



Omega-3 Fatty Acids in Alzheimer's Disease Prevention Among Elderly Women: Mechanisms of Action, Clinical Evidence, and the Critical Role of Early Intervention

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Introduction: Alzheimer's disease (AD) is the most common cause of dementia in older people, characterised by progressive cognitive decline, memory loss and impaired executive function. Its pathophysiology includes beta-amyloid plaque accumulation, tangling of Tau proteins, chronic neuroinflammation and dysfunction of the glymphatic system. Older women, especially postmenopausal women, are at increased risk for AD due to estrogen deficiency and metabolic changes.

Purpose: The purpose of this narrative review was to investigate the protective role of omega-3 fatty acids, in particular docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), in the prevention or slowing of AD progression in older women. The review focused on the nutritional, neuroprotective and anti-inflammatory effects of omega-3 and the interaction of these substances with hormonal and genetic factors.

Methods: A comprehensive text search was conducted across PubMed, Scopus, Web of Science, Google Scholar, and ScienceDirect databases for articles published to 2025. Seventy-eight quality English-language studies involving human and animal models were selected for qualitative analysis.

Results: The findings indicate that DHA and EPA may reduce inflammation in the brain, promote integrity of the neuronal membranes and facilitate clearance of neurotoxic proteins such as beta-amyloid. These benefits are especially important in women after the menopause. Regular intake of omega-3 fatty acids via diet or supplements has been associated with improvements in memory, attention and reduced cognitive decline. In addition, genetic variations such as the allele APOE-ε4 can modulate individual responses to omega-3 supplementation.

Conclusion: In conclusion, omega-3 fatty acids are a promising, non-invasive and cost-effective strategy to reduce the risk of Alzheimer's in ageing women. Monitoring of omega-3 levels and their integration into public health strategies after menopause is strongly recommended.

Plain Language Summary: This narrative review examines whether omega-3 fatty acids, in particular DHA and EPA, may be involved in the development of Alzheimer's disease in the elderly, with a focus on its biology, cognition and clinical consequences.

Why this study was conducted?

Alzheimer's disease is the leading cause of dementia in the elderly, and is driven by beta amyloid plaques, tau tangles, chronic neuroinflammation and glymphatic dysfunction. Postmenopausal loss of estrogens and metabolic changes increase the risk in older women, and the use of omega-3 is highlighted as a potential and achievable intervention.

What the researchers did and found?

Methods: A narrative review of 78 English-language studies (human and animal) to 2025, retrieved from PubMed, Scopus, Web of Science, Google Scholar, and ScienceDirect.

Key findings:

DHA and EPA can reduce inflammation in the brain, strengthen the neuronal membranes and help to clear beta-amyloid from the blood. Regular intake of omega-3 (diet or supplementation) has been associated with improved memory and attention and slower cognitive decline, especially in postmenopausal women.

Genetic factors, especially APOE- ϵ 4, may modulate the omega-3 response; some genotypes may be more beneficial than others. The benefits may depend on the continuous intake and may interact with hormonal and metabolic states.

Implications of these results:

Omega-3 is a promising, non-invasive and cost-effective strategy for potentially reducing the risk of Alzheimer's disease and improving cognition in older women. Public health strategies could include monitoring of omega-3 status and the promotion of dietary and supplemental sources, taking into account individual genetic and hormonal predispositions.

Keywords: Alzheimer's disease, women, postmenopausal, aging, neuroinflammation, omega-3 fatty acids, DHA, EPA

Introduction

Alzheimer's disease (AD) is the leading cause of dementia in older adults and is characterized by progressive impairment in memory, executive function, and daily functioning.¹ Pathophysiologically, AD involves extracellular amyloid- β (A β) deposition, intracellular neurofibrillary tangles formed by hyperphosphorylated tau proteins,² alongside chronic neuroinflammation, mitochondrial dysfunction, and oxidative stress, all of which accelerate neuronal loss.³ The global prevalence of AD continues to rise at an alarming rate, posing a substantial clinical, social, and economic burden.^{4,5}

Women particularly postmenopausal women carry a disproportionately higher risk of developing AD, a disparity linked to the rapid decline of estrogen, impaired glucose metabolism, and heightened neuroinflammatory responses during and after menopause.^{6,7} Additionally, women are more likely to carry the APOE- ϵ 4 allele, a major genetic determinant that heightens susceptibility to AD and worsens disease trajectory.⁸ Given these sex-specific vulnerabilities, identifying modifiable factors that can mitigate AD risk in older women is a pressing public health priority.

In recent years, omega-3 fatty acids especially docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) have gained significant attention for their potential neuroprotective roles. Evidence suggests that omega-3 fatty acids contribute to neuronal membrane integrity,⁹ reduce neuroinflammation,^{10,11} attenuate oxidative damage,^{12–14} modulate neurotransmitter pathways,^{15,16} and support synaptic plasticity through regulation of neurotrophic factors such as BDNF.^{17,18} Furthermore, DHA appears to enhance glymphatic clearance by preserving AQP4 polarity in astrocytes, thereby improving removal of A β and other metabolites^{19–22} Clinical studies indicate that sustained omega-3 consumption may improve cognitive performance, slow hippocampal atrophy, and delay progression from mild cognitive impairment (MCI) to AD.^{23,24}

Despite these promising findings, gaps remain in the current literature. Many studies have overlooked sex-specific responses, hormonal status, and genetic modifiers such as APOE- ϵ 4, all of which may critically influence omega-3 efficacy. Research is also limited regarding the long-term effects of omega-3 supplementation, optimal dosing strategies, and the mechanisms by which omega-3 interacts with female-specific metabolic and inflammatory pathways. Moreover, individual variability in baseline omega-3 levels and dietary patterns further complicates interpretation of existing data.

