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THE IMPACT OF OMEGA-3 SUPPLEMENTS ON THE COGNITIVE FUNCTION IN ALZHEIMER'S PATIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Background: Alzheimer's disease (AD) is a progressive neurodegenerative disorder that leads to severe cognitive decline, especially in the aging population. With limited therapeutic options to reverse disease progression, nutritional interventions such as omega-3 fatty acid supplementation have been investigated for their neuroprotective potential. However, clinical findings remain inconsistent, prompting the need for a systematic synthesis of current evidence to determine the efficacy of omega-3 in improving cognitive function in AD patients.

Objective: To evaluate the impact of omega-3 supplementation on cognitive outcomes in patients with Alzheimer's disease through a systematic review and meta-analysis.

Methods: A comprehensive literature search was conducted across PubMed, ScienceDirect, Scopus, The Cochrane Library, and Google Scholar for relevant studies published until March 2025. Eligible studies included randomized controlled trials assessing the effects of omega-3 supplements in AD patients, with outcomes measured by MMSE and ADAS-Cog. Two independent reviewers performed data extraction and quality assessment. The Cochrane RoB 2.0 tool was used to assess the methodological quality. Meta-analyses were conducted using RevMan 5.4 software under a random-effects model. Publication bias was evaluated using funnel plots. The certainty of evidence was graded using the GRADE framework.

Results: Seventeen studies met the inclusion criteria. The pooled effect size for MMSE scores was 0.10 (90% CI, -0.02 to 0.21; p=0.16; I^2=0%), while for ADAS-Cog scores it was 0.24 (90% CI, -0.45 to 0.94; p=0.56; I^2=0%). The pooled odds ratio for adverse events was 0.95 (90% CI, 0.80–1.14; p=0.67; I^2=0%), indicating no significant safety concerns. No publication bias was identified, but several studies exhibited methodological limitations, leading to moderate certainty of evidence.

Conclusion: Omega-3 supplementation did not significantly improve cognitive function in AD patients. Its role may be better suited as part of a broader multimodal therapeutic strategy.

Keywords: Alzheimer Disease, Cognition Disorders, Docosahexaenoic Acids, Eicosapentaenoic Acid, Memory, Omega-3 Fatty Acids, Randomized Controlled Trials.

INTRODUCTION

Alzheimer's disease (AD) is a multifactorial neurodegenerative disorder marked by progressive neuronal loss, primarily affecting older adults. The disease compromises cognitive and functional capacities, resulting in memory impairment and decline in reasoning, judgment, and behavior (1,2). AD typically progresses from a preclinical phase to noticeable cognitive dysfunction and eventually culminates in dementia (3,4). With global aging trends on the rise, the prevalence and burden of AD have significantly escalated, posing an urgent public health challenge (5). Between 1991 and 2019, the global burden of AD increased by approximately 147.95%. Although a recent trend from 2022 to 2023 indicates a slight annual percentage decline of -1.27%, regions with higher socioeconomic indices and older populations continue to experience an alarming burden (5,6). This trend underscores the critical need for effective preventive and therapeutic strategies to combat the disease. In addition to the devastating personal and societal impacts, AD imposes a massive economic burden, with global costs estimated at USD 321 billion in 2022 and projected to exceed USD 1 trillion by 2050 (7). The disease also exerts a profound emotional and psychological toll on patients, caregivers, and their families, amplifying the need for effective interventions (8). Despite substantial research, AD remains incurable, with existing therapies limited to symptom management rather than halting or reversing disease progression (9). Consequently, preventive strategies have garnered increasing attention, particularly those involving non-pharmacological approaches such as nutritional interventions aimed at mitigating cognitive decline.

Among these, omega-3 polyunsaturated fatty acids (PUFAs) have emerged as a promising dietary intervention due to their fundamental role in brain structure and function (10). These fatty acids are integral to neuronal membrane synthesis and have been associated with anti-inflammatory, neuroprotective, and vascular-modulatory effects (11,12). Specifically, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are critical omega-3 components with demonstrated benefits in preserving cognitive performance, especially in the early stages of AD (13). Conversely, deficiencies in these fatty acids have been linked to impaired brain development and an elevated risk of AD later in life (14). Mechanistically, omega-3s influence neural signaling, membrane fluidity, and gene expression through pathways involving cyclooxygenase modulation, AMPK/SIRT1 activation, and the regulation of nuclear receptors such as PPAR, LXR, TLR-4, and SREBF1c (15). Recent evidence also indicates that omega-3 supplementation may delay or prevent cognitive deterioration, particularly when introduced in the preclinical or mild cognitive impairment stages (16,17). Patients with AD have been found to exhibit lower plasma levels of omega-3, particularly DHA, compared to cognitively healthy individuals (18). However, clinical trial results evaluating omega-3 efficacy in AD remain inconsistent. While some trials report cognitive improvements with supplementation, others demonstrate minimal or no benefit, likely due to heterogeneity in trial design, dosage, duration, supplementation forms, and patient characteristics, including the disease stage at intervention (19). These variations highlight the need for a comprehensive synthesis of existing evidence to clarify omega-3's role in AD management. Given the increasing public health burden of AD and the limitations of current pharmacologic treatments, there is a compelling need to explore and validate alternative interventions. This review aims to systematically evaluate the effectiveness of omega-3 supplementation in improving cognitive function among patients with AD, with particular focus on the question: "Does daily omega-3 supplementation improve memory function in patients with Alzheimer's disease?"

