Review Article

ROLES OF OMEGA-3 FATTY ACIDS IN EYE HEALTH AND DISEASE: A REVIEW

ABSTRACT

Aims and Study design: A literature review of the roles of omega-3 fatty acids (FA) and particularly EPA and DHA, in eye health, and, as disease-preventive and curative agents for various ocular ailments was undertaken.

Place and duration of study: Done between December 2021 and May 2024 at the Department of Food Science and Nutrition, Karatina University, Kenya.

Results: Omega-3 FA are needed for brain and vision development in infants and children, protecting the eye from degenerative damage and conferring anti-inflammatory benefits. They seem to prevent and slow macular degeneration, dry eye disease, and lower the risk of early age-related macular degeneration, glaucoma and retinopathy, thus lowering the risk of early vision loss. Fatty fish from the wild, krill, seaweed and sea algae are rich sources of the ω-3 FA, EPA and DHA, while walnuts, flaxseeds and flaxseed oil, chia seeds, canola and soybean oils, tofu and meat from grass-fed ruminants, are good sources of the nutrients, but as ALA. Commercially-prepared fried fish from restaurants and fast-food establishments, are relatively lower in the omega-3s, but high in trans-fatty acids due to high temperature thermal processing. Boiling in water, broiling or grilling for short periods are recommended for preparing fish for consumption and omega-3 FA retention. Dietary omega-3 FA are more efficacious than omega-3 FA from supplements, probably due to their synergistic interaction with lutein, beta-carotene, Vitamins A, C and E and Zinc.

Conclusion: It seems prudent to incorporate Vitamin A, C, E and Zinc during omega-3 FA supplement manufacture to boost their efficacy. Although health authorities recommend 1-2 meals of fatty fish edible portion/week and a daily intake of 0.5-1 g/day or more of the ω-3 FA for cardiovascular health, no definitive amounts are recommended for eye health and curing the various ocular diseases at present. It is, however, increasingly being recommended that amounts of more than 1 g/day and up to 2 g/day are safe and more beneficial based on age, gender and health condition. The omega-3 index is a useful tool for maintaining the blood status of the omega-3 FA. Although ω-3 FA play important roles in eye health and the prevention of ocular dystrophies, the cardioprotective role of omega-6 FA, especially LA, against coronary heart disease cannot be discounted, such that drastic dietary or supplemental reduction of ω-6 FA may be ill-advised at present, while balancing their ratio with that of the omega-3 FA seems to be appropriate health-wise.

Keywords: Omega-3 fatty acids, eye health, eye disease

Introduction

Food lipids are important for human health and disease prevention. The major types of food lipids include fatty acids (FA), which are divided principally into saturated fatty acids (SAFA), monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA). Linoleic acid, linolenic acid (LA), arachidonic acid (AA), eicosapentaenoic acid (EPA), decosapentaenoic acid (DPA) and docosahexaenoic acid (DHA) are long chain PUFA, with the latter 3 being referred to as omega-3 (ω-3) FA. While our interest in this literature review are the ω-3 FA, the ω-6 FA are an integral part of a healthy diet, and the ratio of the omega-3 to ω-6 FA, is important for human health and disease prevention [1]. Gamma linoleic acid (GLA), linoleic acid (LA), and conjugated linoleic acid (CLA) are the ω-6 FA of interest in human health. This review of the literature provides an overview of the significance of the ω-3 FA, and particularly EPA and DHA, as potential disease-preventive and curative agents for various eye ailments.

The most written about ω-3 FA are EPA, DPA and DHA, but alpha linolenic acid (ALA) is the one other ω-3 FA that one is most likely to obtain through diet; Fish oils, vegetable oils, nuts (especially walnuts), flax seeds and leafy vegetables are good sources of omega-3 FA, with the type in plant foods being mainly ALA [2; 3; 4]; sunflower, peanut, maize and palm oils are good sources of the ω-6 FA, but also contain some ALA. Algae also contain significant amounts of omega-3 FA as ALA [5]. Seafood, and especially fatty fish and various forms of ω-3 supplements, contain fairly high amounts of EPA and DHA. However, the amount of the ω-3 FA in seafood and in supplements varies [6]. Breast milk contains significant amounts of DHA [7], and is therefore a crucial source of the nutrient for babies. The brain and the eye have high DHA content compared to other human organs [8], with the highest concentration being in the grey matter of the brain and in the outer rod segments of the retina [6]. In the brain, it seems to be involved in neuronal signaling [9], while in the eye it affects the quality of vision [10]. It is accumulated in the brain and eye late in pregnancy and in early infancy [11]. A lower DHA content has been linked to poorer cognitive development and visual function [12]. It seems to affect cell and tissue physiology and function through various mechanisms, including alterations in membrane structure and function [13], in membrane protein function and in cellular signalling [9], and, in lipid mediator production [6].

Decosapentaenoic acid is a requirement of healthy nutrition, as infants obtain almost as much DPA as well as DHA from human milk [6]. For the general population, the primary DPA sources are fish oil supplements, oily fish and meat from grass-fed ruminants [14; 6]. Although the DPA levels in fish oils are substantially lower than those of EPA and DHA, concentrated DPA products are now becoming commercially available and DPA-based drugs are under development [15]. Current nutritional advice recommends the supplementation of diets with these products where the natural intake is curtailed or inadequate for one reason or another. Epidemiological studies have shown that similar to EPA and DHA, DPA is linked to various improvements in human health, with studies in mammals, platelets, and cell cultures showing that DPA reduces platelet aggregation [16], improves lipid metabolism and endothelial cell

migration [17], and resolution of chronic inflammation [18]. The ω-3 FA are essential FA.as the body cannot make them and so must be provided in the diet.
The fish get their ω-3 FA by eating phytoplankton, which absorb microalgae. Microalgae are the original sources of the ω-3 rich FA that are found in wild, fatty fish, oysters and mussels. Due to the importance and benefits of marine ω-3 FA, it is important to eat fish or other seafood 1-2 or more times/week, particularly fatty (dark meat) fish that are richer in EPA and DHA [19]. This is especially important for women who are pregnant as a developing child needs a steady supply of DHA to form the brain and other parts of the nervous system, beginning in the third trimester until the second year of life [20].

Foods High in ω-3 FA

As both ω-3 and 6 FA play important roles in human health, it is important to keep the two balanced. Experts and authorities recommend the ratio of omega-6 to omega-3 FA in a healthy diet should be 4:1 [21; 22; 23, 24], though recent evidence shows a lower ratio is healthier and more protective to disease [25]. This advice seems more beneficial as long as it involves the increase of the dietary intake of the omega-3 FA, especially from fish, rather than lowering the intake of the omega-6 FA [26].
Unfortunately, the typical modern diet for most societies often contains more omega-6 than ω-3 FA. This may generally be true where the consumption of fish and other foods of considerable content of the omega-3 FA is low and the dietary intake of vegetable oils, with high amounts of ω-6 FA is considerable and frequent. The oils that are high in the ω-6 FA and which are commonly used for frying, baking, etc. include sunflower, maize and palm oils, whose common utilization may cause an imbalance towards a large ratio of the two fatty acids. It has been shown that ratios of 20:1 (omega-6: omega-3) are common in American diets [27], with the likelihood that the ratio could be similar or lower in other parts of the world. The resulting imbalance of ω-6 to ω-3 FA has been suggested to contribute to a higher risk of developing various health problems, such as heart disease [22; 25], cancer [28], asthma [29], arthritis (30) and depression [31]. But, specifically in atherosclerotic plaque inflammation and stabilization [32], a trigger of high-risk cardiovascular disease (CVD) events [33], and in brain development and function [34; 20]. Though regarded generally as beneficial in cardiovascular disease (CVD) amelioration, there is controversial evidence with regard to the effects of omega-6 PUFA on CVD risk. Despite the beneficial impact of omega-6 PUFA supplementation on CVD outcomes supported by some studies, others still report conflicting results. One plausible mechanism that may explain the relationship between omega-6 PUFAs and CVD is the increased production of 2-series prostaglandins and 4-series leukotrienes due to the high content of omega-6 PUFA in the diet, exerting pro-inflammatory effects and thus potentiating CVD risk [35; 36]. Highly unsaturated FA such as AA appear to be linked to an increase in low-density lipoprotein cholesterol (LDL-C) and very-low density lipoprotein (VLDL) susceptibility to oxidation, thus enhancing their atherogenic effect [35]. But, some studies found no association between omega-6 PUFA intake and CVD risk. In the Sydney Diet Heart Study, a randomized control trial (RCT) of 458 participants aged 30–59 years with a recent coronary event, the replacement of SAFA with LA significantly increased all-cause mortality [37]. Similarly, a meta-analysis of 32 observational studies and 27 RCTs reported no correlation between omega-6 PUFA supplementation and CHD [38).

To improve the dietary intake of the ω-3 FA, it is necessary to eat more foods that are rich in ω-3s, such as fatty fish, flaxseeds, flaxseed oil, walnuts, chia seeds, soybeans, tofu, soybean and canola oils [39]. It seems that, while there are several rich vegetarian sources of- ω-3 FA, the body may not process the ALA in them as easily as the EPA and DHA found in fish [40] as the conversion process is inefficient. While beef is generally low in the omega-FA, meats from grass-fed animals contain higher content of the omega-3 FA, but mainly as ALA. Commercially-prepared and fried fish such as that from restaurants and fast food establishments, should not be relied upon as the main source of the FA, as they tend to be relatively lower in ω-3 FA and high in trans-fatty acids due to the high temperature of frying, which destroys the FA and alters their profiles [26; 41]. Despite the common use of high-ALA vegetable oils including sunflower, maize and palm oil for frying, and the resulting changes in the FA ratio, the convenience and the affordability of these fried foods is enticing for many low-income earners, and those who may not have the time to cook a decent meal. Nevertheless, they are still better than no fish at all, especially where other good sources of the ω-3 FA are inadequate in diets or the knowledge of the benefits of their regular consumption is lacking. The average diet provides adequate ω-6 FA, such that their supplements may not, generally, be necessary. Though rare, a deficiency of the omega-3 FA is manifest as rough, scaly, and red, itchy rash of the skin.

