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Research Paper

Documented Evidence on Omega-3 Fatty Acids for Cognitive Decline Prevention in Older Adults: A Scoping Review

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ABSTRACT

Omega-3 fatty acids have been proposed as potential nutritional interventions to preserve neurological health. However, the evidence on omega-3 fatty acids' influence on neurological biomarkers and cognitive outcomes is inconsistent. The study addresses the following questions: RQ1: What types of cohort studies and bioinformatics approaches have been used to investigate omega-3 fatty acids and cognitive decline in older adults? RQ2: Which neurological outcomes, biomarkers, and study populations have been most frequently investigated? RQ3: What knowledge gaps and future research priorities emerge from the existing evidence?

The scoping review was conducted using PRISMA-ScR guidelines. A literature search (n=33) was done on PubMed and Scopus for articles published from 2015 to 2026. There was consistent improvement in the omega-3 biological markers: plasma DHA, plasma EPA, and erythrocyte DHA and EPA. However, there was heterogeneous improvement in cognitive outcomes. Working memory, episodic memory, and executive function were more frequently observed and were often more prevalent in those with prodromal Alzheimer's disease or low baseline omega-3 status and mild cognitive impairment.

Omega-3 fatty acids have shown beneficial effects on neurological markers but may have inconsistent effects on cognitive outcomes. Further well-designed randomised controlled trials with consistent methodologies and standardised methods are needed for better understanding the role of the fatty acids in reducing cognitive decline in the ageing brain.

Keywords: omega-3 fatty acids; docosahexaenoic acid; eicosapentaenoic acid; neurological biomarkers; cognition; older adults; Alzheimer's disease; scoping review

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Introduction

In the modern century, population ageing has emerged as a significant demographic transition. World Health Organisation (2025) reported that low- and middle-income countries will have an 80% older population by 2050. The population faces significant cognitive degradation. For example, dementia is presently the seventh most common cause of mortality among the ageing population (World Health Organisation, 2026). Similarly, studies found that there are 500 cases of Alzheimer's disease and dementia for every 100,000 older people (Kundu & Bandyopadhyay, 2024). It imposes substantial social, economic, and healthcare costs on families and health systems. The pathological processes underlying Alzheimer's disease are thought to develop approximately 10–20 years before the appearance of clinical symptoms (Livingston et al., 2020). This suggests that

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preventive interventions at a preclinical stage targeting modifiable risk factors may offer greater benefits than treatments initiated after irreversible neuronal damage has occurred. Consequently, there has been growing scientific interest in approaches that can aid in delaying neurodegenerative processes and preserving cognitive function.

Within this context, omega-3 polyunsaturated fatty acids (PUFAs) have attracted considerable attention owing to their fundamental roles in maintaining neuronal integrity and brain function. Some of the prominent examples include eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). A substantial proportion of neuronal membrane phospholipids is made up of DHA and contributes to membrane fluidity, synaptic plasticity, neurotransmission, and neurogenesis (Hashimoto et al., 2017). On the other hand, EPA primarily modulates inflammatory pathways through the production of specialised pro-resolving lipid mediators that attenuate chronic neuroinflammation (Dyall, 2015). Additionally, studies further demonstrate that oxidative stress is reduced by omega-3 fatty acids, inhibiting amyloid-β aggregation and decreasing tau hyperphosphorylation (Sahebi & Rezvani Kakhki, 2025; Tahir & Siddiq, 2025). Thereby, these molecules improve cerebrovascular function and enhance brain-derived neurotrophic factor (BDNF) signalling, providing several biologically plausible mechanisms through which cognitive decline may be attenuated. These mechanistic findings have provided a compelling biological rationale for evaluating whether omega-3 fatty acids can be a potential neuroprotective agent in ageing populations.

Genetic studies have highlighted that there are distinct gene expression patterns related to neuroinflammation, synaptic signalling, and lipid metabolism. Additionally, these patterns are also associated with tau proteins and amyloid-β, along with neurofilament light chain, inflammatory mediators and complement-related proteins (Johnson et al., 2020). In addition, metabolomics and lipidomics have allowed for a detailed characterisation of omega-3-associated metabolic signatures and pathways. It provided more mechanistic insight into the cognitive resilience and neurodegeneration metabolic signatures. Together, these strategies have driven a change in paradigm in research by moving from the analysis of individual biomarkers to the characterisation of complex networks of biological systems involved in cognitive ageing.

Despite this strong mechanistic foundation, the translation of experimental evidence into clinical and epidemiological settings has produced inconsistent findings. Higher dietary fish consumption, greater circulating concentrations of DHA and EPA, or elevated omega-3 indices are linked with reduced incidence of dementia and slower cognitive decline (Sala-Vila et al., 2023). For example, recent analyses from the Cardiovascular Health Study demonstrated that reduced chances of cognitive impairment were linked to greater long-term plasma phospholipid omega-3 concentrations (Li et al., 2020). These findings are biologically plausible because circulating biomarkers better reflect long-term physiological status than self-reported dietary intake, while longitudinal cohort designs capture cumulative exposure throughout ageing rather than isolated interventions.

However, some trials have reported modest improvements in executive function, episodic memory or global cognition among individuals with mild cognitive impairment (Power et al., 2022). Contrarily, many others have demonstrated negligible or no significant benefits in neurologically healthy older adults or patients with established dementia (Andrieu et al., 2017; Baleztena et al., 2018). Thus, the research has shown that omega-3 supplementation has generated considerably more heterogeneous outcomes. Similar inconsistencies have been highlighted by studies in meta-analysis (Mazereeuw et al., 2012). These inconsistencies are unlikely to reflect a simple absence of biological efficacy. Rather, they appear to arise from substantial methodological heterogeneity, including variations in supplementation dosage, EPA-to-DHA ratios, intervention duration, baseline nutritional status, participant health profiles, cognitive assessment tools, and disease stage at intervention. This apparent discrepancy in evidence has important implications for future research.

Cognitive decline develops gradually over decades through complex interactions among genetic susceptibility, vascular health, inflammation, metabolic dysfunction, and environmental influences (Colita et al., 2024). Consequently, relatively short supplementation trials initiated in later life may fail to reverse neuropathological processes that have already become established. For example, RCTs remain the gold standard for evaluating therapeutic efficacy; however, they may inadequately capture the cumulative and lifelong dietary exposures that characterise nutritional epidemiology. Emerging evidence further suggests that responsiveness to omega-3 fatty acids may differ according to individual biological characteristics, including APOE ε4 genotype, systemic inflammatory status, metabolic health, and baseline omega-3 concentrations (Visioli et al., 2026). This evidence highlights the limitations of applying a uniform intervention across biologically heterogeneous populations. Collectively, these findings indicate that the current debate surrounding omega-3 fatty acids should move beyond the simplistic question of whether supplementation is universally effective. As a result, bioinformatics has emerged as an essential

tool to combine disparate information from epidemiological cohorts, transcriptomic data, proteomic profiles and metabolomic data to discover new drug targets and biomarker signatures.

Nonetheless, recent studies comprehensively summarise recent randomised controlled trials and cohort studies highlighting the potential impact of omega-3 on cognition. However, it does not systematically map how different types of evidence have been used to investigate the neuroprotective role of omega-3 fatty acids. With the increasing use of epidemiological databases and omics technologies, there is a need to identify research trends, methodological characteristics, evidence gaps, and future research priorities. A scoping review is appropriate because it aims to map the breadth of available evidence rather than evaluate intervention effectiveness.

RQ1: What types of cohort studies and bioinformatics approaches have been used to investigate omega-3 fatty acids and cognitive decline in older adults?

RQ2: Which neurological outcomes, biomarkers, and study populations have been most frequently investigated?

RQ3: What knowledge gaps and future research priorities emerge from the existing evidence?

This is especially significant because nutritional neuroscience is moving towards precision nutrition. New opportunities arise from the growing availability of biobanks with longitudinal data that connects dietary fatty acids to the molecular mechanisms of cognitive ageing, in the context of genomic, transcriptomic, proteomic, and metabolomic data, as well as electronic health records. Without assessing the scope, it is impossible to determine which areas of the evidence base, limited evidence, and new technologies are being developed. Therefore, the study used a scoping review method as its aim is not to measure pooled intervention effects but to map the existing evidence, clarify the research trends, categorise methodological approaches and identify gaps in knowledge.

2. Methodology

2.1. Study Design

This study adopted a scoping review methodology guided by the frameworks developed by Hadie (2024). Unlike systematic reviews, scoping reviews are not designed to critically evaluate the methodological quality of individual studies or to statistically combine findings through meta-analysis. Rather, they offer an organised method for recognising, characterising, and summarising the range of information that is already available on a given subject while emphasising areas where knowledge is still incomplete and further research is necessary. A scoping review was deemed the best method to thoroughly map the body of research on the relationship between omega-3 fatty acids and cognitive aging due to the wide range of study designs, outcome measures, and biomarker evaluations. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) criteria were followed in the review process and reporting.