METHODS

The present systematic review and meta-analysis was conducted in accordance with the 27-item Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure transparency, reproducibility, and methodological rigor in synthesizing the evidence on the effects of omega-3 supplementation on cognitive function in Alzheimer's disease (AD) patients (20). A comprehensive search strategy was employed to identify relevant literature across multiple electronic databases, including PubMed, ScienceDirect, Scopus, The Cochrane Library, and Google Scholar, covering publications up to March 2025. Keywords and Medical Subject Headings (MeSH) were tailored to capture variations of terms such as "Alzheimer's disease," "omega-3," "omega-3 fatty acids," "eicosapentaenoic acid," "docosahexaenoic acid," "fish oil," "cognitive decline," and "memory loss." The complete search strategy is detailed in Supplementary Table 1 to ensure reproducibility and coverage. Eligibility criteria were defined based on the PICO framework. The population (P) included patients diagnosed with Alzheimer's disease at mild, moderate, or severe stages. The intervention (I) focused on omega-3 supplementation, regardless of form or dosage. The comparator (C) involved clearly defined control groups, including

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placebo, standard care, or no intervention. The primary outcomes (O) of interest were changes in cognitive function, as reported through validated clinical or neuropsychological measures. Eligible studies were limited to original interventional research, including randomized controlled trials (RCTs), observational studies, clinical trials, cohorts, and case-control designs published in English-language peer-reviewed journals. Exclusion criteria encompassed studies with insufficient or incomplete data, non-human or animal research, studies involving non-AD populations, research that did not examine omega-3 interventions, and articles lacking cognitive outcomes. Non-original publications such as reviews, editorials, conference abstracts, and letters to the editor were also excluded to maintain methodological consistency.

The study selection process was independently carried out by two reviewers using a four-stage PRISMA-compliant screening strategy. In the initial stage, 1649 records were retrieved from the selected databases, and 233 duplicates were removed using EndNote reference manager. In the second stage, titles and abstracts of 1416 articles were screened, resulting in the exclusion of 1397 irrelevant studies. Nineteen potentially eligible full-text articles were assessed in the third stage based on predefined inclusion and exclusion criteria, and two were excluded with justified reasons outlined in the PRISMA flowchart. Ultimately, 17 studies were deemed suitable and included for qualitative synthesis and quantitative meta-analysis. Any discrepancies between the two primary reviewers during study selection were resolved by consensus in consultation with a third senior reviewer. Data extraction was performed using a standardized pre-defined form. Two reviewers independently extracted relevant data, including study characteristics (author, publication year, country, study design, sample size), participant demographics (age, gender, comorbidities), disease specifics (AD stage, duration), intervention details (type of omega-3 used, dosage, duration of exposure), and primary outcomes related to cognitive function.

To assess methodological quality, two validated tools were employed. For randomized controlled trials, the Cochrane Risk of Bias tool (RoB 2.0) was applied to evaluate biases across domains such as randomization, deviations from intended interventions, and outcome measurement. Each domain was rated as low risk, some concerns, or high risk. For non-randomized studies, the ROBINS-I tool was utilized, offering a comparable evaluation across study design types (21). Visualization of risk of bias judgments was generated using the robvis web-based application for clarity and interpretability (22,23). Quantitative synthesis was conducted using Review Manager (RevMan) version 5.4 software. Forest plots were created to assess the pooled effect sizes of omega-3 supplementation on cognitive outcomes. Statistical heterogeneity was evaluated using the I^2 statistic, with thresholds of <25%, 26–75%, and >75% indicating low, moderate, and high heterogeneity, respectively. Chi-square tests were used to determine the significance of heterogeneity, with a p-value threshold of <0.10. Funnel plots were used to assess publication bias, with symmetrical distribution indicative of low bias and asymmetry suggesting potential bias. The certainty of the evidence for each outcome was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework. Two independent reviewers rated the quality of evidence as high, moderate, or low, taking into account study limitations, inconsistency, imprecision, indirectness, and potential publication bias. This robust methodological framework ensured a comprehensive and credible synthesis of the current evidence regarding the role of omega-3 supplementation in cognitive enhancement among individuals with Alzheimer's disease.