Lipids of the Human Eye

The major phospholipid of the human lens is dihydrosphingomyelin, but phosphatidylethanolamine (PE) and phosphatidylcholine (PC) are dominant in both the vertebrate retina and in retinal rod outer segment membranes of the human eye [42]. Unusually high levels of cholesterol are a peculiarity in eye lens membranes. The lens membrane contains more cholesterol than any other organ in the human body, as it has a cholesterol-phospholipid ratio of 8:1 in the center of the eye lens [43]. The relative amount of cholesterol is lowest in the outer cortical region of the lens where the molar cholesterol-phospholipid ratio is ~ 1:2 [44]. The cholesterol in the lens is relatively stable and impervious to oxidation compared with unsaturated lipids, possibly adding stability to the membrane. The abundance of cholesterol in the human lens leads to the presence of patches of pure cholesterol in the human eye. Changes in human lens lipid composition occur with age and disease. The composition also reveals the presence of relatively small amounts of other glycerolipids and importantly, they have an ether linkage in the sn-1 chain [45]. About 20% of the phospholipids found in humans possess 1-*O*-alkyl or 1-*O*-alkenyl ether linkages, and inactivation of their synthesis results in numerous pathologies [46; 47]. The 1-*O*-alkenyl ether-linked phospholipids are often referred to as plasmalogens. Plasmalogens serve multiple functions, including their role as potent antioxidants [48]. Lipid oxidation is deleterious to the lens, but the lens membranes have a high sphingolipid content that confers resistance to oxidation, allowing these membranes to stay clear for a relatively longer time than is the case in many other species [49]. Lens lipid composition changes dramatically with cataract. Compared with normal lenses of similar age, the total amount of glycerophospholipids is much less in cataractous lenses, though the total amount of sphingolipids also decreases in cataractous lenses but to a much lesser extent [50], probably due to the preferential oxidation of glycerophospholipids. Lens sphingolipids are 3-4 times more saturated than glycerolipids, and consequently resist oxidation more effectively than unsaturated lipids [51].

Recent studies [45] have clarified previous observations [50] showing that about 35% of the phospholipids in the human lens are predominantly ether-linked (*O*-alkyl but not *O*-alkenyl) phosphatidylethanolamines and phosphatidylserines. Phosphatidylethanolamine (18:1e/18:1) is the most abundant ether-linked phospholipid in the human lens [51]. In the human lens, over two-thirds of the phosphatidylethanolamine and phosphatidylserine [51], if not all [45], are ether-linked. Phosphatidylethanolamine 1-*O*-alkyl ether lipid decreases with age and cataract [51]. The function of ether-linked lipids in the lens is speculative, but they may be important for lens transparency, because in a mouse model, when synthesis of these lipids was inhibited, cataracts developed [52; 53]. It has been suggested that ether-linked lipids are involved in the formation of distinct membrane domains that are required for the regulation of growth, and hence, lens transparency [47]. It appears that phospholipids with either ester- or vinyl-linked chains are preferentially degraded, leaving the more stable ether-linked species in the membrane. Phospholipid oxidation and subsequent degradation could account for the dramatic changes observed in human lens lipid composition with age and cataract. Major changes in lens lipid composition could also cause cataract, influencing membrane permeability properties, the function of membrane proteins and the major lens membrane proteins, the aquaporin. Data suggest that humans have adapted so that their lens membranes have a high sphingolipid content to confer resistance to oxidation, allowing these membranes to stay clear for a relatively longer time than is the case in many other species [49]. An increase in sphingolipid content occurs with increasing age [54] and cataract [50]. In terms of fatty acids, DHA, is the most prevalent fatty acid in photoreceptor outer segment membranes of the eye and it may be important for renewal of the outer segment of photoreceptors and for the synthesis of new membranes [55].

Common Ailments of the Human Eye

Common diseases of the human eye include: a) **Dry Eye Syndrome**: This is a condition that affects tear film, the three layers of tears that cover and protect the surface of the eyes [56]. A smooth and stable tear film is required for clear and comfortable vision, as disruptions to the tear film can cause uncomfortable burning, itching, watering or blurred vision. Many factors can prevent the tear film from working properly as it should, thus leading to dry eye disease (DED). These include: inflammation, malfunctioning of the meibomian layer of the eye, and tear instability, due to several causes as discussed further. There are several types of DED including: (i) **Aqueous deficient dry eye**: This is a condition where eyes do not produce enough tears, which originate from a healthy lacrimal gland (found in the upper, outer corner of each eye). The tears make up the middle, watery layer of the tear film. Inflammation in the lacrimal gland can prevent it from producing enough aqueous tears [57]. (ii) **Evaporative dry eye**: This condition occurs when tears evaporate too fast from the eye. The most common cause of the condition is meibomian gland malfunction [58], a condition in which the glands in the eyelids that produce the outer, oily layer of the tear film malfunction, leading to instability in the oily layer, which can no longer protect the watery layer, resulting in fast drying up of tears. (iii) **Mixed dry eye**: this results from aqueous tear deficiency and tear instability [59] in some individuals. The result is the inability to produce enough tears, combined with an unstable tear film. Both problems produce dry eye symptoms, which include burning or stinging sensation in the eye, light sensitivity, blurred or changed vision, mucus coming out of the eye, and watery eyes, with excess tears running down the cheeks. Many of these symptoms are apparent in the elderly.

b) **Age-related Macular Degeneration** (ARMD): This is the most common cause of severe loss of eyesight among people who are 50 years and older. As only the center of vision is affected by the disease, people rarely go blind from it. ARMD affects central vision, and with it, the ability to see fine details. In advanced stages, people lose their ability to drive, to see faces, and to read smaller print. In its early stages, ARMD is often without signs or symptoms, such that people may not suspect they are suffering from it. The two primary types of ARMD have different causes. (i) **Dry ARMD**: This type is the most common, with about 80% of those with ARMD having the condition. Its exact cause is unknown, though both genetic and environmental factors are thought to play a role [60]. It happens when the light-sensitive cells in the macula slowly break down, generally one eye at a time. The loss of vision through this condition is normally slow and gradual. It is believed that the age-related damage of an important support membrane under the retina contributes to dry ARMD [60].

(i) **Wet ARMD**: Despite this type being less common, it usually leads to more severe vision loss in patients, than dry ARMD [61]. It is the most common cause of severe loss of vision. Wet ARMD happens when abnormal blood vessels start to grow beneath the retina, and they leak fluid and blood, hence the name wet ARMD [61]. The condition can also create a large blind spot in the centre of the visual field [61].

There are several risk factors that can contribute to developing ARMD, including, being 50 years and older, eating a diet that is high in saturated fat, smoking, and high blood pressure or hypertension [60]. The most common symptoms of ARMD include: blurry or fuzzy vision, difficulty in recognizing familiar faces, the appearance of straight lines as wavy, a dark, empty area or blind spot in the center of vision, loss of central vision, which is necessary for driving and reading, and, difficulty in performing close-up work [60; 61]. These symptoms may differ with individuals as not all who suffer from ARMD show similar symptoms. The presence of drusen, which are tiny yellow deposits in the retina, is one of the most common early signs of ARMD [62], with its presence pointing to the eminent risk of developing more severe ARMD.

c) **Glaucoma**: Is a group of eye conditions that damage the optic nerve. The optic nerve sends visual information from the eye to the brain and is therefore vital for good vision. Damage to the optic nerve is often related to high pressure in the eye, although glaucoma can develop even with normal eye pressure [63]. Glaucoma can occur at any age, but is more common in older adults, and is one of the leading causes of blindness in people over the age of 60 [63]. Many forms of glaucoma have no warning signs as the effects are so gradual that one may not realize change in vision until the condition is in its late stages. Regular eye exams that include measurements of eye pressure, can catch glaucoma early. The symptoms of glaucoma depend on the type and stage of the disease. The familiar types and their symptoms are given below.

(i) **Open-angle glaucoma:** This type of the disease does not exhibit any specific **s**ymptoms in its early stage; though patchy, blind spots develop gradually in one's side vision (peripheral vision) [64]. In the late stages, central vision may be lost.

(ii) **Acute angle-closure glaucoma**: this exhibits as severe headache, severe eye pain, nausea or vomiting, blurred vision, halos or coloured rings around lights, and eye redness [65].

(ii) **Normal-tension glaucoma**: the condition does not have any symptoms in the early stages, but blurred vision gradually develops, which eventually leads to loss of side vision [65].

(iii) **Glaucoma in children**: This is seen as dull or cloudy eye, increased blinking, and producing tears without an infant crying. Other symptoms include blurred vision, headaches and nearsightedness that gets worse with time [66].

(d) **Retinopathy** (**disease of the retina**): There are several types of retinopathy, but all types of the condition are diseases of the small retinal blood vessels [67], which as a result, may damage the retina, impairing vision. ARMD is technically included under the umbrella term retinopathy, although it is often discussed as a separate disease [68]. Diabetic retinopathy, a prevalent ocular disorder that results in blindness, has been linked to dysregulation of phosphoinositide 3-kinase (PI3K) [69], especially in older patients commonly due to neurodegeneration. Retinopathy can be broadly categorized into proliferative and non-proliferative types. More often, retinopathy is an ocular manifestation of systemic disease as observed in diabetes or hypertension [70]. Diabetes is the most common cause of retinopathy globally, making the ailment the leading cause of blindness in aging people [71], as it accounts for approximately 5% of blindness worldwide and is therefore designated a priority eye disease by the WHO [72].

Omega-3 FA in eye health

Studies in pre-term and full-term infants suggest that getting enough ω-3 FA in the diet of the mother is essential for optimal visual development (eye and optic nerve development). Studies have shown that animals that do not get enough DHA in their diets, suffer visual impairment and degradation of the retina [73; 74; 75], though one 2-year controlled study recently showed this may be beneficial only in the early stages of loss of retinal integrity and disease onset [76]. Human studies have also shown that low levels of DHA and EPA are found in diabetic retinopathy, ARMD, DED and retinopathy of prematurity [75; 77], thus pointing to the important role that adequate levels of the two omega-3 FA play in retinal health and potential prevention of ocular dsystrophies.