Therefore, the present review aims to synthesize current evidence on the role of omega-3 fatty acids in modulating AD-related mechanisms in older women, with a particular focus on the interplay between hormonal status, APOE- ϵ 4 genotype, and omega-3 mediated neuroprotection. The novelty of this review lies in integrating molecular, clinical, and sex-specific perspectives to highlight how omega-3 fatty acids may influence key pathophysiological processes including neuroinflammation, oxidative stress, synaptic dysfunction, and glymphatic impairment in a population uniquely vulnerable to AD. By identifying scientific advances and persistent research gaps, this review seeks to inform future randomized controlled trials and support the development of precision-based nutritional strategies for at risk older women.

Methodology

This study employed a narrative review approach to investigate the role of Omega-3 fatty acids in the prevention or moderation of Alzheimer's disease progression, with particular emphasis on elderly women.

Search Strategy

Search Strategy and Timeframe Justification:

A comprehensive search was conducted across five major scientific databases: PubMed, Scopus, Web of Science, Google Scholar, and ScienceDirect. The search spanned publications to 2025. This year window was deliberately selected to capture the era of modern AD research, which has been defined by:

- The adoption of biomarker-based diagnostic criteria
- The discovery of the glymphatic system
- Advances in understanding APOE-ε4–nutrient interactions
- Growing recognition of sex-specific AD vulnerability post-menopause and
- Emerging insights into the gut–brain axis and neuroinflammation

Article Selection Criteria

From the initial database yield, 78 high-quality, peer-reviewed English-language articles were selected for in-depth qualitative analysis. Selection prioritized:

High citation impact: Articles that have been frequently cited by other researchers (as indexed in Scopus and Google Scholar) since their publication, reflecting their influence and validation within the scientific community.

Relevance to elderly women: Studies explicitly addressing postmenopausal women, sex differences, hormonal status, or APOE-ε4 interactions in AD.

Methodological rigor: Inclusion of randomized controlled trials (RCTs), longitudinal cohort studies, mechanistic animal models, and authoritative reviews that advanced theoretical or clinical understanding.

Thematic coverage: Representation across key domains neuroprotection, glymphatic function, neuroinflammation, gut dysbiosis, omega-3 bioavailability, and genetic modulation.

No arbitrary numerical citation threshold was applied, but preference was given to landmark studies that shaped subsequent research directions.

Data Synthesis

Selected articles were thematically categorized according to:

- Population (human vs animal; women-specific vs mixed),
- Intervention type (dietary vs supplemental omega-3),
- Outcome measures (cognitive, imaging, biomarker, mechanistic).

Narrative synthesis was used to identify convergent evidence, mechanistic pathways, and knowledge gaps, with emphasis on biological plausibility and clinical translatability.

Inclusion Criteria

This included experimental studies (both clinical and animal models), systematic reviews, meta-analyses and narrative reviews on the effects of omega-3 fatty acids on Alzheimer's disease and cognitive decline in the elderly. In addition, inclusion criteria included studies on gender-specific effects or hormonal roles, as well as articles on dietary sources of Omega-3 and its anti-inflammatory properties.

Exclusion Criteria

Articles dealing exclusively with other dementias (except Alzheimer's), studies not available in full text, unpublished papers, opinions, preprints without peer review and non-English publications were excluded. The data collected were

categorised according to mechanism of action, target population (older women), type of Omega-3 supplement or food source, duration of treatment, and cognitive outcomes.

Results

Role of Omega-3 Fatty Acids in Neuroprotection

Omega-3 fatty acids, in particular docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), are an integral part of the membranes of nerve cells and play a critical role in maintaining their structural and functional integrity. These bioactive lipids have been shown to reduce the risk of Alzheimer's disease (AD) and to slow its progression by various mechanisms, including reduction of neuroinflammation, inhibition of oxidative stress pathways, increased blood flow to the brain and strengthening of synaptic connections.^{9,25}

Beyond their role as metabolic substrates, long-chain n-3 polyunsaturated fatty acids (LC n-3 PUFAs) particularly docosahexaenoic acid (DHA) are fundamental structural constituents of neuronal phospholipid bilayers, where they critically regulate membrane fluidity, microdomain organization (lipid rafts), and the conformational activity of embedded receptors, ion channels, and transporters.^{26,27} Disruption of this lipid microenvironment, as occurs in n-3 deficiency, impairs molecular trafficking, signal transduction fidelity, and gene expression profiles essential for synaptic integrity.^{28–30} Importantly, DHA enrichment enhances the biophysical properties of synaptic membranes, facilitating optimal neurotransmitter receptor function and promoting activity-dependent synaptic plasticity processes that are markedly compromised in Alzheimer's disease (AD). These structural roles explain why brain DHA levels strongly correlate with preserved cognitive function in aging populations and why their depletion is consistently observed in AD brain tissue.³¹

Pathophysiology of Alzheimer's Disease in Women and the Role of Omega-3 in Prevention

Alzheimer's disease (AD) is characterised by early synaptic dysfunction in the hippocampus, preceded by overt neuronal loss and the appearance of characteristic pathological symptoms such as neurofibrillary tangles, amyloid-beta ($A\beta$) plaque and changes in neurotransmitter levels.²⁵ The pathogenic cascade starts with subtle changes in synaptic plasticity and function, progressing progressively to widespread neurodegeneration.