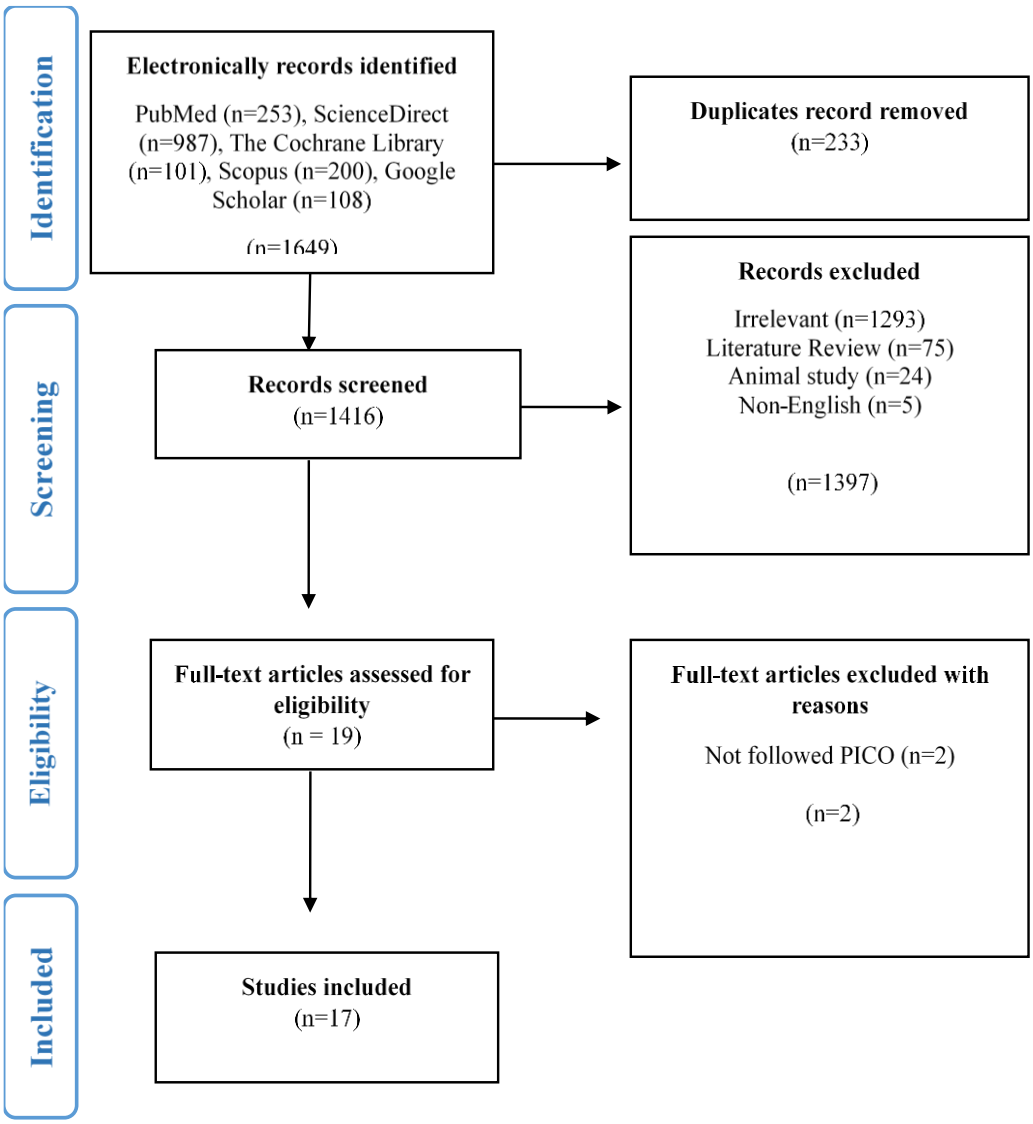

Figure 1: PRISMA flow chart for the selection of the studies

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RESULTS

A total of 1649 records were initially retrieved through systematic searches from multiple databases. After the removal of 233 duplicate entries, 1416 studies were screened based on titles and abstracts. Of these, 1397 were excluded for irrelevance to the study aim. Nineteen full-text articles were assessed for eligibility, out of which 17 met all inclusion criteria and were included in the final qualitative and quantitative synthesis. The entire selection process followed PRISMA guidelines and is illustrated in the PRISMA flow diagram (Figure 1). Among the 17 included studies, all followed a randomized controlled trial design and were conducted in diverse geographical locations. Most studies were reported from the United States (4 studies), followed by Sweden (3), Finland (2), the Netherlands (2), Taiwan (2), and one each from the United Kingdom, France, Japan, and Pakistan. Sample sizes varied considerably, with intervention groups ranging from 12 to 326 participants and control groups ranging from 9 to 311. The participants were elderly, predominantly between the ages of 66 and 76 years, and the majority were female. While some studies documented comorbidities such as hypertension, diabetes, or a family history of dementia, others did not report these details. The trials included patients at various stages of Alzheimer's disease—ranging from mild cognitive impairment and prodromal AD to mild and moderate dementia—thereby capturing a broad clinical spectrum. Table 1 provides an overview of the general characteristics of the included studies.

The intervention across most studies consisted of omega-3 fatty acids, specifically docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), either administered as monotherapy or in combination, and sometimes incorporated into fortified nutritional drinks. Doses varied from 240 mg to 2.3 grams per day, with supplementation periods ranging from 3 to 36 months. Cognitive outcomes were measured using standardized tools such as the Mini-Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog), and the Neuropsychological Test Battery (NTB). Adverse events were generally mild and non-significantly different between intervention and control groups, although a few studies reported serious adverse events occurring in both arms. Table 2 outlines the intervention characteristics, assessment tools, adverse events, and conclusions of each study. The methodological quality of the included studies was assessed using the Cochrane RoB 2.0 tool. Eight studies were categorized as having a low risk of bias, five had a high risk, and four had some concerns. The most frequent source of bias was related to the randomization process, while measurement of outcomes and reporting bias were generally well controlled. One study demonstrated high risk in outcome measurement, and overall, the quality assessment reflected moderate concerns regarding internal validity. These assessments are summarized in Table 4.

The primary outcome analysis focused on the impact of omega-3 supplementation on MMSE and ADAS-Cog scores. For MMSE, the pooled estimated mean difference at baseline was 0.09 (90% CI: -0.04 to 0.22; $p = 0.25$), and after 24 weeks, it was 0.15 (90% CI: -0.13 to 0.43; $p = 0.38$). The overall effect size was 0.10 (90% CI: -0.02 to 0.21; $p = 0.16$), with consistently low heterogeneity across all models ($I^2 = 0\%$). Similarly, for ADAS-Cog, baseline pooled difference was 0.11 (90% CI: -0.71 to 0.94; $p = 0.82$), and at 24 weeks it was 0.55 (90% CI: -0.72 to 1.82; $p = 0.47$), with an overall non-significant effect size of 0.24 (90% CI: -0.45 to 0.94; $p = 0.56$) and low heterogeneity ($I^2 = 0\%$). These results suggest no statistically significant improvement in cognitive outcomes as measured by MMSE and ADAS-Cog following omega-3 supplementation. The forest plots illustrating these findings are shown in Figures 2 and 3. Adverse events were also quantitatively analyzed, with the pooled odds ratio of complications between omega-3 and control groups calculated at 0.95 (90% CI: 0.80–1.14; $p = 0.67$), again showing no significant difference and low heterogeneity ($I^2 = 0\%$). The safety profile of omega-3 was consistent across studies, suggesting it is generally well tolerated (Figure 4).

Assessment of publication bias through funnel plot analysis revealed symmetrical distribution of studies for MMSE, ADAS-Cog, and complications, indicating a low likelihood of publication bias (Figure 5). Certainty of evidence, evaluated using the GRADE approach, was rated as moderate for all primary outcomes due to the presence of low to high risk of bias, despite low heterogeneity and minimal publication bias. Effect sizes for MMSE, ADAS-Cog, and complications remained small and non-significant, with confidence intervals crossing the null value. Table 5 presents a summary of the certainty of evidence for each outcome. Collectively, the findings suggest that while omega-3 supplementation appears safe and well tolerated in elderly AD patients, its impact on cognitive improvement remains inconclusive, with only a subset of studies demonstrating statistically significant benefits. The moderate certainty of evidence supports the need for further well-designed, large-scale trials to clarify the potential role of omega-3 in managing cognitive decline associated with Alzheimer's disease.

