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Article

The Role of Omega-3 Fatty Acids in Mitigating Metabolic Risk Factors Associated with Alzheimer's Disease: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Alzheimer's disease (AD) is linked to metabolic conditions like obesity and hypertension, which share inflammation and oxidative stress as common factors. Omega-3 fatty acids (EPA and DHA) may have neuroprotective and anti-inflammatory benefits.
Objective: This study aims to review the effectiveness of omega-3 supplements in reducing metabolic risk factors and slowing cognitive decline in people with AD.
Methods: Following PRISMA guidelines, a comprehensive search was conducted in PubMed, ScienceDirect, and Google Scholar for randomized controlled trials (RCTs) published until July 2025. Eligible studies included older adults (≥65 years) with AD or mild cognitive impairment (MCI) and assessed the impact of omega-3 supplements on cognitive and/or metabolic outcomes. The risk of bias was evaluated using the Cochrane ROB-2 tool. Data were analyzed with Review Manager 5.4 using fixed-effects models for continuous outcomes.
Results: Five RCTs with a total of 490 participants were included. Meta-analysis of four trials (326 participants) revealed that omega-3 supplementation significantly improved Mini-Mental State Examination (MMSE) scores compared to placebo (mean difference: 0.21; 95% CI: 0.02–0.41; P = 0.03; I^2 = 0%). No significant effects were found for ADAS-Cog scores (mean difference: 0.11; 95% CI: –0.40 to 0.62; P = 0.68; I^2 = 46%) or IADL scores (mean difference: 0.48; 95% CI: –0.17 to 1.13; P = 0.15; I^2 = 36%).
Conclusion: Omega-3 fatty acids may offer modest cognitive benefits in AD, though heterogeneity among studies limits general conclusions. Future well-designed RCTs should consider metabolic profiles and standardized dosing to identify populations most likely to benefit from omega-3 supplementation.

Keywords: Alzheimer's Disease, Omega-3 Fatty Acids, Cognitive Function, EPA, DHA

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INTRODUCTION

Globally, the life expectancy of the elderly population is increasing, where according to the World Health Organization (WHO) by 2030, 1 in 6 people in the world will be ≥60 years old, by 2050 there will be 2.1 billion people aged ≥60 years old, and 420 million people aged ≥80 years old (Decade of Healthy Ageing: Plan of Action, n.d.). The increase in the elderly population is also accompanied by an increase in the burden of degenerative diseases, one of which is Alzheimer's disease which mostly occurs in the population ≥65 years old, which is also called late onset Alzheimer's dementia (Safiri et al., 2024). Alzheimer's disease is a progressive neurodegenerative disease that can cause memory loss and cognitive

impairment in language, learning, and visual-spatial abilities, as well as changes in behavior (Safiri et al., 2024). Alzheimer's disease is the main cause of dementia with an increasing prevalence, where in 2018 there were 50 million people experiencing this disease and it is estimated that by 2050 this number will increase three times (Scheltens et al., 2021). Until now, there is no effective therapy to cure Alzheimer's disease, which not only causes high mortality and decreased quality of life for patients and families, but also a high economic burden.

The hallmark of Alzheimer's disease is the accumulation of beta-amyloid peptide (Aβ) outside neurons, and hyperphosphorylation and aggregation of Tau protein inside neurons. In addition, there is atrophy of the hippocampus and neocortex of the brain, as well as a decrease in acetylcholine, norepinephrine, and dopamine. The causes of Alzheimer's disease are multifactorial. In addition to non-modifiable risk factors such as old age, female gender, and genetic disorders such as trisomy 21, there are modifiable risk factors in the form of metabolic syndrome, which includes hypertension, dyslipidemia, obesity, and diabetes mellitus (Ezkurdia et al., 2023). Alzheimer's disease and metabolic syndrome share chronic inflammation, oxidative stress, and impaired metabolic signaling. Obesity and insulin resistance lead to beta-amyloid aggregation and hyperphosphorylation of Tau protein, which exacerbates neuroinflammation and neuronal dysfunction. This relationship leads to the possibility of nutritional intervention that can improve metabolic syndrome and ultimately improve Alzheimer's disease (Yavari et al., 2025).

