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A Review on Potential Properties and Therapeutic Applications of DHA and EPA



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ABSTRACT

Omega-3 [(n-3)] long-chain PUFA, together with EPA and DHA, are dietary fats with an array of health edges. They are incorporated in several components of the body together with cell membranes and play a task in antiinflammatory processes and within the viscousness of cell membranes. EPA and DHA are crucial for correct craniate development and healthy aging.

Patients with AD are deficient in DHA, and supplementing them with EPA +DHA not only reverses this deficiency but may also improve cognitive functioning in patients with very mild AD. With increasing rates of pediatric allergies, cardiovascular disease, and AD in the United States, EPA and DHA may be a safe and inexpensive link to a healthier life



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INTRODUCTION

Omega-3 [(n-3)] long-chain PUFA, together with EPA and DHA, are dietary fats with an array of health edges (1). They are incorporated in several components of the body together with cell membranes (2) and play a task in antiinflammatory processes and within the viscousness of cell membranes (3,4). EPA and DHA are crucial for correct craniate development and healthy aging (5). DHA may be a key part of all cell membranes and is found in abundance within the brain and membrane (6). EPA and DHA are the precursors of many metabolites that are potent lipid mediators, thought of by several investigators to be useful within the hindrance or treatment of many diseases (7). It is often difficult to induce a suitable intake of EPA and DHA through diet alone, even if EPA and DHA are made by water plants like protocists and are rife in marine animals. A shorter chain polyunsaturated fatty acid carboxylic acid, α -linolenic acid (ALA),⁶ may be an outstanding part of our diet as it is found in several land plants that are ordinarily consumed, but it doesn't give the health edges seen with EPA and DHA. though it's doable for the body to convert ALA to EPA and DHA by elongase and desaturase enzymes, analysis suggests that solely a little quantity is often synthesized in the body from this method (8). as an example, one study prompt that solely w2 to 100% of ALA is regenerate to epa or DHA (9), and alternative studies found even less: Goyens et al. (10) found an ALA conversion of w7% for epa, but only 0.013% for DHA; Hussein et al. (11) found an ALA conversion of solely zero.3% for EPA and <0.01% for DHA. The current yank diet has modified over time to be high in SFA and low in polyunsaturated fatty acid fatty acids (12). this variation in uptake habits is focused on nourishment containing high amounts of saturated fat, that has tiny amounts of essential polyunsaturated fatty acid PUFA compared with food ready within the home (13). food sources like fish and fish-oil supplements are the first contributors of the two biologically necessary dietary polyunsaturated fatty acid fatty acids, EPA and DHA (14–16). This low intake of dietary EPA and DHA is believed to be related to enlarged inflammatory processes furthermore as poor craniate development, general vas health, and risk of the event of Alzheimer's illness (AD). This review focuses on the various edges of EPA and DHA supplementation throughout life, together with use throughout pregnancy for correct craniate development and full-term gestation, to cut back several cardiovascular issues.

The two major categories of unsaturated fatty acids (PUFAs) are omega-3 fatty acid and polyunsaturated fatty acid fatty acids. Like all fatty acids, PUFAs contain long chains of carbon atoms with a group at one finish of the chain and an alkyl group at the opposite. PUFAs are distinguished from saturated and monounsaturated carboxylic acids by the presence of 2 or a lot of double bonds between carbons at intervals the fatty acid chain.

Omega-3 fatty acids (omega-3s) have a carbon-carbon covalent bond situated 3 carbons from the methyl radical finish of the chain. Omega-3s, typically observed as "n-3s," is a gift in bound foods like linseed and fish, also to dietary supplements like animal oil. many different omega-3s exist, however, the bulk of the research project focuses on three: omega-3 fatty acid (ALA), omega-3 fatty acid (EPA), and omega-3 (DHA). ALA contains eighteen carbon atoms, whereas EPA and DHA are thought of "long-chain" (LC) omega-3s as a result of EPA contain twenty carbons and DHA contains twenty-two.

