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Review

Omega-3 Long-Chain Polyunsaturated Fatty Acids in the Elderly: A Review

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Abstract

The omega-3 long-chain polyunsaturated fatty acids (omega-3 LC-PUFAs) family includes eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and docosapentaenoic acid (DPA). Although seafood is the richest source of omega-3 LC-PUFAs, because diet alone is often insufficient in older people, they may require food supplements and enriched food as sources of omega-3 LC-PUFAs. It has been reported that long-term intake of 3-5 g/d EPA + DHA as supplements is safe for adults; omega-3 LC-PUFAs exert cardio-metabolic protective effects and improve cognitive health, mood, diabetes, insulin resistance, and vascular endothelial cell function. Furthermore, these acids exert beneficial effects on heart disease, hypertension, diabetes, arthritis, inflammatory problems, autoimmune disease, and cancer. Their pleiotropic nature is manifested as reduced triglyceride levels, management of hypertension, and obesity/metabolic syndrome, and reduced mortality. These key nutrients modulate inflammation and platelet aggregation and are effective in preventing and treating negative consequences of aging. A recent meta-analysis of EPA trials revealed a higher reduction in the relative risk in cardiovascular outcomes for EPA than for EPA + DHA. This review analyzes the influence of omega-3 PUFAs on the brain, heart, metabolism, vascular endothelial and immune functions, and muscle and bone health in the elderly.

Keywords
Elderly; omega-3 fatty acids; eicosapentaenoic acid; docosapentaenoic acid; docosahexaenoic acid; cardio-metabolic prevention; mortality

1. Introduction

Optimal nutrition and lifestyle factors contribute to reducing the risk of disability, maintaining physical and mental functions, and promoting a better quality of life in both men and women. Therefore, these are major determinants of healthy aging [1]. Age-related reduced nutrient consumption and age-dependent decrease in absorption and metabolism can affect nutrient intake [2]. Specific nutrients, such as omega-3 long-chain polyunsaturated fatty acids (LC-PUFAs), could benefit older adults and the population in general by preventing and reducing comorbidities and mortality [3].

Interestingly, a normal Western diet contains around 10 times more omega-6 PUFAs than omega-3 PUFAs [4]. Omega-6 PUFAs are largely derived from refined vegetable oils that are added to processed foods [5].

Over the last 150 years, the intake of omega-6 has increased with a parallel decline in the intake of omega-3 due to an increase in the incidence of heart disease. Thus, an "ideal" ratio of omega-6 to omega-3 fatty acids in the diet was developed [6]. According to certain researchers, the optimal omega-6 to omega-3 ratio is close to 2:1 [5]; however, the ratio associated with a reduced risk of heart disease has not yet been identified. Certain experts now suggest that the ratio is less important than the absolute levels of intake [6]. Furthermore, omega-6 and omega-3 compete for the same enzymes (delta-4, 5, 6 saturase, and elongase) that convert fatty acids into their biologically active forms [7, 8]. Therefore, a balanced diet should be poor in vegetable oils and rich in omega-3. A pioneering study performed some years ago demonstrated that a diet rich in omega-3 is safe and healthy-based; the authors reported a low incidence of cardiovascular disease in the Eskimo population, whose diet comprised foods rich in LC-PUFAs [9]. The cardioprotective function of PUFAs was subsequently confirmed in certain interventional studies [10, 11].

The omega-3 LC-PUFA family includes eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and the less prevalent docosapentaenoic acid (DPA) [12, 13]. All the three acids are derived from alpha-linolenic acid (ALA), which is converted to EPA in humans (20:5ω3) (only 1-10%) and less commonly to DHA (22:6ω3) (0.5-5%). The conversion rate is higher in women, probably due to the influence of estrogen. Moreover, there exist genetic differences, even if the available evidence is relatively limited; APOE and FADS are among the most important genotypes [14]. Conversion is also likely reduced in conditions such as insulin resistance, which is highly relevant in the context of aging [15].

LA and ALA are present in several plant foods, such as walnuts, corn, purslane, spinach, soybeans, safflower, sunflower, pumpkin seeds, and other seeds (i.e., flax, hemp, and chia), and in certain animal fats [7, 15]. The conversion of linoleic acid (18:2ω6) and ALA (18:3ω3) to long-chain (≥C20) PUFAs is inefficient in humans [12]. However, omega-6 PUFAs are abundant in the food supply, whereas the intake of omega-3 LC-PUFAs in the general population, and in particular in older people, is considerably low. Due to the imbalance between omega-6 and omega-3, the supplementation of

omega-3 is safe and important for healthy aging. Omega-3 PUFAs have a double bond located at three carbon atoms from the methyl end [16]. Arachidonic acid (AA) is synthesized via the LA pathway from two intermediate metabolites, namely, gamma-linolenic acid (18:3ω-6) and dihomo-gamma-linolenic acid (20:3ω-6), [7]. AA reacts with molecular oxygen through cyclooxygenase, lipoxygenase, and cytochrome P450 pathways, leading to the generation of eicosanoids, which include prostaglandins, thromboxanes, and leukotrienes—important mediators of the inflammatory response. The majority of AA released is promptly incorporated back into the membrane phospholipids, and therefore, it is less available for oxidation [7].

EPA and DHA exert positive effects on multiple metabolic pathways, such as those involved in reducing serum triglycerides and glucose, platelet aggregation, regulation of the inflammatory response, vascular endothelial function, and improvement of the myocardial, brain, and immune functions [17].

Seafood is the most important dietary source of omega-3 LC-PUFA. In particular, herring, sardines, tuna, trout, and salmon are rich sources of omega-3 PUFAs [11]. Other sources include human milk, marine mammals, marine algae, and krill. Because diet alone is often insufficient for older people to obtain adequate amounts of omega-3, they usually require supplements. Moreover, in 2012, the European Safety Food Authority (ESFA) panel concluded that supplemental intakes of EPA and DHA at doses up to 5 g a day do not raise safety concerns for adults [16]. Omega-3 PUFAs may exert cardio-protective effects, namely, anti-hyperlipidemic, anti-thrombotic, anti-hypertensive, anti-arrhythmic, and anti-inflammatory effects [18-20]. Therefore, scientific opinion recognizes omega-3 PUFAs as potential key nutrients for healthy aging [21, 22]. Furthermore, the Omega-3 Index, that is, the EPA + DHA content of erythrocyte membranes, was recognized as a marker for the risk of coronary heart disease and is expressed as a percentage of total fatty acids. The optimal Omega-3 Index is 8% or more, with ≥8% being associated with the highest protection and ≤4% with the least [23].