Chronic inflammation may play a role in the development of many common, degenerative and potentially devastating eye conditions like macular degeneration and diabetic retinopathy, but the ω-3 FA seem to play a key role in the body's ability to regulate and balance inflammation [78]. EPA and DHA seem to play an important role in regulating the signaling molecules and hormone receptors that are implicated in inflammation, abnormal retinal neovascularization, vascular permeability, leading to edema [79; 80], all being indicators of-retinal disease. People who had a regular intake of ω-3 FA in their diets were shown to halve their risk of developing the wet form of ARMD [81]. Over the 12 years that participants were followed in the landmark AREDS (Age-Related Eye Disease Study), conducted by the US National Eye Institute, those that reported the highest intake of omega-3 FA in their diets, were 30% less likely to develop central geographic atrophy or wet ARMD [82]. However, when the follow-up AREDS2 study investigated if ω-3 supplementation would have an additional benefit in reducing progression of macular degeneration, the researchers did not find a significant benefit over 5 years. This led to the speculation that many of the participants may have met their dietary intake of ω-3 FA, thus annulling any benefit from the additional supplementation. This further points to the positive benefits of the ω-3 FA in eye health. A good supply of omega-3 FA was also observed to help maintain a tear film on the surface of the eye [83]. Tears help clean and lubricate the eye, while the tear film interface, focuses light on the retina and plays a role in maintaining visual acuity. A recent study in Australia showed that taking a daily ω-3 supplement, significantly reduced eye pressure.in individuals with abnormal eye pressure [84]. Omega-3 FA may thus prevent or slow down the development of glaucoma. A 2019 meta-analysis of 17 randomized clinical trials (3363 people with

DED) reported that supplementation with ω-3 FA significantly reduced dry eye signs and symptoms, suggesting that ω-3 FA supplementation may have a beneficial role in the treatment for DED [85].

Developmental, Wellness and Curative Role of ω-3 FA

It seems that ω-3 intake by an expectant mother is essential for brain and eye (neurological and visual) development of the foetus [20]. As ω-3 FA are significant components of breast milk, they may be necessary for infant nutrition and healthy development [86], as research has established that the addition of EPA and DHA to the diet of pregnant women, has a positive effect on visual and cognitive development of the baby [87]. However, another study [88], showed that maternal DHA supplementation did not improve neurodevelopmental outcomes at 18 to 22 months' gestational age in breastfed, preterm neonates, though subgroup analyses in the same study suggested a potential benefit for language acquisition in preterm neonates born before 27 weeks' gestational age. Also, Strømmen et al. [89] found that enhanced nutrient supply to very low birth weight infants (<1500 g birth weight), resulted in improved white matter maturation and head growth, thus implying some benefits to the neonate of ω-3 FA.

The rods and cones, are responsible for low night vision, while the cones are more active at higher light, but also have a role in colour vision. In a prospective controlled study, it was evident that cell membranes of the rods and cones require ω-3 FA, specifically DHA, to develop and function well in preterm infants [90]. DHA accounts for more than 50% FA content of rod outer segments, implying that DHA may help to renew the outer segment of photoreceptors and synthesize new membranes [55]. A study also showed that the efficiency of visual signaling was dependent on the presence of DHA in the rod outer segment membranes [9]. Chronic inflammation has been shown to play a role in the development of many common, degenerative and potentially damaging eye conditions like ARMD and diabetic retinopathy, through the ω-3 FA role in regulating inflammation [91; 92]. EPA and DHA have been observed to play an important role in regulating the signaling molecules and hormone receptors that are implicated in inflammation, and particularly abnormal retinal neovascularization and vascular leakage [93], which are indications of retinal disease. Studies show that consuming adequate amounts of EPA and DHA can improve dry eye disease by decreasing the rate of tear evaporation and increasing tear secretion [94]. In the age-related eye disease study (AREDS), it was evident that regularly consuming ω-3 FA can lower risk of ARMD [82]. Supplementing with DHA therefore seems to preserve healthy retinal function, lowers occurrence of inflammation and supports visual acuity recovery [55;-9]. Omega-3 FA supplementation has also been observed to decrease healing time due to abrasions of the corneal epithelium [95], arising from eye injuries when the outer surface of the eye gets scraped by objects. The optimal ratio of dietary ω-6 to ω-3 is considered to be approximately 4 to 1 [80; 22], though the lower ratio of 2:1 seems appropriate for better physiological outcomes [96]. Excessive consumption of foods that are rich in ω-6 FA, can shift the ω-6: ω-3 to a higher ratio than 4:1. However, it has been reported that adults in many parts of the World may not be getting the daily, recommended dietary intake of long-chain ω-3 FA for optimal health [82; 97], meaning that a significant percentage of their populations misses the health benefits of adequate ω-3 FA consumption. Diets that are rich in long-chain ω-3 FA have been suggested to provide long-term benefits for several chronic ocular conditions, including DED and ARMD [98]. These FA are observed to also help ensure the eyes drain fluids properly, which can help to prevent the onset of glaucoma, high pressure build-up in the eyes and retinopathy [84].

In a systematic review of meta-analysis and randomized controlled studies, ω-3 FA seemed useful for the treatment of DED [99], though the DREAM study funded by the US National Eye Institute did not show any significant benefit of omega-3 FA supplementation to keep DED incidence low over a 2-year observation period [100] as the results were similar to those of the placebo. This result was also arrived at in another randomized clinical trial with over 23,000 US adults over a 5.3-year period with marine omega-3 FA [101]. Therefore, clinical trials assessing the effects of ω-3 FA supplementation on DED, presented contradictory results. While a possible role seems to exist for long-chain ω-3 FA supplements in managing DED, the available evidence is inconsistent and inconclusive. The role of ω-3 FA in the management of DED and other ocular ailments, is thus a study area of continuing debate that requires further inquiry.
DHA is implicated in maintaining the structural and functional properties of the retina, in addition to its observed anti-inflammatory effects [80]. Although epidemiological studies have associated dietary long-chain ω-3 FA intake with a lower risk of developing early-stage ARMD and its progression to the late-stages of the disease [102], ω-3 FA nutritional supplements were shown in one study not to confer the same benefit of reducing the risk of developing ARMD as whole foods [103]. The difference in efficacy may be due to the potential synergistic interaction of the ω-3 FA with other nutrients that are present in whole foods, but not in supplements [104]; these nutrients include zinc, Vitamins A, C, E and D [104]. These differences should therefore be considered when recommendations relating to the efficacy of ω-3 FA as supplements in the treatment and management of ARMD and other ocular diseases are made.

Potential ω-3 FA Intake for Eye Health

During manufacture as supplements, EPA and DHA are often combined and presented as EPA+DHA. The recommended optimal ratio of dietary omega-6 to omega-3 for cardiovascular health is considered to be approximately 4:1 or lower [105]. Excessive consumption of foods that are rich in omega-6 FA, can shift the omega-6 to omega-3 ratio higher than 4:1 [106], an occurrence that would be undesirable from a health viewpoint. As wild fish are the best source of EPA and DHA, various authorities recommend slightly different amounts that should be eaten when available (1-2 times/week commonly), though 2-4 servings per week for pregnant women would be more beneficial for the foetus [107], in view of the critical role of DHA in foetal brain and visual development [20]. The WHO recommends the intake of 0.3–0.5 g/day, while the US Food and Drug Administration (FDA) and the AHA recommend a regular intake of 0.9–1.0 g/day of fish edible portion for cardiovascular health. Anchovies, salmon, sardines contain > 1200 mg/100 g of EPA+DHA in cooked edible portion, while trout and swordfish contain about 400-500 mg/100 g of edible portion; the common aquaculture fishes of the tropics such as tilapia and catfish, ocean going fishes such as the groupers, mahi mahi, cod, halibut and haddock, contain less than 250 mg/100 g of cooked edible portion [2; 3; 4]. The low omega-3 FA content in aquaculture-produced fish is due to the inclusion of a high proportion of grain in fish feeds. Consuming less than the 100 g of edible portion of these tropical and ocean-going fish may require that one seeks supplementation, though mixed diets may just supply the required amounts. The National Academy of Medicine [108] recommends that men consume 1.6 grams of ALA daily and 1.1 grams per day for women, with individuals who are pregnant or breastfeeding needing about 1.4 g/day. The AHA recommends eating two servings of fish, particularly fatty fish, per week to help reduce the risk of heart disease and stroke, with two servings equalling about 170 g of cooked edible fish portion. Ideally, people should get the ω-3 FA from food, though dietary supplements, such as fish oil, are an alternative, especially for those who don't eat fish. AHA advised that ω-3 FA fish oil supplements may slightly lower the risk of dying after a recent heart attack, but they do not prevent heart disease [109]. Further, the AHA advised in 2019 [110] that consuming 4 grammes per day of prescription fish oil supplements as a safe and an effective method to lower triglycerides, in people with elevated lipid levels. The same advisory warned consumers not to take unregulated supplements. A-2022 analysis published in the Journal of the AHA (JAHA) found consuming 2-3 grammes each day of EPA and DHA, in food or supplement form, may be the ideal dose to help lower blood pressure [111].

The specific amounts of the ω-3 FA for eye health and curing ocular disease have yet to be agreed upon. It is apparent that in most countries of the world, the omega-3 index is low, except for coastal and fishing communities or those who have not adopted western type diets or those who due to their good economic situation or knowledge, maintain their consumption of the omega-3 FA at appropriate levels. They thus may not miss out on most benefits of adequate intake of the omega-3 FA. In a global survey of omega-3 index (O3I) in blood sample data, regions with high blood levels of EPA + DHA were found in distinct regions with countries on the Sea of Japan (Japan, South Korea, and Primorsrky Krai region of Russia), Scandinavia (Denmark, Norway, and Greenland) and regions with indigenous populations or populations that are not fully adapted to “Western pattern” diets (Northern Russia, Alaska, Greenland, Papua New Guinea, Fiji, Nigeria, and the St. Helena Bay region of South Africa) [97]. Moderate blood levels of EPA + DHA were observed in Northern Canada (Cree/Inuit populations), Chile, Iceland, Finland, Sweden, Tunisia, Hong Kong, Mongolia and French Polynesia. Europe had eight countries with low EPA + DHA blood levels (Belgium, Czech Republic, France, Germany, Scotland, Spain, and The Netherlands) while Israel, some countries in Asia (China, Russia, and Singapore), Oceania (Australia and New Zealand) and South Africa and Tanzania, were observed to have low levels as well. Very low blood levels with O3I of <4%) were observed in North America (Canada and USA), Central and South America (Guatemala and Brazil), Europe (Ireland, UK, Italy, Greece, Serbia, and Turkey), the Middle East (Iran and Bahrain), Southeast Asia (India) and Africa (Kenya) [97]. Diets that are rich in the ω-3 FA have been suggested to provide long-term benefits for several chronic ocular conditions, including DED and ARMD [98]. To improve the dietary intake of the omega-3 FA it is advisable that one eats more omega-3 FA rich foods and less of those that are high in the omega-6s, while there are several rich vegetarian sources of omega-3 FA, the body may not process their ALA fatty acid, as easily as the EPA and DHA found in fish [112]. The conversion of ALA into EPA and DHA is inefficient, such that the better option is to consume fish and fish oil. For those who do not consume fish for some reason, the purchase of supplements as a source of the ω-3 FA is advised. However, consumers should be aware that the efficacy of the omega-3s from whole foods is higher than that from supplements, due to the presence of such nutrients as lutein, beta carotene, Vitamin A, C, E and zinc, mainly from fruits and vegetables [113; 114]. Most of these nutrients are known antioxidants, which play a role in regulating inflammation. It therefore seems that dietary emphasis should be on increasing the intake of the omega-3 FA from fish, other seafood and limiting the intake of the omega-6 FA from processed seed and nut oils and not drastically cutting down the intake of the omega-6 FA from whole foods. Other factors that influence the efficacy of the omega-3s include the manner of processing of the food, especially the extent of thermal processing. It also seems that determining the