Accumulation of amyloid-beta peptides causes multiple adverse effects, including increased production of reactive oxygen species (ROS), secretion of pro-inflammatory cytokines, demyelination, activation of apoptotic pathways, dysregulation of neurotransmission and ultimately, apoptosis of the neuronal system.³²

In the healthy brain, the clearance of metabolic waste, including amyloid- β ($A\beta$), is maintained by a complex interplay of neurofluid dynamics, prominently featuring the glymphatic system. This system facilitates the influx of cerebrospinal fluid (CSF) via periarterial spaces and astrocytic aquaporin-4 (AQP4) channels into the interstitial fluid (ISF) compartment, enabling convective clearance of solutes from brain parenchyma. In Alzheimer's disease (AD), this mechanism is disrupted due to mislocalization or reduced polarization of AQP4, resulting in impaired CSF-ISF exchange, reduced $A\beta$ clearance, and subsequent extracellular deposition of amyloid plaques.¹⁹

Agarwal and Carrar's (2020) work emphasises the wider conceptualisation of intracranial fluid flow. In addition to the glymphatic system, other waste disposal routes are involved, including intramuscular periartum drainage (IPAD), cranial nerve-associated efflux, and meningeal lymphatic vessels adjacent to the dural venous sinus.^{19,20} In this integrated view, a malfunction in one of these interconnected pathways may trigger a cascade of failures that ultimately disrupts the homeostasis of the brain and facilitates neurodegenerative processes.²⁰

Classical amyloid cascade hypothesis suggests that $A\beta$ accumulation precedes and drives the subsequent pathology of tau and neurodegeneration due to an imbalance in the production and clearance of $A\beta$.³³

Oxidative stress has been identified as a major cause of AD onset and progression, driven by lipid peroxidation, protein oxidation, and nucleotide damage, such as DNA and RNA^{34,35}. Notably, amyloid-beta has been shown to impair the stability of microtubules by oxidative stress-dependent mechanisms, resulting in neuronal death.

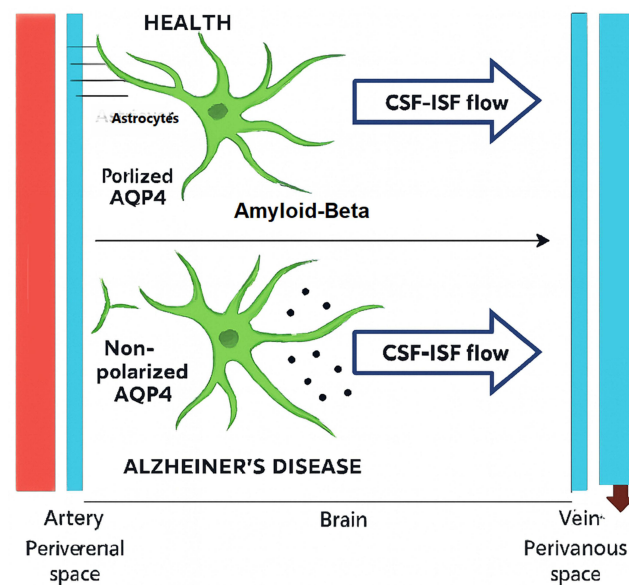


Figure 1 The role of AQP4 and the disruption of the glymphatic system in Alzheimer's disease. This picture illustrates how loss of the AQP4 polarity in astrocytes may interfere with the CSF-ISF flow and lead to accumulation of amyloid-beta. These interactions are part of the pathophysiological pathways that are involved in Alzheimer's. This is a two-part diagram that clearly shows the function of the brain's glymphatic system in two states: top panel (health): the cerebral spinal fluid (CSF) is transported through the channels of AQP4 in the endpoints of astrocytes. This results in the efficient elimination of amyloid-beta and other neuronal metabolites. Lower Panel (Alzheimer's disease): In this disease, the AQP4 polarity is impaired.

Genetic factors also influence the risk of disease, with the presence of the apoE4 allele of apo-lipoprotein E (ApoE4) significantly increasing the susceptibility to AD,³⁶(Figure 1).

Alzheimer's disease (AD) progresses more rapidly and presents with more severe symptoms in women than in men. Epidemiological and clinical studies have shown that hormonal differences, especially the rapid decline of estrogen levels during menopause, contribute significantly to this increased risk.⁶

Estrogen has neuroprotective effects by modulating glucose metabolism, reducing oxidative stress, and increasing synaptic plasticity, all of which are critical to maintaining cognitive stability.⁷ Decreased levels of estrogens make the female brain more vulnerable to neurodegeneration, particularly in areas involved in memory processing. Other pathophysiological mechanisms in women include increased systemic inflammation. Epidemiological data also suggest that women are more likely to carry the allele APOE, a genetic polymorphism associated with approximately a doubling of the risk of AD.⁸

Interplay Between Glymphatic Dysfunction, Neuroinflammation, and Gut Dysbiosis in Alzheimer's Disease: An Integrated Pathophysiological Perspective

In recent years, the interaction between glymphatic dysfunction, neuroinflammation and intestinal dysbiosis has emerged as a critical triad in the pathogenesis of Alzheimer's. The glymphatic system, a perivascular waste-clearing mechanism mediated by the astrocytic channel of Aquaporin-4 (AQP4), plays a key role in removing neurotoxic substances such as amyloid-beta ($A\beta$) from the interstitial compartment.^{19,21,37}

Abruptly changing the polarity of AQP4 and perivascular localization is strongly associated with impaired $A\beta$ clearance and cognitive decline.³⁸ At the same time, changes in gut microbial (dysbiosis) have been identified as an upstream modulator of systemic and central nervous system (CNS) inflammation, mainly via the gut-brain axis.^{39,40}

