS-Cog test; and iv) study type: RCTs.

Statistical analysis. Data analysis was conducted using RevMan 5.3 software (https://revman.cochrane.org/info). The outcomes were treated as continuous variables and analyzed using the random effects model. The point estimate for continuous variables was the mean difference (MD) along with the corresponding 95% confidence intervals (CIs). To impute a standard deviation of the change from baseline for the experimental intervention, an appropriate formula was used according to the Cochrane Handbook for Systematic Reviews of Interventions (10). Statistical homogeneity was evaluated with the Chi-squared test and the I^2 test. A value of $P<0.05$ was considered to indicate a statistically significant difference. Sensitivity analysis was also performed by successively deleting each study and reanalyzing the data set for all remaining studies.

Quality assessment and data extraction. The Revised Cochrane risk of bias tool for randomized trials (RoB 2.0) (10) was used to assess the methodological quality of the included studies. Two researchers (TVK and KD) independently used a standardized form to collect data on the RCTs. The form included data on the names of authors, year of publication, study design, study characteristics (sample size, and age and sex of the study participants, duration of the intervention), intervention (type of omega-3 FA and dosage), outcome assessment and results. Discrepancies between the two reviewers were resolved through discussion and consensus with a third senior reviewer (DK). The grading of retrieved evidence for the efficacy outcome (improved cognition) was performed in accordance with the GRADE framework (11).

Results

Selected studies. Initially, 143 results were retrieved from the PubMed database and 192 results from the Cochrane Library database. After removing duplicate records and evaluating the titles and abstracts to identify relevant articles, five studies (12-16) met the eligibility criteria and were included in the qualitative synthesis, with four of these studies (12-15) being included in the present meta-analysis. The study by Shinto *et al* (16) was excluded from the quantitative synthesis, as the results were not presented in an appropriate format. Data were collected from a total of 702 patients with AD, with 376 participants assigned to omega-3 FA supplementation and 326 participants assigned to a placebo. A flow diagram illustrating the study selection process is presented in Fig. 1.

Characteristics of selected studies. The five clinical studies were conducted between 2006 and 2022. The age of the study participants ranged from 64 to 85 years. The clinical trials varied in duration from 24 weeks to 24 months. Omega-3 FAs (DHA, EPA, or combinations thereof) were administered orally in the form of capsules. Both females and males were included in the studies. The ADAS-Cog test was performed at the beginning of the studies and at the final time endpoint in all studies. All the studies included were RCTs. The characteristics of the included studies are presented in Table I.

Table I. Summary of the baseline characteristics of the participants, which are of interest, across the selected trials.

Characteristic	Authors (Refs.)				
	Freund-Levi *et al* (12)	Chiu *et al* (15)	Quinn *et al* (13)	Shinto *et al* (16)	Lin *et al* (14)
No. of participants on omega-3 FAs	89	20	238	13	123
No. of participants on the placebo	85	15	134	13	40
Age of the participants (years) on omega-3 FAs	72.6±9	74.0±3.9	76±9.3	75.9±8.1	EPA group, 77.80±8.49; DHA group, 78.95±7.89; EPA + DHA group, 76.73±9.15
Age of the participants (years) on the placebo	72.9±8.6	76.5±4.7	76±7.8	75.2±10.8	78.10±8.59
Females on omega-3 FAs (n, %)	51 (57%)	65%	47.1%	39%	EPA group, 32.5%; DHA group, 29.27%; EPA + DHA group, 35.71%
Females on the placebo (n, %)	39 (46%)	46.7%	59.8%	54%	37.50%
Omega-3 FA	DHA + EPA	EPA + DHA	DHA	DHA + EPA	EPA, DHA and EPA + DHA
Route of administration	Oral (capsules)	Oral (capsules)	Oral (capsules)	Oral (capsules)	Oral (capsules)
Dosage	430 mg DHA+150 EPA	1,080 mg EPA + 720 mg DHA	2 g DHA	675 mg DHA + 975 mg EPA	EPA group, 1.6 g; DHA group, 0.7 g; EPA + DHA group, 0.8 g EPA + 0.35 g DHA
Duration	6 months	24 weeks	18 months	12 months	24 months
ADAS-Cog baseline for omega-3 FA supplementation	25.7±10.1	9.17±7.19	23.77 (8.9)	31.8 (9.4)	EPA group, 15.29±8.48; DHA group, 14.60±6.38; EPA + DHA group, 16.33±8.46
ADAS-Cog baseline for placebo supplementation	27.2±10.1	7.99±7.13	23.96 (9.2)	32.2 (9.5)	14.76±6.98
ADAS-Cog final for omega-3 FA supplementation	27.7±11.1	5.90±5.63	31.75±11.8	-	EPA group, 17.93±6.43; DHA group, 17.53±7.17; EPA + DHA group, 18.7±3.68
ADAS-Cog final for placebo supplementation	28.3±10.8	5.57±4.76	32.23±10.32	-	15.61±4.03

FA, fatty acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale.