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Table 1: Summary of general characteristics of included studies

Author ID	Country	Study design	Sample size	Gender (M: F)	Age	Comorbidities	Alzheimer's patient condition
Freund-Levi, Eriksdotter-Jönhagen (24)	Sweden	RCT	Intervention group=89, Control group=85	Intervention group=38:51, Control group=46:39	Intervention group=72.6, Control group=72.9	Diabetes	Mild to moderate
Kotani, Sakaguchi (35)	Japan	RCT	Intervention group=12, Control group=9	Intervention group=9:3, Control group=3:6	Intervention group=66.9, Control group=69.7	NA	MCI
Chiu, Su (32)	Taiwan	RCT	Intervention group=23, Control group=23	Intervention group=65% F, Control group=46.7% F	Intervention group=74, Control group=76.5	NA	Mild to moderate
Quinn, Raman (20)	USA	RCT	Intervention group=238, Control group=164	Intervention group=126:112, Control group=66:98	Intervention group=76, Control group=76	NA	Mild to moderate
Yurko-Mauro, McCarthy (23)	USA	RCT	Intervention group=219, Control group=218	Intervention group=44%:56%, Control group=40%:60%	Intervention group=70, Control group=70	Family history of dementia	Age-related cognitive decline
Scheltens, Kamphuis (29)	Netherland	RCT	Intervention group=106, Control group=106	Intervention group=54:52, Control group=52:54	Intervention group=74.1, Control group=73.3	Hypertension	Mild
Shah, Kamphuis (21)	USA	RCT	Intervention group=265, Control group=262	Intervention group=126:139, Control group=127:135	Intervention group=76.6, Control group=76.9	NA	Mild to moderate
Scheltens, Twisk (30)	Netherland	RCT	Intervention group=130, Control group=129	Intervention group=68:62, Control group=64:65	Intervention group=74.4, Control group=73.2	Hypertension	NA
Shinto, Quinn (22)	USA	RCT	Intervention group=13, Control group=13	Intervention group=39% F, Control group=54% F	Intervention group=75.2, Control group=75.9	NA	NA
Phillips, Childs (19)	UK	RCT	Intervention group=37, Control group=39	Intervention group=16:21, Control group=18:21	Intervention group=71.1, Control group=71.1	NA	NA
Eriksdotter, Vedin (25)	Sweden	RCT	174	79:86	74	NA	Mild to moderate
Soininen, Solomon (27)	Finland	RCT	Intervention group=153,	Intervention group=81:72,	Intervention group=71.3,	NA	Prodromal

Author ID	Country	Study design	Sample size	Gender (M: F)	Age	Comorbidities	Alzheimer's patient condition
			Control group=158	Control group=73:85	Control group=70.7		
Chhetri, de Souto Barreto (34)	France	RCT	Intervention group=326, Control group=311	Intervention group=119:207, Control group=107:204	Intervention group=75.5, Control group=75.2	Hypertension	AD with dementia
Jernerén, Cederholm (26)	Sweden	RCT	Intervention group=88, Control group=83	Intervention group=46:37, Control group=38:50	Intervention group=72.5, Control group=72.9	Family history of AD	Mild to moderate
Soininen, Solomon (28)	Finland	RCT	Intervention group=152, Control group=157	Intervention group=25:20, Control group=19:17	Intervention group=71.9, Control group=69.9	NA	Prodromal
Lin, Cheng (31)	Taiwan	RCT	Intervention group=41, Control group=40	NA	NA	NA	Mild
Fiaz, Hanif (33)	Pakistan	RCT	Intervention group=92, Control group=92	NA	Intervention group=70, Control group=72.2	NA	NA

Abbreviations: AD= Alzheimer's disease, MCI=Mild cognitive impairment, USA=United States of America, UK=United Kingdom, NA=Not Available

Table 2: Summary of characteristics of intervention and outcomes

Author ID	Intervention	Dose	Control /Placebo	Assessment method	Complications/adverse events	Follow-up	Key findings	Conclusion
Freund-Levi, Eriksdotter-Jönhagen (24)	Omega-3 fatty acids	DHA =1.7 g EPA= 0.6 g	Isocaloric placebo oil (corn oil=1 g, linoleic acid=0.6 g)	MMSE ADAS-Cog	NA	12 months	Significant (P <0.05) reduction in MMSE decline	Administration of omega -3 fatty acids did not delay the rate of cognitive decline
Kotani, Sakaguchi (35)	ARA DHA	240 mg/day	Olive oil	Japanese version of RBANS	NA	3 months	Significant improvement of the immediate memory and attention score	ARA and DHA supplementation can improve cognitive dysfunction

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Author ID	Intervention	Dose	Control /Placebo	Assessment method	Complications/adverse events	Follow-up	Key findings	Conclusion
Chiu, Su (32)	Omega-3 PUFAs monotherapy	1.8 g/day	Olive oil	CIBIC-plus ADAS-Cog MMSE HRDS	No serious events occurred in either group	24 weeks	Non-significant difference among both groups	Omega-3 fatty acids did not improve cognitive outcomes
Quinn, Raman (20)	DHA	2 g/day	Corn or soy oil	MMSE ADAS-Cog	Major adverse events and hospitalization in both groups	18 months	DHA supplementation had no beneficial effect	DHA supplementation did not slow the rate of cognitive
Yurko-Mauro, McCarthy (23)	DHA	900 mg/day	Corn or soy oil	MMSE	Non-significant difference between both groups	24 weeks	Non-significant difference (p=0.86) in MMSE scores	Improvement in learning and memory was observed, while no improvement in cognitive outcomes
Scheltens, Kamphuis (29)	Souvenaid (DHA and EPA)	EPA=300 mg DHA=1200 mg/day	Placebo	MADAS-Cog	No significant (P =0.28) difference	24 weeks	Significant improvement in the delayed verbal recall task	Improvement was observed in intervention group
Shah, Kamphuis (21)	Souvenaid (DHA and EPA)	125 ml/day	Iso-caloric	MMSE ADAS-Cog	Non-significant difference	24 weeks	Non-significant difference between study groups	Supplementation did not slow cognitive decline in persons treated for mild-to-moderate AD
Scheltens, Twisk (30)	Souvenaid (DHA and EPA)	DHA =300 mg EPA= 1200 mg/daily	Iso-caloric	NTB MMSE	145 patients (56.2%) had AE	24 weeks	The NTB memory domain Z-score was significantly increased	Souvenaid improves memory performance
Shinto, Quinn (22)	Omega-3 Fatty Acids	DHA =675 mg EPA= 975 mg EPA/ daily	Soybean oil	MMSE ADAS-Cog	Two serious adverse events occurred in each group	12 months	Non-significant difference	The combined treatment instead of omega alone slowed cognitive improvement