Omega-3 is known to have anti-inflammatory and neuroprotective effects. In a meta-analysis, Jang et al. reported that docosahexaenoic acid (DHA) is associated with a reduced risk of metabolic syndrome (Jang & Park, 2020). In contrast, Mirmiran et al. reported that omega-3 intake was positively correlated with brain volume and MMSE scores, signaling improvements in cognitive function in elderly patients with metabolic syndrome (Mirmiran et al., 2023).

METHODS

Data Sources and Search Strategy

This systematic review was completed in 2025 by following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Data sources were systematically retrieved by searching for relevant articles through PubMed, ScienceDirect, and Google Scholar. Articles retrieved spanned 2006–2025, with the last article search conducted in July 2025. The search was conducted using a combination of keywords: (Alzheimer's disease) AND (metabolic syndrome OR obesity OR hypertension OR insulin resistance) AND (omega-3 OR EPA OR DHA). These articles were subsequently filtered using predefined inclusion and exclusion criteria.

Eligibility Criteria

The inclusion criteria for the selected studies were original randomized controlled trial papers published in the last 15 years, studies involving older adults ≥65 years old, studies related to the effect of omega-3 consumption on Alzheimer's disease with or without comorbid metabolic diseases, and availability in English.

Exclusion criteria were studies that were not available in full text and were not relevant to the research topic.

Critical Appraisal of Risk of Bias

The quality of the included studies was evaluated with the Risk of Bias 2 (ROB-2) tool, which is used for studies of randomized controlled trials (RCTs). The ROB-2 assessment includes five bias domains: randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result.

Data Extraction

The data extraction process was conducted independently. The selected articles were carefully reviewed, and relevant information was extracted for use in the study. The author recorded various study characteristics, including the author(s), year of publication, location, study design, study period, intervention, outcome, assessment, and result.

Data Analysis

Data were analyzed using Review Manager (RevMan) version 5.4 (The Cochrane Collaboration). The effect size was calculated as the mean difference (MD) with 95% confidence intervals (CIs) for continuous outcomes. A fixed-effects model was applied due to low statistical heterogeneity, as indicated by the Chi-square test and I^2 statistic. Heterogeneity was assessed using Cochran's Q test (Chi^2) and the I^2 statistic, where I^2 values greater than 50% were interpreted as indicating high heterogeneity. A P-value < 0.05 was considered statistically significant. Forest plots were generated to visualize individual study effects and the overall pooled estimate.

RESULTS

Study Selection

An initial 267 articles were found by searching PubMed, Google Scholar, and ScienceDirect databases. After the elimination of 13 duplicate articles, 254 articles remained for the initial screening stage. At this stage, titles and abstracts were reviewed, resulting in 225 articles being eliminated because they did not meet the criteria. Next, 29 articles were examined in full-text form. Of these, 12 articles were excluded because the topic was irrelevant, 6 articles because the research subjects were inappropriate, 3 articles because the interventions used were inappropriate, and the remaining 3 articles were not available in full text. Finally, 5 articles were selected for inclusion in this systematic review and further analyzed for risk of bias using the ROB-2 assessment tool.