Meta-analysis. As demonstrated in Fig. 2, omega-3 FA supplementation compared to a placebo resulted in a non-significant impact on the ADAS-Cog score (MD=1.37; 95% CI, 0.00-2.73). The included studies were similar (I^2=35%; P=0.17). The test for overall effect (Z=1.96; P=0.05) confirmed no statistically significant difference. No heterogeneity was demonstrated for the comparison. Publication bias was assessed with funnel plots and the risk was low (Fig. 3). Egger's test was also performed. It yielded a value of 0.07 (>0.05) with a regression coefficient of -1.5; the results demonstrated no major publication bias, but a possible sign against publication of smaller size studies.

Quality assessment. The risk of bias assessment of the included trials according to the revised Cochrane risk of bias tool for randomized trials (RoB 2.0) is presented in Table II. The study by Freund-Levi *et al* (12) was reported as being randomized without describing the exact method of randomization; thus, the risk of bias regarding the randomization process could not be adequately assessed. Both the intervention and placebo groups received the intended interventions, and the effect of assignment to the intervention was estimated using both intention-to-treat and per-protocol analyses. As regards outcome measurement, the assessor was not blinded (the study was not triple-blinded). The overall risk was stated as 'some

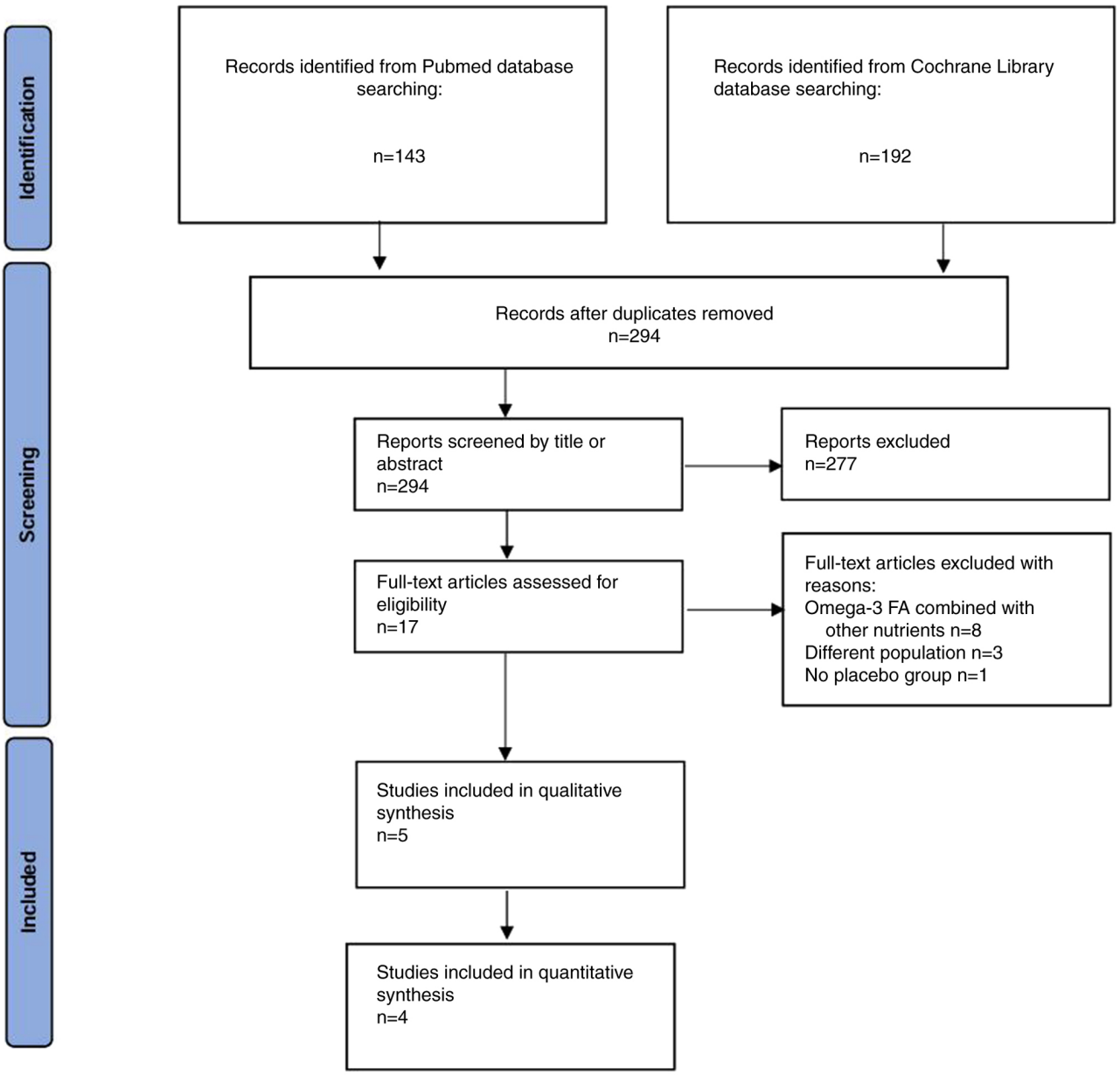

Figure 1. Flow diagram illustrating the study selection process.

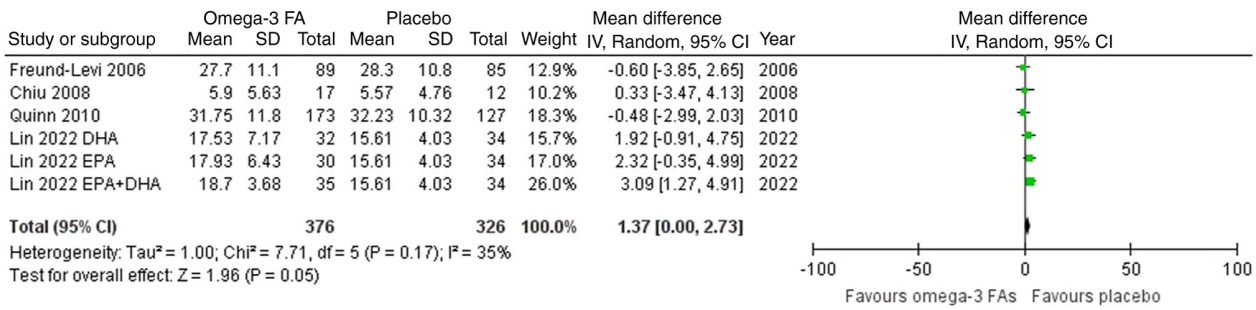

Figure 2. Forest plot for the impact of omega-3 FA supplementation on the Alzheimer's Disease Assessment Scale-Cognitive score. FA, fatty acid. The studies presented in the forest plot are as follows: Freund-Levi *et al* (12), Chiu *et al* (15), Quinn *et al* (13) and Lin *et al* (14).

concerns.' The study by Chiu *et al* (15) did not elaborate on the process used to achieve randomization, so the randomization bias risk could not be measured. The assessor of the outcome was not blinded in this study either. The overall risk was characterized as some concerns.' Shinto *et al* (16) did not describe the randomization process, but provided a detailed table with

Table II. Quality assessment of the included interventional trials.

Authors	Randomization process	Deviation of intended intervention	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall	(Refs.)
Freund-Levi *et al*	Unclear	Low risk	Low risk	Some concerns	Low risk	Some concerns	(12)
Chiu *et al*	Unclear	Low risk	Low risk	Some concerns	Low risk	Some concerns	(15)
Shinto *et al*	Unclear	Low risk	Low risk	Some concerns	Low risk	Some concerns	(16)
Quinn *et al*	Low risk	Low risk	Low risk	Some concerns	Low risk	Some concerns	(13)
Lin *et al*	Unclear	Low risk	Low risk	Some concerns	Low risk	Some concerns	(14)