PUFAs are oftentimes selected by their range of carbon atoms and double bonds. ALA, as an example, is understood as C18:3n-3 as a result of its eighteen carbons and three double bonds and is an n-3, or omega-3, fatty acid. Similarly, EPA is understood as C20:5n-3 and DHA as C22:6n-3. polyunsaturated fatty acid carboxylic acids (omega-6s) have a carbon-carbon covalent bond that's six carbons off from the methyl radical finish of the fatty acid chain. linolic acid (C18:2n-6) and arachidonic acid (C20:4n-6) are 2 of the foremost omega-6s.

The organic structure will solely type carbon-carbon double bonds when the ninth carbon from the methyl radical finish of a carboxylic acid [1]. Therefore, ALA and linolic acid are thought of as essential fatty acids, which means that they need to be obtained from the diet [2]. ALA may be reborn into EPA and so to DHA, however, the conversion (which happens primarily within the liver) is extremely restricted, with reportable rates of but 15 august 1945 [3]. Therefore, overwhelming EPA and DHA directly from foods and/or dietary supplements are that the solely sensible thanks to increasing levels of those fatty acids within the body.

ALA is a gift in plant oils, like linseed, soybean, and canola oils [3]. DHA and EPA are gifted in fish, fish oils, and malacostracan crustacean oils, however, they're originally synthesized by microalgae, not by the fish. once fish consume a plant that consumed microalgae, they accumulate the omega-3s in their tissues [3].

After the bodily function, dietary lipids are hydrolyzed within the viscous lumen [1]. The chemical reaction products—monoglycerides and free fatty acids—are then incorporated into bile-salt-containing micelles and absorbed into enterocytes, for the most part by passive diffusion. The method is economical, with an absorption rate of concerning ninety-fifths, which is analogous to it of different eaten fats [1]. At intervals viscous cells, free fatty acids are primarily incorporated into chylomicrons and enter the circulation via the vascular system [1,4]. Once within the blood, conjugated protein particles flow into at intervals the body, delivering lipids to numerous organs for resulting oxidization, metabolism, or storage in fatty tissue [4,5].

Omega-3s play necessary roles within the body as elements of the phospholipids that type the structures of cell membranes [5]. DHA, specifically, is particularly high within the membrane, brain, and gamete [3,5,6]. Additionally, to their structural role in cell membranes, omega-3s (along with omega-6s) offer energy for the body and are wont to type eicosanoids. Eicosanoids are communication molecules that have similar chemical structures to the fatty acids from that they're derived; they need wide-ranging functions within the body's vessel, pulmonary, immune, and endocrine systems [1,2].

The eicosanoids made up of omega-6s are usually less attackable mediators of inflammation, constriction, and protoplasm aggregation than those made up of omega-3s, though there are some exceptions [3,7]. As a result of each category of fatty acids contend for identical desaturation enzymes, ALA may be a competitive substance of linolic acid metabolism and the other way around [8]. Similarly, EPA and DHA will contend with arachidonic acid for the synthesis of eicosanoids. Thus, higher concentrations of EPA and DHA than arachidonic acid tip the eicosanoid balance toward less inflammatory activity [9].

Some researchers propose that the relative intakes of omega-6s and omega-3s—the omega-6/omega-3 ratio—may have necessary implications for the pathological process of the many chronic diseases, like disorder and cancer [8], however the best ratio—if any—has not been outlined [10]. Others have all over that such ratios are too non-specific and are insensitive to individual carboxylic acid levels [11-13]. Most agree that raising EPA and DHA blood levels are much a lot of necessary than lowering linolic acid or arachidonic acid levels.