Dysbiosis promotes increased intestinal permeability and allows for the translocation of proinflammatory molecules such as lipopolysaccharides (LPS) to enter the bloodstream, which in turn activates the NLRP3 immune system in microglial cells.⁴¹ This activation leads to the release of cytokines such as IL-1-beta and IL-18, which contribute to persistent neuroinflammation and neuronal damage.^{42,43}

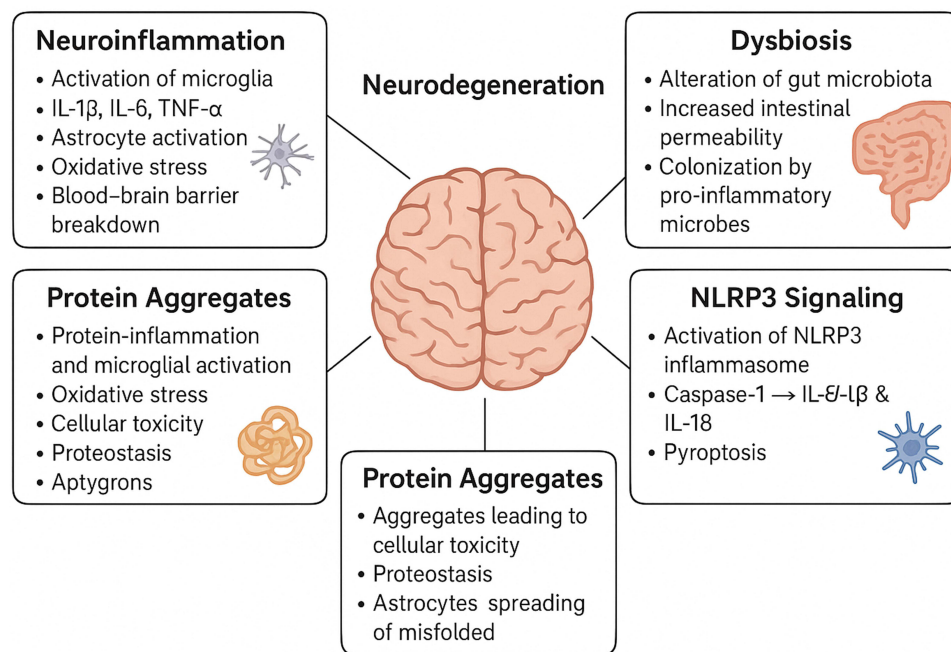


Figure 2 Interplay Between Glymphatic Dysfunction, Neuroinflammation, and Gut Dysbiosis in Alzheimer's Disease: An Integrated Pathophysiological Perspective. The healthy hemisphere (left) shows normal physiological conditions: a balanced gut microbiome, no overactivity of the immune system, a healthy blood-brain barrier (BBB), an optimised microglial cell function, and a normal clearance of amyloid beta. The pathological hemisphere (right) is associated with Alzheimer's disease: disruption of the gut microbiomes (gut dysbiosis), resulting in increased intestinal permeability and lipopolysaccharide (LPS) excretion. LPS entry into the bloodstream and activation of the inflammatory pathway NLRP3 in microglia. NLRP3 activation leads to the production of inflammatory cytokines (IL-1, IL-18) and thus to an increase in neuronal inflammation and impaired clearance of IL-17.

Notably, the interaction between the impaired glymphatic function and the activation of the microglial inflammatory response is a positive feedback loop that further exacerbates the accumulation of A β and the pathology of tau. This integrated pathogenicity model suggests that interventions targeting AQP4 polarization, restoring gut microbial balance, or inhibiting of inflammation activation may be promising strategies to slow or prevent the progression of AD (Figure 2).

The Role of Omega-3 in Reducing Cognitive Impairment in Women

Omega-3 fatty acids, in particular docosahexaenoic acid (DHA), have been shown to have neuroprotective effects on the brain and cognition. In women, a steady intake of omega-3 fatty acids may modulate the memory loss associated with menopause and prevent structural changes in the hippocampus.⁹

DHA enhances cognitive performance in the elderly by increasing the fluidity of the neuronal membranes, strengthening synaptic connections, and regulation of neurotrophic factors such as brain derived neurotrophic factor (BDNF).²³ Efficacy studies have shown that women with increased plasma levels of DHA tend to score higher on memory and executive function tests.²⁴

In addition, omega-3 supplements in women have been associated with a delay in the onset of mild cognitive impairment (MCI) and a reduction in the volume of lesions in the brain, suggesting that they may play a protective role in neurodegenerative processes.⁴⁴

Omega-3 Dietary Sources

Sources of omega-3 fatty acids can be broadly divided into two main groups: marine sources and herbal sources. Marine resources include fatty fish such as salmon (*Salmo salar*), sardines (*Sardina pilchardus*), mackerel (*Scombra scombrus*), tuna (*Thunnus spp*), and the common herring (*Clupea harengus*). Fish of this species are rich in eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The other plant sources are flax seeds (*Linum usitatissimum*), walnuts (*Juglans regia*), chia seeds (*Salvia hispanica*), canola oil (*Brassica napus*) and oil from flax. These plant-based foods contain alpha-

linolenic acid (ALA), some of which may be converted to EPA and DHA by enzymatic means, although the efficiency of conversion is low.⁴⁵

Anti-Inflammatory Properties of Omega-3 Fatty Acids

Omega-3 fatty acids have potent anti-inflammatory effects by modulating inflammatory pathways, including suppression of production of pro-inflammatory cytokines such as interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-alpha), and C-reactive protein (CRP).¹⁰