To establish the review eligibility criteria and guide the search strategy, the Population–Concept–Context (PCC) framework was applied (Peters et al., 2021). The PCC framework facilitated the systematic definition of the review question and ensured that the literature search was comprehensive and aligned with the objectives of the review.

- **Population**: Community-dwelling and clinical populations of older adults aged 60 years and above.
- **Concept**: The relationship between omega-3 fatty acids obtained through dietary intake, fish oil supplementation, or biomarker assessment, and neurological health, cognitive function, or cognitive decline.
- **Context**: Evidence generated from cohort studies, randomized controlled trials, longitudinal population-based studies.

2.2 Eligibility Criteria

The predetermined PCC criteria were used to select eligible studies. The population focused on older adults aged 60 years with no restrictions on sex, ethnicity or geography.

Inclusion Criteria

The following prospective and retrospective cohort studies, longitudinal observational studies and population-based epidemiological studies investigating the relationship between cognitive outcomes and omega-3 fatty acids were considered for inclusion. Research projects using bioinformatics analysis, transcriptomics, genomics, proteomics, metabolomics, lipidomics, systems biology or network pharmacology to explore the biological mechanisms of how omega-3 can achieve neuroprotection were also included. Common neurological outcomes of interest were MCI, executive function, cognitive decline, Alzheimer's disease, dementia, memory performance, as well as other validated cognitive assessments. Where applicable, studies that assessed circulating markers, inflammatory markers, neuroimaging markers, genetic polymorphisms, and markers of molecular pathways related to omega-3 metabolism and cognition were included.

Exclusion Criteria

Studies that contained animal or in-vitro experiments, paediatric or adult studies that were under 60 years old, editorials, conference abstracts without full-text publications, opinion papers, narrative reviews, commentaries, case reports, or non-English studies were excluded. Randomised controlled trials and systematic reviews were found

in the search process, but were not included in the present review as the aim of the present review was to map observational and molecular evidence and not to assess the efficacy of interventions.

2.3. Search Strategy

The most successful approach is to adopt a search strategy that uses information sources to locate the information needed. A search was conducted on PubMed/MEDLINE and Scopus. To ensure that these databases covered the biomedical sciences, nutrition, neuroscience, psychology and epidemiology, these databases were chosen. Studies published from January 2015 to December 2026 were searched to ensure that the data included more recent advances in multi-omics approaches and precision nutrition and longitudinal cohort research. Medical Subject Headings [MeSH] and Emtree terms with free-text keywords were used to develop the search strategy. Table 1 shows the important key terms used.

Group	Terms
omega-3 fatty acids	“omega-3", DHA, EPA, fish oil
Older adults	"aged", "older adults", elderly
methodological approaches	cohort, longitudinal, epidemiology, bioinformatics, genomics, transcriptomics, proteomics, metabolomics, lipidomics, and network pharmacology
cognitive outcomes	"cognitive decline", dementia, Alzheimer's disease, mild cognitive impairment

Phrase searching, truncation, Boolean operators, and database-specific syntax were used to maximise the number of hits while avoiding false hits. All cited studies and relevant review articles were hand-screened in the reference lists for further eligible papers. The search strings are provided in Table 1 below.

Table 2. Search Strategy applied

Database	Search
Scopus	TITLE-ABS-KEY((omega-3* OR "fish oil" OR DHA OR EPA OR "docosahexaenoic acid" OR "eicosapentaenoic acid") AND ("cognitive decline" OR dementia OR cognition OR "mild cognitive impairment" OR Alzheimer* OR neurodegenerative) AND ("older adults" OR elderly OR ageing OR aging OR aged) AND (cohort OR longitudinal OR prospective OR epidemiology OR bioinformatics OR genomics OR transcriptomics OR proteomics OR metabolomics OR lipidomics OR "network pharmacology"))
PubMed	(("Fatty Acids, Omega-3"[Mesh] OR "Fish Oils"[Mesh] OR omega-3*[tiab] OR "omega 3"[tiab] OR DHA[tiab] OR EPA[tiab] OR "docosahexaenoic acid"[tiab] OR "eicosapentaenoic acid"[tiab] OR "fish oil"[tiab] OR "marine oil"[tiab]) AND ("Cognitive Dysfunction"[Mesh] OR "Cognition Disorders"[Mesh] OR "Alzheimer Disease"[Mesh] OR "Dementia"[Mesh] OR "Mild Cognitive Impairment"[Mesh] OR "cognitive decline"[tiab] OR cognition[tiab] OR dementia[tiab] OR Alzheimer*[tiab] OR "mild cognitive impairment"[tiab] OR MCI[tiab] OR neurodegenerat*[tiab]) AND ("Aged"[Mesh] OR elderly[tiab] OR "older adults"[tiab] OR aging[tiab] OR ageing[tiab] OR seniors[tiab]))

2.4 Study Selection

The studies were screened using Covidence. All articles that were potentially relevant were searched for full text, and then assessed independently for final inclusion. The research selection process was recorded using the PRISMA-ScR flow diagram, which is depicted in Figure 1. Finally, thirty-three studies were included.

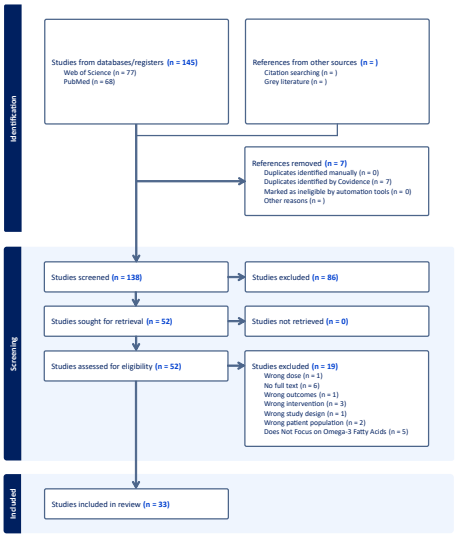

Figure 1. Screening of studies shown in PRISMA-Sc

2.5. Data Extraction and Data Synthesis

Data were extracted following the JBI recommendations (Peters et al., 2021). Information retrieved consisted of author, year of publication, study design, study participants, omega intervention, any biomarkers studied, key findings, and limitations of the study. The data of extraction is presented in Table 2 in the Appendix.

No formal methodological quality appraisal was done as this was not the intent of a scoping review, which aims to observe the available evidence (Munn et al., 2018; Peters et al., 2021). The data were analysed through narrative synthesis. The trends in research, geographical distribution, commonly studied biomarkers, emerging applications of bioinformatics and multi-omics technologies and the need for more evidence were identified using frequencies and descriptive summaries. The results were then related to the aim of the review to pinpoint gaps in the methodology and suggest future research

avenues for the field of Omega-3 and cognitive ageing.

3. Results

Following the screening, thirty-three studies were selected for the study. The table of extraction below shows the details of the findings from the selected studies.

3.1. Types of cohort studies and bioinformatics approaches used to investigate Omega-3 fatty acids and cognitive decline in older adults

The studies included showed significant variability in the types, composition, dose, duration of administration, and mode of delivery of omega-3 fatty acids. Evidence included randomised controlled trials of omega-3 supplementation, prospective observational cohort studies of plasma omega-3 levels, and secondary analyses of clinical trials that explored the effects of modifying variables on the outcomes of omega-3 interventions. These interventions were mostly based on DHA; alpha-linolenic acid (ALA); a combination of EPA and DHA; or the assessment of the endogenous status of omega-3 fatty acids by observation alone.

Several randomised controlled trials evaluated DHA as the only omega-3 fatty acid administered, reflecting its recognised role as the predominant structural lipid within neuronal membranes (Bischoff-Ferrari et al., 2020). DHA dosages ranged from 300 mg/day up to 2 g/day, and the length of supplementation varied between 12 and 24 months. The largest dose used in the trials was in the PreventE4 trial, where 2 g/day DHA was used among older adults who were cognitively normal but at higher risk for developing dementia. Contrarily, in other trials, daily DHA supplementation generally varied between 800 and 1,500 mg. In all these studies, DHA supplementation was found to significantly increase the blood and CSF DHA levels, which indicated good treatment adherence and biological uptake of DHA. There was less uniformity in improvements of cognitive outcomes, however. While some studies found no significant relationship with global cognition, other studies showed small- to moderate-sized benefit in subgroups or cognitive domains or modest effect overall with large omega-3 blood levels. This variability implies that a simple increase in exposure to DHA is not likely to lead to measurable cognitive effects in relatively short periods of intervention, especially in cognitively normal groups.