O3I is a good way to track the intake of the ω-3 FA for optimal health outcomes, with an index ≥8% being recommended [115]. The O3I is a measure of the level of omega-3 fatty acids, specifically, EPA and DHA in the red blood cells. It is expressed as a percentage and serves as a valuable indicator of one's overall cardiovascular health. Not all fish oils give the same beneficial health outcomes. In a feeding experiment with mice on a high-fat diet using eel, cod, sardine and trout oil for 60 days, it was found that eel was the best source of the ω-3 FA, with a balance of omega-6 FA to the ω-3 FA, that ameliorated high fat diet-induced mixed hyperlipidemia [116]. Subgroup analysis showed that the cardiovascular benefit of ω-3 FA was primarily attributable to the prescription of EPA ethyl ester. In addition, prescription omega-3 acid ethyl ester had a good safety profile, despite the prescription EPA ethyl ester likely to induce bleeding [117]. The meta-analysis supported the use of prescription EPA ethyl ester formulations to prevent cardiovascular disease, but the potential risk of atrial fibrillation and bleeding was a concern [117]. The same study recommended that the ω-3 FA should be applied with caution in patients with previous myocardial infarction, while the increased risk of stroke may be expected. So, while omega-3 fatty acid supplements are relatively safe and in general do not increase gastrointestinal problems, attention should be paid to the risk of bleeding with prescription EPA ethyl ester formulations [117]. While the WHO recommends 0.3–0.5 g/day, the US FDA and the AHA recommending an intake of 0.9–1.0 g/day of omega-3 FA for cardiovascular health [118: 80], the amount for eye health and that needed to slow the progression of the common ocular ailments has not been determined. It is apparent that the efficacy of the ω-3 FA depends on the source. In critical reviews from Jan 2010 to Sep 2020, it was established that high dose flaxseed or echium seed oil supplements, provided no increases to the O3I and some studies showed reductions [119]. However, microalgal oil supplementation increased O3I levels in all the studies. The results indicate that for vegetarians and vegans to benefit from DHA supplements, it is useful to maintain their regular consumption [119]. Based on data evaluated from another study, practical recommendations to improve O3I to ≥8% are the consumption of 1,000-1,500 mg for at least 12 weeks [115].

Adverse Effects of Excessive Intake of ω-3 FA

High doses of the ω-3 FA >2000 mg but less than 4000 mg/day, are generally regarded to be safe and are well tolerated, though there are reported adverse effects of their consumption as supplements [120; 121; 122]. A systematic review of RCTs published between 1987 and 2023 concluded that the adverse effects of ω-3 PUFA containing EPA or DHA, or both compared with controls (a placebo or a standard treatment), combinations of the 2 FA had significantly higher odds of occurrence of diarrhoea, dysgeusia, and bleeding tendency, but lower rates of back pain [123]. The most common and significant side effects are gastrointestinal (e.g., nausea and bloating), dermatological (e.g., skin itching), and haematological (e.g., anticoagulatory effects) [121]. Nonetheless, systematic reviews that examined the safety profile of ω-3 FA, when doses of up to 4000 mg/day were consumed, concluded that supplementation is well tolerated and that associated adverse events were of no clinical significance [107; 123]. Other reported side effects of high dose consumption of the ω-3 FA in clinical trials, included increased bleeding risk [124], increased LDL-C production (though it increases LDL density) [125], and the inability to control blood sugar levels [126], implying that there would be no benefit of ω-3 FA supplementation for diabetic patients. Other risks associated with excessive consumption of supplemental *n*-3 PUFA include altered platelet function. The presence of EPA and DHA leads to the production of thromboxane

A_3, which is a less potent platelet activator than thromboxane A_2 [107], which leads to an antithrombotic effect that is detrimental to wound healing [121]. The adverse effects on wound healing may be at their greatest, immediately after trauma or surgery, being also dependent on the amount and the duration of supplementation, and, the severity of the wound. Another side effect is the potential for lipid peroxidation. Long-chain, highly unsaturated fatty acids such as EPA and DHA, are at high risk of peroxidation. Membrane phospholipid fatty acids can be vulnerable to peroxidation, resulting in free radical-formation, which can be detrimental to proteins and DNA integrity [120]. The authors found out that, although a ratio of dietary (n-6) to (n-3) fatty acids of 1.4:1 depresses the cell-mediated immune response and PGE (prostaglandin E_2) production, compared to the ratio of 31:1 of n-6:n-3 FA. It seemed to increase lipid peroxidation and lower vitamin E concentration. However, in a study (though short), on growing horses fed 60 mg/Kg of body weight daily for 60 days, n-3 FA supplements did not negatively affect vitamin E status or promote lipid peroxidation. Elevated vitamin E status in the horses fed FISH, coupled with lower serum F2-isoprostanes, further suggests that the longer-chain, highly unsaturated n-3 FA, EPA and DHA, may actually reduce lipid peroxidation [127]. *N*-3 PUFA supplementation has been contra-indicated during antiplatelet and anticoagulant treatment due to the synergistic effect on bleeding times, when administered together with aspirin (simvastatin) [128]. Nevertheless, potential risks should be assessed versus the potential benefits, with the adverse effects likely to be dose-dependent. Also, most side effects are apparent only with the consumption of supplements as the amounts of the ω-3 FA in diets are normally low, with amounts varying depending on the nature of food and the manner of processing. To avoid undesirable side effects, consumers should eat as much of the plant sources of omega-3 FA, as any adverse side effects from their consumption are minimal. Also, for individuals who do not consume fish, EPA and DHA are manufactured commercially from microalgae, which is an excellent source of the ω-3 FA. Algal oil is another vegan source of these FA. Algae are the original source of the ω-3 FA that are consumed by fish and other phytophagous marine organisms. Algae or algal oil are also acceptable sources of the ω-3 FA as they do not have the smell of fish which can put off some consumers. To reduce the generation of trans fatty acids through high temperature thermal processing, one should broil or bake and grill fish instead of frying. Doing so optimizes ω-3 FA retention, thereby benefiting dietary intake.

Sustaining Omega-3 FA Supply

The increasing knowledge on the role of ω-3 FA in the aetiology of many diseases of mankind, is driving the quest for industry to supply increasing amounts of ω-3 FA for human needs. Marine fish and fish oils are regarded as the best sources of ω-3 FA [3; 6]. Algae, algal oil and seaweed are good source of these FA [108] for vegans. However, other marine organisms are also likely to provide the ω-3 FA for human health requirements. But the question of sustainable supplies is one that industry has to answer as demand for the ω-3 FA increases due to their acclaimed health benefits. The dwindling natural fish stocks and the low-ω-3 FA in aquaculture-produced fish (due to the incorporation of considerable amounts cereals in fish feeds), despite the rising global production of aquaculture-produced fish, makes the provision of adequate quantities of the ω-3 FA for human consumption seem a daunting task. The Antarctic Krill may be one answer to the potential increasing demand for ω-3 FA. It is reported that less than 1% of the krill biomass has been exploited [129] versus 20% of marine fish stocks [130]. The abundant biomass of this organism in Antarctica, may just be the answer for the time being to the sustainable supply of the ω-3 FA for human needs, alongside farming of algae and other organisms on an increasing scale. However, Krill are sensitive to ocean acidification and the effects of climate change can drastically upset its survival. In Krill, 30–65% of EPA and DHA are in phospholipid fatty acids, while in fish or fish oil, EPA and DHA are mainly in triglycerides (sn-2 position) [131; 132]. This implies better bioavailability of the ω-3 FA from Krill meal and oil, compared to those from fish oil, as was demonstrated in a randomized, single dose, single-blind, cross over trial with 15 healthy volunteers [133], though further long-term and bigger clinical trials are needed. Also, a recent study. Mozzafarian et al. [134], found that an ω-3 phospholipid ester/free fatty acid, a novel krill oil–derived ω-3 formulation, reduced triglyceride levels and was safe and well tolerated in 520 patients with severe hypertriglyceridemia, thus pointing to sensory acceptability and therefore potential benefits from the consumption of krill oil-derived products, as they also do not have the fishy smell of fish, fish oils or fish oil supplements.

Conclusion

The ω-3 and 6 FA are an integral part of a healthy diet, and their recommended ratio in diets currently stands at 1:4, though lower ratios are increasingly being considered for optimal health. Fatty fish from the wild, fish oils and fish oil supplements are the best sources of the ω-3s, particularly EPA and DHA, with flax seed and its oil, walnuts, chia seeds, soybean and its oil, tofu, other soya products, canola oil, and, meat from grass-fed ruminants being good sources of ALA. All the fish do not have similar amounts of ω-3 FA and all fish oils are not equally efficacious. AHA advises that ω-3 FA fish oil supplements may slightly lower the risk of dying after a recent heart attack, but they do not prevent heart disease. The considerable consumption of plant foods that are good sources of ω-6 FA and less fish, may shift the ratio higher than 1:4, which may be undesirable health-wise. In view of the influence of one on the other for optimal health outcomes, the maintenance of a good balance of the omega-3 to omega-6 FA seems critical for optimal health outcomes and well-being. The amounts of the ω-3 FA in diets are normally low, with amounts varying with the nature of food and the manner of processing. To avoid any undesirable side effects from supplements, consumers should eat as much of the plant sources of ω-3 FA, as any adverse effects from their consumption are minimal. EPA and DHA are required for brain and vision development in infants and children and have also been shown to prevent DED and slow down the progression of ARMD, glaucoma and retinopathy.