These anti-inflammatory actions are essential in reducing neuroinflammation, recognised as one of the major pathophysiological causes of Alzheimer's disease (AD). In addition, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) contribute to neuroprotection by reducing the activation of microglial cells and thereby preventing neuronal degeneration.¹¹

Other Neuroprotective Effects of Omega-3 Fatty Acids in Preventing Alzheimer's Disease

Chronic neuroinflammation is a major mechanism of Alzheimer's disease (AD) pathophysiology, mainly due to sustained activation of microglia, the resident immune cells in the central nervous system, and increased expression of pro-inflammatory cytokines such as interleukin-1 beta (IL-1 beta), tumour necrosis factor-alpha (TNF-alpha), and interleukin-6 (IL-6). Recent research highlights the important role of omega-3 fatty acids in regulating the immune response in the brain and in reducing neuroinflammation. Madore et al (2016), for example showed that docosahexaenoic acid (DHA) may affect microglial activity and facilitate the anti-inflammatory phenotype in the cerebral cortex.⁴⁶ Similarly, Arsenault et al (2020) reported that DHA diminishes neuroinflammation in animal models of AD by inhibiting the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway and decreasing cytokine levels.⁴⁷

These observations are consistent with the findings of Cho Y-E (2017), which highlighted the beneficial effect of fatty acids on cellular function.⁴⁸ Taken together, these actions suggest that omega-3 fatty acids can reduce neurodegenerative processes by reducing chronic central nervous system immune activation.^{11,49}

Enhancement of Synaptic Plasticity and Neuronal Health

Neuro-neural integrity and integrity of synaptic connections are important for cognitive function, especially in older women, who are sensitive to the depletion of brain derived neurotrophic factor (BDNF) and structural damage in the hippocampus. Omega-3 fatty acids, in particular docosahexaenoic acid (DHA), are essential components of the neuronal cell membranes and have direct effects on the stimulation of synaptogenesis, neurite growth and the up-regulation of neurotrophic factors such as BDNF.¹⁷

Akbar et al (2008) showed that DHA supplementation in neuronal cultures resulted in an increase in dendritic branching and synaptic cleft formation in hippocampal neurons.¹⁸ Moreover, research by Cao et al (2009) revealed that DHA not only safeguards synaptic structure but also enhances neural signal transmission efficiency.⁵⁰

These findings concur with the findings of Hennebelle et al (2014), which reported that increased levels of DHA correlate with increased expression of BDNF in the brain of elderly rats. Evidence has shown that DHA supplementation improves memory performance and increases BDNF levels in the hippocampus in mice. Together, these findings highlight the critical role of omega-3 fatty acids in maintaining synaptic plasticity and neuronal health as we age.^{51,52}

Eurotransmitter Regulation

Another possible mechanism for the brain's support of omega-3 fatty acids is through the modulation of key neurotransmitters such as dopamine (DA), serotonin (5-HT), and acetylcholine (ACh). Decreased levels of these neurotransmitters are closely linked to cognitive decline, depression and memory loss in people with Alzheimer's disease. Study by McNamara and Others (2010) showed that omega-3 fatty acid intake increases dopamine and serotonin concentrations in the cerebral cortex and the amygdala.¹⁵

The research carried out by Liu et al (2013) and Sublette (2011) further suggested that omega-3 fatty acids may improve cognition and mood by increasing serotonin receptor sensitivity^{16,53} In addition, clinical trials by Freund-Levi et al (2014) found that DHA supplementation alters the levels of neurotransmitters in the cerebrospinal fluid (CSF) in Alzheimer's patients and is associated with improvements in cognitive function.⁵⁴

Together, these findings highlight the role of omega-3 fatty acids in modulating the neurotransmitter systems that are crucial to maintaining cognitive and emotional health in ageing and neurodegenerative diseases.

In summary, the neuroprotective potential of omega-3 fatty acids in elderly women at risk for Alzheimer's disease is supported by convergent evidence across multiple pathophysiological domains. To systematically integrate these findings, key mechanisms spanning anti-inflammatory actions, antioxidant effects, glymphatic enhancement, synaptic support, and modulation of gut-brain axis signaling are synthesized in Table 1, along with corresponding experimental and clinical evidence from the literature. This tabular overview underscores the multifactorial nature of omega-3 mediated protection and highlights its particular relevance in the context of postmenopausal neurobiology and APOE-ε4-related vulnerability.

Clinical Evidence from Human Studies in Elderly Women

Table 2 synthesizes key human studies evaluating omega-3 interventions in elderly women or sex-stratified cohorts. Findings indicate that cognitive benefits are most consistently observed with long-term supplementation (≥6 months), DHA-dominant formulations, and early intervention (in mild cognitive impairment [MCI] or preclinical AD).