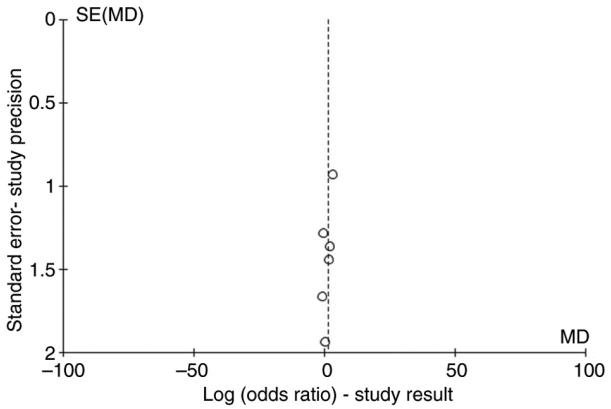

Figure 3. Funnel plot for the impact of omega-3 fatty acid supplementation on the Alzheimer's Disease Assessment Scale-Cognitive score.

the number of dropouts in each group without mentioning an intention-to-treat analysis. The overall risk of bias of the study was stated as some concerns.' Quinn *et al* (13) adequately described the randomization process, but the outcome assessor was not blinded. The overall risk was stated as some concerns.' Lastly, the study conducted by Lin *et al* (14) did not provide a detailed description of the randomization process and did not include a blinded outcome assessor. Overall, the risk of bias was stated as some concerns.'

Discussion

AD is the leading cause of dementia and a significant public health concern globally, particularly as the population ages. It is a multifactorial neurodegenerative disease characterized by a continuous and slow progression that affects the brain and interferes with independent living. Currently, no curative treatment is available, and the pathophysiological cellular and molecular mechanisms responsible for the development of AD remain unclear (1).

Cyclooxygenase and lipooxygenase pathways, along with cytochrome P450 enzymes, are critical for the metabolism of omega-3 dietary long-chain polyunsaturated FAs. These nutrients may have beneficial properties, such as anti-inflammatory, anti-apoptotic, antioxidant and neurotrophic effects. Specifically, omega-3 FAs inhibit the activities of cyclooxygenase-2 and nitric oxide synthase-2, and suppress nuclear factor-κB, leading to decreased levels of cytokines and monocytic chemotactic protein-1, thus enhancing anti-inflammatory activity. Omega-3 FAs also prevent neuronal apoptosis by lowering caspase levels, exert antioxidant effects by inducing transcription factors, and increase nerve growth factor levels (17). Despite the growing interest and extensive research in nutrition over recent years, with common assumptions that diet and nutrients may affect the progression of AD, available data from studies evaluating omega-3 FA supplementation remain controversial and limited. Several research groups worldwide have used different animal models over the last two decades to examine the potential association between omega-3 FA supplementation and Aβ pathology and cognitive decline. Despite notable heterogeneity, evidence suggests that these dietary components can protect against cognitive deterioration in AD and associated neuropathology.

The systematic review and meta-analysis conducted by Hooijmans *et al* (18) in 2012 revealed that long-term omega-3 FA supplementation (≥10% of the expected lifespan in rats and mice) reduced brain Aβ levels, neuronal loss, and improved cognitive functions in animal models of AD. Subgroup analysis indicated potential differences between species (mice and rats) and sex (18). In humans, a key risk factor for AD development is the loss of sex steroid hormones, specifically androgens and estrogens, with age. Cognitive decline is slower, and females exhibit improved verbal abilities than males (19).

Freund-Levi *et al* (12) conducted a randomized, double-blind, placebo-controlled study with 6 months of follow-up. The treatment group received 1,720 mg DHA plus 600 mg EPA daily, while the placebo group received 4,000 mg isocaloric corn oil daily for 6 months. ADAS-Cog was assessed at baseline and at 6 months. No statistically significant difference was observed between the groups on the ADAS-Cog ($P>0.05$) at 6 months. However, a significant reduction in decline rate was noted in a subgroup of patients with very mild cognitive dysfunction (n=32) in the omega-3 FA group compared to placebo ($P=0.01$) (12).

Chiu *et al* (15) conducted a randomized, double-blind, placebo-controlled study with 24 weeks of treatment. Patients received 1,080 mg EPA plus 720 mg DHA daily, while the placebo group received olive oil esters. Cognitive evaluation was performed at baseline and weeks 6, 12, 18 and 24 using ADAS-Cog. No significant cognitive improvement was observed in the treated group (15).

Quinn *et al* (13) conducted an 18-month randomized, double-blind, placebo-controlled trial. The intervention group received 2 g DHA daily, while the placebo group received corn

or soy oil. ADAS-Cog assessment was conducted at baseline, six months, and 12 months. No statistically significant difference was found between the groups regarding ADAS-Cog (P=0.41) after 18 months (13).