Table 1. *Characteristics of included studies*

No	Author(s); Year	Study design; Location	Sample size	Intervention; Duration	Outcome Assessment	Result
1	Freund-Levi et al.; 2006	DB-RCT; Sweden	174 Intervention: 89 Placebo: 85	Omega-3 FA (2.3 g/day: 1.7 g DHA + 0.6 g EPA); 6 months double-blind, followed by 6 months open-label	Cognitive tests (MMSE, ADAS-cog), neuropsychiatric inventory	No overall difference in cognition; subgroup with very mild AD showed slower cognitive decline (p=0.01); no effect in moderate AD
2	Freund-Levi et al.; 2014	DB-RCT; Sweden	37 Intervention: 20 Placebo: 17	Omega-3 supplementation: 1.7 g DHA + 0.6 g EPA per day vs. placebo (corn oil); 6 months	Urinary F2-isoprostanes (8-iso-PGF2α) as oxidative stress marker and 15-keto-dihydro-PGF2α as inflammatory marker	No significant effect of omega-3 on biomarkers; F2-isoprostanes increased in placebo group but not in omega-3 group; no between-group difference
3	Shinto et al.; 2013	DB-RCT; USA	39 Omega-3 group: 13 Omega-3 + ALA group: 13 Placebo group: 13	Omega-3 (675 mg DHA + 975 mg EPA/day) ± ALA 600 mg; 12 months	ADAS-cog, MMSE, ADCS-ADL	Combination omega-3 + ALA group showed slower decline in ADL vs placebo (p=0.01); delayed MMSE decline in combined intervention group (p<0.01); no significant difference in ADAS-cog
4	Lin et al.; 2022	DB-RCT; Taiwan	163 EPA group: 40 DHA group: 41 EPA+DHA group: 42 Placebo group: 40	0.7 g/day DHA, 1.6 g/day EPA, or 0.8 g EPA + 0.35 g DHA per day for 24 months	Cognitive (ADAS-cog, MMSE), functional (ADCS-ADL, QOL), mood (GDS), blood biomarkers (cytokines, CCL4)	No overall significant effects on cognition or function; EPA reduced CCL4 levels (p<0.001); EPA and DHA improved certain subdomains (constructional praxis and spoken language)
5	Nolan et al.; 2022	DB-RCT; Ireland	77 Intervention: 50 Placebo: 27	1 g fish oil (500 mg DHA, 150 mg EPA), 22 mg carotenoids (10 mg lutein, 10 mg meso-zeaxanthin, 2 mg zeaxanthin), 15 mg vitamin E daily; 12 months	MMSE, DSRS, skin and serum carotenoids, omega-3 FA and vitamin E levels, clinical collateral, QoL, frailty score	Significant improvements in skin and blood carotenoids, omega-3, and vitamin E levels in active group. Better memory and mood outcomes. Trend toward improved MMSE category (p = 0.074).

DB-RCT: double-blind randomized controlled trial; MMSE: Mini-Mental State Examination; ADAS-cog: Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCS-ADL: Alzheimer's Disease Cooperative Study-Activities of Daily Living; ALA: alpha-lipoic acid; GDS: Geriatric Depression Scale; DSRS: Dementia Severity Rating Scale.

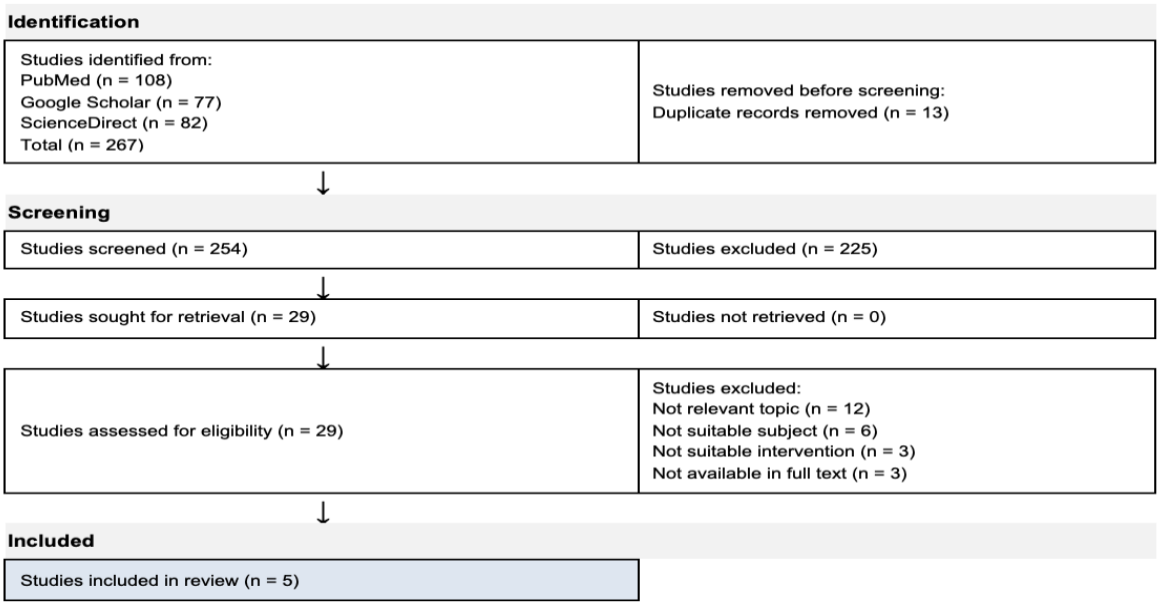

Figure 1. PRISMA flow diagram

Study Characteristics

A total of 490 participants were included in five randomized controlled trials assessing the impact of omega-3 fatty acids on cognitive and inflammatory outcomes in individuals with Alzheimer's disease (AD) or mild cognitive impairment (MCI). Although metabolic comorbidities were not consistently defined as inclusion criteria, preliminary data suggest a substantial prevalence of diabetes, hypertension, overweight/obesity, and subclinical dyslipidemia — factors that have considerable relevance to the neuroinflammatory processes involved in AD pathophysiology.