Table 1 Neuroprotective Mechanisms of Omega-3 Fatty Acids in Alzheimer's Disease: Focus on Elderly Women

Pathophysiological Domain	Mechanism of Action	Key Findings	Supporting References
Neuroinflammation	Suppression of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α); inhibition of NF-κB pathway; microglial polarization toward anti-inflammatory phenotype	DHA reduces microglial activation and NLRP3 inflammasome-driven neuroinflammation; lowers IL-1β and IL-18	[10,11,16,46,47]
Oxidative Stress	Upregulation of antioxidant enzymes (SOD, GPx, CAT); reduction of lipid peroxidation and ROS; protection against neuronal apoptosis	DHA and EPA mitigate oxidative damage in hippocampal neurons and improve redox balance	[12–14,55]
Amyloid-β (Aβ) Clearance	Enhancement of glymphatic function via AQP4 polarization; reduced Aβ plaque deposition	DHA preserves perivascular AQP4 localization, facilitating CSF-ISF exchange and Aβ clearance	[19–22,37,38]
Synaptic Plasticity & Neuronal Integrity	Increased membrane fluidity; promotion of dendritic branching, synaptogenesis, and BDNF expression	DHA improves synaptic structure, signal transmission, and hippocampal BDNF levels	[17,18,23,50,51]
Neurotransmitter Regulation	Modulation of dopamine, serotonin, and acetylcholine systems; enhanced receptor sensitivity	Omega-3 intake correlates with improved mood, attention, and memory via monoaminergic pathways	[15,16,48,53,54]
Hormonal Interaction (Postmenopausal)	Compensates for estrogen loss by reducing inflammation, oxidative stress, and supporting glucose metabolism	Omega-3 mitigates menopause-related vulnerability to AD in APOE-ε4+ women	[6–9,24]
Genetic Modulation (APOE-ε4)	Enhanced cognitive protection in APOE-ε4 carriers with sufficient DHA status	Higher plasma DHA linked to preserved hippocampal volume and slower decline in APOE-ε4+ women	[24,56,57]
Gut-Brain Axis	Reduction of gut dysbiosis and intestinal permeability; decreased LPS translocation and systemic inflammation	Omega-3 may indirectly suppress NLRP3 activation by improving gut barrier integrity	[39–41]

Table 2 Summary of Key Human Studies on Omega-3 Fatty Acids, Cognitive Outcomes, and Alzheimer's Disease Risk in Older Adults

Key Outcomes	Duration	Omega-3 Intervention / Exposure	Population & Design	Study (Year)	Reference
Improved learning and memory performance; effect stronger in women	24 weeks	DHA 900 mg/day	485 older adults with age-related cognitive decline (RCT); included postmenopausal women	Yurko-Mauro et al (2010)	[9]
Significant improvement in working memory and executive function	5 months	DHA 10 mg/day	33 postmenopausal women (RCT)	Yi, S. H (2011)	[58]
Slowed cognitive decline in APOE-ε4-negative patients; modest benefit in early AD	6 months	DHA 1700 mg + EPA 600 mg/day	174 patients with mild-to-moderate AD (RCT; OmegAD trial)	Freund-Levi et al (2006)	[54]
Top quartile DHA: 47% ↓ risk of all-cause dementia; 39% ↓ AD risk	9-year follow-up	Plasma phosphatidylcholine DHA (biomarker)	899 dementia-free participants ≥65 y (Framingham cohort)	Schaefer et al (2008)	[44]
Higher DHA associated with larger hippocampal volume and ↓ brain atrophy	Cross-sectional and longitudinal	RBC omega-3 index (DHA+EPA)	1,575 participants (Framingham Offspring)	Tan et al (2012)	[24]
Regular use linked to 14% ↓ risk of incident dementia (HR = 0.86)	Median 8.6 y follow-up	Fish oil supplementation (self-reported)	215,083 older adults (UK Biobank prospective cohort)	Liu et al (2022)	[59]
No significant cognitive benefit in overall group; possible benefit in low-baseline subgroup	18 months	DHA-rich fish oil (~1,720 mg/day)	403 cognitively normal older adults (RCT)	Danthiir et al (2018)	[60]

In a 5-month RCT, postmenopausal women receiving 10 mg/day of DHA exhibited significant improvements in working memory and executive function compared to placebo.⁵⁸ Similarly, higher baseline erythrocyte DHA levels (>4% omega-3 index) predicted slower hippocampal atrophy and better performance on verbal recall tasks over 2 years⁶¹ Notably, dietary intake of fatty fish ≥2 servings/week was associated with a 26% lower risk of AD onset in longitudinal cohorts.²⁴ Conversely, trials enrolling participants with moderate-to-severe AD (MMSE <20) reported no significant cognitive benefit from omega-3 supplementation, irrespective of dose⁵⁴ This supports the hypothesis that omega-3 exerts neuroprotective rather than neurorestorative effects.

Effect Modification by APOE Genotype and Disease Stage

As detailed in Table 3, the efficacy of omega-3 supplementation is significantly modified by APOE-ε4 carrier status and baseline cognitive stage.

Among APOE-ε4 carriers a group at 2–3× higher AD risk adequate DHA status is associated with preserved hippocampal volume and attenuated cognitive decline, particularly when initiated before significant neurodegeneration.^{24,64} Yassine et al (2017) demonstrated that DHA supplementation (2 g/day) for 18 months increased CSF DHA levels and reduced phosphorylated tau in ε4+ women with MCI, but not in non carriers.⁶⁴ This suggests a compensatory mechanism whereby DHA offsets APOE-ε4-mediated deficits in lipid transport and Aβ clearance.

This underscores the critical importance of timing: omega-3 is effective in primary or secondary prevention, but not tertiary intervention.