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Author ID	Intervention	Dose	Control /Placebo	Assessment method	Complications/adverse events	Follow-up	Key findings	Conclusion
Phillips, Childs (19)	Omega-3 PUFAs monotherapy	EPA=600 mg DHA=625 mg/day	Olive oil	MMSE	NA	4 months	Both EPA and DHA improved in intervention group	No benefit on cognitive outcomes
Eriksdotter, Vedin (25)	DHA	2.3 g/day	Corn oil=1 g, Linoleic acid=0.6 g	ADAS-cog MMSE	NA	6 months	Significant association in increasing plasma omega-3 fatty acid levels	Improvement was observed in intervention group
Soininen, Solomon (27)	Drink containing Fortasyn Connect	125 ml/day	Isocaloric	NTB	Adverse events were reported in both groups	24 months	Non-significant mean change in NTB	The intervention had no significant effect on the NTB
Chhetri, de Souto Barreto (34)	Omega-3	NA	Without omega-3	FCSRT MMSE	NA	36 months	Significant improvement	Might be beneficial
Jernerén, Cederholm (26)	DHA and EPA	DHA=1.7 g/day, EPA=0.6 g/day	Corn oil=1 g linoleic acid=0.6 g	MMSE	NA	6 months	Significant interactions (p=0.04) between supplementation and tHcy on cognition	Improvement was observed in intervention group
Soininen, Solomon (28)	Drink containing Fortasyn Connect	125 ml/day	Isocaloric	NTB	Adverse events were reported in both groups	36 months	Significant reductions in decline were observed for NTB	Improvement was observed in intervention group
Lin, Cheng (31)	DHA and EPA	DHA=0.7 g/day, EPA=1.6 g/day	Olive oil	Cognitive assessment	NA	24 months	Non-significant difference in both groups	Intervention did not reduce cognitive outcomes
Fiaz, Hanif (33)	Omega-3 PUFAs	EPA+DHA	Olive oil	MMSE ADAS-Cog	NA	6 months	Significant improvement in	Improvement was observed in intervention group

Author ID	Intervention	Dose	Control /Placebo	Assessment method	Complications/adverse events	Follow-up	Key findings	Conclusion
	monotherapy	= 2:1 (1 g)					MMSE and ADAS-Cog	

Abbreviations: ARA-Arachidonic acid, DHA=Docosahexaenoic acid, EPA=Eicosapentaenoic acid, RBANS=Repeatable Battery for Assessment of Neuropsychological Status, CIBIC=Clinician's Interview-Based Impression of Change Scale-plus, ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive, MMSE= Mini Mental Status Examination, HRDS=Hamilton Depression Scale, PUFAs=Polyunsaturated Fatty Acids, MADAS-Cog=Modified Alzheimer's Disease Assessment Scale–cognitive, NTB=Neurphysiological Test Batterey, FCSRT=Free and Cued Selective Reminding Test, NA=Not Available

Table 3: Methodological quality assessment of included studies

Author ID	Randomization process	Deviation from intended intervention	Missing outcome data	Measurement of the outcome	Selection of reported results	Overall
Freund-Levi, Eriksdotter-Jönhagen (24)	High	Low	Low	Low	Low	High
Kotani, Sakaguchi (35)	High	Low	Low	Low	Low	High
Chiu, Su (32)	Low	Low	Low	Low	Low	Low
Quinn, Raman (20)	Low	Low	Low	Low	Low	Low
Yurko-Mauro, McCarthy (23)	Some concerns	Low	Low	Low	Low	Some concerns
Scheltens, Kamphuis (29)	High	Low	Low	Low	Low	High
Shah, Kamphuis (21)	Low	Low	Low	Low	Low	Low
Scheltens, Twisk (30)	Low	Low	Low	Low	Low	Low
Shinto, Quinn (22)	Low	Low	Low	Low	Low	Low
Phillips, Childs (19)	Some concerns	Low	Low	Low	Low	Some concerns
Eriksdotter, Vedin (25)	Some concerns	Low	Low	Low	Low	Some concerns
Soininen, Solomon (27)	Low	Low	Low	Low	Low	Low
Chhetri, de Souto Barreto (34)	Low	Low	Low	Low	Low	Low
Jernerén, Cederholm (26)	High	Low	Low	Low	Low	High
Soininen, Solomon (28)	Some concerns	Low	Low	Low	Low	Some concerns
Lin, Cheng (31)	Low	Low	Low	Low	Low	Low
Fiaz, Hanif (33)	High	Low	Low	High	Low	High

Table 4: Certainty of evidence using the GRADE framework

Outcomes	Studies	RoB	Inconsistency	Indirectness	Imprecision	Publication bias	Mean diff./OR (95% CI)	Certainty of evidence
Impact on MMSE scores	Baseline=10, After 24 weeks=4	Low to high	Not serious (I^2=0%)	Not serious	Not serious	Not suspected[a]	7.04 (95% CI, 4.59-10.1)	Moderate ΘΘΘ
Impact of ADAS-Cog scores	Baseline=6, after 24 weeks=3	Low to high	Not serious (I^2 =0%)	Not serious	Not serious	Not suspected[a]	0.20 (95% CI, 0.12-0.33)	Moderate ΘΘΘ
Complications/adverse events	9	Low to high	Not serious (I^2=0%)	Not serious	Not serious	Not suspected[a]	0.33 (95% CI, 0.18-0.60)	Moderate ΘΘΘ