Furthermore, the most commonly investigated intervention approaches were combining EPA and DHA. Most intervention trials evaluated combined DHA and EPA supplementation rather than single-fatty-acid formulations. The administered omega-3 dose ranged from approximately 520 mg/day (430 mg DHA and 90 mg EPA) to 3.36 g/day (1.86 g EPA and 1.50 g DHA), and supplementation periods lasted for as long as three years. EPA/DHA treatments were administered in various doses, such as fish oil capsules, fish oil ethyl esters and fortified nutritional beverages. Some trials used omega-3 fatty acids alone, while others used them combined with other nutrients such as carotenoids, vitamins, phospholipids, uridine monophosphate, choline or cocoa flavanols. This meant that sometimes it was difficult to attribute the observed neurological effects to omega-3 fatty acids.

Across intervention studies, overall, DHA and EPA supplementation increased levels of DHA and EPA, plasma DHA, plasma EPA, and the Omega-3 Index in blood. This evidence indicates high compliance overall. However, clinical results were still variable. Several trials found an improvement in executive function, verbal fluency, working memory or a decrease in subjective cognitive complaints (Malik et al., 2023). Others found no significant effect on global cognition, hippocampal volume or progression of dementia. Positive intervention effects were more prominent in those participants who had early cognitive decline, low baseline omega-3 status, high vascular risk, or specific genetic factors including APOE ε4 carriage, indicating that baseline participant factors may play a role in response to supplementation.

A few of the studies included examined omega-3 fatty acids from plants. The principal ALA intervention was 12 weeks of 2.2 g/day of ALA through flaxseed oil among older adults with normal cognitive function (Ogawa et al., 2023; Assmann et al., 2018). Evidence for ALA was less than for DHA and EPA. The available trial revealed slight benefits in verbal fluency but no significant effects in the wider cognitive domains, such as memory, executive functioning or processing speed. Moreover, no biological markers of omega-3 were used to verify the formation of longer-chain omega-3 fatty acids from conversion of ALA. Thus, it makes mechanistic interpretation difficult. Therefore, the existing evidence base is much less robust for ALA compared to marine-based DHA and EPA for neurological outcomes among ageing and older adults.

Several prospective cohort studies that did not use omega-3 supplements, but rather looked at the correlation between endogenous omega-3 status and neurological outcomes using objective biomarkers. The studies mainly estimated the amount of DHA or EPA in red blood cells or fatty acids in serum or the Omega-3 Index, which enabled the evaluation of long-term omega-3 exposure at normal levels of consumption. In observational studies, each increase in DHA or EPA by 10% was consistently found to be related with a decreased risk of incident Alzheimer's disease, cognitive decline or dementia. Interestingly, the biomarker of red blood cell DHA was consistently linked to positive neurological outcomes, while the results for EPA and ALA were not as consistent. However, these studies were observational in nature and thus did not

prove causation. Nonetheless, they serve as valuable evidence for the possible association of long-term omega-3 status with neurological health.

Dosages of omega-3 supplementation ranged widely between intervention studies, depending on the different study goals, subjects, and formulations of the supplements. The dose of DHA ranged from 300 mg/day to 2,000 mg/day, EPA from 90 mg/day to about 1,860 mg/day and ALA up to 2.2 g/day. The total intake of marine omega-3s was thus estimated to be between 520 mg/day and 3.36 g/day (Table 2). Even though this wide range of dosage was used, no dose–response relationship was found. The cognitive results of high-dose supplementation did not always show any differences from low-dose supplementation. For instance, trials that delivered 2 g/day of DHA had a consistent positive effect on increasing circulating levels and CSF levels of DHA; however, the positive effect on cognition was not observed in all studies. Several studies provided moderate-dose DHA supplementation with positive effects in a few cognitive domains. These especially included executive function, working memory, and verbal fluency. Results indicate that baseline nutritional status, disease stage, length of the intervention, genetic susceptibility and metabolic health may contribute significantly to intervention efficacy beyond dose.

The length of time an intervention takes to be effective has varied between 36 months to 12 weeks. Most of the randomised controlled trials (RCTs) have been for 6 to 24 months. Short duration studies (≤12 weeks) mostly reported cognitive effects or circulating biomarkers, and longer studies also reported structural MRI results, incidence of dementia, and rate of cognitive decline. Moreover, extended supplementation did not always lead to improved clinical outcomes, but longer periods of supplementation would allow more time for the remodelling of neuronal membranes and the neuroprotective effects to take place. A couple of studies over 24–36 months showed minimal or no improvement in global cognition despite continued increase in omega-3 status. Shorter studies, however, have sometimes reported benefits in executive function or verbal fluency after as few as 12 weeks. This engagement variability indicates that the efficacy of interventions is not solely dependent on the duration of the intervention, and suggests that cognitive ageing and neurodegeneration are a multifactorial process. Therefore, the heterogeneity of formulations, dosage, length of intervention, participant characteristics, and co-supplementation techniques must be noted when interpreting the effects of sources on neurological health in older adults.

3.2. Investigated neurological outcomes, biomarkers, and study populations

In the studies included, a wide range of neurological biomarkers was used to impact of omega-3 fatty acids on neurological health among older adults. Blood-based biomarkers, genetic markers, neuroimaging outcomes, biomarkers in cerebrospinal fluid (CSF) and other physiological or metabolic parameters were all broadly classified as biomarkers. The range of biomarkers highlights the multi-faceted nature of cognitive ageing and neurodegeneration and the absence of a biomarker that has become the standard marker of the efficacy of omega-3.

The most common category was blood biomarkers (22% of studies included). The most commonly reported measures were RBC fatty acid composition, including the Omega-3 Index, fatty acids DHA and EPA. These were associated with long-term dietary consumption and incorporation of omega-3 fatty acids (Hooper et al., 2017; Howe et al., 2018; Kühn et al., 2022; Sala-Vila et al., 2022; Maltais et al., 2022; Mengelberg et al., 2022). Other studies measured plasma or serum phospholipids or serum EPA and DHA levels. These were considered to be more reflective of recent dietary intake and were still used as a measure of intervention adherence (Power et al., 2022; Sueyasu et al., 2023; van Soest et al., 2022; Vauzour et al., 2023). In both types of biological matrix used in the intervention studies, the increase in the concentrations of EPA and DHA in plasma was consistently reported and indicative of the successful biological uptake of the supplement. However, there was no consistent evidence of improvements in neurological outcomes associated with enhanced peripheral fatty acid status, and this was an inadequate predictor of clinical benefit (Yassine et al., 2026; Shinto et al., 2024). Conversely, inverse relationships were repeatedly reported between elevated baseline levels of either RBC DHA or serum EPA and incident dementia orr Alzheimer's disease (van Lent et al., 2021; Sala-Vila et al., 2022). This implied that omega-3 status over an extended period of time may prove to be a more powerful prognostic factor than a short-term supplement

APOE ε4 genotype was included in many intervention and observational studies (Soininen et al., 2017; Hooper et al., 2017; Ichinose et al., 2021; Sala-Vila et al., 2022; van Soest et al., 2022; Yassine et al., 2026; Shinto et al., 2024). APOE ε4 was not a primary outcome but was mainly explored as an effect modifier. There was a dichotomy in the studies regarding the effect of omega-3 supplementation on the genotype effect. While some suggested that it was detrimental, others found it to be beneficial, whereas several studies reported that APOE ε4 carriers had higher degrees of decline in cognition or neurodegeneration compared to non-carriers (Vyas et al., 2024; Maltais et al., 2022). In a similar study, Yassine et al. (2026) showed that high doses of DHA, rather than low doses, raised CSF DHA concentrations regardless of whether participants had an APOE genotype that promoted or opposed

DHA delivery. In addition to APOE, few studies examined other epigenetic or genetic markers. For example, LINE-1 DNA methylation was investigated by Karimi et al. (2017). It was also found to be a significant gap in the evidence on other molecular mechanisms of omega-3 responsiveness.

A variety of neuroimaging biomarkers were broadly used to assess brain structural and functional alterations. Hippocampal volume, whole-brain volume, ventricular enlargement, temporal lobe volume, cortical thickness and white matter lesion burden were the conventional structural MRI outcomes (Soininen et al., 2017; Barnes et al., 2021; Emam et al., 2026; Shinto et al., 2024). Neuronal integrity was assessed using more advanced neuroimaging techniques. These included dynamic contrast-enhanced MRI (DCE), cerebral blood flow assessment and β-amyloid positron emission tomography (PET), diffusion tensor imaging (DTI) (Hooper et al., 2017; Howe et al., 2018; Kuszewski et al., 2020; He et al., 2023). Despite the advances in methodology, the results of the neuroimaging studies remained inconsistent. Other trials have shown preservation of hippocampal volume and/or slowed white matter degeneration after omega-3 supplementation (Soininen et al., 2017; Shinto et al., 2024). Contrarily, others have reported no significant structural changes with substantial elevations in peripheral omega-3 biomarkers (Yassine et al., 2026). This difference implies that the results of neuroimaging studies may need longer intervention periods or earlier therapeutic interventions before a measurable change in structure occurs.