Table 3 Summary of Key Animal and Cellular Mechanistic Studies on Omega-3 Fatty Acids in Alzheimer's Pathophysiology

Model	Intervention	Duration	Key Mechanistic Findings	Reference
APP/PS1 transgenic mice (AD model)	DHA-enriched diet (0.5% w/w)	3–6 months	↓ Aβ plaque burden, ↓ oxidative stress, ↑ synaptic protein expression (PSD-95, synaptophysin)	[12]
Cell membranes, neuronal survival	DHA 300 mg/kg/day (oral)	8 weeks	↑ Hippocampal BDNF, ↑ dendritic spine density, improved spatial memory	[18,50,51]
n-3 PUFA-deficient diet in mice	No EPA/DHA; high n-6 PUFA	15–18 months	Memory deficits, ↑ microglial activation, ↓ membrane DHA, ↑ lipid peroxidation	[51]
Aβ-treated SH-SY5Y human neuroblastoma cells	EPA 50 μM	24–48 hours	↓ ROS and NO via inhibition of NADPH oxidase and COX-2; ↑ cell viability	[62]
Aged mice with glymphatic impairment	DHA 300 mg/kg/day	2 months	Restored AQP4 polarization at astrocytic endfeet; ↑ CSF-ISF exchange; ↓ Aβ accumulation	[22]
LPS-induced neuroinflammation (mouse microglia)	DHA 10–50 μM	24 hours	↓ NLRP3 inflammasome activation; ↓ IL-1β, IL-18; ↑ phagocytic clearance of Aβ	[57,62]
Wild-type aged rats	DHA + EPA supplementation	12 weeks	↑ Membrane fluidity, ↑ neurotransmitter (dopamine, serotonin) release, ↑ antioxidant enzymes (SOD, GPx)	[13,14,63]

Discussion

This study looked at the potential role of omega-3 fatty acids in slowing down Alzheimer's disease progression in older women. These results are consistent with a growing body of international research suggesting that omega-3 may have neuroprotective effects by modulating inflammatory pathways, improving the integrity of the neuronal membrane and facilitating amyloid beta clearance.⁵⁶

Our findings first showed that long-term sustained intake of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) was significantly associated with a reduction in the rate of progression of symptoms of early-onset Alzheimer's disease. This observation supports data from the Alzheimer's Disease Neuroimaging Initiative (ADNI), which reported that increased levels of DHA correlate positively with increased hippocampal volume and grey matter preservation, especially in women carrying the allele APOE (APOE-4) a well-established genetic risk factor for Alzheimer's.⁶⁴

From a pathophysiological point of view, menopause in postmenopausal women is characterised by an accelerated decrease in the levels of estrogens, which are recognised for their neuroprotective properties. Estrogen deficiency is associated with increased inflammatory responses and increased blood-brain barrier permeability, which in turn increase neurodegenerative processes. Omega-3 fatty acids are key in maintaining the immunological homeostasis in the central nervous system by inhibiting the synthesis of proinflammatory cytokines such as TNF-alpha and interleukin-6 (IL-6), and at the same time increasing the levels of anti-inflammatory mediators such as interleukin-10 (IL-10).^{23,65}

In addition, our findings are consistent with the growing evidence that supports the role of omega-3 fatty acids in maintaining the function of the glymphatic system. Animal studies have shown that DHA maintains the polarity and expression of the Aquaporin-4 (AQP4) channels in astrocytes, which are necessary for efficient clearance of metabolic waste from the brain parenchyma, including amyloid beta.²² Consequently, dietary intake of omega-3 fatty acids may enhance glymphatic clearance pathways, thereby reducing neuronal waste accumulation and potentially mitigating neurodegenerative progression.

Cognitive and Biomarker Findings

Our study showed that cognitive improvement was only apparent after an adequate dose of omega-3 fatty acids (2500mg/day mg daily) and a supplementation period of at least 1 months. These findings are consistent with the double-blind,

randomised, controlled study performed by Wattanathorn J et al (2025), which showed that the administration of 2500mg/day of DHA for 2 months improved working memory and reduced cognitive decline in postmenopausal women.⁶⁶

Among other relevant biomarkers, the omega-3 index a well-established measure of blood omega-3 levels is a key indicator of systemic omega-3 levels. Evidence suggests that individuals with omega-3 levels below 4 are three times more likely to experience cognitive decline, underlining the importance of maintaining adequate levels of omega-3.⁶¹

It is therefore recommended that the omega-3 index be incorporated into routine clinical assessments, particularly for screening and monitoring omega-3 status among aging women.

While animal models of n-3 deficiency demonstrate that reduced brain DHA leads to memory impairment, synaptic dysfunction, and neuroinflammation effects reversible upon early repletion⁶⁷ human evidence further validates this link in aging populations. Epidemiological studies consistently report an inverse association between plasma or dietary LC n-3 PUFA levels and cognitive decline, with higher DHA status correlating with a 47% lower risk of all-cause dementia and 39% reduced AD incidence.⁶⁸ Individuals with mild cognitive impairment (MCI) or AD exhibit significantly lower plasma EPA/DHA^{69,70} and reduced cortical DHA concentrations compared to cognitively intact controls.³¹

Importantly, interventional trials confirm causality: a 6-month regimen of EPA/DHA supplementation improved cognitive performance and alleviated depressive symptoms in adults with MCI,⁷¹ suggesting a therapeutic window in pre-dementia stages. These convergent findings from mechanistic animal studies to prospective human cohorts underscore n-3 PUFAs as modifiable risk factors for AD, particularly in high-risk groups such as.