Currently, most clinicians don't assess omega-3 fatty acid standing, however, it may be done by measure individual omega-3s in plasma or bodily fluid lipids and expressing them because of the share of total phospholipid fatty acids by weight [14-16]. Specialists haven't established traditional ranges, however, mean values for bodily fluid or plasma lipid EPA and DHA among U.S. adults not taking omega-3 fatty acid supplements are concerning 3%–4% [14-16]. Plasma and bodily fluid carboxylic acid values, however, will vary well supported an individual's most up-to-date meal, so that they don't replicate semipermanent dietary consumption [3,17].

It is additionally doable to assess omega-3 fatty acid standing via analysis of RBC fatty acids, a measure that reflects longer-term intakes over just about the previous one hundred twenty days [18,19]. The “omega-3 index” planned by Harris and von Schacky reflects the content of EPA and DHA in RBC membranes expressed as a share of total RBC fatty acids [20,21]. This index may be used as a surrogate for assessing tissue levels of EPA and DHA [16,22,23]. EPA and DHA usually comprise concerning 3%–5% of RBC fatty acids in Western populations with low fish intakes. In Japan, wherever fish consumption is high, RBC EPA and DHA levels are concerning doubly those of Western populations [3].

Omega 3,6, 9 Uses:

Infant health and neurodevelopment Numerous studies have examined the effects of maternal seafood and omega-3 intakes on infant birth weight, length of gestation, visual and cognitive development, and other infant health outcomes. High concentrations of DHA are present in the cellular membranes of the brain and retina [5], and DHA is important for fetal growth and development. The accumulation of DHA in the retina is complete by birth, whereas accumulation in the brain continues throughout the first 2 years after birth.

Evidence from observational research: Observational studies indicate that maternal consumption, during pregnancy and breastfeeding, of at least 8 ounces per week of seafood that contains DHA is associated with better infant health outcomes [77]. For example, in a prospective cohort study of 341 mother-child pairs in the United States, maternal fish consumption more than twice per week compared to no weekly consumption was associated with improved visual-motor skills in their children at age 3 after adjustment for covariates such as maternal age, education, maternal smoking and alcohol use during pregnancy, paternal

education, and fetal growth [83]. In another observational cohort study in the United Kingdom in 11,875 pregnant women who reported seafood intakes ranging from none to more than 340 g (about 12 ounces) per week, lower consumption of seafood during pregnancy was associated with an increased risk of suboptimal communication skills in the offspring at ages 6 and 18 months and suboptimal verbal IQ and prosocial behavior at age 7–8 years [84]. It is not possible to establish causality, however, because all of these studies were observational.

Seafood contains varying levels of methylmercury [31]. However, results from numerous studies, including a systematic review of the literature on maternal fish intake and subsequent neurodevelopmental outcomes, show that the health benefits of consuming moderate amounts of seafood during the prenatal period outweigh the risks [84-87].

Randomized controlled trials of omega-3 supplementation: Several randomized controlled trials have examined whether supplementation with fish oil, EPA, and/or DHA during pregnancy and early infancy is beneficial for infant health and neurodevelopment.

One of these trials examined the effects of fish oil supplementation in 2,399 pregnant women on the subsequent clinical outcomes and neurodevelopment of their children [88]. Pregnant women received daily supplements of either fish oil (providing 800 mg DHA and 100 mg EPA) or placebo from less than 21 weeks' gestation until the birth of their child. Compared to the placebo group, children of mothers who received fish oil were heavier at birth and less likely to be born very preterm (less than 34 weeks' gestation). However, assessments of 726 of the children (all 96 preterm children and 630 randomly selected full-term children) found no differences between groups in mean cognitive composite scores or mean language composite scores at age 18 months. A follow-up study of the children at age 4 years found no differences between groups in general conceptual ability score or other assessments of cognition, language, and executive functioning [89]. Another study found no benefits on visual function at age 7 years when very preterm infants (less than 33 weeks' gestation) consumed human milk with a higher DHA concentration than normal (lactating mothers took 900 mg/day DHA supplements) for the first months of life until full term [90]. In a clinical trial in 420 healthy full-term infants, those who received either DHA-enriched fish oil (250 mg DHA and 60 mg EPA) or placebo daily from birth to 6 months had similar scores on neurodevelopment assessments at 18 months [91].