Recommendations

Ideally, people should get the ω-3 FA from food, though dietary supplements, such as fish oil, are an alternative, but not for those who do not eat fish and who should therefore seek non-fish oil supplements. It is recommended that men consume 1.6 grammes of ALA daily and 1.1 grammes per day for women, but with women who are pregnant or breastfeeding needing about 1.4 g/day. The AHA recommends eating two servings of fish, particularly fatty fish, per week to help reduce the risk of heart disease and stroke, with two servings equalling about 170 g of cooked edible fish portion It is recommended that men consume 1.6 grammes of ALA daily and 1.1 grammes per day for women, with women who are pregnant or breastfeeding needing about 1.4

g/day. The AHA recommends eating two servings of fish, particularly fatty fish, per week to help reduce the risk of heart disease and stroke, with two servings equalling about 170 g of cooked edible fish portion. Nevertheless, the recommended WHO and AHA daily intake of the ω-3 FA for optimal health and specially for cardiac health, currently stands at 0.5-1 g/day as EPA+DHA, but that for optimal ocular health and the treatment of the common eye diseases is currently undetermined, though it cannot be higher than that recommended for optimal well-being, A daily intake higher than 1 g/day and up to 2 g/day of EPA+DHA as supplements, is recommended as safe, based on age, gender and health condition, though caution currently restricts the upper limit to approximately 4 g/day. The omega-3 index of ≥8% in red blood cells seems to be a good measure of the ω-3 FA status as necessary to maintain good cardiac health and general well-being. Despite marine, fatty fish from the wild and fish oil supplements being the best source of the ω-3 FA, frying fish destroys the fatty acids and alters their profile and may even reduce their bioavailability. As fried fish may therefore be lower in the ω-3 FA and high in trans fatty acids, boiling in water, baking or grilling are recommended methods for preparing fish for human consumption. Good manufacturing practice during the manufacture of ω-3 FA supplements could incorporate Vitamins A, E, C, and Zinc as synergistic nutrients, as they have been found to boost the efficacy of the ω-3s. The proportion and mechanism of action of the synergist nutrients with the ω-3 FA in supplements, could be an area of future research. Future ocular clinical research with ω-3 FA should also include ω-6 FA as part of the regimen.

REFERENCES

1. Nigam D, Yadav R & Tiwari U. Omega-3 Fatty Acids and Its Role in Human Health. First Online: 13 October 2018. Chapter 9 in: Rani V and Yadav U.C.S. (editors) in Functional foods and human health, pp 173-198, Springer Nature, Singapore PTE Ltd., 2018.
2. Das UN. Essential fatty acids: biochemistry, physiology and pathology. *Biotech. J.* 2006;1(4):420–439.
3. Hughes CL & Dhiman TR. Dietary compounds in relation to dietary diversity and human health. *J. Medic. Food* 2002;5(2):51–68.
4. Benatti P, Peluso G, Nicolai R & Calvani M. Polyunsaturated fatty acids: biochemical, nutritional and epigenetic properties. *J. Amer. Coll. Nutr.* 2004;23(4):281–302.
5. Borowitzka MA. High-value products from microalgae—their development and commercialisation. *J Appl Phycol* **25**, 743–756 (2013). https://doi.org/10.1007/s10811-013-9983-9
6. Wang H & Daggy BP. The role of fish oil in inflammatory eye diseases. BioMed. Hub J. 2017;2(1):1-12. Available at: https:/doi:10.1159/000455818 46.
7. Bzikowska-Jura A, Czerwonogrodzka-Senczyna A, Jasińska-Melon E, Mojska H, Olędzka G, Wesołowska A & Szostak-Węgierek D. The Concentration of Omega-3 Fatty Acids in Human Milk Is Related to Their Habitual but Not Current Intake. Nutrients. 2019 Jul 12;11(7):1585. doi: 10.3390/nu11071585.

8. Walchuk C & Suh M. Nutrition and the aging retina: A comprehensive review of the relationship between nutrients and their role in age-related macular degeneration and retina disease prevention. Adv. Food Nutr. Res. 2020; 93:293-332. DOI: 10.1016/bs.afnr.2020.04.003 47.
9. Hou TY, McMurray DN & Chapkin RS. Omega-3 fatty acids, lipid rafts, and T cell signaling. Eur J Pharmacol. 2016;785: 2-9. doi: 10.1016/j.ejphar.2015.03.091.
10. Eilander A, Hundscheid DC, Osendarp SJ, Transler C & Zock PL. Effects of n-3 long chain polyunsaturated fatty acid supplementation on visual and cognitive development throughout childhood: A review of human studies. Prost. Leukotr. Essent. Fatty Acids. 2007;76: 189-203.
11. Wani AL, Bhat SA & Ara A. Omega-3 fatty acids and the treatment of depression: a review of scientific evidence. Integr. Med. Res. 2015; 4(3): 132-141. doi: 10.1016/j.imr.2015.07.003.
12. Byelashov OA, Sinclair AJ & Kaur G. Dietary sources, current intakes and nutritional role of omega-3 decosapentaenoic acid. Lipid Technol. 2015; 27(4): 79-82. DOI: 10.1002/lite.201500013 49.
13. Stillwell, S.R. Wassall. Docosahexaenoic acid: membrane properties of a unique fatty acid. Chem. Phys. Lipids; 126 (2003): 1-27.
14. Daley CA, Abbott A, Doyle PS, Nader GA, Larson S. A review of fatty acid profiles and antioxidant content in grass-fed and grain-fed beef. Nutr. J. 2010 Mar 10;9:10. doi: 10.1186/1475-2891-9-10.
15. Frigerio F, Pasqualini G, Craparotta I, Marchini S, van Vliet EA, Foerch P, et al. n-3 decosapentaenoic acid-derived protectin D1 promotes resolution of neuroinflammation and arrests epileptogenesis. Brain. 2018;141(11): 3130-3143. Available at: https://doi.org/10.1093/brain/awy 247 50.
16. Kaur G, Garg M & Sinclair AJ. Decosapentaenoic acid (22:5n-3): A review of its biological effects. Prog. Lipid Res. 2011;50(1):28-34. Accessed 10th June, 2021 Available at: https://doi.org/10.1016/j.plipres.2 010.07.004.
17. Bäck M & Hansson GK. Omega-3 fatty acids, cardiovascular risk and the resolution of inflammation. FASEB Journal. 2019;33(2):1536-1539. DOI: 10.1096/fj.201802445R.
18. DiNicolantonio JJ & O'Keefe JH. Effects of dietary fats on blood lipids: A review of direct comparison trials. Open Heart. 2018;5: e000871. DOI: 10.1136/openhrt-2018-000871 5.
19. Calder PC. n-3 polyunsaturated fatty acids, inflammation, and inflammatory diseases. Amer. J. Clin. Nutr. 2006;83(6):1505S-1519S. DOI: 10.1093/ajcn/83.6.1505S70.

20. Rahul Mallick, Sanjay Basak, Asim K. Duttaroy**.** Docosahexaenoic acid, 22:6n-3: Its roles in the structure and function of the brain. Int. J. Developmental NeuroScience.

First published: 17 October 2019. **https://doi.org/10.1016/j.ijdevneu.2019.10.004**

21. Kris-Etherton PM & Innis S, Position of the American Dietetic Association and Dietitians of Canada: Dietary fatty acids, J Am Diet Assoc, 2007; 107:1599-1611.

22. Simopoulos AP. The importance of the omega-6/omega-3 fatty acid ratio in cardiovascular disease and other chronic diseases. Exp Biol Med (Maywood). 2008 Jun;233(6):674-88. doi: 10.3181/0711-MR-311.
23. American Heart Association Nutrition Committee, Diet and lifestyle recommendations revision 2006: a scientific statement from the American Heart Association Nutrition Committee, Circulation, 2006; 114:82-96.
24. US Department of Health and Human Services, US Department of Agriculture, Dietary Guidelines for Americans, 2005, US Department of Health and Human Services website. http://www.health.gov/dietaryguidelines/dga2005/document/default.htm,
25. DiNicolantonio JJ & OKeefe J. Importance of maintaining a low omega-6/omega-3 ratio for reducing platelet aggregation, coagulation and thrombosis. Open Heart 2019 May 2;6(1):e001011. doi: 10.1136/openhrt-2019-001011.
26. American Heart Association Nutrition Subcommittee; Council on Cardiovascular Nursing; and Council on Epidemiology and Prevention. American Heart Association Science Advisory Omega-6 fatty acids and risk of cardiovascular disease. Circulation, 2009; 119:0-0.
27. Blasbalg TL, Hibbeln JR, Ramsden CE, Majchrzak SF & Rawlings RR. Changes in consumption of omega-3 and omega-6 fatty acids in the United States during the 20th century. Am J Clin Nutr. 2011 May;93(5):950-62. doi: 10.3945/ajcn.110.006643.
28. Brasky TM, Till C, White E, Neuhouser ML, Song X, Goodman P, Thompson IM, King IB, Albanes D & Kristal AR. Serum phospholipid fatty acids and prostate cancer risk: results from the prostate cancer prevention trial. Am J Epidemiol. 2011 Jun 15;173(12):1429-39. doi: 10.1093/aje/kwr027.
29. Reisman J, Schachter HM, Dales RE, Tran K, Kourad K, Barnes D, Sampson M, Morrison A, Gaboury I & Blackman J. Treating asthma with omega-3 fatty acids: where is the evidence? A systematic review. BMC Complement Altern Med. 2006 Jul 19;6:26. doi: 10.1186/1472-6882-6-26.
30. Kostoglou-Athanassiou I, Athanassiou L & Athanassiou P. The Effect of Omega-3 Fatty Acids on Rheumatoid Arthritis. Mediterr J Rheumatol. 2020 Jun 30;31(2):190-194. doi: 10.31138/mjr.31.2.190.
31. Wani AL, Bhat SA, Ara A. Omega-3 fatty acids and the treatment of depression: a review of scientific evidence. Integr Med Res. 2015 Sep;4(3):132-141. doi: 10.1016/j.imr.2015.07.003.
32. Cawood A, Ding R, Napper FL, Young RH, Williams JA, Ward M.J, Gudmundsen O., Vige R., Payne SP & Ye S., et al. Eicosapentaenoic acid (EPA) from highly concentrated n-3 fatty acid ethyl esters is incorporated into advanced atherosclerotic plaques and higher plaque EPA is associated with decreased plaque inflammation and increased stability. Atherosclerosis 2010;212:252–259. doi: 10.1016/j.atherosclerosis.2010.05.022
33. Nicholls SJ., Lincoff AM, Garcia M, Bash D, Ballantyne CM, Barter PJ, Davidson MH, Kastelein JJ, Koenig W & McGuire DK. Effect of high-dose omega-3 fatty acids vs corn oil on major adverse cardiovascular events in patients at high cardiovascular risk: The STRENGTH randomized clinical trial. JAMA 2020;324:2268–2280 doi: 10.1001/jama.2020.22258.
34. Lauritzen L, Brambilla P, Mazzocchi A, Harsløf LB, Ciappolino V & Agostoni C. DHA effects in brain development and function. *Nutrients* 2016;8:6. doi: 10.3390/nu8010006.
35. Russo GL. Dietary n-6 and n-3 polyunsaturated fatty acids: from biochemistry to clinical