Accounting to the invasive procedure of CSF puncture, only a few studies included CSF biomarkers. The majority of those measured the CSF concentration of CSF amyloid-β42, the ratio CSF amyloid-β42/CSF amyloid-β40, CSF total tau, CSF phosphorylated tau and CSF DHA, respectively (Soininen et al., 2017; Arellanes et al., 2020; Yassine et al., 2026). High-dose DHA supplementation was found to be effective at engaging the central nervous system (CNS) with an elevation in CSF DHA and CSF DHA to arachidonic acid ratios. These findings were consistent across all studies. However, there was no consistent link between these biochemical effects and measures of cognition or MRI outcomes, indicating that appropriate delivery of DHA to the brain does not equate to any measurable clinical effects in the timeframe of the current trials.

Other studies evaluated inflammatory, vascular and metabolic markers, as well as classic neurological markers. Other markers that were added as supporting markers to better characterise mechanisms of cognitive ageing were homocysteine, inflammatory cytokines, C-reactive protein (CRP), lipid profiles, glucose metabolism, carotenoids, brain-derived neurotrophic factor (BDNF), and immune-inflammatory indices (Bo et al., 2017; Daďová et al., 2022; Kuszewski et al., 2020; McNamara et al., 2018; Power et al., 2022; He et al., 2023). However, these measures were not always included. Consequently, this made comparison difficult between studies, and also highlighted a high level of methodological heterogeneity in the existing evidence.

Moreover, there was significant variability in outcome selection as well. A large number of different validated cognitive tests and neuroimaging measures were used to evaluate neurological outcomes. Global cognition was the most common domain assessed, and was typically assessed with the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), Mini-Mental Status Examination (MMSE), or composite neuropsychological scores (Soininen et al., 2017; Vyas et al., 2024; Yassine et al., 2026). Although omega-3 biomarkers in circulation showed consistent improvement after supplementation, there was a relatively small improvement in global cognition. However, the majority of randomised controlled trials (RCTs) found there is no distinction between placebo and treatment (Power et al., 2022; Vauzour et al., 2023; Yassine et al., 2026). Additionally, there were minor effects compared to placebo in cognitively unimpaired participants. In contrast, evidence from observational studies indicated that individuals with higher baseline concentrations of EPA or DHA experienced a decreased risk of incident dementia or decline in cognition (Sala-Vila et al., 2022; van Lent et al., 2021). These findings imply that maintaining higher long-term DHA and EPA status may contribute to preserving cognitive function and reducing dementia risk.

Memory outcomes were assessed in most intervention studies and comprised episodic memory, verbal memory, visual memory and delayed recall. Memory had more consistent evidence of responsiveness to omega-3 supplementation, but was less responsive than global cognition. This was mainly attributed to improvements in participants with subjective cognitive decline (SCD), or prodromal Alzheimer's disease (PAD) or mild cognitive impairment (MCI) (Soininen et al., 2017; Sueyasu et al., 2023; Gustafson et al., 2020; Deshmukh et al., 2024). On the other hand, studies involving cognitively healthy older adults tended to report minimal effects (Power et al., 2022). This pattern indicated that pretreatment cognitive deficits might modulate the magnitude of treatment effects.

Another common domain assessed was executive function. This involved tests of planning, cognitive flexibility, and verbal fluency/inhibitory control. Multiple randomised trials showed improvements in executive function with omega-3 supplementation (Power et al., 2022; Daďová et al., 2022). However, no significant differences between

intervention and placebo groups were reported by other study (Vauzour et al., 2023). These inconsistencies were also noted for attention and processing speed, assessed with the Trail Making Tests, Stroop tests, Digit Symbol Substitution Tests and computerised cognitive batteries. While there were scattered reports of low levels of improvement, the results were not always consistent throughout the larger body of evidence.

Brain imaging results included objective measures of neurodegeneration beyond cognitive testing, such as hippocampal atrophy, cortical thickness, ventricular enlargement, progression of white matter lesions, neuronal integrity and cerebral perfusion (Soininen et al., 2017; Barnes et al., 2021; Shinto et al., 2024; Emam et al., 2026). Findings from the structural brain outcomes showed limited sensitivity to omega-3 supplementation, with positive results only in specific subgroups, such as those with prodromal Alzheimer's disease or low baseline omega-3 status. As such, although omega-3 supplementation showed consistent benefit on biochemical measures of fatty acid status, the benefits for clinically relevant cognitive performance and structural brain integrity were largely inconsistent across the studies. However, the types of intervention, the diversity of the study groups, the variety of biomarkers used and the outcome measures analysed highlight the heterogeneity of the existing evidence. Thus, it highlights the important factors to be considered when evaluating the effectiveness of the fatty acid intervention for maintaining neurological health as people age.

3.3. Knowledge gaps and future research priorities emerging from the existing evidence

With regard to the scope of this review, multiple common gaps in knowledge across studies were identified. Some of the most obvious drawbacks were the significant variations in study design, participant characteristics, intervention type, dosage, duration, biomarker selection, and cognitive outcomes measures across studies (Soininen et al., 2017; Power et al., 2022; Shinto et al., 2024). Although most intervention studies showed that there were significant changes in the levels of circulating omega-3s, consistent improvements in any cognitive or neuroimaging outcomes were not consistently observed. These indicated the need for more precise identification of clinically meaningful biomarkers of treatment response.

Some studies also stressed on the questions surrounding the proper dosage, form, and length of omega-3 supplementation. The interventions included moderate dose DHA/EPA supplementation, high-dose DHA supplementation or multi-nutrient formulations, but no optimal therapeutic strategy could be determined (Soininen et al., 2017; Vauzour et al., 2023; Yassine et al., 2026). Additionally, many trials added other nutrients (carotenoids, vitamins, cocoa flavanols, or B vitamins) to the omega-3 fatty acids, which made it difficult to separate the effects observed from those of the omega-3 fatty acids alone (Power et al., 2022; Sueyasu et al., 2023; Vauzour et al., 2023). Another common deficiency was the lack of assessment of biological factors which could affect therapeutic response. While APOE ε4 genotype was often studied, the effects of this genotype as a modifier of the omega-3 efficacy did not always agree across studies (Sala-Vila et al., 2022; Vyas et al., 2024; Yassine et al., 2026). Similarly, few studies included cerebrospinal fluid markers, sophisticated neuroimaging measures or longitudinal measures of structural brain change. Thus, the body of evidence suggests that larger, well-designed RCTs is needed. It can use standardised biomarker panels, standardised cognitive assessments and longer follow-up periods. These would help in further clarifying the neurological effects of omega-3 fats and to increase the comparability of future studies.

4. Discussions

Omega-3 fatty acids consumption increased serum levels of both EPA and DHA. However, supplementation effects on cognitive performance are inconsistent across older adults. The evidence highlights that generally significant increases in blood-based markers (Omega-3 Index, plasma DHA and erythrocyte EPA) were observed. This aligns with the findings from existing studies (Suh et al., 2024). Additionally, significant increases in global cognition were observed less consistently across studies depending on baseline cognition, treatment characteristics and participant risk profiles. Dose–response in the last few years have yielded comparable findings, with no overall benefits for cognitive function in cognitively normal older adults from omega-3 supplementation, despite recognised benefits reported. Rather, cognitive improvements seemed to be limited to certain domains of cognitive function, especially executive function, and to be moderated by the length of the intervention, its dose and the baseline level of omega-3.

Current findings also confirm a now-established pattern of more positive outcomes for cognitive decline in individuals with higher risk than cognitively healthy individuals when taking omega-3 supplements (Wei et al., 2023). Several studies included in this review reported more favourable outcomes among participants with early-stage cognitive impairment, self-reported cognitive complaints, reduced baseline omega-3 status, or a greater burden of vascular risk factors. These findings are consistent with the meta-analysis conducted by Suh et al. (2024), which demonstrated that DHA and EPA supplementation was associated with significant improvements in overall cognitive performance in older adults with MCI or dementia, whereas benefits for executive functioning and

language abilities were less pronounced. In general, these observations suggest that pre-treatment neurological status might be an important predictor of treatment response and explain some of the conflicting findings reported in intervention trials.