However, infants receiving fish oil had significantly better performance on language assessments, indicating some benefit for early communication development.

The authors of a systematic review and meta-analysis of 11 randomized controlled trials concluded that the evidence neither supports nor refutes the benefits of LC omega-3 supplementation during pregnancy for cognitive or visual development in infants [92]. Another systematic review and meta-analysis that included two randomized controlled trials in women with a previous preterm birth found no significant differences in rates of recurrent preterm birth between women who took omega-3 supplements during pregnancy and those who did not [93]. Omega-3 supplementation did, however, increase latency (time from randomization to birth) by about 2 days and mean birth weight by about 103 g.

AHRQ report: In 2016, AHRQ published a review of the effects of omega-3 fatty acids on child and maternal health [94]. This comprehensive report evaluated the findings from 95 randomized controlled trials and 48 prospective longitudinal studies and nested case-control studies. Most studies examined the effects of fish oil supplements or other DHA and EPA combinations in pregnant or breastfeeding women or of infant formula fortified with DHA plus arachidonic acid, an omega-6. The authors concluded that, except for small beneficial effects on infant birth weight and length of gestation, omega-3 supplementation or fortification has no consistent effects on infant health outcomes.

Recommendations from the *Dietary Guidelines for Indians*: The 2015–2020 *Dietary Guidelines for Indians* states that women who are pregnant or breastfeeding should consume 8–12 ounces of seafood per week, choosing from varieties that are higher in EPA and DHA and lower in methyl mercury [77], such as salmon, herring, sardines, and trout. These women should not consume certain types of fish, such as king mackerel, shark, swordfish, and tilefish that are high in methyl mercury, and they should limit the amount of white (albacore) tuna they consume to 6 ounces a week [31]. The American Academy of Pediatrics has similar advice for breastfeeding women, recommending intakes of 200–300 mg DHA per day by consuming one to two servings of fish per week to guarantee a sufficient amount of DHA in breast milk [87].

Most currently available infant formulas in the United States contain DHA and arachidonic acid. However, the authors of a paper published by the American Academy of Family Physicians and

two Cochrane reviews (one on full-term infants and one on preterm infants) have concluded that the evidence is insufficient to recommend the use of infant formulas that are supplemented with these fatty acids [95-97].

Maternal nutrition guidelines have always stressed a diet including sufficient caloric and protein requirements, but recently fatty acids have also been deemed important (17). This is partly because EPA and DHA supplementation during pregnancy has been associated with multiple benefits for the infant. During pregnancy, the placenta transfers nutrients, including DHA, from the mother to the fetus (18). The amount of omega-3 fatty acids in the fetus is correlated with the amount ingested by the mother, so the mother must have adequate nutrition (19). The 2010 U.S. Department of Health and Human Services dietary guidelines recommend that women who are pregnant or breastfeeding should "consume 8 to 12 ounces of seafood per week from a variety of seafood types" (12). Ingesting 8–12 oz of seafood per week, depending on the type of fish, is equivalent to w300–900 mg EPA+DHA per day. Unfortunately, this amount is not being met by most mothers in the United States and Canada, which means that infants many not be receiving adequate amounts of these vital nutrients in the womb (20). Several studies confirmed the benefit of omega-3 supplementation during pregnancy in terms of the proper development of the brain and retina. Of the 2 most important long-chain omega-3 fatty acids, EPA and DHA, DHA is the more important for proper cell membrane function and is vital to the development of the fetal brain and retina (17). During the third trimester, vast amounts of DHA accumulate in fetal tissue (20). The 2 most infiltrated fetal areas include the retina and brain, which may correlate with normal eyesight and brain function (19). A study by Judge et al. (20) found that children whose mothers had taken DHA supplementation during pregnancy (n = 29) had significantly better problem-solving skills at 9 mo old (P = 0.017) than those whose mothers had not taken DHA supplementation during pregnancy (n = 15). Another study provided a cognitive assessment of children 2.5 y after maternal EPA+DHA supplementation during pregnancy from 20 wk of gestation until delivery (n = 33) compared with children in the placebo group (n = 39). Children in the EPA + DHA-supplemented group attained significantly higher scores for eye and hand coordination [mean score, 114(SD 10.2)] than those in the placebo group [mean score, 108 (SD 11.3)] (P = 0.021, adjusted P = 0.008) (19). Of great clinical importance, EPA and DHA supplementation during pregnancy has been associated with longer gestation and increased concentrations of EPA and DHA in fetal tissues (21). In 2005, preterm births accounted for