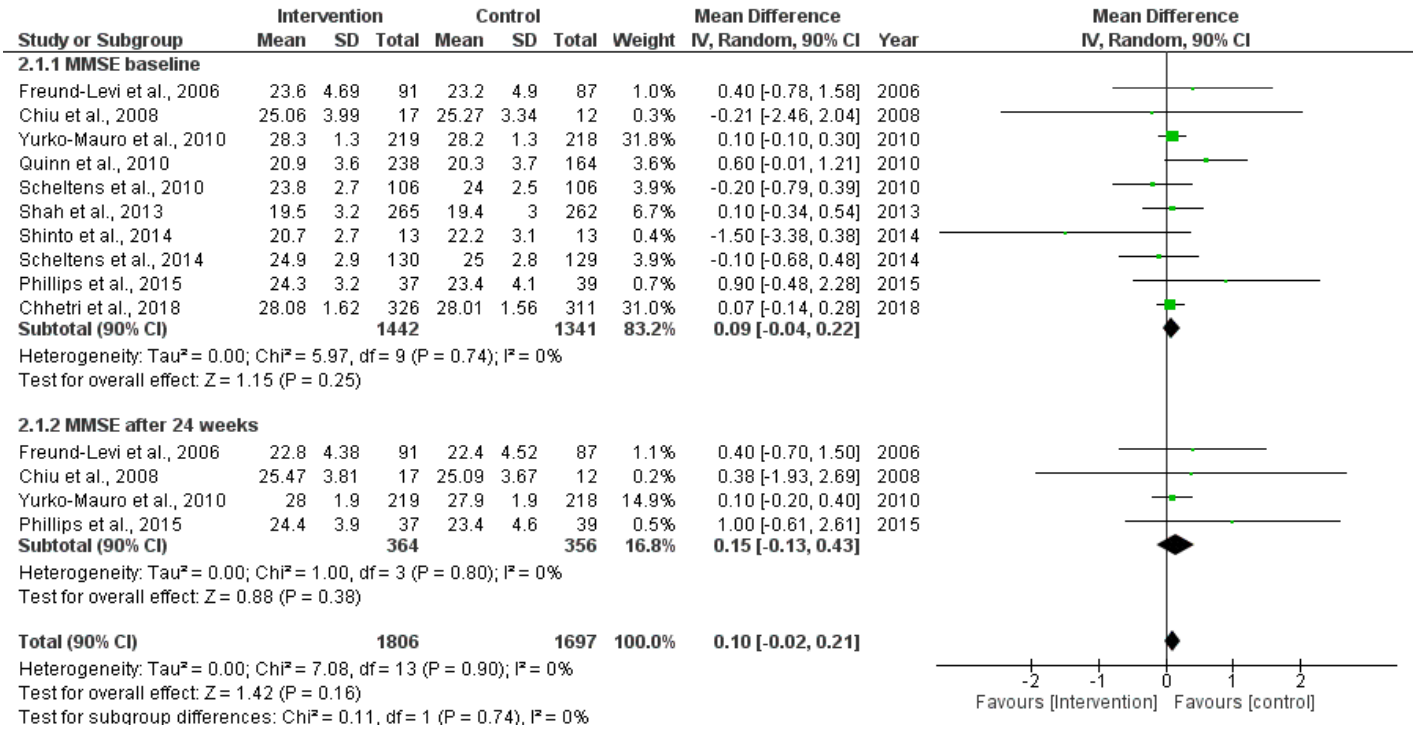

Figure 2: Forest plot for MMSE scores at baseline and after 24 weeks of omega-3 supplementation in AD patients for the improvement of cognitive outcomes.

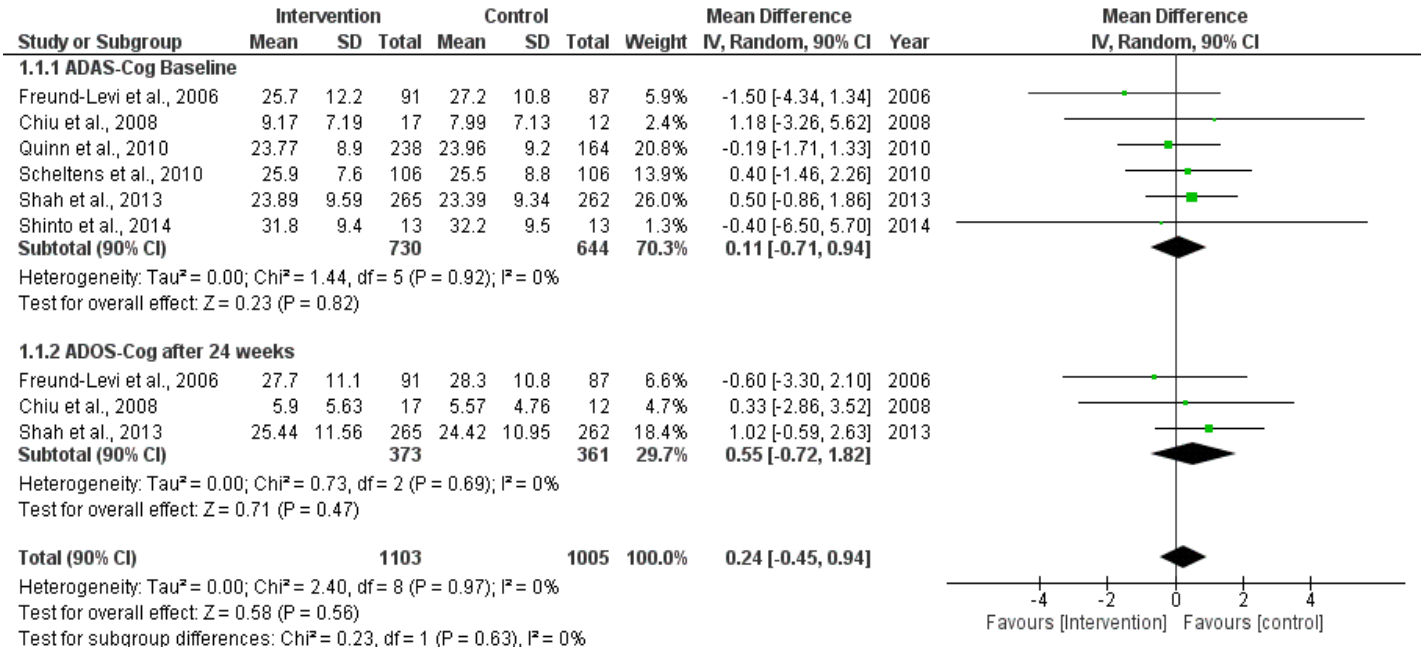

Figure 3: Forest plot for ADAS-Cog scores at baseline and after 24 weeks of omega-3 supplementation in AD patients for the improvement of cognitive outcomes.