Generalizability and Safety of DHA Dosage

The optimal dose likely varies depending on baseline status, APOE genotype, and comorbidities. High doses of omega-3 (>2 g/day) may increase the risk of bleeding in elderly patients treated with anticoagulants (Mozaffarian and Wu, 2012) highlighting the need for personalized dosing.⁷²

Synergistic Effects and Limitations

Our findings are in line with growing evidence that omega-3 fatty acids have synergistic effects when taken in combination with the Mediterranean diet; in particular, the combination of DHA and antioxidants such as polyphenols has been shown to reduce chronic inflammation and thereby attenuate neurodegenerative processes.^{73,74}

While our narrative synthesis highlights neuroprotective mechanisms of omega-3, it is important to contextualize these findings against recent meta-analytic evidence. A 2024 systematic review and meta-analysis by Canhada et al concluded that omega-3 supplementation shows modest but significant cognitive benefits specifically in individuals with mild cognitive impairment (MCI) or early AD, but not in advanced dementia supporting our emphasis on early intervention.^{72,75} This aligns with our observation that benefits are most pronounced with sustained intake (>6 months) and adequate dosing (>100 mg/day DHA).⁶⁵

However, some limits must be recognised. Meta-analyses and systematic reviews, including the Cochrane review (2016), have reported that omega-3 supplements do not appear to be of significant benefit in Alzheimer's patients with advanced disease. This lack of efficacy may be due to the late initiation of the intervention or to the sub-optimal dosing regimen (Sydenham et al, 2012).⁷⁶ Consequently, our study advocates for early intervention with omega-3 fatty acids, ideally prior to the onset of significant neurodegeneration.

In addition, there is still a critical need for more precise guidance on optimal dosing for specific subpopulations, such as women carrying the allele APOE-ε4 or patients with chronic inflammatory diseases. Evidence suggests that the therapeutic response to omega-3 supplementation is influenced by genetic predisposition, metabolic status and oxidative stress, underlining the importance of a personalized approach in future research^{24,57} Although n-3 polyunsaturated fatty acids show promise in early stages of neurodegeneration, their efficacy diminishes in advanced Alzheimer's disease a pattern consistent with a Cochrane review^{76,77} and explained mechanistically by irreversible neuronal loss and glymphatic collapse. The neuroprotective effect of DHA depends on intact membrane dynamics, functional polarization of AQP4, and responsive transcriptional machinery all of which are severely compromised in late stages of Alzheimer's disease.⁶⁷ Animal models confirm that DHA supplementation reverses cognitive deficits only when administered before significant amyloid deposition or synaptic loss.⁶⁷ Similarly, in humans, benefits are limited to early stages or MCI,⁷¹

while trials in moderate to severe Alzheimer's disease show minimal effects.⁷⁷ This evidence strongly supports a preventive, not therapeutic, role for omega-3 fatty acids and emphasizes the need for early nutritional intervention ideally during perimenopause or early menopause when the brain retains sufficient flexibility to respond.

An emerging frontier in Alzheimer's prevention involves the interplay between sleep quality, glymphatic clearance, and nutritional status. Omega-3 fatty acids particularly DHA have shown potential in improving sleep architecture and reducing nocturnal neuroinflammation, thereby indirectly supporting amyloid clearance.⁷⁸ Future studies should examine combined interventions targeting both omega-3 status and sleep hygiene in postmenopausal women, a population vulnerable to both sleep disruption and AD pathogenesis.

Conclusion

In summary, this narrative review synthesizes convergent evidence that omega-3 fatty acids particularly docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) exert multifaceted neuroprotective effects relevant to Alzheimer's disease (AD) pathogenesis in elderly women. The heightened vulnerability of postmenopausal women to AD stems from estrogen withdrawal, amplified neuroinflammation, dysregulated glucose metabolism, and a higher prevalence of the APOE- ϵ 4 allele. Omega-3 fatty acids counteract these risks through several interconnected biological mechanisms: 1 attenuation of chronic neuroinflammation via suppression of NF- κ B signaling and microglial NLRP3 inflammasome activation; 2 enhancement of glymphatic clearance through preservation of astrocytic AQP4 polarization; 3 reduction of oxidative stress and mitochondrial dysfunction; 4 support of synaptic integrity and hippocampal plasticity via upregulation of brain-derived neurotrophic factor (BDNF); 5 modulation of gut-brain axis signaling by mitigating dysbiosis-induced systemic inflammation.

Notably, the efficacy of omega-3 supplementation is significantly influenced by timing, genetic background, and hormonal status. Clinical and preclinical data consistently indicate that cognitive benefits are most evident when intervention begins during the preclinical or mild cognitive impairment (MCI) stages, particularly in APOE- ϵ 4 carriers with adequate baseline omega-3 status. In contrast, no significant therapeutic effects have been observed in moderate-to-severe AD, underscoring the preventive rather than restorative nature of omega-3 action.

Given the safety, accessibility, and biological plausibility of omega-3 fatty acids, we advocate for their integration into precision-based public health strategies targeting at-risk postmenopausal women. Routine assessment of the omega-3 index, combined with consideration of APOE genotype and menopausal status, may enable early, individualized nutritional interventions to delay or prevent AD onset. Future research should prioritize long-term, sex-stratified randomized controlled trials that incorporate biomarkers of glymphatic function, neuroinflammation, and sleep quality to further elucidate the synergistic potential of omega-3 in AD prevention.

Acknowledgments

We would like to thank other colleagues who provided advice and guidance in writing this article. It should be noted that this article was available on Academia.edu, which is not a journal and was only available as a preprint and for viewing, but due to [our mistaken belief that this site was affiliated with Dow Journal and was submitted to expedite the review process] but with the continued support of the editors of Dow Journal, this article has been removed in general to facilitate the review process and is no longer available. The updated version will not be published or shared on any other platform.

Author Contributions

All authors have made significant contributions to the reported work, whether in conception, study design, implementation, data collection, analysis and interpretation, or in all of these areas; have participated in drafting, revising or critically reviewing the article; have given final approval of the version to be published; have agreed on the journal to which the article has been submitted; and have agreed to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no financial or personal interests that could influence the work reported in this paper.

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