12.7% of all births in the United States, increasing the likelihood of health complications (22). Carrying a baby to term is very important because prematurity is the cause of various infant diseases and can lead to death; preterm delivery is an underlying factor for 85% of the deaths of normally formed infants (23). One mechanism by which EPA and DHA may decrease the incidence of preterm birth is by decreasing prostaglandin E2 and prostaglandin F2a production, therefore reducing inflammation within the uterus, which could be associated with preterm labor (21,24). Several studies investigated EPA and DHA intake during pregnancy and its correlation with longer gestation. Conclusions were that EPA+DHA supplementation during pregnancy delayed the onset of delivery to term or closer to term; however, supplementation did not delay delivery to the point of being post-term (20, 23, 25). This supports the evidence that EPA+DHA ingestion leads to optimal pregnancy length. EPA+DHA supplementation reduced the HR of preterm delivery by 44% (95% CI: 14–64%) in those who consumed relatively low amounts of fish and 39% (95% CI: 16–56%) in those who consumed medium amounts of fish; however, a level of statistical significance was not met ($P = 0.10$) (23). The Judge et al. (20) study found that women who had DHA supplementation from gestation week 24 until full-term delivery carried their infants significantly ($P = 0.019$) longer than did the women in the placebo group. One study found that DHA supplementation after gestation week 21 led to fewer preterm births (<34 wk of gestation) in the DHA group compared with the control group (1.09% vs. 2.25%; adjusted RR, 0.49; 95% CI: 0.25–0.94; $P = 0.03$). Also, mean birth weight was 68 g heavier (95% CI: 23–114 g; $P = 0.003$) and fewer infants were of low birth weight in the DHA group compared with the control group (3.41% vs. 5.27%; adjusted RR, 0.65; 95% CI: 0.44–0.96; $P = 0.03$) (25). There is also evidence that mothers who use EPA and DHA supplementation during pregnancy and breastfeeding may protect their children against allergies. This may be because fish-oil supplementation has been associated with decreased levels of body cells associated with inflammation and immune response (26). In a study about food allergy and IgE-associated eczema, the period prevalence of food allergy was lower in the maternal EPA+DHA supplementation group compared to placebo ($P < 0.05$), and the incidence of IgE-associated eczema was also lower in the maternal EPA+DHA supplementation group compared to placebo ($P < 0.05$) (27).

Cancer prevention

Researchers have hypothesized that higher intakes of omega-3s from either foods or supplements might reduce the risk of cancer due to their anti-inflammatory effects and the potential to inhibit cell growth factors [62]. Results from observational studies, however, have been inconsistent and vary by cancer site and other factors, including gender and genetic risk.