One key point from this review was the high frequency of the biochemical target engagement to clinical outcome mismatch. The DHA levels in the CSF were always high following supplementation, and in some cases, this was associated with biochemical markers that did not reflect measurable cognitive changes or structural neuroimaging changes. These findings are echoed by recent evidence syntheses which found that circulating omega-3 levels do not accurately predict cognitive benefits (Welty, 2023). On the other hand, a successful intervention may require that sufficient tissue levels of omega-3 are reached before significant neurodegeneration has taken place. Furthermore, recent reviews of each of these analyses show that the greater the baseline or post-intervention Omega-3 Index, the more likely the improvements in cognition will be. It suggests that biological response to intervention, rather than the intervention itself, may be an important element in clinical effectiveness.

More recent research has included newer cognitive tests with the addition of CSF markers, APOE genotype and metabolomic profiling. In contrast to the earlier studies, newer studies included traditional cognitive measures, CSF markers, APOE genotype and metabolomic profiling plus neuroimaging. There is a lot of variety among methodology. There was also significant variability in the formulations of the supplements, intervention duration, the tools used for cognitive assessment, as well as the selection of the biomarkers used in recently conducted systematic reviews. The results of this review support such concerns, highlighting the lack of standardisation of outcome measures across studies and protocols of interventions.

An interesting point of study was the importance of personal nutrition. Reviews of the studies show that genetic factors, starting levels of omega-3 and metabolic health may be determinants of treatment response. The results relating to APOE ε4 modification were mixed, but is consistent with the more recent literature that favours precision nutrition rather than a universal omega-3 approach (Loong et al., 2023). The interest of interventions in the future should be to stratify based on baseline nutritional status, genetic profile, and disease stage to maximise the number of people supplemented.

The present study results add to the existing evidence. It indicates that the biological actions of ω3 fatty acids are present but that clinical effectiveness is good to weak. To date, no evidence challenges the neurobiological importance of DHA and EPA. Contrarily, consistency of methodology, baseline nutrition and timing of interventions are suggested as factors that might impact intervention success. To improve the comparability and clinical relevance of results, future studies should be aimed at the standardisation of biomarker assessment, harmonisation of cognitive outcome measures and at using sufficiently large sample sizes and being specifically designed for populations at highest risk of cognitive decline.

5. Conclusion

The evidence together strongly supported the consistent improvement of biological markers of an omega-3 status with omega-3 supplementation, particularly formulations containing EPA and DHA. There were also reports of positive increases in CSF DHA concentrations, demonstrating effective target engagement in the CNS following supplementation. The neurological function, however, showed far more variable biochemical effects, even with these consistent biochemical changes. There was a general trend of enhancing cognitive function in specific domains instead of global cognition across the studies included. In the domain of episodic memory, working memory, executive function, and verbal fluency, benefits from omega-3 supplementation were most frequently reported, while benefits for overall cognitive performance were less consistent. There was greater evidence of beneficial impact in those with prodromal Alzheimer's disease, subjective cognitive decline, mild cognitive impairment, low levels of baseline omega-3 and high dementia risk than among cognitively normal older adults. Likewise, observational studies all found a lower likelihood of cognitive deterioration, dementia incidence and Alzheimer's disease as linked to higher endogenous concentrations of EPA and DHA. However, randomized controlled trials yielded inconsistent results, and gains in omega-3 fatty acids in blood did not always lead to improvements in cognition or brain structure in the relatively limited duration of the most common trials.

From a clinical and public health perspective, the findings suggest that omega-3 fatty acids may serve as a valuable component of strategies aimed at maintaining cognitive health in older adults, particularly those with an elevated risk of cognitive deterioration. Blood and CSF omega-3 biomarkers have increased consistently following supplementation, suggesting a biological effect of supplementation, and positive results have been seen in certain high-risk populations. Thus, a greater clinical benefit can be achieved from targeted as opposed to universal supplementation. The review further emphasises the need to integrate objective biomarkers, such as the Omega-3 Index, neuroimaging markers, CSF markers and genetic markers, into clinical practice. Additionally, research in the future need to improve the ability to assess the response to intervention and disease progression more precisely. Moreover, the results

provide evidence for a shift toward the development of individual nutritional interventions that take into account the initial nutritional status, cognitive function, vascular risk factors, and genetic susceptibility when developing preventive strategies for cognitive decline.

Furthermore, several intervention studies evaluated omega-3 fatty acids in combination with additional bioactive nutrients, including carotenoids, vitamins, flavanols, and phospholipids. Consequently, the independent contribution of omega-3 supplementation to the observed outcomes cannot be clearly distinguished. Third, there was significant variation in the use of biomarkers and neuropsychological assessment. Thus, it can make it difficult to detect common trends in the studies. Finally, this review was a scoping review, and so was not intended to formally evaluate the methodological quality of studies or to quantify treatment effects through meta-analysis of the evidence.

Future studies should focus on larger, well-powered randomised controlled studies using standardised intervention protocols and cognitive assessments as well as harmonized biomarker panels. More follow-up is also needed to see if improved omega-3 benefits are translated into clinically significant decreases in incidence of cognitive decline or dementia. Additional studies are warranted to examine the effect of baseline omega-3 status, APOE genotype, vascular health, and other biological modifiers. This would provide insight on whether the supplement has an impact on individuals to determine which individuals are most likely to benefit from supplementing with omega-3s. These research priorities will help build the evidence base and help inform the development of more tailored, effective nutrition approaches to support neurological health and the burden of age-related cognitive decline.

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Appendix

Table 2. Data Extracted from Selected studies

Covidence #	Study ID	Authors	Year of publication	Aim of study	Study design	Participants	Health Status	Omega Exposure	Biomarkers	Key findings	Study limitations
144	Soininen 2017	Soininen et al.	2017	To evaluate whether Fortasyn Connect slows cognitive decline and neurodegeneration in pro	Randomised controlled trial	311 prodromal Alzheimer's adult patients aged 55-85 years (mean age 71 years)	Alzheimer's disease-related mild cognitive impairment, biomarker-positive, no dementi	Daily 125 mL Souvenaid (Fortasyn Connect). It contains EPA, choline, DHA, uridine monop	Plasma DHA/EPA, CSF AÎ²42, AÎ²42/AÎ²40, total tau, phosphorylated tau, APOE Îµ4 genotype, MRI hipp	No significant improvement in the primary NTB outcome (P=0.166); significa	Underpowered primary endpoint, slow cognitive decline in controls, NTB sensitivity

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16 % less ven tric ular enl arg em ent, incr eas ed pla sm a DH A/ EP A con fir min g adh ere

											nce, no difference in dementia conversion, and good safety profile
138	Hooper 2017	Hooper et al.	2017	To investigate whether plasma homocysteine is associated with cortical Î²-amyloid burden and	Randomised controlled trial	177 community-dwelling adults aged 70 years at risk of dementia	subjective memory complaints among patients with other dementia risk factors	Baseline erythrocyte omega-3 index (EPA + DHA)	RBC omega-3 index, plasma homocysteine, Î²-amyloid PET (SUVR), APOE Îµ4	Homocysteine was not associated with amyloid overall. However, it was related wit	Cross-sectional design, small exploratory subgroup, no longitudinal imaging, no dietary assessm

whether this association is modified by omega-3 status.

hcortical Î²-amyloid positively. It suggested omega-3 may modify amyloid-related ent, exploratory analyses without correction for multiple testing.

ted pathology.

131	Assmann 2018	Assmann et al.	2018	To investigate whether midlife dietary intakes of unsaturated fatty acids, particularly omega-3 polyunsaturated fatty acids (PUFAs), are associated with cognitive performance 13 year	Cohort study	3,362 French adults (Mean age= 65.5 Â± 4.6 years)	Community-dwelling adults Free-living general population No requirement for dementia or MCI at enrolment Cognitive function assessed in later life using a standardized neuropsychological	Total omega-3 PUFAs Alpha-linolenic acid (ALA) EPA DHA	-	Higher total omega-3 PUFA intake was associated with better cognitive performance, but only among participants who supplementation. ALA intake	Cognitive function was not measured at baseline, preventing assessment of cognitive decline over time. Participants were volunteers in a nutrition trial and generally healthier and more educate

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12 2	Howe PRC 2018	How et al.	2018	To investigate whether DHA-rich omega-3 supplementation improves cerebrovascular function, cerebrovascular reactivity, and cognition in mildly hypertensive older adults	Randomised controlled trial	38 adults (40â€“85 years; mean â‰ˆ 64 years) with mild hypertension and low omega-3 intake	Mildly hypertensive, cognitively healthy, low fish intake	DHA 1600 mg/day + EPA 400 mg/day for 20 weeks	Erythrocyte EPA, DHA, Omega-3 Index, cerebrovascular responsiveness, cerebral blood flow, pulsatility index	Improved cerebrovascular function and neurovascular coupling, but no significant improvements in cognition or mood; erythrocyte EPA/DHA increased significantly	Small sample, short duration, cognitively healthy participants, included adults younger than 60 years, sex-specific findings need confirmation