In the study by Freund-Levi et al. (2006) (N=174), 13% of participants in the omega-3 group and 6% in the placebo group had diabetes, while 39.3% and 32.6% were classified as overweight (BMI >25 kg/m²). The mean systolic blood pressure was 137 mmHg in both groups, indicating borderline hypertension. Although not initially stratified by metabolic status, this group represents a mixed population with underlying cardiometabolic risks (Freund-Levi et al., 2006).

In the Freund-Levi et al. (2014) study (N = 37), the mean BMI was 26.4 ± 2.9 kg/m² in the omega-3 group and 29.5 ± 4.2 kg/m² in the placebo group, indicating overweight to obese status. Inflammatory markers such as hs-CRP and TNF-α were elevated in all groups, supporting the presence of chronic low-grade inflammation, which may be due to adiposity or unreported metabolic conditions (Freund-Levi et al., 2014).

The Shinto et al. (2013) study (N=39) allowed the inclusion of participants with hypertension and dyslipidemia; although precise prevalence data were not reported, these comorbidities were not excluded, implying the possible presence of metabolic risk factors in the study population (Shinto et al., 2013).

The study by Nolan et al. (2022) (N=77) explicitly characterized comorbidities: 18.4% of participants had diabetes, 78.9% had hypertension, and 30.6% were obese in the active group, while in the placebo group the values were 10.5%, 84.2%, and 17.6%, respectively. Waist circumference and BMI confirmed the presence of central obesity. These parameters correspond to established definitions of metabolic syndrome, making this study highly relevant for evaluating the metabolic–inflammation–cognition axis (Nolan et al., 2022).

Finally, Lin et al. (2022) (N=163) reported biochemical data consistent with early-stage metabolic dysregulation. Across groups, fasting glucose levels ranged from 95.9 ± 30.7 to 111.0 ± 33.3 mg/dL, while triglyceride levels ranged from 110.9 ± 66.0 to 133.8 ± 98.3 mg/dL, and LDL cholesterol ranged from 101.6 ± 26.5 to 108.3 ± 30.0 mg/dL. These values are suggestive of prediabetic and dyslipidemic profiles common in early metabolic syndrome (Lin et al., 2022).

Regarding clinical and biochemical outcomes, omega-3 supplementation, administered as EPA, DHA, or a combination, produced modest but favorable effects on cognitive function and inflammation. In Lin et al. (2022), EPA significantly reduced serum CCL4 levels ($p < 0.001$), a chemokine associated with AD-related neuroinflammation. Similarly, Shinto et al. (2013) showed that co-supplementation of omega-3 and alpha-lipoic acid significantly slowed the decline in MMSE and instrumental ADL scores compared to placebo ($p < 0.01$). However, Freund-Levi et al. (2006, 2014) reported no significant improvement in global cognitive outcomes

or oxidative stress markers, although subgroup analysis in the 2006 study indicated cognitive preservation in patients with very mild AD.

The Effect of Omega-3 on Alzheimer's Disease

Four randomized controlled trials involving a total of 326 participants (175 receiving omega-3 and 151 receiving placebo) assessed the impact of omega-3 supplementation on MMSE scores. As shown in Figure 3, omega-3 supplementation was associated with a statistically significant increase in MMSE scores compared to placebo (mean difference: 0.21; 95% CI: 0.02 to 0.41; P = 0.03). Heterogeneity among studies was low ($Chi^2 = 0.84$, df = 3, P = 0.84; $I^2 = 0\%$), suggesting consistent findings across trials.

Three studies with a total of 269 participants (137 in the omega-3 group and 132 in the placebo group) reported outcomes on ADAS-Cog scores. As presented in Figure 4, omega-3 supplementation did not result in a statistically significant improvement in cognitive performance compared to placebo (MD: 0.11; 95% CI: –0.40 to 0.62; P = 0.68). Moderate heterogeneity was observed ($Chi^2 = 3.71$, df = 2, P = 0.16; $I^2 = 46\%$).