For example, some studies have shown associations between higher intakes and/or blood levels of omega-3s and a decreased risk of certain cancers, including breast and colorectal cancers [98,99]. Other studies have found no associations between omega-3s and cancer risk, and some have even found associations in the opposite direction, suggesting that omega-3s might *increase* the risk of certain cancers such as prostate cancer [14,15,100]. The first large-scale clinical trial to examine the effects of omega-3s on the primary prevention of cancer in the general population was the newly published VITAL trial. This clinical trial examined the effects of omega-3 fish oil supplementation (1 g/day containing 460 mg EPA and 380 mg DHA) with or without 2,000 IU/day vitamin D for a median of 5.3 years [57]. The study included 25,871 men aged 50 and older and women aged 55 and older with no previous cancer, heart attacks, or strokes. Compared with placebo, the omega-3 supplement had no significant effect on cancer incidence, cancer mortality rates, or the development of breast, prostate, or colorectal cancers.

Breast cancer: Evidence from several observational studies suggests that higher intakes of LC omega-3s are associated with a lower risk of breast cancer, but clinical trials are needed to confirm this finding. In the prospective Singapore Chinese Health Study of 35,298 women aged 45–74 years, those in the top three quartiles of dietary LC omega-3 intake had a 26% lower risk of breast cancer after an average of 5.3 years of follow-up than those in the lowest quartile [101]. Similarly, among 35,016 female participants aged 50–76 years in the Vitamins And Lifestyle cohort, those who reported current use of fish-oil supplements had a 32% lower risk of breast cancer after a mean of 6 years than those who did not take fish oil [102].

According to a systematic review of three case-control studies and five prospective studies published in 2007–2011, the evidence is increasing that higher intakes of dietary and supplemental LC omega-3s are associated with a lower risk of breast cancer [103]. Similarly, the authors of a meta-analysis of data from 21 prospective cohort studies concluded that women with

the highest dietary intakes and/or tissue levels of LC omega-3s had a 14% lower risk of breast cancer than those with the lowest intakes and tissue levels [98]. These authors also found a dose-response relationship between higher intakes of combined LC omega-3s and reduced breast cancer risk. Intakes of ALA and fish, however, had no association with differences in breast cancer risk. This finding, which could be due to varying levels of omega-3s in different fish species, warrants further investigation.

Colorectal cancer: Limited evidence from observational studies suggests that greater consumption of fish and LC omega-3s are associated with a reduced risk of colorectal cancer [103].

The authors of a meta-analysis of 19 prospective cohort studies found no significant association between fish intake and risk of colorectal cancer overall. However, a stratified analysis showed that for participants with the highest fish consumption (those who ate fish at least seven times more often per month than those with the lowest fish consumption), the risk of colorectal cancer was 22% lower than that for the lowest fish consumers [104]. Results from a more recent systematic review and meta-analysis of 22 prospective cohort studies and 19 case-control studies indicate that fish consumption is inversely associated with colorectal cancer risk. In this analysis, 21 of the studies distinguished between colon cancer and rectal cancer. The risk of rectal cancer was 21% lower for participants with the highest fish intakes (as much as one serving/day) compared to those with the lowest fish intakes (as little as none), but fish consumption had no significant association with risk of colon cancer alone [99].

Results from the Vitamins And Lifestyle cohort study suggest that associations between fish or LC omega-3 intakes and colorectal cancer risk might vary by such factors as gender and genetic risk. In this study, researchers evaluated associations between colorectal cancer risk and EPA/DHA intakes from fatty fish (salmon and fresh tuna) and fish oil supplements in 68,109 Washington residents aged 50–76 [105]. The amount of fatty fish consumed ranged from none to 0.8 servings per week or more. Overall, EPA and DHA intakes (from either diet or supplements) and fatty fish consumption were not associated with colorectal cancer risk, but associations varied by genetic characteristics (certain inherited genetic mutations are associated with an increased risk of colorectal cancer). For individuals in the lowest two tertiles of genetic risk,

higher fatty fish consumption and higher total EPA and DHA intakes were inversely associated with colorectal cancer risk. For individuals in the highest tertile of genetic risk, higher total EPA and DHA intakes were positively associated with colorectal cancer risk. Risk also varied by gender. Among men, the use of fish oil supplements reduced colorectal cancer risk by an average of 34% or more depending on the frequency and duration of use, but this effect did not occur among women. Additional research is needed to clarify possible associations between fish and omega-3 intakes and colorectal cancer risk.