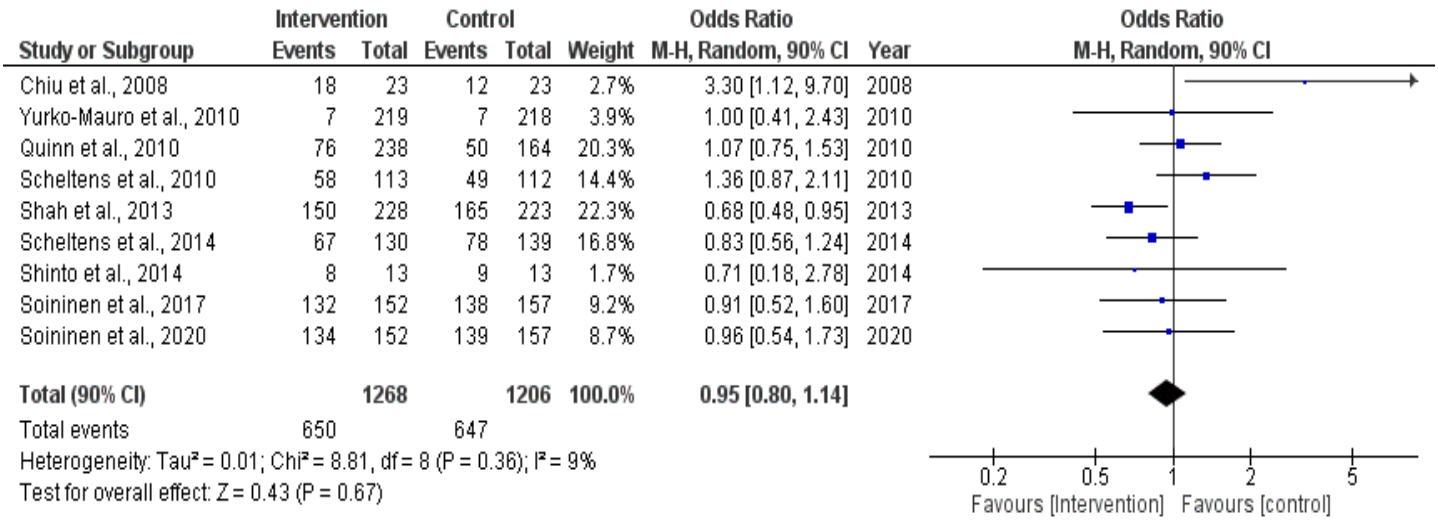

Figure 4: Forest plot for complications/adverse events after the administration of omega-3 supplementation in AD patients for the improvement of cognitive outcomes.