Two randomized controlled trials involving a total of 95 participants (48 in the omega-3 group and 47 in the placebo group) assessed IADL scores. As shown in Figure 5, the pooled analysis revealed no statistically significant difference between omega-3 and placebo groups (MD: 0.48; 95% CI: –0.17 to 1.13; P = 0.15). Moderate heterogeneity was present ($Chi^2 = 1.55$, df = 1, P = 0.21; $I^2 = 36\%$).

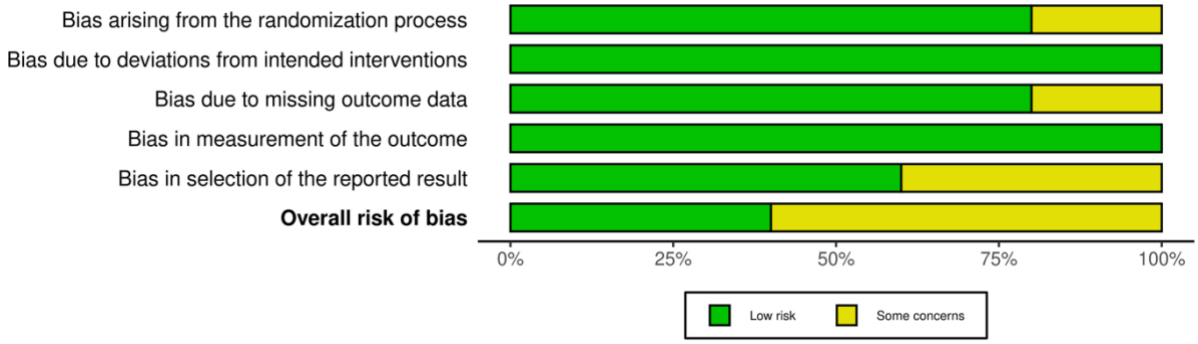

Figure 2. Risk of bias assessment for the included RCTs using ROB-2

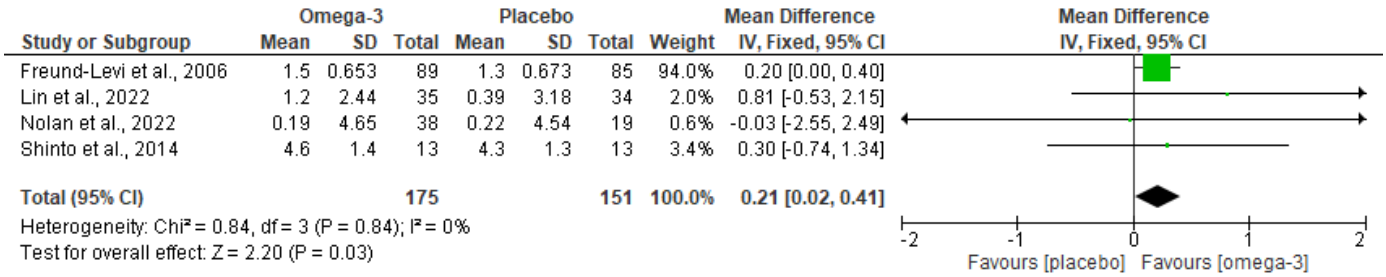

Figure 3. Forest plot showing the effect of omega-3 supplementation on Mini-Mental State Examination (MMSE) scores compared to placebo

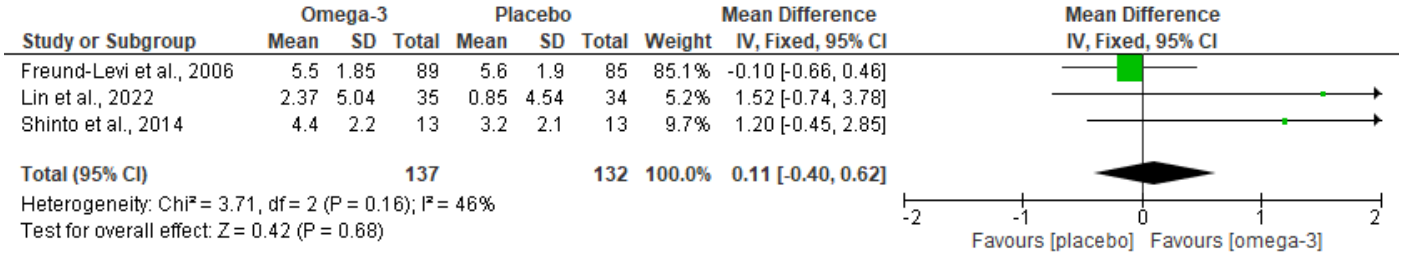

Figure 4. Forest plot showing the effect of omega-3 supplementation on Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) scores compared to placebo