The United States Food and Drug Administration states that omega-3 supplements containing EPA and DHA are safe if doses do not exceed 3 g/d. The EFSA notes that long-term intakes of 3 to 5 g/d of EPA + DHA from supplements are safe in adults. In addition, supplemental intakes of EPA alone, up to 1.8 g/d, do not raise safety concerns for adults [4]. However, adverse effects are bleeding episodes, decreased immune function, impaired lipid and glucose metabolism, and increased lipid peroxidation [12]. In addition, increasing evidence indicates both independent and shared effects of EPA and DHA [24].

EPA, DPA, and DHA differ in their biochemistry and metabolism. DHA is the most important omega-3 PUFA in the brain and has been shown to have a remarkable function in the neuronal membrane. DHA is neuroprotective and is required for the maintenance of normal brain function in adults and for improving learning ability [16]. Interestingly, EPA is a stronger indicator of omega-3 PUFA intake than DPA or DHA, probably due to the different ways in which it is incorporated into membrane phospholipids. The EPA content is determined primarily by exchange with plasma lipoproteins, whereas DPA and DHA are largely present in the inner membrane and are mostly influenced by erythrocyte turnover [25].

A meta-analysis of several studies confirmed the function of EPA rather than DHA or DPA in reducing cardiovascular mortality and depression [26, 27].

The present review aims to analyze the possible pleiotropic effects of omega-3 PUFAs on the health of older adults. We will discuss evidence regarding the effects of omega-3 LC-PUFAs on brain

functions, cardiovascular system, metabolism, skeletal system, and immune function. Furthermore, we will discuss the function of omega-3 supplements in non-alcoholic fatty liver disease and the molecular forms of omega-3 supplementations.

2. Brain Functions

2.1 Cognition, Dementia, and Mood

PUFAs have a pivotal function in mediating cognition, learning, and memory functions, probably by exerting stabilizing and protective effects on the structure and function of neuronal membranes. In addition, a beneficial effect was reported on white matter microstructural integrity and gray matter volume in specific brain areas [28].

The deficiency of PUFAs in the brain can lead to cognitive deficits, whereas their supplementation could help people with cognitive deficits [29]. The brain is enriched with two polyunsaturated fatty acids, namely, AA and DHA, which are esterified to phospholipids and are released from the membrane. In addition, they are biotransformed into active molecules, participate in cell signaling, and modulate cell survival, neurogenesis, brain inflammation, and synaptic function [30].

In patients with dementia, low levels of EPA, DHA, and total omega-3 PUFAs have been found in peripheral blood tissues [31, 32]. DHA plays a pivotal role in maintaining the normal brain structure and function and exerts neuroprotective effects. Furthermore, studies in rats have demonstrated that the incorporation of radiolabeled DHA into the brain from the plasma is an *in vivo* marker of brain DHA metabolism and neurotransmission [33]. In other words, the incorporation rate of DHA into the brain equals the rate of brain DHA consumption. DHA signaling is probably mediated by calcium-independent phospholipase A(2) (iPLA(2)). Experiments performed on mice knocked out for this enzyme showed that iPLA(2) is pivotal for muscarinic cholinergic signaling involving DHA [33].

Furthermore, post-mortem studies reported a lower DHA content in the brains of patients with Alzheimer's disease (AD) as compared to the brains of healthy people [34, 35].

In a subgroup of the Framingham Heart Study, a higher plasma phosphatidylcholine DHA level was associated with a 47% lower risk of developing all-cause dementia and a 39% lower risk of developing AD [36].

The OmegAD study reported beneficial effects of omega-3 PUFA supplementation in 174 patients with mild-to-moderate AD. Furthermore, the subgroup analysis revealed beneficial effects, especially in patients with very mild cognitive decline at baseline [37, 38].

In the Three-City Study conducted in Bordeaux, France (1,214 non-dementia participants followed up for 4 years), 65 patients developed dementia. After adjustment for age, education, apolipoprotein E epsilon4 allele, diabetes, and baseline plasma vitamin E and triacylglycerol, the authors found that higher plasma EPA concentrations were associated with a lower incidence of dementia (hazard ratio [HR] = 0.69; 95% confidence interval [CI]: 0.48-0.98) in these patients, independently of the depressive status. Interestingly, higher ratios of AA to DHA and of omega-6 to omega-3 PUFAs were related to an increased risk of dementia, especially in 90 patients affected with depression (HR: 2.65; 95% CI: 1.07-6.56 and 1.61; 95% CI: 1.04-2.47, respectively) [39].

A systematic review and meta-analysis by Yurko-Mauro et al. [40] revealed that DHA, alone or in combination with EPA, can improve memory function in older adults with mild memory complaints. This research involved healthy adults and was conducted using the Ovid MEDLINE and EMBASE databases. Episodic memory outcomes in people with mild memory complaints were significantly

improved with DHA/EPA supplementation ($p < 0.004$), whereas >1 g/d DHA/EPA improved episodic memory ($p < 0.04$) despite cognitive status at baseline. Moreover, DHA was shown to be significantly successful in semantic and working memory changes from baseline. The research followed another study from the same author, a double-blind, placebo-controlled clinical study, which reported beneficial effects of DHA in 485 patients with age-related cognitive decline. Patients were aged ≥55 years, had a Mini-Mental State Examination (MMSE) score >26, and a baseline Logical Memory (Wechsler Memory Scale III) score ≥1 standard deviation below that of younger adults. The patients were randomly assigned to 900 mg/d DHA orally or placebo for 24 weeks. Positive effects were observed in the treated group for immediate and delayed verbal recognition memory scores ($p < 0.02$), whereas no benefits were found for working memory and executive function [41].