implications in cardiovascular prevention. *Biochem Pharmacol.* 2009;77:937–46.
36. Siriwardhana N, Kalupahana NS, Fletcher S, Xin W, Claycombe KJ, Quignard-Boulange A, Zhao L, Saxton AM & Moustaid-Moussa N. n-3 and n-6 polyunsaturated fatty acids differentially regulate adipose angiotensinogen and other inflammatory adipokines in part via NF-κB-dependent mechanisms. J Nutr Biochem. 2012 Dec;23(12):1661-7. doi: 10.1016/j.jnutbio.2011.11.009.
37. Ramsden CE, Zamora D, Leelarthaepin B, Majchrzak-Hong SF, Faurot KR, Suchindran CM, Ringel A, Davis JM & Hibbeln JR. Use of dietary linoleic acid for secondary prevention of coronary heart disease and death: evaluation of recovered data from the Sydney Diet Heart Study and updated meta-analysis. BMJ 2013 Feb 4;346:e8707. doi: 10.1136/bmj.e8707. Erratum in: BMJ. 2013;346:f903.
38. Chowdhury R, Warnakula S, Kunutsor S, Crowe F, Ward HA, Johnson L, Franco OH, Butterworth AS, Forouhi NG, Thompson SG, Khaw KT, Mozaffarian D, Danesh J & Di Angelantonio E. Association of dietary, circulating, and supplement fatty acids with coronary risk: a systematic review and meta-analysis. Ann Intern Med. 2014 Mar 18;160(6):398-406. doi: 10.7326/M13-1788. Erratum in: Ann Intern Med. 2014 May 6;160(9):658.
39. Tur JA, Bibiloni MM, Sureda A & Pons A. Dietary sources of omega 3 fatty acids: public health risks and benefits. Br. J. Nutr. 2012 Jun;107 Suppl 2:S23-52. doi: 10.1017/S0007114512001456.
40. Baker EJ, Miles EA, Burdge GC, Yaqoob P & Calder PC. Metabolism and functional effects of plant-derived omega-3 fatty acids in humans. Prog Lipid Res. 2016 Oct; 64:30-56. doi: 10.1016/j.plipres.2016.07.002.
41. Meng L. How fish is cooked affects heart-health benefits of omega-3 fatty acids. American Heart Association (AHA), Scientific Conference, Hawaii, Manoa, 2009
42. Fliesler SJ. Lipids and lipid metabolism in the eye. J. Lipid Res. Vol. 51(1), 1-3. Published online, Jan. 2010. DOI: https://doi.org/10.1194/jlr.E003533.
43. Rujoi M., Jin J, Borchman D, Tang D & Yappert MC. 2003. Isolation and lipid characterization of cholesterol-enriched fractions in cortical and nuclear human lens fibers. Invest. Ophthalmol. Vis. Sci. 44: 1634–1642.
44. Jacob RF. Cenedella RJ & Mason RP. 1999. Direct evidence for immiscible cholesterol domains in human ocular lens fiber cell plasma membranes. J. Biol. Chem. 274: 31613–31618.
45. Estrada R, Puppato A, Borchman D & Yappert MC. 2009. Re-evaluation of the phospholipid composition in membranes of adult human lenses by 31-P NMR and MALDI-MS. Biochim. Biophys. Acta-Biomembranes. 1798: 301–311.
46. McOmtyre TM, Snyder F, Marathe GK, Dennis EV & Jean EV. Biochemistry of Lipids, Lipoproteins and Membranes. 5th edition Elsevier, San Diego, 2018.
47. Gorgas K, Teigler A, Komljenovic D & Just WW. The ether lipid-deficient mouse: tracking down plasmalogen functions. Biochim. Biophys. Acta. 2006; 1763: 1511–1526.
48. Nagan N & Zoeller RA. Plasmalogens: biosynthesis and functions. Prog. Lipid Res. 2001; 40: 199–229.
49. Borchman D, Yappert MC & Afzal M. Lens lipids and maximum lifespan. *Exp. Eye Res.* 2004;79:761–768.
50. Huang L, Rasi V, Grami V. Marrero Y, Borchman D, Tang D & Yappert MC. Human lens phospholipid changes with age and cataract. *Invest. Ophthalmol. Vis. Sci.* 2005;46:

1682–1689.
51. Deeley JM, Mitchell TW, Wei X, Korth J, Nealon JR, Blanksby SJ & Truscott RJ. 2008. Human lens lipids differ markedly from those of commonly used experimental animals. Biochim. Biophys. Acta. 2008; 1781: 288–298.
52. Rodemer C, Thai TP, Brugger B, Gorgas K & Just WW. 2003a. Targeted disruption of ether lipid synthesis in mice. Adv. Exp. Med. Biol. 544: 355–368.
53. Rodemer C, Thai TP, Brugger B, Kaercher H, Werner KA, Nave F, Wie l, Gorgas K and Just WW. 2003b. Inactivation of ether lipid biosynthesis causes male infertility, defects in eye development and optic nerve hypoplasia in mice. Hum. Mol. Genet. 12: 1881–1895.
54. Yappert MC, Rujoi M, Borchman D, Vorobyov I, Estrada R. Glycero- versus sphingo-phospholipids: correlations with human and non-human mammalian lens growth. Exp Eye Res. 2003 Jun;76(6):725-34. doi: 10.1016/s0014-4835(03)00051-4.
55. Huber T, Rajamoorthi K, Kurze VF, Beyer K & Brown MF. Structure of docosahexaenoic acid-containing phospholipid bilayers as studied by (2)H NMR and molecular dynamics simulations. J Am Chem Soc. 2002 Jan 16; 124(2):298-309. https://www.ncbi.nlm.nih.gov/pubmed/11782182
56. Messmer EM. The pathophysiology, diagnosis, and treatment of dry eye disease. Dtsch Arztebl Int. 2015 Jan 30;112(5):71-81; quiz 82. doi: 10.3238/arztebl.2015.0071.
57. Zoukhri D. Effect of inflammation on lacrimal gland function. Exp Eye Res. 2006 May;82(5):885-98. doi: 10.1016/j.exer.2005.10.018.
58. Inoue S, Kawashima M, Arita R, Kozaki A & Tsubota K. Investigation of Meibomian Gland Function and Dry Eye Disease in Patients with Graves' Ophthalmopathy. J Clin Med. 2020 Aug 31;9(9):2814. doi: 10.3390/jcm9092814.
59. Şimşek C, Doğru M, Kojima T & Tsubota K. Current Management and Treatment of Dry Eye Disease. Turk J Ophthalmol. 2018 Dec 27;48(6):309-313. doi: 10.4274/tjo.69320.
60. Stahl A. The Diagnosis and Treatment of Age-Related Macular Degeneration. Dtsch Arztebl Int. 2020 Jul 20;117(29-30):513-520. doi: 10.3238/arztebl.2020.0513.
61. Takahashi K, Iida T, Ishida S, Crawford B, Sakai Y, Mochizuki A, Tsujiuchi R, Tanaka S & Imai K. Effectiveness of Current Treatments for Wet Age-Related Macular Degeneration in Japan: A Systematic Review and Pooled Data Analysis. Clin Ophthalmol. 2022 Feb 25; 16:531-540. doi: 10.2147/OPTH.S345403.
62. Lin, JB, Halawa, OA., Husain, D. *et al.* Dyslipidemia in age-related macular degeneration. *Eye* **36**, 312–318 (2022). https://doi.org/10.1038/s41433-021-01780-y.
63. Mohamed-Noriega J & Sekhar GC. Defining and diagnosing glaucoma: a focus on blindness prevention. Community Eye Health 2021;34(112):32-35.
64. Schuster AK, Erb C, Hoffmann EM, Dietlein T & Pfeiffer N. The Diagnosis and Treatment of Glaucoma. Dtsch Arztebl Int. 2020 Mar 27;117(13):225-234. doi: 10.3238/arztebl.2020.0225.

65. National Eye Institute. 2021. Types of glaucoma. Available at:
https://www.nei.nih.gov/learn-about-eye-health/eye-conditions-and-diseases/glaucoma/types-glaucoma.updated September 10th, 2021.
66. Shen R, Li VSW, Wong MOM & Chan PPM. Pediatric Glaucoma-From Screening, Early Detection to Management. Children (Basel). 2023 Jan 18;10(2):181. doi: 10.3390/children10020181.
67. Das T, Takkar B, Sivaprasad S, Thanksphon T, Taylor H, Wiedemann P, Nemeth J, Nayar PD, Rani PK & Rajiv K. Recently updated global diabetic retinopathy screening guidelines: commonalities, differences, and future possibilities. *Eye* 2021; Vol. 35, pages 2685–2698.
68. Anon. Definition of Retinopathy". www.merriam-webster.com. Retrieved *2023-03*-01.
69. Chen K, Li Y, Zhang X. *et al.* The role of the PI3K/AKT signalling pathway in the corneal epithelium: recent updates. *Cell Death Dis* **13**, 513 (2022). Available at: https://doi.org/10.1038/s41419-022-04963-x.
70. Ophthalmology, American Academy of *(2012). "Retina and vitreous". American Academy of Ophthalmology (2011–2012 ed.). p. 271. ISBN 9781615251193.*
71. Cheung, Ning; Mitchell, Paul; Wong, & Tien Yin (2010). *"Diabetic retinopathy". The Lancet.* ***376*** *(9735): 124–136. doi:10.1016/S0140-6736(09)62124-3.*
72. World Health Organization. Blindness and vision impairment: The key facts. 2019. https://www.who.int/en/news-room/fact-sheets/detail/blindness-and-visual-impairment.
73. Saunders EF, Reider A, Singh G, Gelenberg AJ & Rapoport SI. Low unesterified:esterified eicosapentaenoic acid (EPA) plasma concentration ratio is associated with bipolar disorder episodes, and omega-3 plasma concentrations are altered by treatment. Bipolar Disord. 2015 Nov;17(7):729-42. doi: 10.1111/bdi.12337.
74. Daniëlle Swinkels & Myriam Baes. The essential role of docosahexaenoic acid and its derivatives for retinal integrity. Pharmacology and Therapeutics 2023; Vol. 247. Available at: https://www.sciencedirect.com/science/article/abs/pii/S0163725823001043.
75. Weir N, Guan W, Karger AB, Klein BEK, Meuer SM, Cotch MF, Guo X, Li X, Tan J, Genter P, Chen YI, Rotter JI, Ipp E & Tsai MY. Omega-3 Fatty Acids are Associated with Decreased Presence and Severity Of Diabetic Retinopathy: A Combined Analysis of MESA and GOLDR Cohorts. Retina. 2023 Jun 1;43(6):984-991. doi: 10.1097/IAE.0000000000003745.
76. García P, Hernández Martínez FJ, Aznárez López N, Castillón Torre L & Tena Sempere ME. Supplementation with a Highly Concentrated Docosahexaenoic Acid (DHA) in Non-Proliferative Diabetic Retinopathy: A 2-Year Randomized Double-Blind Placebo-Controlled Study. Antioxidants (Basel). 2022 Jan 5; 11(1):116. doi: 10.3390/antiox11010116.
77. Sugasini D, Yalagala PCR & Subbaiah PV. Efficient Enrichment of Retinal DHA with Dietary Lysophosphatidylcholine-DHA: Potential Application for Retinopathies. Nutrients. 2020 Oct 12;12(10):3114. doi: 10.3390/nu12103114. Erratum in: Nutrients. 2021 Jun 24;13(7).
Available at; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7601701/.
78. Niu SL, Mitchell DC, Lim SY, Wen ZM, Kim HY, Salem N Jr & Litman BJ. Reduced G