Shinto *et al* (16) conducted a 12-month, three-arm, parallel-group, randomized, double-blind, placebo-controlled pilot clinical trial. Participants received omega-3 FA fish oil concentrate containing 675 mg DHA and 975 mg EPA daily, while the placebo group received soy oil. Cognitive subscale evaluation was conducted at baseline and 12 months. No significant difference in cognitive performance was observed between the omega-3 FA and placebo groups (P=0.86) (16). Lin *et al* (14) conducted a randomized, double-blind, placebo-controlled trial with four groups: The placebo, DHA 0.7 g daily, EPA 1.6 g daily, or EPA 0.8 g plus DHA 0.35 g daily for 24 months. Overall, omega-3 FA supplementation did not improve cognitive outcomes (14).

Phillips *et al* (20) conducted a 4-month randomized, double-blind, placebo-controlled study. The intervention group received 625 mg DHA and 600 mg EPA daily, while the placebo group received olive oil. Cognitive assessment was conducted using the MMSE at 1 and 4 months. No significant difference in cognition was observed between the groups (P<0.05) over the 4-month period (20).

The fact that through time several studies have presented conflicting results regarding the efficacy of omega-3 FA in the management of AD may be attributed to different study designs, different population characteristics, different types of interventions, differences in duration of intervention, methodological differences, such as the lack of blinding and randomization, discrepancies in statistical analysis and various other environmental and contextual factors.

Previous studies have indicated uncertain associations between omega-3 FA supplementation and cognitive improvement, with no significant outcomes reported (12,13,15,16,20). AD is a high-burden disease with an increasing prevalence as the population ages. It is a clinically complex, age-related neurodegenerative disorder with significant pathological brain changes and no curative treatment. Current therapeutic approaches primarily alleviate symptoms rather than halt disease progression. Nutritional interventions may enhance pharmaceutical treatment outcomes. The present systematic review and meta-analysis aimed to determine whether dietary omega-3 FA administration could improve cognitive parameters, as indicated by the ADAS-Cog test, in patients with AD.

The authors aimed to address the need for a clearer discussion of the clinical impact of the findings and the potential benefits of omega-3 fatty acids in AD. While the findings of the present meta-analysis do not demonstrate significant cognitive benefits of omega-3 FA supplementation for patients with AD, the clinical implications remain noteworthy. Omega-3 FAs, particularly DHA and EPA, are recognized for their anti-inflammatory, neuroprotective and antioxidant properties, which may provide neurobiological benefits beyond measurable cognitive outcomes. Although the evidence does not support their routine use in AD treatment, omega-3 FAs could potentially play a preventative role by mitigating early pathological processes such as neuroinflammation and oxidative stress. Furthermore, the observed subgroup effects, such as reduced cognitive decline in patients with very mild cognitive dysfunction, highlight the need for targeted interventions at earlier disease stages. Future studies are required to investigate the timing, dosage and population-specific factors that may optimize the therapeutic or preventative utility of omega-3 FAs in patients with AD.

The limited number of RCTs included small sample sizes, limited statistical power, and varying omega-3 FA types, dosages and ratios used restricted subgroup analysis. Future studies are thus warranted to address these limitations. The heterogeneity observed (I^2 35%) may be attributed to differences in treatment duration (6 months to 24 months), the type of FAs used (DHA + EPA or DHA alone), differences in demographics (male-female composition of each intervention and comparator group, and mean age), small sample sizes [Shinto *et al* (16) and Chiu *et al* (15)].

In conclusion, omega-3 FA supplementation does not appear to significantly benefit cognition in patients with AD. Therefore, omega-3 FA supplementation should not be recommended for the treatment of AD, although the results should be cautiously interpreted due to the limited number of included studies. Larger RCTs and further investigation are required to explore the potential beneficial role of omega-3 FAs in preventing cognitive deterioration in individuals at risk of developing AD. Developing nutrition strategies to maintain cognitive function and improve the quality of life for AD patients should be a research priority.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

KD and DK conceptualized the study. TVK KD, DK, GF, VEG and DAS made a substantial contribution to data interpretation and analysis and wrote and prepared the draft of the manuscript. DK and KD analyzed the data and provided critical revisions. All authors contributed to manuscript revision and have read and approved the final version of the manuscript. VEG and TVK confirm the authenticity of all raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

DAS is the Editor-in-Chief for the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article. The other authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, AI tools were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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