112	Kuszewski 2020	Kuszewski et al.	2020	o evaluate the independent and combined effects of fish-oil and curcumin supplementation on	Randomised controlled trial	126 overweight/obese adults, 50-80 years (mean ~66 years), cognitively healthy	Community-dwelling, cognitively normal, overweight/obese	Fish oil (2000 mg DHA + 400 mg EPA/day) for 16 weeks, with or without curcumin	Omega-3 Index, CRP, lipids, blood pressure, cerebrovascular responsiveness, cerebral blood flow measures	Fish oil improved processing speed and cerebrovascular responsiveness in males;	Healthy baseline cognition, short intervention, sex-specific effects, relatively high baseline Omega-3 Index	cognitive performance in overweight or obese middle-aged and older adults	no overall cognitive benefit; no added benefit from curcumin combination	3 Index

111	Malik 2021	Malik et al.	2021	To determine whether long-term high-dose EPA and DHA supplementation prevent	Randomised control trial	285 cognitively healthy adults with stable CAD; mean age 63.4 years; 83% male	Stable coronary artery disease; cognitively healthy (MMSE â‰¥29)	EPA 1.86 g/day + DHA 1.50 g/day (3.36 g/day total) for 30 months	-	High-dose EPA/DHA improved verbal fluency, language, memory, and visual-motor	Secondary outcome analysis, open-label design, predominantly male CAD population, no	s cognitive decline and improves cognitive function in cognitively healthy adults with	or coordination over 30 months compared with control, with	neurological biomarkers, potential practice effects on memory testing.

												le CAD.
110	McNamara 2018	McNamara et al.	2018	To determine whether fish oil (EPA+DHA), blueberry supplementation, or their combination	Randomised controlled trial	94 enrolled (76 completed intervention); adults aged 62-80 years with subjective cognitive decline but no MCI or	Community-dwelling older adults with subjective cognitive decline and normal objective	Fish oil providing EPA 1.6 g/day + DHA 0.8 g/day for 24 weeks	Erythrocyte EPA, DHA, total EPA+DHA; plasma EPA, DHA, AA; AA/EPA+DHA ratio; APOE genotype;	Fish oil increased erythrocyte EPA+DHA and reduced subjective cognitive complaints	Small sample size, participant attrition, cognitively healthy population limiting detectable cha	effects on global cognition or RAVLT measures.

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											ned supplementation provided no additional cognitive benefit.
109	Balezt ena 2018	Balezt ena et al.	2018	To determine whether a multinutrient supplement rich in omega-3 PUFAs improves cog	Randomised controlled trial	99 participants (Mean=75)	Very old institutionalized adults No dementia Some participants had MCI	Participants received one capsule three times daily for 12 months. Each capsule containe	-	No significant improvement in global cognitive function after one year of supplemе	Small sample size (only 99 randomized; 78 completed), limiting statistical power. Intervention was mul

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106	Ichinose 2021	Ichinose et al.	2021	To determine whether daily consumption of a DHA-enriched milk beverage improves	Text and opinion	53 healthy elderly Japanese adults (mean age 69.1 years; MMSE 28)	Cognitively healthy older adults	297 mg DHA + 137 mg EPA/day in a milk beverage for 12 months	Erythrocyte DHA, EPA, DHA/AA ratio, APOE genotype, TRACP-5b, BAP	Improved erythrocyte omega-3 levels, preserved MMSE scores, better recall and orie	Small sample, healthy participants, single-country study

				cognitive function and alters erythrocyte fatty acid composition and bone metabolism in heal							ntation, reduced bone resorption marker

				thy elderly individuals.								
105	KÃ¼hn 2022	KÃ¼hn et al.	2022	To determine whether adding omega-3-rich fish to a modified MIND diet for 12 weeks improv	Randomised controlled trial	57 cognitively intact older adults; mean age 72 Â± 7 years	Cognitively healthy, independently living older adults	Fish-based modified MIND diet providing ~2.2 g/day omega-3 PUFA for 12 weeks	RBC total omega-3 LCPUFA, RBC EPA, RBC DPA, RBC DHA, arachidonic acid	Fish intake improved CASI scores and increased RBC EPA/DPA, indicating improv	Small sample, short duration, screening-based cognitive assessment, self-reported diet

												es cognition in cognitively intact, independently living, resource-limited older adults.	ed cognition and adherence
104	Sala-Vila 2022	Sala-Vila et al.	2022	To determine whether RBC DHA predicts incident Alzheimer's disease and all-cause dem	Cohort study	1,490 dementia-free adults aged 65 years	Community-dwelling, dementia-free older adults	Baseline RBC DHA (objective biomarker of long-term dietary DHA intake); addition	RBC DHA, RBC EPA, Omega-3 Index, APOE-Îµ4 genotype	Highest RBC DHA (>6.1%) was associated with a 49% lower risk of Alzheimer	Observational design, single biomarker measurement, residual confounding, limited APOE-Îµ4

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103	Gustafson 2020	Gustafson et al.	2020	To investigate whether dietary fatty acid intake, classified according to chain length and degree of saturation, is associated with the risk of developing Alzheimer's disease (AD) and	Cohort study	2,612 Age: 65 years	Dementia-free older adults at baseline. Participants underwent standardized neurological examinations	The primary omega-3 exposures were: Docosahexaenoic acid (DHA) Eicosapentaenoic acid (EPA) Total omega-3 polyunsaturated fatty acids	-	During a mean follow-up of 4.5 years, 380 of 2,612 participants developed Alzheimer's disease and AD were diagnosed	Observational design; causality cannot be established. Dietary intake was assessed once at baseline using and neuropsychological assessments. Incident Alzheimer's disease and AD were diagnosed	oic acid (EPA) Total omega-3 polyunsaturated fatty acids	's disease. Higher dietary DHA intake was independently associated with a 27% low	g and FFQ, which is subject to recall and measurement error.

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's disease (HR = 0.74, 95% CI 0.57-“0.95; P = 0.021). Participants with higher EPA and DHA intakes demonstrated longer Alzheimer's disease eâ€“free survival.

				To investigate whether omega-3 polyunsaturated fatty acid (n-3 PUFA) supplementation improved	Randomised controlled trial	Total participants: 183 Omega-3 group: 98 Placebo group: 85 Age: 70 years	Participants were: Free from clinical dementia At risk of dementia Reported subjective memory	Intervention: Docosahexaenoic acid (DHA): 800 mg/day Eicosapentaenoic acid (EPA): up to	Fatty acid biomarker Red blood cell (RBC) omega-3 index Calculated as EPA + DHA (% of total RBC fatty	Omega-3 supplementation results in significantly less decline in executive function, memory	Post hoc secondary analysis, meaning the subgroup analysis was not pre-specified in the original MA
102	Hooper 2017 et al.	2017										

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					Tests A or B Clinical Dementia Rating (CDR-SB).							
101	Vyas 2024	Vyas et al.	2024	To determine whether APOE-Îµ4 is associated with cognitive decline and whether it modifi	Randomised control trial	743 community-dwelling U.S. adults aged 60 years (mean age 67.1 years); 24.9% APOE-Îµ4 carriers	Generally healthy older adults without dementia or major neuropsychiatric disorders	Marine omega-3 supplementation: 1 g/day fish oil containing 460 mg EPA + 380 mg DHA	APOE genotype (genetic biomarker); no plasma or red blood cell omega-3 biomarkers measured	APOE-Îµ4 carriers had greater decline in global cognition and episodic memory. Omega	Secondary analysis; limited APOE-Îµ4 homozygotes; healthy and predominantly non-Black

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100	Vauzour 2023	Vanzour et al.	2023	To determine whether combined DHA-rich fish oil and cocoa flavanol supplementation improves cognition and brain structure in older adults	Randomised control trial	259 randomized older adults (mean age 65.5 years) with subjective cognitive impairment or mild cognitive impairment	Older adults with SCI or MCI, without dementia	Daily supplementation with 1.1 g DHA + 0.4 g EPA (1.5 g/day total omega-3) plus 500 mg/day cocoa flavanols for 12 months	Plasma NEFA and DHA, LPCEPA and DHA, phosphatidylcholine omega-3 species, urinary flavanol metabolites, BDNF, lipid profile, glucose	Supplementation significantly increased plasma EPA and DHA but did not improve cognition, hippocampal volume, or overall brain structure. Executive function and alertness;	Combined DHA-rich fish oil and cocoa flavanol supplementation prevents isolation of omega-3 effects; mixed SCI/MCI cohort; 20% attrition; 12-month duration may be insufficient; MRI subset only; no body weight assessment.