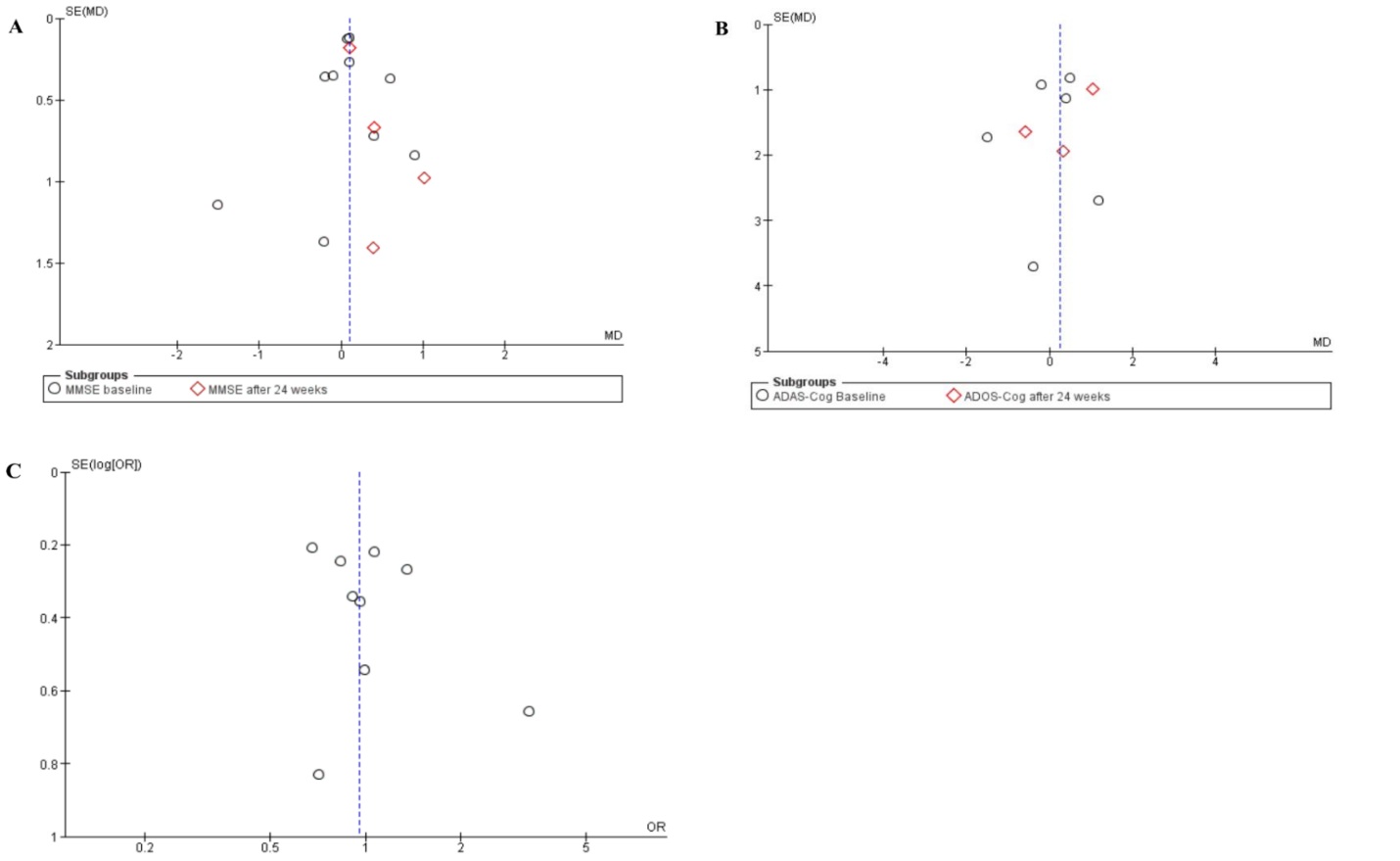

Figure 5: Publication bias A. MMSE, B. ADAS-Cog, C. Complication

DISCUSSION

The present meta-analysis aimed to assess the effectiveness of omega-3 supplementation on cognitive function in patients with Alzheimer's disease (AD), focusing on commonly used assessment tools such as MMSE and ADAS-Cog. After pooling data from 17 randomized controlled trials, the findings revealed a statistically non-significant impact of omega-3 supplementation on both MMSE and ADAS-Cog scores. These results suggest that omega-3 supplementation did not produce measurable cognitive improvement when compared to placebo or standard care in patients with mild to moderate AD. This outcome is consistent with multiple previously published meta-analyses and systematic reviews, which similarly reported non-significant differences in MMSE scores after six months of supplementation, despite minor variations in effect sizes and confidence intervals (24-26). While the overall findings align with several previous studies, other systematic reviews have highlighted potential cognitive benefits of omega-3, particularly in specific domains such as executive function, verbal memory, and hippocampal volume preservation (27,28). These discrepancies may reflect variations in the population baseline characteristics, such as age, stage of disease, dietary intake of omega-3, genetic predisposition, and comorbidities. Additionally, variations in dosage, formulation, and the duration of intervention further complicate the interpretation of results. Some evidence suggests that earlier supplementation, before significant neurodegeneration occurs, may yield more favorable outcomes, particularly in individuals with prodromal or mild cognitive impairment stages (29,30). However, when cognitive decline has already progressed, the neuroprotective effects of omega-3 may not be sufficient to overcome the underlying pathology of AD.

In terms of adverse events, the pooled analysis showed no significant difference between intervention and control groups, with an odds ratio of 0.95 (90% CI, 0.80–1.14; p=0.67), confirming the safety and tolerability of omega-3 supplements. Minor complications such as

gastrointestinal discomfort was reported, and serious adverse events, including hospitalizations, occurred at similar frequencies in both groups. These findings are corroborated by existing literature, which consistently supports the favorable safety profile of omega-3 supplementation in elderly populations, including those with neurodegenerative conditions (31-33). The study's major strength lies in its comprehensive synthesis of evidence across a broad geographical and demographic spectrum, thereby enhancing the external validity of the findings. The inclusion of randomized controlled trials, low heterogeneity across outcome measures, and the application of standardized tools for risk of bias and evidence certainty contribute to the methodological robustness of this analysis. Additionally, the use of GRADE to assess the quality of evidence adds transparency and reliability to the interpretation of the results.

However, several limitations must be acknowledged. The inability to statistically differentiate the effects of DHA and EPA as individual components of omega-3 supplementation represents a significant gap, primarily due to the limited number of studies evaluating these fatty acids separately. Most studies utilized combined formulations or commercial products, which may obscure the distinct neuroprotective contributions of each compound. Moreover, cognitive function was evaluated in aggregate terms using broad scales such as MMSE and ADAS-Cog, without isolating specific cognitive domains like working memory, executive function, or verbal recall. Such domain-specific analyses could have provided a more nuanced understanding of cognitive responses to supplementation. Another notable limitation was the lack of consideration for concurrent medications administered to AD patients, which could potentially interact with or confound the effects of omega-3 supplementation. Furthermore, the short duration of some included trials may not have been sufficient to capture the long-term cognitive effects of omega-3, especially in a condition characterized by slow but progressive decline (34,35). The baseline dietary intake of omega-3, which was not uniformly reported across studies, also limits the interpretation of supplementation efficacy, as individuals with adequate dietary intake may exhibit diminished responsiveness to additional supplementation. In conclusion, while this meta-analysis reinforces the safety of omega-3 supplementation in AD patients, it does not support its efficacy in significantly improving cognitive function, as measured by MMSE and ADAS-Cog. Future research should aim to conduct long-term, large-scale, multicenter trials that stratify participants by disease severity, dietary habits, genetic markers, and cognitive subdomains. Additionally, separate evaluation of DHA and EPA, as well as their interaction with pharmacological treatments, would provide deeper insights into the potential of omega-3 as a preventive or adjunctive therapy in Alzheimer's disease.

CONCLUSION

This study concludes that omega-3 supplementation, while safe and well-tolerated, does not significantly improve cognitive function in patients with Alzheimer's disease as measured by standard clinical tools. Although previous qualitative findings suggested potential benefits, the present meta-analysis did not demonstrate a statistically significant impact on cognitive scores or adverse event rates. These findings underscore the complexity of cognitive decline in AD and highlight the need for more targeted, long-term research to explore the therapeutic potential of omega-3, particularly in earlier stages of the disease or as part of comprehensive, multifaceted interventions.

AUTHOR CONTRIBUTION

Author	Contribution
Aiman Abdullah Sanosi*	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published

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