Another 12-month, randomized, double-blind, placebo-controlled study was conducted on 36 elderly patients with low socioeconomic status and affected with MCI (mild cognitive impairment) and used fish oil supplementation with DHA. Patients were randomly assigned to receive either concentrated DHA fish oil ($n = 18$) or placebo ($n = 18$) capsules. In the treated group, a significant improvement was recorded in short-term and working memory ($p < 0.0001$), immediate verbal memory ($p < 0.05$), and delayed recall ability ($p < 0.05$), with minimal and self-limiting adverse effects [42].

A similar study assessed 86 individuals with MCI aged ≥60 years; 44 were randomly assigned to receive DHA 480 mg/d and EPA 720 mg/d, and 42 received placebo capsules (olive oil). The study concluded that omega-3 PUFAs could improve cognitive function in patients with MCI. However, more studies involving larger samples and different fish oil dosages are necessary to consolidate the evidence for using PUFAs in individuals with cognitive impairment [43]. Other studies showed the effects of 4-month supplementation with DHA 800 mg/d plus lutein 12 mg/d in older women; this combination enhanced the verbal fluency and memory scores, although no effect on mood and mental processing speed was recorded [44].

An improvement in the MMSE score and semantic verbal fluency was observed following 12 weeks' administration of an emulsion of DHA-phospholipids containing melatonin and tryptophan in 25 elderly patients with MCI. Surprisingly, a significant improvement in the Mini Nutritional Assessment score was observed [45].

In patients with AD, omega-3 PUFAs have been reported to increase the clearance of β-amyloid peptides and exert neurotrophic, neuroprotective, and anti-inflammatory effects. Supplementation with PUFAs was associated with dementia in eight studies; however, five studies reported the trivial effect of omega-3 PUFAs in patients affected by dementia [46]. The authors concluded that patients with mild cognitive impairment can be treated using long-term and higher intakes of omega-3 PUFAs [46].

Furthermore, the beneficial effects of EPA and DHA intake have been observed in patients affected with depression which can increase the risk of progression from MCI to dementia. For example, a 6-month double-blind, randomized controlled trial conducted in 50 people aged > 65 years with MCI showed improvement in the Geriatric Depression Scale scores and mental health, whereas an increased DHA intake was found to improve self-reported physical health. These results need further investigation in larger samples of patients with depression and MCI [47].

In a cross-over placebo-controlled study, including 40 healthy middle-aged to elderly patients, 3 g/d omega-3 PUFA supplementation for 5 weeks resulted in better performance in the working

memory test than placebo ($p < 0.05$). Furthermore, omega-3 PUFAs were found to be effective in lowering the levels of plasma triglycerides ($p < 0.05$) and systolic blood pressure ($p < 0.0001$) [48].

Interestingly, an experimental mouse model of brain ischemia induced with 20 min of bilateral common carotid artery occlusion showed that combination treatment with citicoline 40 mg/kg/d and DHA 300 mg/kg/d synergistically improved the learning and memory ability in ischemic mice compared with each product administered alone [49]. This finding indicates a possibility of possible combination in humans following brain ischemia.

The importance of long-term administration was studied. The 3-year supplementation with omega-3 PUFAs, lycopene, and *Ginkgo biloba* improved the cognitive function in 41 individuals aged ≥65 years, both in APOE4 carriers and non-carriers; thus, indicating the absence of influence of the APOE genotype [50].

In contrast, a 4-month, randomized, double-blind, placebo-controlled study conducted on 57 participants with cognitive impairment, no dementia (CIND), and 19 with AD randomized to receive either omega-3 PUFAs (600 mg EPA and 625 mg DHA per day) or placebo (olive oil) revealed a negligible effect on cognition and mood. The authors concluded the importance of assessing the effects of different doses of PUFAs in a larger sample [51].

In 1,390 participants from the Three-City Study conducted in Bordeaux, France (mean age 74.6 years), the plasma levels of EPA were found to be lower in patients affected with depressive symptoms compared with controls (0.85% vs. 1.01%; $p = 0.001$). Moreover, the plasma levels of EPA were inversely associated with the severity of depressive symptoms (beta = -0.170; $p = 0.040$) in patients assuming antidepressants. The authors concluded that higher levels of plasma EPA were associated with less severe depressive symptoms in elderly patients, especially those taking antidepressants [52].

However, numerous studies have investigated the relationship between the blood levels of PUFAs and the risk of cognitive impairment. Higher plasma EPA levels, but not DPA or DHA levels, were associated with lower gray matter atrophy in the hippocampus and amygdala of individuals aged ≥65 years [53], as well as with slower cognitive decline [54], lower risk of dementia [39], and depressive symptoms in the elderly [52]. Moreover, a recent meta-analysis reported that even if blood levels of DHA, EPA, and total omega-3 PUFAs were significantly reduced in patients affected with dementia, only EPA levels were significantly lower in patients with the pre-dementia syndrome. This implied that the plasma levels of EPA might be not only a marker of disease state but also a risk factor for cognitive impairment [32].

Recent double-blind randomized controlled trials indicated that EPA, mainly at dosages of 1 or 2 g/d, was better than placebo. In addition, DHA could be used as monotherapy or adjuvant therapy in treating mild-to-moderate depression [55, 56]. A systematic review of the literature was conducted using PubMed and EMBASE (articles published before 20 December 2017) to estimate the efficacy of DHA and EPA in improving depression [29]. The search yielded 180 articles, although only 26 studies (2,160 participants) eventually met the eligibility criteria. The dosage of EPA supplementation ranged from 180 mg/d to 4000 mg/d. The EPA-pure and EPA-major groups were separated by dosage (≤1 g/d and >1 g/d). Treatment demonstrated significant beneficial effects on depression. This finding was in accordance with a review by Song et al. [56], who found that EPA is more efficacious regarding its antidepressant effect than DHA [29] (most effective ratio of EPA to DHA for depression: 2:1 or 3:1). Unlike DHA, EPA is not highly concentrated in the human brain; it can enter the brain quickly as free fatty acids and is rapidly metabolized and beta-oxidized; thus, it

is not re-acetylated into phospholipid membrane stores. Both DHA and EPA lead to decreased production of pro-inflammatory cytokines, i.e., tumor necrosis factor α and interleukins 1β, 2, and 6, and may reduce inflammation through their precursor AA [29]. In contrast, the role of inflammation, in particular neuroinflammation, is remarkable in neurodegeneration, as well as in cognitive impairment [57]. It is usually associated with oxidative stress and significant cell energy metabolism. Neuroinflammation is defined as the reactive response of the central nervous system (CNS) against elements that interfere with homeostasis, inside or outside the CNS. Furthermore, this response is involved in all neurological diseases, including neurodegenerative diseases such as AD [58]. Neuroinflammation is linked to the activation and proliferation of non-neuronal cells (in particular, astrocytes, microglia, and mast cells) and is associated with the release of pro-inflammatory mediators, which, in turn, can change the synaptic plasticity. In line with their anti-inflammatory properties, EPA and DHA supplementations can directly act on inflammatory cells through membrane receptors to decrease inflammatory responses [7].