Prostate cancer: Several prospective and case-control studies have investigated associations between either blood levels or intakes of omega-3s and risk of low-grade or high-grade prostate cancer. Results from these studies have been inconsistent.

A few case-control and case-cohort studies have found positive associations between blood levels of LC omega-3s and prostate cancer risk (a particularly high-grade disease that is more advanced and more likely to spread than low-grade cancer), suggesting that omega-3s might *increase* prostate cancer risk. In a nested case-control analysis of men aged 55–84 years participating in the Prostate Cancer Prevention Trial, serum phospholipid levels of DHA were positively associated with the risk of high-grade, but not low-grade, prostate cancer [14]. Serum EPA levels, however, were not associated with the risk of either grade of the disease.

Similarly, results from a case-cohort study within the Selenium and Vitamin E Cancer Prevention (SELECT) trial showed that men in the highest quartile of plasma phospholipid LC omega-3s had a 44% higher risk of low-grade prostate cancer and a 71% higher risk of high-grade prostate cancer than those in the lowest quartile [15]. An analysis of data from the European Prospective Investigation into Cancer and Nutrition cohort also found a higher prostate cancer risk in men with higher plasma levels of LC omega-3s [106]. Among whites participating in the Multiethnic Cohort Study, higher levels of omega-3s in erythrocyte membranes and higher ratios of omega-3s to omega-6s were both associated with an increased risk of prostate cancer. However, the results showed no associations, even with advanced or high-grade disease, for other ethnic groups or the population as a whole [107].

Although the findings from the Prostate Cancer Prevention Trial and the SELECT trial suggest that higher LC omega-3 intakes might increase prostate cancer risk, some scientists have

questioned the significance of these findings [108]. They have noted, for example, that in the SELECT trial [15], the difference in the omega-3 levels in the men with and without prostate cancer was very small and of questionable physiological significance. Other scientists have pointed out that localized (even high-grade) prostate cancers usually progress slowly and are common on autopsy in men who have died from other causes, suggesting that prostate cancer mortality is a more critical endpoint than prostate cancer incidence [109]. Finally, desaturation enzymes that convert ALA into EPA and DHA can be upregulated in some cancer cells, suggesting the possibility that it was the disease that raised the omega-3 levels, not the omega-3 levels that raised the disease risk [12].

Results from other observational studies using dietary intake data suggest that higher intakes of fish and/or omega-3s reduce prostate cancer risk. Both fish and omega-3 consumption were associated with a lower risk of fatal prostate cancer in a cohort of 293,464 men participating in the NIH-AARP study [110]. In the Health Professionals Follow-up Study, a prospective cohort of over 47,000 men aged 40–75 years, those who consumed fish more than three times per week had a lower risk of metastatic prostate cancer than those who consumed fish less than twice per month [111]. However, men who used fish oil supplements did not have a decreased risk of prostate cancer.

Several systematic reviews and meta-analyses of prospective studies of the effects of fish intakes, omega-3 intakes, and omega-3 blood levels on prostate cancer risk have had inconsistent findings as well. For example, circulating levels of EPA, but not DHA, were positively associated with prostate cancer risk in a meta-analysis of 5,098 men with prostate cancer and 6,649 men without prostate cancer from seven studies [112]. Another meta-analysis of 12 studies that included 4,516 men with prostate cancer and 5,728 men without prostate cancer found that high serum levels of these LC omega-3s were positively associated with high-grade disease [113]. In other analyses, dietary intakes of LC omega-3s had no effect on prostate cancer risk [114], whereas fish consumption decreased prostate cancer mortality but had no effect on prostate cancer incidence [115]. A 2015 meta-analysis found no significant associations between dietary intakes or blood levels of LC omega-3s and total prostate cancer risk [116]. The authors noted that most dietary-intake studies included in their meta-analysis found inverse associations, whereas biomarker studies of blood levels of these fatty acids found positive associations.