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99	vanSoestAPM 2022	van Soest et al.	2022	To determine whether baseline plasma omega-3 status (DHA and EPA) modifies the cog	Randomised controlled trial	191 community-dwelling Dutch adults aged 65 years (mean 71.6 years) with elevated homocysteine	Cognitively healthy older adults with combined omega-3 concentrations (observa	Baseline plasma phospholipid DHA and EPA measured by GC-FID; additional measures included homocysteine, folate,	Higher baseline DHA status enhanced the beneficial effect of B-vitamin supplementation on cognitive effects of B-vitamin supplementation in healthy older adults	Post-hoc exploratory analysis; small sample; baseline biomarker measurement only; plasma phospholipid biomarkers may not reflect long-term omega-3 status; short follow-up; findings requ		

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				cts were observed for individual cognitive domains.							
97	Karimi 2017	Karimi et al.	2017	To determine whether long-term DHA-rich omega-3 supplementation alters global DN	Randomised controlled trial	63 patients with mild-to-moderate Alzheimer's disease; mean age ~73 years	Alzheimer's disease	Daily supplementation for 6 months: DHA: 1.7 g/day EPA: 0.6 g/day Fish oil con	LINE-1 DNA methylation, plasma DHA, EPA, DPA, APOE4, sIL-1R2	Omega-3 supplementation increased plasma DHA/EPA and reduced global DNA	Small biomarker sample, short duration, peripheral biomarker measurements

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93	Ogawa 2023	Ogawa et al.	2023	To evaluate whether ALA-rich flaxseed oil improves cognitive function in healthy older	Randomised controlled trial	60 healthy adults aged 65-80 years (30 intervention, 30 placebo)	Cognitively healthy community-dwelling older adults (MSE 27, CDR=0)	Flaxseed oil providing 2.2 g/day alpha-linolenic acid (ALA) vs corn oil placebo for 12	-	Significant improvement in verbal fluency (FAB lexical fluency) with ALA supple	Small sample, short duration, healthy population, no biochemical biomarkers, benefit limited	adults	weeks	mentation; no significant effects on other cognitive domains	to one cognitive outcome.

92	Yassine 2026	Yassine et al.	2026	To determine whether 2 g/day DHA achieves CNS target engagement and improves brain structure and cognition in older adults at risk for dementia	Randomised controlled trial	365 community-dwelling adults aged 55-80 years (mean age 66.4 years), cognitively unimpaired, low dietary DHA intake	Cognitively normal older adults at increased dementia risk with low baseline DHA intake	DHA 2,000 mg/day for 24 months versus corn oil/soybean oil placebo	CSF DHA/AA ratio, CSF DHA, plasma DHA, plasma DHA/AA, RBC DHA/AA, Omega-3 Index, brain DHA intake, cardiovascular risk factor	DHA significantly increased CSF DHA/AA ratio ($P < 0.001$) and markedly increased plasma AD biomarkers, APOE Îµ4 genotype	Single-centre design, 38% attrition, relatively healthy population with minimal cognitive decline, 24-month follow-up may be too short, and DHA monotherapy may not address multifactorial	

target dementia engagement mechanisms. However, no significant improvements were observed in cognition, orientation, hippocampal volume, cortical thickness, and APOEÎµ4 status did not modify

												treatment effects. DHA supplementation was safe and well tolerated.
91	Arellanes 2020	Arellanes et al.	2020	To determine whether high-dose DHA supplementation (2,152 mg/day) increases brai	Randomised controlled trial	33 cognitively unimpaired adults aged 55 years (median age 69 years) with a first-degree family history of dem	Cognitively normal adults at increased risk of Alzheimer's disease due to family history	2,152 mg/day DHA (approximately 2 g/day) for 6 months versus placebo (corn/soy oil). All	Primary biomarker: CSF DHA concentration. Secondary biomarkers: CSF EPA, plasma DHA, plasma EPA,	DHA supplementation significantly increased CSF DHA by 28% and CSF EPA	Small sample size (pilot RCT); short intervention period

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ces DHA brain delivery. non-carriers, suggesting reduced brain delivery of omega-3 fatty acids. However, no significant improvements were observed in hippocampal volume, entorhinal

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												meaningful brain delivery, particularly in APOE Îµ4 carriers.
90	Maltais 2022	Maltais et al.	2022	To determine whether baseline homocysteine modifies the relationship between RBC ome	Rand omised control led trial	782 participants (cross-sectional); 370 participants (longitudinal); community-dwelling adults aged 70 years	Older adults without dementia but at risk of cognitive decline (memory complaints, slow	DHA 800 mg/day + EPA 225 mg/day for 3 years; baseline RBC EPA+DHA measured by	RBC EPA, RBC DHA, total RBC omega-3 PUFA, plasma homocysteine, APOE Îµ4	Lower homocysteine enhanced the positive association between RBC Omega-3	Secondary analysis, multiple testing, baseline-only homocysteine measurement, no vitamin B asse

ga-3 status and cognition, and whether influences cognitive responses to long-term	gait and/or IADL limitations)	gas chromatography	status and executive function. Omega-3 supplementation improved executive function	ssment, limited generalisability of the homocysteine threshold.
ome ga-3 supplementation.				and CDR only in participants with lower homocysteine, suggesting homocysteine

												modifies the neuroprotective effects of omega-3 fatty acids.
84	Sueyasu 2023	Sueyasu et al.	2023	To evaluate whether supplementation with ARA, DHA, EPA, lutein, and zeaxanthin improv	Randomised controlled trial	312 healthy Japanese adults aged 55-79 years with subjective memory complaints (120 in Trial 1; 192 in Trial 2)	Community-dwelling older adults without dementia; subgroup with cognitive decline (Mo	DHA 300 mg/day + EPA 100 mg/day + ARA 120 mg/day, combined with lutein and zeaxanthin; dietary fatty acid intake	Plasma phospholipid DHA, EPA, ARA; serum lutein and zeaxanthin; dietary fatty acid intake	No significant cognitive benefit in the overall cohort, but significant improvement in Japanese-only population; explo	Combined nutrient intervention limits attribution to omega-3 alone;

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83	Mengelberg 2022	Mengelberg et al.	2022	To evaluate whether high-dose DHA supplementation improves cognition and well-being in older adults with MCI and Apoε4 genotype, modifies the response.	Randomised controlled trial	72 randomized (60 completed); adults aged 60-90 years with mild cognitive impairment	Community-dwelling older adults with MCI and preserved independent functioning	DHA 1491 mg/day + EPA 351 mg/day for 12 months	RBC DHA, EPA, DPA, ARA, LA, ALA, Omega-3 Index, ARA:EPA ratio, ARA:DHA ratio, APOE ε4 genotype, vitamin B12, ferritin	DHA significantly increased RBC DHA, EPA, and Omega-3 Index but did not improve cognitive performance. APOE ε4 carriers showed improved depression and anxiety	Small sample, high baseline cognitive reserve, heterogeneous MCI subtypes, high baseline DHA status, and absence of neuroimaging or neurodegenerative biomarkers.

												scores, and DHA attenuated increases in systolic blood pressure.
81	Power 2022	Power et al.	2021	To evaluate whether combined omega-3, carotenoid, and vitamin E supplementation improves cognition in healthy	Randomised controlled trial	To evaluate whether combined omega-3, carotenoid, and vitamin E supplementation improves cognitively healthy older adults with normal MoCA and RBANS scores	Cognitively healthy older adults	Fish oil (1 g/day) containing 430 mg DHA + 90 mg EPA, plus carotenoids and vitamin E, versus	Plasma DHA, plasma EPA, serum lutein, zeaxanthin, meso-zeaxanthin, vitamin E, macular pigment	Significant improvements in working memory with increased plasma DHA/EP	Combined intervention limits attribution to omega-3 alone; small sample size; single-center

cognition in healthy older adults	older adults	placebo for 24 months	optical volume, skin carotenoid score	And carotenoid biomarkers; biomarker improvements correlated with better working kingmemory performance	study; healthy population only; no multiple-comparison adjustment.	