Furthermore, EPA supplementation has been associated with increased levels of N-acetyl-aspartate in the brain, a marker for neuronal homeostasis, suggesting its role as a neuroprotective agent [59].

Eventually, a systematic review demonstrated that the most beneficial effects of EPA + DHA supplementation were observed in the early stages of the disease [60], implying that earlier treatment with PUFA supplementation is better than that started later. In addition, a meta-analysis of six RCTs with a range of duration between 3 and 40 months and using 0.14 to 1.8 g EPA + DHA administered daily reported a slower rate of cognitive decline in patients receiving omega-3 LC PUFAs [61].

In summary, although clinical observations are not homogeneous, the majority of studies report a positive correlation between omega-3 supplementation and brain functions [22].

3. Cardiovascular System

3.1 Vascular Endothelial Cell Function, Heart Disease, and Hypertension

A low ratio of EPA-DHA to AA PUFAs has been associated with cardiovascular events and progression to coronary atherosclerosis. This was evaluated using virtual histology intravascular ultrasound in patients with coronary artery disease and treated with statins. A study performed on 101 patients at the time of the percutaneous coronary intervention and 8 months after the statin therapy revealed the percentage change in the plaque volume to be negatively correlated with changes in the EPA to AA ratio (r = -0.190, p = 0.05), DHA to AA ratio (r = -0.231, p = 0.02), and EPA + DHA to AA ratio (r = -0.240, p = 0.02) in patients treated with pravastatin [62]. Progression of atheroma was observed in 46 patients (45.5%), and regression of atheroma after 8-months of follow-up was observed in the remaining 55 patients (54.5%) [62].

A 2012 study assessed whether omega-3 PUFA supplementation, in addition to optimal medical therapy, reduced the increased platelet and endothelial activity in 150 patients affected with intermittent claudication who were already on aspirin and statin therapy. This randomized double-blind study compared the 6-week supplementation with EPA/DHA 850-882 mg with a placebo. The supplementation exerted no effect on the markers of inflammation or platelet and endothelial activation, whereas high-sensitivity C-reactive protein, s-ICAM, and IL-6 remained unchanged [63].

Differences have been reported in the composition of phospholipid fatty acids between stroke and non-stroke patients and between non-cerebral atherosclerotic stenosis and intracranial atherosclerotic stenosis in patients with stroke. For example, Kim et al. [64] reported a higher risk of intracranial atherosclerotic stenosis at lower amounts of plasma DHA (more specifically, there was an inverse relation with the levels of phospholipid DHA).

DHA prevents arteriosclerosis and inhibits the development of inflammation in endothelial cells [65, 66]. In addition, it regulates vascular biomarkers, reduces cardiovascular risk, and controls the production of nitric oxide and endothelin 1 in endothelial cells, thus, regulating vascular relaxation and constriction [65]. Other possible actions of DHA on vascular endothelial cell function involve the expression of oxidized low-density lipoprotein (LDL) receptor 1, plasminogen activator inhibitor 1, thromboxane A2 receptor, and adhesion molecules, i.e., vascular cell adhesion molecule-1, monocyte chemoattractant protein-1, and intercellular adhesion molecule 1 [65]. A new mechanism of action of DHA has been reported to be mediated via the endothelial free fatty acid receptor 4, which is associated with the induction of heme-oxygenase-1 by nuclear factor erythroid 2-related factor 2 (Nrf2)—an emerging regulator of cellular resistance to oxidants [65]. Thus, increasing evidence suggests that low serum levels of DHA could serve as a marker of endothelial dysfunction.

PUFAs exert a remarkable effect on arrhythmias. For example, supplementation with 1 g/d omega-3 for 6 months in patients with a history of myocardial infarction reduced isolated ventricular contractions and ventricular tachycardia and exerted favorable effects on heart rate variability and the red blood cell omega-3 index [67]. Interestingly, a combination of PUFAs and vitamins C and E in patients aged >65 years planned for cardiac surgery with extracorporeal circulation markedly reduced postoperative atrial fibrillation in older patients and enhanced glutathione peroxidase activity [68]. The GISSI-HF study (Gruppo Italiano per lo Studio della Sopravvivenza nell' Insufficienza Cardiaca) enrolled patients with heart failure with any cause and severity. Twenty-four--hour Holter recordings (range, 16-24 h) in 388 patients at baseline were obtained after 3 and 12 months. Omega-3 PUFA supplementation partially restored autonomic modulation in patients affected with chronic heart failure, with a maximal effect after 3 months of treatment [69]. Moreover, lower rates of mortality and hospitalization for heart failure and coronary heart disease were associated with higher blood levels of PUFAs [66]. Supplementation with 2 g/d PUFAs for 5 months prevented the decline in heart rate variability related to particulate matter measuring ≤2.5 μ in nursing home (NH) residents aged 60 years old or older [70].

Next, PUFAs were assessed for their role in reducing mortality. Importantly, long-chain omega-3 PUFA in red blood cells was associated with a lower risk for total mortality in a community-dwelling population in their mid-60s. The Framingham Offspring Cohort participants without cardiovascular disease and available red blood cell fatty acid measurements were assessed in an 11-year follow-up study. A systematic evaluation was performed to examine the relationship between 8 standard risk factors (age, sex, hypertension, systolic blood pressure, diabetes, total cholesterol, HDL cholesterol, and smoking status) and 28 fatty acid metrics and all-cause mortality. The results were remarkable because 4 of the 28 fatty acid metrics (14:0, 16:1n-7, 22:0, and omega-3 index [031; 20:5n-5 + 22:6n-3]) were remarkable predictors of all-cause mortality and as predictive as standard risk factors such as lipid levels, hypertension, smoking, and diabetes [71].