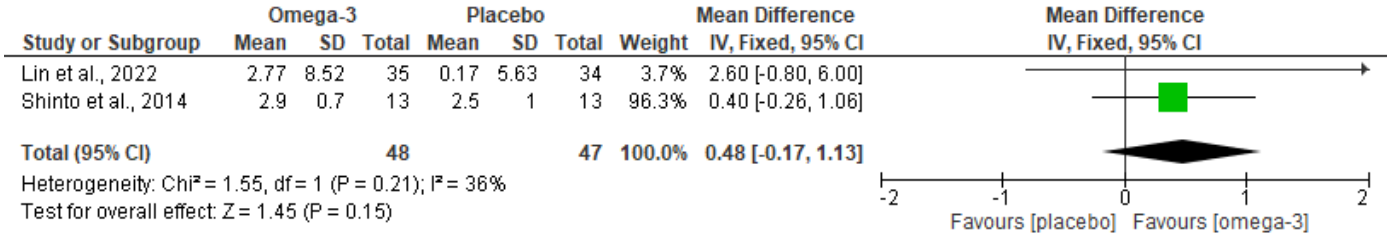

Figure 5. Forest plot showing the effect of omega-3 supplementation on Instrumental Activities of Daily Living (IADL) scores compared to placebo

DISCUSSION

This systematic review identified five randomized controlled trials examining the effects of omega-3 fatty acid supplementation on cognitive outcomes and inflammatory markers in individuals with Alzheimer's disease (AD). Of these, three studies reported beneficial effects, including Lin et al. (2022), who found a significant reduction in serum CCL4 levels following EPA supplementation, and Shinto et al. (2013), who demonstrated a slower decline in MMSE and IADL scores with omega-3 plus alpha-lipoic acid. Additionally, Freund-Levi et al. (2006) observed preserved cognition in a subgroup of participants with very mild AD. However, two studies (Freund-Levi et al., 2006, 2014) reported no significant improvements in global cognitive or oxidative markers.

These findings are partially consistent with a recent meta-analysis by Kalamara et al. (2025), which pooled data from five randomized controlled trials and found no statistically significant overall effect of omega-3 supplementation on ADAS-Cog scores (mean difference = 1.37; 95% CI: 0.00–2.73; p = 0.05). However, the authors noted a trend toward cognitive benefit, particularly in individuals with mild cognitive impairment (MCI) rather than established AD (Kalamara et al., 2025). This nuance is important, as it suggests that the therapeutic effect of omega-3 may depend on the stage of cognitive decline, with greater efficacy possible during prodromal or very early stages.

This stage-dependent response may be further modulated by underlying metabolic status. Epidemiological evidence has increasingly linked metabolic syndrome — comprising insulin resistance, central obesity, dyslipidemia, and hypertension — to an elevated risk of developing Alzheimer's disease. A large population-based study demonstrated that individuals with metabolic syndrome,

particularly women, exhibited a significantly higher incidence of AD, highlighting metabolic dysfunction as a potentially modifiable risk factor in neurodegenerative diseases (Jang & Park, 2020). These associations provide a compelling rationale to explore omega-3 fatty acids as a therapeutic agent targeting both systemic and neuroinflammatory pathways in metabolically vulnerable AD populations.

Metabolic syndrome, particularly insulin resistance, has emerged as a key contributor to Alzheimer's disease (AD) risk. As highlighted by Ezkurdia et al. (2023), insulin resistance disrupts neuronal insulin signaling via the IRS-1–PI3K–Akt pathway, leading to impaired glucose metabolism, enhanced tau phosphorylation through GSK-3β activation, and increased amyloid-β accumulation. Additionally, chronic systemic inflammation associated with insulin resistance promotes neuroinflammation through elevated TNF-α and IL-6, potentially exacerbating AD pathology (Ezkurdia et al., 2023).