79	Bischoff-Ferrari 2020	Bischoff-Ferrari et al.	2020	To determine whether vitamin D supplementation (2000 IU/day), omega-3 fatty acid supplementation (1 g/day marine omega-3 fatty acids for 3 years, consisting of 330 mg EPA + 660 mg DHA, compared with placebo, within the factorial design.	Randomised controlled trial	2,157 adults who were 70 years. Switzerland, France, Germany, Portugal, and Austria (mean age= 74.9)	Relatively healthy, community-dwelling older adults without major comorbidities.	Plasma polyunsaturated fatty acids (including omega-3 fatty acids) measured by liquid chromatography mass spectrometry (LC-MS)	After 3 years, omega-3 supplementation did not produce a statistically significant improvement in cognitive function (MoCA) compared with placebo. Likewise, no	Participants were generally healthy with high baseline cognitive performance, creating potential ceiling effects; the omega-3 dose (1 g/day) may have been insufficient for neuroprotection;

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58	Bo 2017	Bo et al.	2017	To investigate the impact of n-3 PUFA supplementation on cognitive function in Chinese	Randomised controlled trial	86 Chinese adults aged 60 years with mild cognitive impairment; mean age approximately 71 years	Mild cognitive impairment (MCI)	480 mg DHA + 720 mg EPA daily (total 1.2 g/day) for 6 months.	Plasma phosphatidylcholine fatty acid profile (EPA, DHA and other fatty acids); inflammatory biomarkers	Compared with placebo, omega-3 supplementation significantly enhanced total	Small sample size (n=86), relatively high dropout rate (~25%), short intervention period

older adults with MCI.	(IL-6, IL-10, TNF-Î); inflammatory enzyme activities (COX, LOX, sPLA2).	BCAT score, working memory spatial imagery efficiency, and perceptual speed after 6 months.	Recognition memory and mental arithmetic efficiency did not significantly

											improve.
47	Barnes 2021	Barnes et al.	2021	To investigate whether long-chain omega-3 fatty acids which are associated with blo	Cross sectional study	45 older adults (mean age 76.8)	Healthy aging adults without acute neurological disease. Participants with Parkinson's disease, stroke,	Exposure was erythrocyte long-chain omega-3 status.	Blood-brain barrier integrity measured by Ktrans using dynamic contrast-enhanced MRI. Additional biom	Higher erythrocyte EPA + DHA levels were significantly associated with better	cross-sectional design and small sample size; prevents causal inference; participants were

od-brain barrier (BBB) integrity, with cognitive performance in healthy older adults.

brain tumours, multiple sclerosis, diabetes, kidney disease, or other neurological disorders

arkers: Erythrocyte EPA, DHA, omega-3 index, omega-6 index, whitematter lesion volume.

BBB integrity (lower Ktrans) in the internal capsule (r = â’’0.525, p = 0.004). Post hoc exclude

exceptionally healthy, highly educated, and predominantly vegetarian, limiting generalizability

analyses showed that both EPA and DHA contributed to this association, with EP

A demonstrating the strongest relationship. Positive trends were observed between omega-3 levels and memory (p = 0.058) and language (p = 0.083), although no

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46	Emam 2026	Emam et al.	2026	To investigate the relationship between circulating fatty acid levels and temporal lobe volume	Cross sectional study	Total participants: 414 Alzheimer's disease (AD): 80 patients having normal cognition: 134 Mild cognitive impairment	Participants were classified into three diagnostic groups: CN, MCI and AD.	Circulating serum total PUFAs measured using the Nightingale Health Nuclear Magnetic Res	Fatty acid biomarkers: Serum total omega-3 PUFAs Serum total omega-6 PUFAs Omega-6:omega-3 ratio	higher circulating omega-3 PUFA concentrations were significantly related with low	The design of the study did not allow causal inference. Potential reverse causality in cognitively normal individuals, patients	(MCI): 200 Age: 55-90 years	nance (NMR) metabolomics platform.	MUFAs SFAs Neuroimaging biomarker: Temporal lobe volume assessed using tensor-based morpho	temporal lobe volume in participants with AD. A lower omega-6:omega-3

metry (TBM) MRI Cognitive biomarkers/outcomes: Alzheimer's Disease Assessment Scale Cognitiv	3 ratio was also significantly associated with reduced temporal lobe volum
e Subscale (ADAS-Cog 11 and ADAS-Cog 13) Clinical Dementia Rating Sum of Boxes (CDR-SB)	e in the ADgroup. No significant association between omega-3 PUFAs and Participan

Genetic biomarker: APOEÎµ4 carrier status	ts with MCI or cognitively normal persons showed differences in temporal lobe volume after multivariable adjustment. Omega-3 PUFAs were not significantly rela

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45	AlzheimersDisNeuroimaging 2023	Bao-Zhen et al.	2023	To investigate the longitudinal associations between blood omega-3 biomarkers and omega-3 supplementation and the risk of incident Alzheimer's disease, and to evaluate the	Cohort study	Individuals were aged 55-90 years and were followed for 6 years.	Healthy patients and mild cognitive impairment (MCI) patients.	Self-reported supplementation (fish oil, DHA, EPA, ALA, omega-3 fatty acids or PUFA supplements). Participants using omega-3 supplements for >1 year were classified as exposed,	Plasma total docosahexaenoic acid (DHA), omega-3 fatty acids and alpha-linolenic acid (ALA) measured. APOE Î¼4 genotype was also assessed as an important covariate and effect modifier.	Long-term omega-3 supplementation (10 years) was related decreased with a 64% lower risk of Alzheimer's disease. Overall omega-3 supplementation was	(1) Residual confounding from unmeasured factors such as diet and physical activity; (2) Supplementation data were self-reported, and dose information was unavailable—only duration of use was

asso ciati ons bet wee n diet ary ome ga- 3 inta ke, blo od bio mar kers , and the risk of dem enti a or wit h lon g- ter m use defi ned as 10 year s. Blo od con cent rati ons of tota l ome ga- 3, DH A, and AL A wer e also mea sure d usin g NM R met abol omi cs. uce d AD risk afte r mul tiva riab le adj ust me nt. Pro tect ive effe cts wer e stro nge st am ong cog niti ve decl ine usin g evid enc e fro m pros pect ive coh ort stud ies. reco rded ; (3) Om ega- 3 exp osur e was mea sure d only at base line, so cha nge s over time coul d not AP OE Îµ4 carr iers , old er adu lts (â ‰¥ 65 yea rs), mal es, and part icip ant s wit h MC I. be capt ured

Plasma omega-3, DHA, and ALA concentrations were not significantly associated with incident AD in the ADNI cohort.	d

20	Shinto 2024	Shinto et al.	2024	To determine whether EPA+DHA supplementation slows white matter lesion progression and neuronal integrity decline among older adults who had low omega-3 status, and	Rand omised control led trial	102 adults (mean age 81 years), without dementia but with MRI-confirmed white matter lesions and low omega-3	Mild or healthy cognitive impairment (CDR 0.5), cerebral small-vessel disease, sub optimal	1.65 g/day omega-3 PUFA (675 mg DHA+ 975 mg EPA) for 3 years versus soybean	Plasma EPA, DHA, whole-blood omega-3 status, APOE Îµ4 genotype, MRI-derived WML volume, neuronal integrity	No significant reduction in WML progression or overall neuronal integrity decline; not powered for	Small sample size, possible insufficient power, homogeneous population, not powered for APOE statuses	omega-3 levels	oil placebo	DTI-FA, brain volumes	APOE Îµ4 carriers showed significantly reduced DTI-FA decline (P = .04); treatment	subgroup comparisons, MRI scanner upgrade during follow-up.

												nt was safe and well tolerated
16	vanLent 2021	Melo van Lent et al.	2021	To determine whether serum omega-6 fatty acid and omega-3 fatty acid concentrations pre	Cohort study	1,264 dementia-free German adults (mean age 84 years)	Dementia-free older adults recruited from primary care	Baseline serum phospholipid EPA, DHA, and ALA concentrations (observational biomar	Serum phospholipid EPA, DHA, ALA, LA, DGLA, and AA measured by gas chromatography	Higher serum EPA concentrations were independently associated with lower inci	Observational design; baseline biomarker measurement only; possible residual confounding and reve

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											no significant association were observed for AL A or omega-6 fatty acids.
2	He 2023	He et al.	2023	To comprehensively investigate whether plasma polyunsaturated fatty acid (PUFA) levels and	Cohort study	440,750 dementia-free UK Biobank participants	Community-dwelling adults free of dementia at baseline. Incident cases of all-cause dementia,	Plasma concentrations of total omega-3 PUFAs and DHA measured by nuclear magnetic reso	Metabolomic biomarkers: plasma total PUFAs, omega-3 PUFAs, DHA, omega-6 PUFAs, linoleic acid (NMR	During follow-up, 7,768 participants developed dementia. Higher plasma omega-3	Plasma PUFAs reflect relatively short-term status and may not represent long-term exp

fish oil supplementation are associated with the risk of incident dementia	Alzheimer's disease (AD), and vascular dementia (VD) were identified using linked ICD	nance (NMR) metabolomics	platform). Immune biomarkers: neutrophils, lymphocytes, monocytes, neutrophil-to-lymphocyte ratio (NLR),	PUFA levels were associated with a lower risk of incident dementia (HR 0.90,	osure as accurately as erythrocyte fatty acids. Fish oil supplementation was self-reported
-10 records during follow-up.	lymphocyte-to-monocyte ratio (LMR), systemic immune-inflammation index (SII), platelet-to-lymphocyte	95% CI 0.86â€“0.95 per SD increase), whilehigher DHA was also protective (HR	no information on dose, formulation, frequency, or duration.

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