A recent systematic review and meta-analysis was conducted to assess the effects of EPA and DHA on cardiovascular outcomes. A broad search involving PubMed, ClinicalTrials.gov, EMBASE, and the Cochrane library databases up to June 7, 2021, yielded 798 eligible articles. Of these, 760 were

removed according to *a priori* study selection criteria, leaving 38 randomized controlled trials on omega-3 PUFAs. Notably, the trials were stratified by EPA monotherapy and EPA + DHA therapy, with the key outcomes being non-fatal cardiovascular outcomes, cardiovascular mortality, bleeding, and atrial fibrillation. The protocol was registered in PROSPERO.

A total of 149,051 participants were involved, and the results showed notably reduced cardiovascular risk after EPA monotherapy compared with EPA + DHA [27]. The dose of omega-3 PUFAs ranged from 0.4 g/d to 5.5 g/d, whereas doses in the EPA trials ranged from 1.8 to 4.0 g/d, and those of EPA + DHA ranged from 0.4 to 5.5 g/d [27].

Overall, omega-3 PUFAs are associated with reduced cardiovascular mortality, non-fatal myocardial infarction and related events, and major adverse cardiovascular events. In particular, trials of EPA compared with those of EPA + DHA showed higher relative reductions in cardiovascular outcomes.

The Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial was performed in patients with atherosclerotic cardiovascular disease or those at high risk of this condition (diabetes with at least 1 additional risk factor) [72, 73]. Surprisingly, the use of icosapent ethyl, a highly purified ethyl ester of EPA, resulted in a significant 25% relative reduction in primary endpoints (cardiovascular death, non-fatal myocardial infarction and stroke, coronary revascularization, and unstable angina). Furthermore, secondary endpoints of cardiovascular death, myocardial infarction, or stroke were significantly reduced by 26%, and death from cardiovascular causes was reduced by 20% [73]. The results of this recent meta-analysis are reported in detail in Table 1.

Table 1 Results of a recent review and meta-analysis confirm the remarkable role of omega-3 FAs, particularly EPA, in reducing cardiovascular events and mortality [73].

	Use of omega-3 FA
Cardiovascular mortality	Reduced (RR, 0.93 [0.88-0.98]; $p = 0.01$)
Non-fatal MI	Reduced (RR, 0.87 [0.81-0.93]; $p = 0.0001$)
CHD	Reduced (RR, 0.91 [0.87-0.96]; $p = 0.0002$)
MACE	Reduced (RR, 0.95 [0.92-0.98]; $p = 0.002$)
Revascularization	(RR, 0.91 [0.87-0.95]; $p = 0.0001$)
	EPA monotherapy vs. EPA + DHA
Cardiovascular mortality	Higher RR reductions with EPA monotherapy (0.82 [0.68-0.99]) EPA + DHA (0.94 [0.89-0.99])
Non-fatal MI	(EPA: 0.72 [0.62-0.84]; EPA + DHA: 0.92 [0.85-1.00])
CHD events	(EPA: 0.73 [0.62-0.85]; EPA + DHA: 0.94 [0.89-0.99])
MACE and revascularization	(EPA: 0.78 [0.71-0.85]; p = 0.00000001); EPA + DHA: 0.99 [0.95-1.02]; $p = 0.48$
AF	Increased risk of AF (RR, 1.26 [1.08-1.48])
Risk of total bleeding	Higher risk with EPA monotherapy vs. control (RR, 1.49 [1.20-1.84]) Higher risk with EPA monotherapy vs. control (RR, 1.35 [1.10-1.66])

AF = atrial fibrillation; CHD = coronary heart disease; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; FA = fatty acids; MACE = major adverse cardiovascular events; MI = myocardial infarction; RR = relative risk

Regarding hypertension, DHA and, to a lesser extent, EPA reduced the blood pressure in people affected by essential hypertension, even at high doses (6 g/d). A cross-sectional study of 4,680 individuals in China, Japan, the United Kingdom, and the USA showed that PUFAs were inversely associated with blood pressure [74, 75].

A systematic literature search was performed using PubMed and Scopus to assess the differential effects of EPA and DHA on blood pressure and inflammatory mediators [76]. EPA significantly reduced systolic blood pressure (-2.6 mmHg; 95% CI, -4.6 to -0.5 mmHg), in particular in patients affected by dyslipidemia (-3.8 mmHg; 95% CI: -6.7 to -0.8 mmHg), whereas DHA significantly decreased the diastolic blood pressure in patients with dyslipidemia (-3.1 mmHg; 95%CI: -5.9 to -0.2 mmHg). Both EPA and DHA significantly reduced the concentrations of C-reactive protein, especially in dyslipidemic patients, and higher baseline concentrations of C-reactive protein.

Similarly, in blood coagulation parameters, PUFAs reduced collagen-stimulated platelet aggregation [77]. Furthermore, an analysis of eight clinical studies involving 600 patients treated, even at short-term doses of up to 10 g/d EPA + DHA or above 1.5 g/d up to 52 weeks, revealed no increase in the risk of bleeding manifestations. This is held true for vulnerable and sensitive populations, for example, intensive care patients or patients affected with gastrointestinal cancer [78, 79]. Table 2 summarizes the primary findings on the cardiovascular effects of PUFAs.

Table 2 Primary cardiovascular effects of EPA, DHA, and DPA in humans [65-79].

	EPA	**DHA**	**DPA**
Plasma lipids	↓ TG levels	↓ TG levels ↑ LDL particle size	//
Arrhythmias	Restoration of autonomic modulation in patients with chronic health failure	↓ Arrhythmias	No clear effects
Hypertension	↓ BP	↓ BP	//
Endothelial function	↑ Nitric oxide and ↓ peroxynitrite (ONOO-)	↑ Nitric oxide, ↑ PGI2, ↓ endothelin-1 production, ↓ MMP-2, ↑ O2*	//
Inflammation	↓ Inflammation	↓ Inflammation	↓ Inflammation
Thrombosis and coagulation	↓ Collagen-stimulated platelet aggregation; no increased risk of bleeding	↓ Collagen-stimulated platelet aggregation; no increased risk of bleeding	↓ Collagen-stimulated platelet aggregation; no increased risk of bleeding
All-cause mortality	↓ Mortality	↓ Mortality	↓ Mortality

EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid; DPA = docosapentaenoic acid; PGI2 = prostacyclinI2; MMP2 = matrix metalloprotease 2; O2* = superoxide anion

4. Metabolism

4.1 Diabetes and Insulin Resistance

The effects of dietary omega-3 PUFAs on glycemic regulation in type 2 diabetes mellitus have been investigated in randomized, controlled interventional studies in humans.