Beyond insulin resistance, other components of metabolic syndrome such as obesity and hypertension have been implicated in Alzheimer's disease pathogenesis. Obesity fosters neuroinflammation and tau/Aβ dysregulation via microglial activation and oxidative stress (Thomas et al., 2015), while hypertension contributes to white matter lesions, blood–brain barrier breakdown, and cerebral hypoperfusion (Canavan & O'Donnell, 2022). These multifaceted metabolic and vascular effects, alongside the central anti-inflammatory actions of omega-3 fatty acids, provide a robust biological rationale for their potential utility in AD patients with metabolic comorbidities.

Considering the interplay between metabolic dysfunction and Alzheimer's disease (AD), omega-3 polyunsaturated fatty acids (PUFAs) offer a biologically plausible intervention targeting both peripheral and central pathways. Metabolic syndrome-related factors, especially insulin resistance and low-grade systemic inflammation, contribute to neuroinflammation, oxidative stress, and amyloid accumulation. Omega-3 PUFAs, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), modulate these mechanisms through complementary actions. EPA primarily reduces peripheral inflammation by downregulating TNF-α and IL-6, while DHA supports neuronal integrity by enhancing synaptic plasticity, limiting glial activation, and promoting brain-derived neurotrophic factor (BDNF). These dual effects are particularly relevant in early AD with metabolic comorbidities (Devassy et al., 2016).

While omega-3 fatty acids show therapeutic promise in targeting both metabolic and neurodegenerative pathways, the evidence across clinical trials remains heterogeneous. Variability in study populations, particularly in the severity of Alzheimer's disease and the presence or absence of metabolic comorbidities, may influence treatment responsiveness. Some trials demonstrated benefits primarily in early-stage AD or metabolically at-risk individuals, yet many lacked detailed reporting of baseline metabolic status, limiting subgroup interpretation. Differences in omega-3 formulations, dosages, EPA/DHA ratios, and use of co-interventions such as antioxidants further contribute to outcome variability. Additionally, the use of diverse cognitive assessment tools across studies complicates comparisons. These methodological and clinical inconsistencies highlight the importance of more

standardized, stratified research to clarify which patient subgroups are most likely to benefit from omega-3 supplementation.

This review highlights the potential utility of omega-3 fatty acids in early-stage Alzheimer's disease (AD), where cognitive benefits have been more consistently observed. Although participants' metabolic status was not systematically reported in most studies, the mechanistic overlap between metabolic dysfunction and AD supports the rationale for targeting individuals with emerging metabolic risk. Given their favorable safety profile and dual anti-inflammatory and neuroprotective effects, omega-3s may serve as adjunctive therapy in early cognitive decline, particularly in patients with subtle metabolic alterations. Future trials should stratify participants by metabolic risk to clarify who stands to benefit most and inform personalized treatment strategies.

This review has several limitations. First, although the included studies targeted Alzheimer's disease broadly, beneficial effects of omega-3 fatty acids were primarily observed in early-stage AD, limiting the generalizability of findings across the disease spectrum. Second, metabolic profiles of participants were often not systematically reported, hindering analysis of treatment response in metabolically at-risk individuals. Third, heterogeneity in intervention protocols, such as omega-3 composition, dosage, and use of co-interventions, alongside diverse cognitive assessment tools, complicates direct comparisons. Lastly, most studies had relatively small sample sizes, reducing statistical power and increasing the risk of type II errors.

CONCLUSION

This systematic review suggests that omega-3 fatty acid supplementation may offer modest cognitive and biological benefits in individuals with Alzheimer's disease (AD), particularly in the early stages. Although none of the included studies explicitly enrolled patients with metabolic syndrome, the mechanistic overlap between metabolic dysfunction and AD provides a biological rationale for targeting metabolically vulnerable populations. Across studies, effective interventions commonly involved daily doses ranging from 2 to 2.4 grams, with DHA-dominant formulations administered for at least 6 months. While these parameters may serve as a preliminary reference, optimal dosing strategies remain to be confirmed.

The current evidence is constrained by small sample sizes, heterogeneity in intervention protocols, and limited reporting of metabolic status. Future trials should adopt stratified designs that consider metabolic risk and test standardized omega-3 regimens over sufficient durations. If validated, such approaches could support more personalized, metabolism-informed interventions in early cognitive decline.

CONFLICT OF INTEREST

The authors stated there is no conflict of interest in this study.

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