protein-coupled signaling efficiency in retinal rod outer segments in response to n-3 fatty acid deficiency. J Biol Chem 2004; 279:31098-104. https://www.ncbi.nlm.nih.gov/pubmed/15145938
79. Calder PC. Omega-3 fatty acids and inflammatory processes. Nutrients.2010 Mar;2(3):355-374.doi: 10.3390/nu2030355.
80. Querques G, Forte R & Souied EH. Retina and omega-3. J Nutr Metab. 2011;2011:748361. doi: 10.1155/2011/748361.
81. Ausgood C, Chakravarthy U, Young I, Vioque J, de Jong PT, Bentham G, Rahu M, Seland J, Soubrane G, Tomazzoli L, Topouzis F, Vingerling JR & Fletcher AE. Oily fish consumption, dietary docosahexaenoic acid and eicosapentaenoic acid intakes, and associations with neovascular age-related macular degeneration. Am J Clin Nutr. 2008 Aug;88(2):398-406. Doi. https://www.ncbi.nlm.nih.gov/pubmed/18689376.
82. SanGiovanni JP, Agron E, Meleth AD, Reed GF, Sperduto RD, Clemons TE, et al. ω-3 Long-chain polyunsaturated fatty acid intake and 12-y incidence of neovascular age-related macular degeneration and central geographic atrophy: AREDS report 30, a prospective cohort study from the Age-Related Eye Disease Study. Am J. Clin. Nutr. 2009; 90: 1601-7. https://www.ncbi.nlm.nih.gov/pubmed/19812176
83. Georgakopoulos CD, Makri OE, Pagoulatos D, Vasilakis P, Peristeropoulou P, Kouli V, Eliopoulou MI & Psachoulia C. Effect of Omega-3 Fatty Acids Dietary Supplementation on Ocular Surface and Tear Film in Diabetic Patients with Dry Eye. J. Am. Coll. Nutr. 2017 ;36(1):38-43. doi: 10.1080/07315724.2016.1170643.
84. Downie LE & Vingrys AJ. Oral Omega-3 Supplementation Lowers Intraocular Pressure in Normotensive Adults. Transl Vis Sci Technol. 2018 May 1;7(3):1. https://www.ncbi.nlm.nih.gov/pubmed/29736322. Accessed on 4th June, 2023.
85. Giannaccare G, Pellegrini M, Sebastiani S, Bernabei F, Roda M, Taroni L, Versura P & Campos EC. Efficacy of Omega-3 Fatty Acid Supplementation for Treatment of Dry Eye Disease: A Meta-Analysis of Randomized Clinical Trials. Cornea 2019 Jan 29. https://www.ncbi.nlm.nih.gov/pubmed/30702470.
86. Mosca F., Giannì M.L. Human milk: Composition and health benefits. *Pediatr. Med. Chir.* 2017;39:155. doi: 10.4081/pmc.2017.155.
87. Delgado-Noguera M.F., Calvache JA & Bonfill Cosp X. Supplementation with long chain polyunsaturated fatty acids (LCPUFA) to breastfeeding mothers for improving child growth and development. *Cochrane Database Syst. Rev.* 2010:Cd007901. doi: 10.1002/14651858.CD007901.pub2.
88. Guillot M, Synnes A, Pronovost E, Qureshi M, Daboval T, Caouette G, Olivier F, Bartholomew J, Mohamed I, Massé E, Afifi J, Hendson L, Lemyre B, Luu TM, Strueby L, Cieslak Z, Yusuf K, Pelligra G, Ducruet T, Khairy AB, Ndiaye T, Angoa G, Sériès T, Piedboeuf B, Nuyt AM, Fraser W, Mâsse B, Lacaze-Masmonteil T, Lavoie PM & Marc I. Maternal High-Dose DHA Supplementation and Neurodevelopment at 18–22 Months of Preterm Children. Pediatrics 2022; 150(1): e2021055819. Available at: https://doi.org/10.1542/peds.2021-055819.
89. Strømmen K, Blakstad EW, Moltu SJ, Almaas AN, Westerberg AC, Amlien IK, ... & Iversen, P. O. (2014). Enhanced nutrient supply to very low birth weight infants is associated with improved white matter maturation and head growth. *Neonatology*, *107*(1), 68-75.
90. O'Connor DL, Hall R, Adamkin D, Auestad N, Castillo M, Connor WE, Connor SL, Fitzgerald K, Groh-Wargo S, Hartmann EE, et al.. 2001. Growth and development in preterm

infants fed long-chain polyunsaturated fatty acids: a prospective, randomized controlled trial. *Pediatrics.* 108: 359–371.
91. James MJ, Gibson RA & Cleland IG. Dietary polyunsaturated fatty acids and inflammatory mediator production. *Am J Clin Nutr.* 2000;71(1 Suppl):343S–348S.
92. Mahmood AM & Al-Swailem SA. Essential fatty acids in the treatment of dry eye syndrome: A myth or reality? Saudi J Ophthalmology. 2014 Jul;28(3):195-7. doi: 10.1016/j.sjopt.2014.06.004.
93. Vitale S, Agrón E, Clemons TE, Keenan TDL, Domalpally A, Danis RP Jr, Chew EY. Association of 2-Year Progression Along the AREDS AMD Scale and Development of Late Age-Related Macular Degeneration or Loss of Visual Acuity: AREDS Report 41. JAMA Ophthalmol. 2020 Jun 1;138(6):610-617. doi: 10.1001/jamaophthalmol.2020.0824.
94. Joon-Young Hyon and Sang-Reom Han. The protective role of polyunsaturated fatty acids against dry eye disease: a literature review. Appl. Sci. 2021; 11(10){ 4519. https//doi.org/10.3390/app11104519.
95. Bucolo C, Maugeri G, Giunta S, D'Agata V, Drago F & Romano GL. Corneal wound healing and nerve regeneration by novel ophthalmic formulations based on cross-linked sodium hyaluronate, taurine, vitamin B6, and vitamin B12. Front Pharmacol. 2023 Feb 2;14:1109291. doi: 10.3389/fphar.2023.
96. DiNicolantonio JJ, O'Keefe J. The Importance of Maintaining a Low Omega-6/Omega-3 Ratio for Reducing the Risk of Inflammatory Cytokine Storms. Mo Med. 2020 Nov-Dec;117(6):539-542.

97. Ken D. Stark, Mary E. Van Elswyk, M. Roberta Higgins, Charlie Weatherford, Norman Salem Jr. Global survey of the omega-3 fatty acids, docosahexaenoic acid and eicosapentaenoic acid in the blood stream of healthy adults. Prog. Lipid Res. 2016; 63:132-152.
98. SanGiovanni JP, Chew EY. The role of omega-3 long-chain polyunsaturated fatty acids in health and disease of the retina. Prog Retin Eye Res. 2005 Jan;24(1):87-138. doi: 10.1016/j.preteyeres.2004.06.002.
99. Wang WX & Ko ML Efficacy of Omega-3 Intake in Managing Dry Eye Disease: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. J. Clin. Med. 2023 Nov 10;12(22):7026. doi: 10.3390/jcm12227026.
100. Hussain M, Shtein RM, Pistilli M, Maguire MG, Oydanich M & Asbell PA. The Dry Eye Assessment and Management (DREAM) extension study – A randomized clinical trial of withdrawal of supplementation with omega-3 fatty acid in patients with dry eye disease. The Ocular Surface 2020; Volume 18, Issue 1, pages 47-55.
101. Christen WG, Cook NR, Manson JE, et al. Efficacy of Marine ω-3 Fatty Acid Supplementation vs Placebo in Reducing Incidence of Dry Eye Disease in Healthy US Adults: A Randomized Clinical Trial. *JAMA Ophthalmol.* 2022;140(7):707–714. doi:10.1001/jamaophthalmol.2022.1818.
102.. García-Layana A, Cabrera-López F, García-Arumí J, Arias-Barquet L, Ruiz-Moreno JM. Early and intermediate age-related macular degeneration: update and clinical review. Clin Interv Aging. 2017 Oct 3;12:1579-1587. doi: 10.2147/CIA.S142685.