Both marine and vegetable oils have high concentrations of PUFAs and, therefore, can affect glycemic regulation. However, the majority of the studies examined have documented the lack of effect, maybe owing to an inappropriate control group. More studies are required, and it is not yet possible to draw valid conclusions [80].

A study performed a few years ago demonstrated that insulin resistance is related to a diet high in saturated fatty acids, whereas PUFAs slightly enhanced insulin sensitivity. The insulin resistance in a diet high in saturated fatty acids was associated with high diacylglycerol content and an increase in the saturation of muscle triacylglycerol. PUFAs improved insulin sensitivity, possibly via increased incorporation into triacylglycerol [81].

In an experimental high-fat-diet murine model, supplementation with EPA, DPA, or DHA prevented fatty liver and high serum cholesterol and glucose levels and prevented high liver cholesterol levels. DPA (but not EPA or DHA) was reported to be associated with a significant improvement in a homeostatic model of assessing insulin resistance (HOMA-IR) compared with the high-fat-fed mice. Furthermore, supplementation with both DPA and DHA prevented increased serum alanine aminotransferase levels compared with EPA and the high-fat group, probably owing to down-regulation of the TLR-4/NF-κB signaling pathway and decreased lipogenesis in the liver [82].

In a double-blind, placebo-controlled, randomized clinical trial in 67 overweight patients with type 2 diabetes mellitus, 3 months of supplementation with EPA exerted a beneficial effect on glycemic indices in patients affected with type 2 diabetes mellitus and improved insulin sensitivity. In addition, it decreased serum insulin, fasting plasma glucose, HbA1c, and the HOMA-IR value [83].

Nevertheless, more studies are required to assess the effects of omega-3 PUFAs on glycemic control and insulin resistance.

5. Skeletal System

5.1 Muscle Performance and Bone Health

Sarcopenia is the progressive loss of muscle mass and function that can occur with aging and is a major public health concern. It is associated with the accumulation of intramuscular fat, muscle atrophy, and decreased peripheral cell proliferation [84]. Sarcopenia during aging can be managed using omega-3 PUFA supplementation, thus, stimulating the synthesis of muscle proteins. Supplementation with omega-3 PUFAs for 8 weeks in 16 older adults was shown to cause a hyper-aminoacidemia-hyperinsulinemia-induced increase in muscle protein synthesis, as well as in muscle mTOR and p70s6 k phosphorylation [85]. In addition, a systematic review and meta-analysis of 123 studies showed a positive effect of omega-3 LC PUFA supplementation on body muscle mass and, interestingly, on muscular strength [4].

A cross-sectional study on 118 men and 129 women residing in the community or an assisted living facility with a mean omega-3 PUFA intake of 1.27 g/d demonstrated a higher bone mineral density, although no independent association was associated between PUFA intake and lower extremity muscle function [86]. Importantly, the grip strength was closely associated with the consumption of fatty fish. Moreover, for each additional portion of fatty fish consumed per week, an increase in grip strength of 0.43 kg in men (p = 0.005) and 0.48 kg in women (p < 0.001) was observed [87]. The InCHIANTI study, a population-based study on older Italians involving 330 participants, reported significantly decreased lower extremity performance (defined as a Summary Physical Performance Battery [SPPB] score ≤9). Individuals with an SPPB score > 9 had higher levels of total PUFAs and both omega-3 and omega-6 PUFAs. Furthermore, baseline SPPB scores were associated with omega-3 PUFAs (beta = 0.148, p = 0.031), whereas the 7-min walk time was associated with total PUFAs (beta = -0.068, p = 0.008). A higher omega-6/omega-3 ratio was associated with an increased risk of poor physical performance and slower walking speed [88].

PUFAs have been implicated in preserving skeletal integrity during aging. Weiss et al. [89] reported a significant inverse correlation between the ratio of dietary linoleic acid to ALA and bone mineral density at the hip in 642 men and 564 women not using hormone therapy and 326 women using hormone therapy.

EPA and DHA supplementation could exert a beneficial effect on cancer cachexia, although further studies are required. The possibly involved mechanisms are an anti-inflammatory action, the stimulation of the anabolic pathway through muscle mTOR and p70s6 k phosphorylation, and the suppression of the catabolic pathway through NF-kb and FOX 03 [90].

6. Immune System

6.1 Immune Function

Omega-3 PUFA supplementation exerts significant effects on immune functions. For instance, linoleic acid (LA) and ALA are known to modulate T-cell proliferation in older adults. The best proliferative response was observed at an LA:ALA ratio of 8.70 with a diet based on soybean oil, leading to changes in the fatty acid composition of phospholipids in the immune cell membrane [91]. Forty enterally fed patients aged 60 to 80 years were recruited 48 h after admission to the intensive care unit; short-term intravenous administration of fish oil--based lipid emulsion (0.2 g/kg) over 6 h for 3 days was shown to modulate certain inflammatory markers [92]. Similarly, a prospective randomized controlled trial performed on cardiac surgery patients who received three infusions of 0.2 g/kg fish oil emulsion or saline (control) 12 and 2 h before and immediately after the surgery showed significantly increased PUFA concentrations in the platelets and atrial tissue membranes. The increase was recorded within 12 h of the first administration, with a simultaneous decrease in both biological and clinical signs of inflammation [93].

Furthermore, in healthy older individuals, a supplementation comprising very low doses of marine oil (600 mg/d) with 150 mg DHA plus 30 mg EPA for 6 weeks significantly decreased the proliferative responses of lymphocytes to mitogens at day 42 and reduced glutathione peroxidase activity compared with controls (p < 0.01). These results show that even very low doses of omega-3 PUFAs can influence the immune response in elderly individuals [94].