103. Lawrenson JG & Evans JR. Omega-3 fatty acids for preventing or slowing the progression of age-related macular degeneration. Cochrane Database Syst Rev. 2015 Apr 9;2015(4):CD010015. doi: 10.1002/14651858.CD010015.pub3.
104. Agrön E, Mares J, Clemons T, Swaroop A, Chew EY, Tiarnan DL Keenan, for the ARDS and AREDFS2 research group. Dietary nutrient intake and progression of to late-age-related macular degeneration in the age-related eye disease 1 and 2 study for AREDS 1 and AREDS 2 research group. Ophthalmology 2020; 128(3):425-442.
105. Olivier MC, Vanessa L & Isabelle A. Why and how meet n-3 PUFA dietary recommendations? *Gastroenterology Research and Practice.* 2011;2011:11-15.
106. Djuricic, I & Calder PC. Beneficial Outcomes of Omega-6 and Omega-3 Polyunsaturated Fatty Acids on Human Health: An Update for 2021. Nutrients. 2021 Jul 15;13(7):2421. doi: 10.3390/nu13072421.
107. Gammone MA, Parrinello RGG & D'Orazio N. Omega-3 Polyunsaturated fatty acids: benefits and endpoints in sport. Nutrients. 2018 Dec 27;11(1):46. doi: 10.3390/nu11010046.
108. Institute of Medicine (National Academy of Medicine). Food and Nutrition Board. Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids (macronutrients). Washington, DC: National Academy Press; 2005. Available at: https://ods.od.nih.gov/factsheets/Omega3FattyAcids-HealthProfessional/.
109**.** Siscovick DS, Barringer TA, Fretts AM, Wu JH, Lichtenstein AH, Costello RB, Kris-Etherton PM, Jacobson TA, Engler MB, Alger HM, Appel L, & Mozaffarian D. American Heart Association Nutrition Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Epidemiology and Prevention; Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; and Council on Clinical Cardiology. Omega-3 Polyunsaturated Fatty Acid (Fish Oil) Supplementation and the Prevention of Clinical Cardiovascular Disease: A Science Advisory From the American Heart Association. Circulation. 2017 Apr 11;135(15):e867-e884. doi: 10.1161/CIR.0000000000000482.
110**.** Skulas-Ray AC, Peter W, Wilson F, Harris WS, Brinton EA, Kris-Etherton PM, Richter CK, Jacobson TA, Engler MB, Miller M, Robinson JG, Blum CB, Leyva DB, de Ferranti SD, & Welty FK. On behalf of the American Heart Association Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Lifestyle and Cardiometabolic Health; Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; and Council on Clinical Cardiology. Omega-3 Fatty Acids for the Management of Hypertriglyceridemia: A Science Advisory From the American Heart Association. Circulation 2019, Vol. 140(12**),** available at: https://doi.org/10.1161/CIR.0000000000000709Circulation. 2019; 140:e673–e691.
111. Xin Zhang, Jennifer A. Ritonja, Na Zhou, Bingshu E, C**hen and Xinzhi Li.** Omega□3 Polyunsaturated Fatty Acids Intake and Blood Pressure: A Dose□Response Meta□Analysis of Randomized Controlled Trials. JAHA Jun 2022. 11:e025071.

https://doi.org/10.1161/JAHA.121.025071

112, Mori T.A. Marine OMEGA-3 fatty acids in the prevention of cardiovascular disease. *Fitoterapia.* 2017;123:51–58. doi: 10.1016/j.fitote.2017.09.015.
113. Merle BMJ, Colijn JM, Gregoire AC, de Koning-Backus APM, Delyfer MN, Kiefte-de Jong JC, Meester-Smoor M, Feart C, Verzijden T, Samieri C., et al. Mediterranean Diet and Incidence of Advanced Age-Related Macular Degeneration: The EYE-RISK Consortium. *Ophthalmol.* 2018;126:381–390. doi: 10.1016/j.ophtha.2018.08.006.
114. De Koning-Backus APM, Buitendijk GHS, Kiefte-de Jong JC, Colijn JM, Hofman A, Vingerling JR, Haverkort EB, Franco OH & Klaver CCW. Intake of Vegetables, Fruit, and Fish is Beneficial for Age-Related Macular Degeneration. *Am. J. Ophthalmol.* 2019;198:70–79. doi: 10.1016/j.ajo.2018.09.036.
115. Dempsey M, Rockwell MS & Wentz LM. The influence of dietary and supplemental omega-3 fatty acids on the omega-3 index: A scoping review. Front Nutr. 2023 Jan 19;10:1072653. doi: 10.3389/fnut.2023.1072653.
116. Kontostathi M, Isou S, Mostratos D, Vasdekis V, Demertzis N, Kourounakis A, Vitsos A, Kyriazi M, Melissos D, Tsitouris C, Karalis E, Klamarias L, Dania F, Papaioannou GT, Roussis V, Polychronopoulos E, Anastassopoulou J, Theophanides T, Rallis MC & Black HS. Influence of Omega-3 Fatty Acid-Rich Fish Oils on Hyperlipidemia: Effect of Eel, Sardine, Trout, and Cod Oils on Hyperlipidemic Mice. J Med Food. 2021 Jul;24(7): 749-755. doi: 10.1089/jmf.2020.0114.
117. Yan J, Liu M, Yang D. *et al.* Efficacy and Safety of Omega-3 Fatty Acids in the Prevention of Cardiovascular Disease: A Systematic Review and Meta-analysis. *Cardiovasc Drugs Ther* 2022. https://doi.org/10.1007/s10557-022-07379-z.
118. Whelton SP, He J, Whelton PK & Muntner P. Meta-analysis of observational studies on fish intake and coronary heart disease. Am J Cardiol. 2004; 93: 1119– 1123: https://www.ncbi.nlm.nih.gov/pubmed/15110203.
119. Lane KE, Wilson M, Hellon TG & Davies IG. Bioavailability and conversion of plant based sources of omega-3 fatty acids - a scoping review to update supplementation options for vegetarians and vegans. Crit Rev Food Sci Nutr. 2022;62(18):4982-4997. doi: 10.1080/10408398.2021.1880364.
120. Wander RC, Hall JA, Gradin JL, Shi-Hua Du & Jewell DE. The Ratio of Dietary (n-6) to (n-3) Fatty Acids Influences Immune System Function, Eicosanoid Metabolism, Lipid Peroxidation and Vitamin E Status in Aged Dogs. J. Nutr. 127(6): 1198-1205.
121. Wensing AG, Mensink RP & Hornstra G. Effects of dietary n-3 polyunsaturated fatty acids from plant and marine origin on platelet aggregation in healthy elderly subjects. *Br. J. Nutr.* 1999;82:183–191.
122 Jane Pei-Chen Chang, Ping-Tsao Tseng, Bing-Syuan Zeng, Cheng-Ho Chang, Huanxing-Su, Po-Han Chou & Kuan-Pin Su. Safety of supplementation of omega-3 polyunsaturated fatty acids: a systematic review and meta-analysis of randomized controlled trials. Advances in Nutrition 2023; Vol 14 (6), P1326-P1336. DOI. https://doi.org/10.1016/j.advnutr.2023.08.003.
123. Dighriri IM, Alsubaie AM, Hakami FM, Hamithi DM, Alshekh MM, Khobrani FA, Dalak FE, Hakami AA, Alsueaadi EH, Alsaawi LS, Alshammari SF, Alqahtani AS, Alawi IA, Aljuaid AA & Tawhari MQ. Effects of Omega-3 Polyunsaturated Fatty Acids on Brain

Functions: A Systematic Review. Cureus 2022 Oct 9;14(10):e30091. doi: 10.7759/cureus.30091.

124. Bhatt DL, P. Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB & Doyle RT, Jr., for the REDUCE-IT Investigators. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. New Eng. J. Med. 2019; 380(1):11-22. DOI: \10.1056/NEJMoa1812792.

125**.** Calabresi DD, Pazzucconi F, Sirtori CR & Franceschini G. Omacor in familial combined hyperlipidemia: effects on lipids and low density lipoprotein subclasses. Atherosclerosis. 2000 Feb;148(2):387-96. doi: 10.1016/s0021-9150(99)00267-1.

126. Bowman L, Mafham M, Wallendszus K, Stevens W, Buck G, Barton J, Murphy K, Aung T, Haynes R, Cox J, Murawska A, Young A, Lay M, Chen F, Sammons E, Waters E, Adler A, Bodansky J, Farmer A, McPherson R, Neil A, Simpson D, Peto R, Baigent C, Collins R, Parish S & Armitage J. ASCEND Study Collaborative Group; Effects of n-3 Fatty Acid Supplements in Diabetes Mellitus. N Engl J Med. 2018 Oct 18;379(16):1540-1550. doi: 10.1056/NEJMoa1804989.

127. White-Springer SH. Vineyard KR, Kivipelto J & Warren LK. Dietary omega-3 fatty acid supplementation does not impair vitamin E status or promote lipid peroxidation in growing horses. J Anim Sci. 2021 Jul 1;99(7): skab177. doi: 10.1093/jas/skab177.

128. Harris WS, Silveira S & Dujovne CA. The combined effects of N-3 fatty acids and aspirin on hemostatic parameters in man. *Thromb. Res.* 1990;57:517–526. doi: 10.1016/0049-3848(90)90069-O.

129. Rosemary R Climate Change and Antarctic Fisheries: Ecosystem Management in CCAMLR. Ecology Law Quarterly 2018; 45(1): 53-81.Doi.org/10.15779/Z381834271.

130. Ritchie H & Roser M. Fishing and overfishing. How are fish stocks changing across the world? How much is overfished? 2021; Found at: https://ourworldindata.org/fish-and-overfishing#long-term-trends-in-fish-catch. Accessed on 27th April, 2024.

131. Ulven SM, Kirkhus B, Lamglait A, Basu S, Elind E, Haider T, Berge K, Vik H & Pedersen JI. Metabolic effects of krill oil are essentially similar to those of fish oil but at lower dose of EPA and DHA, in healthy volunteers. Lipids. 2011 Jan;46(1):37-46. doi: 10.1007/s11745-010-3490-4.

132. Schuchardt JP & Hahn A. Bioavailability of long-chain omega-3 fatty cids. *Prostaglandins Leukot Essent Fatty Acids.* 2013;**89**:1–8. doi: 10.1016/j.plefa.2013.03.010.

133. Köhler A, Sarkkinen E, Tapola N, Niskanen T & Bruheim I. Bioavailability of fatty acids from krill oil, krill meal and fish oil in healthy subjects--a randomized, single-dose, cross-over trial. Lipids Health Dis. 2015 Mar 15;14:19. doi: 10.1186/s12944-015-0015-4.

134. Mozaffarian D, Maki KC, Bays HE, Aguilera, F., Gould G, Hegele RA, Moriarty PM, Robinson JG, Shi P, Tur JF, Jean-François L, Aziz S & Lemieux P, for the TRILOGY (Study of CaPre in Lowering Very High Triglycerides) investigators. Effectiveness of a Novel ω-3 Krill Oil Agent in Patients With Severe Hypertriglyceridemia: A Randomized Clinical Trial. *JAMA Network Open.* 2022;5(1): e2141898. doi:10.1001/jamanetworkopen.2021.41898.