In a randomized, double-blind, placebo-controlled trial involving healthy individuals aged 55 to 75 years who took placebo oil (80:20 mix of palm and sunflower seed oils) or a mixture of placebo

oil and oils rich in ALA (2 g), gamma-linolenic acid (770 mg), AA (680 g), DHA (720 mg), or EPA (1 g) plus DHA (720 mg), revealed that the natural killer (NK) cell activity was insignificantly affected by placebo, ALA, gamma-linolenic acid, AA, or DHA. In contrast, fish oil significantly reduced the NK cell activity. The authors concluded that a moderate amount of EPA, but not other omega-6 or omega-3 PUFAs, decreased the NK cell activity in healthy individuals [95]. NK cells not only participate in controlling several viral infections and tumors but also function as regulatory cells during inflammation and influence the consequent adaptive immune responses.

The anti-inflammatory function of EPA and DHA is linked to the decreased activation of the pro-inflammatory transcription nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) [7]. In addition, EPA and DHA are precursors for the synthesis of novel specialized pro-resolving mediators; these include resolvins, maresins, and protectins (SPMs). Resolvins are part of the metabolic pathway of both EPA and DHA, whereas maresins and protectins are derived from DHA [96-98].

SPMs are remarkable because they activate the resolution of inflammation and increased intakes of EPA and DHA, resulting in their higher concentrations in human blood and tissues [99]. Both EPA and DHA can regulate the antioxidant signaling pathways (cyclooxygenase [COX], lipoxygenase [LOX], cytochrome c oxidase activity, increase in manganese-dependent superoxide dismutase activity). High doses of omega-3 LC PUFAs induce several clinical benefits in rheumatoid arthritis (RA), for example, in reducing pain; a higher blood level of EPA has been reported to be associated with greater treatment efficacy of anti-TNF antibodies in patients with RA [7, 100-102].

Furthermore, for the last 2 years, the world has been shocked by the COVID-19 pandemic, a severe viral disease often associated with an uncontrolled release of pro-inflammatory cytokines and excessive coagulation [103]. The current treatment for COVID-19 infection is aimed to address inflammation and thrombosis. Therefore, omega-3 fatty acids, and in particular EPA and DHA, could be a safe and effective therapeutic strategy for their anti-inflammatory properties and their ability to promote SPMs synthesis and regulate platelet aggregation and thrombosis [7]. In addition, they upregulate the functions of certain cells that are parts of the innate immune response, such as macrophages, neutrophils, NK cells, mast cells, basophils, and eosinophils, and promote antigen-specific responses mediated by T-cells and B-cells [7, 104]. Interestingly, a scoping review selected four studies on the possible function of omega-3 fatty acid supplementation on COVID-19 through an extensive search using PubMed, Google Scholar, Springer Link, and Emerald Insight databases between January 31, 2020, and September 1, 2021 [105]. It was found that omega-3 supplementation exerted a potential effect on COVID-19 management. Another interesting pilot study by Asher et al. reported that patients with an omega-3 index higher than 5.7% had about 75% lower risk for mortality due to COVID-19 infection [106]. The stronger effects could be seen at higher doses of EPA + DHA supplementation, unlike the doses used so far [7, 107].

7. Other Possible Functions

7.1 The Role of Omega-3 Supplements in Non-alcoholic Fatty Liver Disease

Non-alcoholic fatty liver disease (NAFLD) is commonly found in Western countries (20-30%), especially among individuals aged over 50 years [108]. It is often associated with obesity, type 2 diabetes, dyslipidemia, and cardiovascular disease [109, 110]. NAFLD is characterized by the presence of steatosis, with lipid droplets present in more than 5% of hepatocytes [111], and can

potentially progress to steatohepatitis (NASH) and fibrosis [112]. Physical activity and a healthy diet are the primary support for counteracting NAFLD effects. Furthermore, a deficiency of n-3 PUFAs, with a higher n-6/n-3 ratio, has been found in patients with NAFLD [113]. A meta-analysis of 10 studies involving 577 patients affected with NAFLD/NASH revealed that n-3 PUFAs can optimize liver fat, liver enzymes (gamma-glutamyl-transpeptidase, GGT), and blood lipids (triglycerides, HDL), whereas no significant effects were found on transaminase levels (AST and ALT) [114]. Another metanalysis of seven RCTs showed that n-3 PUFAs reduced the amount of liver fat observed on ultrasound, improved hypertriglyceridemia, reduced inflammation, and enhanced insulin sensitivity [115]. More studies with a larger sample size and a well-defined design are warranted for assessing the effects of PUFA supplementation.

7.2 Other Effects

Marine omega-3 PUFAs can activate the transcription factor peroxisome-activated receptor-γ which in turn regulates the expression of adiponectin. Alsaleh et al. [116] investigated the interaction of dietary omega-3 PUFAs with single-nucleotide polymorphism (SNP) genotypes in the adiponectin gene (*ADIPOQ*) as a factor influencing the serum concentrations of adiponectin. Serum adiponectin was measured in healthy individuals aged 45 to 70 years who had received 0.45, 0.9, and 1.8 g/d EPA plus DHA for 12 months. The -11391 A-allele was found to be associated with a higher serum adiponectin concentration at baseline (n = 290; p < 0.001), whereas homozygous individuals for the +45 T-allele aged > 58 years experienced a 22% increase in serum adiponectin concentration compared with baseline after the highest PUFA dose (p-treatment effect = 0.008) [117]. Therefore, a diet high in omega-3 PUFAs could be recommended for older individuals, especially carriers of the +45 TT genotype, who are at an increased risk of hypoadiponectinemia, type 2 diabetes, and obesity [92]. Furthermore, diets high in monounsaturated fatty acids have been associated with a lower prevalence of age-related macular degeneration in the general population [118].

8. Molecular Forms of Omega-3 Supplementations

The nature of the dietary carrier used is remarkable for EPA and DHA levels and their steady-state inside the body [119, 120]. In other words, the oral bioavailability of LC-PUFA is different according to the different molecular forms used (ethyl ester, sn-1(3)-MonoAcylGlycerol [MAG], TriAcylGlycerols [TAG], and free fatty acids [FFA]) [121]. Ethyl ester (EE) of omega-3 fatty acids supplements have become more prevalent in the market because they are cheaper. They are easier to work with; however, they are the least bioavailable forms of omega-3s as compared to triglyceride forms. They are produced using industrial alcohol to form a synthetic substrate with crude fish oil in a free fatty acid form (mico distillation). The ethyl esters are metabolized in the liver, where the ethanol is removed, and the body must rebuild the resulting FFAs back into a triglyceride (TG). This is a longer process compared to the direct intake of a natural TG form; furthermore, TG fish oils result in about 50% more EPA and DHA after absorption compared to EE forms [119-121]. EE forms are rapidly oxidized to harmful oxidation products. The side effects (i.e., infections, flu symptoms, altered taste, skin rash, back pain and possibly burping, vomiting, and pancreatitis) are primarily attributed to the ethanol release [121]. The difference is in our history: EE forms have been in the human food chain for approximately 20 years, unlike TG fatty acids (about 600 million years).

In conclusion, the omega 3 (OM3)-MAG and omega 3(OM3)-FFA have significantly higher bioavailability when compared with the ethyl ester carrier [121]. Because EEs are a poor substrate of pancreatic lipase, the incorporation of fatty acids into mixed micelle is decreased [122, 123]. Conversely, OM3-FFA and OM3-MAG are directly absorbed in the small intestine before entering the circulatory system [119, 124]. They should be considered when therapeutic high doses of OM3 are required. Furthermore, the OM3-MAG carrier provides significantly higher bioavailability for EPA and not DHA compared with the OM3-TAG carrier [121]. Overall, the improved bioavailability observed with both carriers could result in higher TAG lowering effects and provide greater beneficial effects on human health [121].

Future studies should consider the cis-trans-and positional isomers of the OM3 EPA and DHA present in natural OM3 sources and blood metabolites [121].

9. Conclusions

Available studies suggest that omega-3 PUFAs exert pleiotropic effects on cognitive decline, mood, the cardiovascular system, bone and muscle health, vascular endothelium, and immune function (Figure 1). Although EPA, DPA, and DHA have considerable differences in biochemistry and metabolism, EPA is a more important indicator of omega-3 PUFA intake than DPA or DHA, probably owing to the different ways it is incorporated into membrane phospholipids. The intake of EPA up to 3 g/d is safe and effective, and EPA, mostly at dosages of 1 or 2 g/d, has been reported to be superior to placebo and DHA as monotherapy or adjuvant therapy in mild-to-moderate depression [49, 50]. A recent meta-analysis of 149,051 individuals demonstrated that the cardiovascular risk reduction observed for omega-3 PUFAs is more prominent with EPA in monotherapy (doses ranging from 1.8 to 4.0 g/d) than with EPA + DHA [81]. The meta-analysis confirmed the function of omega-3 PUFAs, specifically EPA, in the current treatment for residual cardiovascular risk reduction in patients with atherosclerotic cardiovascular diseases and encourages the investigators to further explore the cardiovascular effects of EPA and PUFAs. Figure 1 summarizes the primary effects of omega-3 PUFAs in older adults.

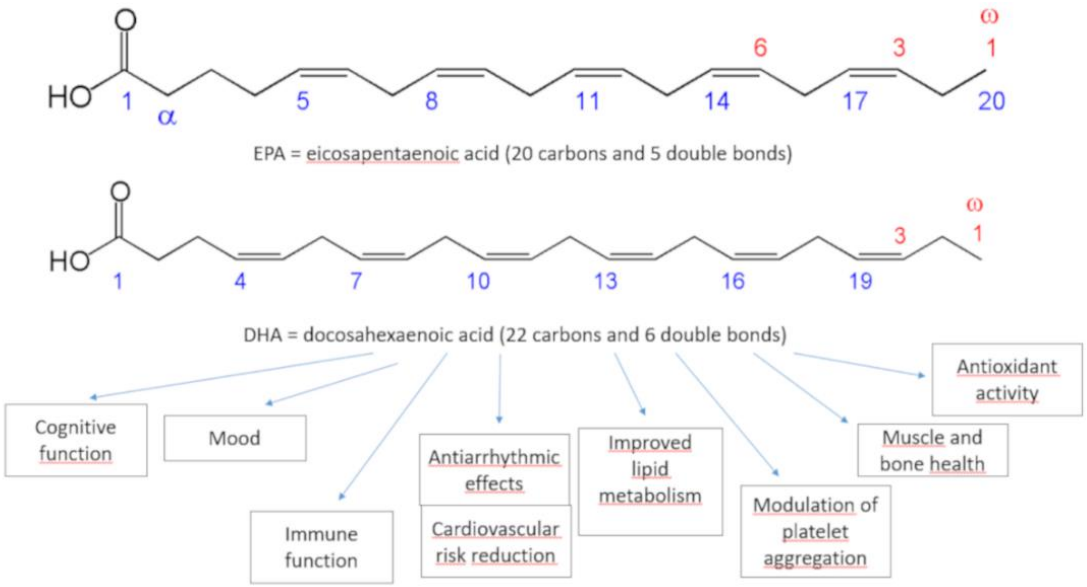

Figure 1 Schemes follow the same formatting.

In conclusion, high intakes of omega-3 LC PUFAs up to 3-5 g/d are safe, although longer-term studies are required to demonstrate the benefits of these clinical outcomes and establish their influence on the quality of life [118]. EPA is a more important indicator of omega-3 PUFAs than DPA or DHA; however, the pleiotropic effects of these agents are objects of future research and can represent an added value to their more extensive use.

Institutional Review Board Statement

The research was in accordance with national requirements and conform to the principles embodied in the 1964 Declaration of Helsinki (http:/www.wma.net) as well as to the International Ethical Guidelines for Biomedical Research Involving Human Subjects and the International Guidelines for Ethical Review for Epidemiological Studies (http:/www.cioms.ch). Ethical review and approval were waived for this study, as well as informed consent, because it involved studies and reported data already published in the literature.

Author Contributions

The author meets the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, takes responsibility for the integrity of the work as a whole, and has given approval for this version to be published.

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Competing Interests

The author disclosed receipt any actual or potential conflict of interest including any financial, activities, additional affiliations, personal or other relationship.

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