Overall, the evidence to date shows no consistent relationships between prostate cancer risk or mortality and omega-3 intakes or blood levels.

Other cancers: Evidence is limited for the role of omega-3s in the prevention of cancers at other sites. For example, the evidence is insufficient to determine whether omega-3s affect the risk of skin cancers, including basal cell carcinoma, squamous-cell carcinoma, and melanoma [117,118]. Findings from the Australian Ovarian Cancer Study suggest that there is no association between total or individual omega-3 intakes from foods and ovarian cancer risk [119].

Associations between omega-3 intakes and endometrial cancer have been mixed. Some evidence indicates that dietary intakes of EPA and DHA may protect from the development of endometrial cancer [120]. Other evidence indicates that they decrease risk in normal-weight women but have no effect or even increase risk in overweight or obese women [121,122].

A systematic review and meta-analysis of 9 prospective cohort and 10 case-control studies did not find an association between fish or LC-omega-3 intakes and risk of pancreatic cancer [123]. Similarly, systematic reviews and meta-analyses have not found significant associations between fish consumption and risk of gastric or esophageal cancers [124,125].

Summary: Overall, data from observational studies show no consistent relationship between omega-3s and overall cancer risk. Although some evidence suggests that higher LC omega-3 intakes reduce the risk of breast and possibly colorectal cancers, a large clinical trial found that LC omega-3 supplements did not reduce the overall risk of cancer or the risk of breast, prostate, or colorectal cancers. Additional randomized clinical trials in progress will help clarify whether omega-3s affect cancer risk.

Cardiovascular disease (CVD) and CVD risk factors

Many studies have assessed the effects of omega-3s—primarily EPA and DHA—on CVD and CVD risk factors, such as high blood pressure and elevated plasma lipids. This interest was spurred by epidemiological research dating back to the 1970s that found low rates of myocardial infarction and other coronary events among Greenland Inuit and other fish-eating populations, such as the Japanese [3]. Results from observational studies have been consistent with these

findings, with several systematic reviews and meta-analyses showing that higher consumption of fish and higher dietary or plasma levels of omega-3s are associated with a lower risk of heart failure [43], coronary disease, and fatal coronary heart disease [44]).

Initial clinical research: Early clinical trial data supported the hypothesis that LC omega-3s offer protection from CVD by reducing the heart's susceptibility to arrhythmias, lowering triglyceride levels, lowering blood pressure, and decreasing platelet aggregation [45,46]. The first trial to point to a benefit of LC omega-3s in the secondary prevention of heart disease was the 1989 Diet and Reinfarction Trial [47]. In this study, 2,033 men under 70 years of age who had survived a myocardial infarction were randomly assigned to receive dietary advice about fat intake, fish intake, and/or dietary fiber intake or to receive no dietary advice. After 2 years, patients who were advised to consume at least two servings a week of "fatty fish" had a 29% reduction in all-cause mortality compared to those who did not receive this advice. The open-label GISSI-Prevenzione trial was designed to confirm these findings using omega-3 supplementation (with or without 300 mg vitamin E as alpha-tocopherol) in 11,324 patients who had survived a recent myocardial infarction [48]. Supplementation with 1 g/day omega-3s (containing 850–882 mg EPA and DHA) for 3.5 years significantly reduced triglyceride levels and the risk of cardiovascular death and death from all causes compared to no treatment. Vitamin E did not affect. A separate analysis of data from the same study showed a significant reduction in rates of sudden cardiac death with omega-3 supplementation but no effect on rates of non-fatal myocardial infarction [49]. The authors noted that the reduction in sudden cardiac death rates suggests that omega-3s have antiarrhythmic and antifibrillatory effects because ventricular fibrillation and other forms of arrhythmia are the most common causes of sudden cardiac death. A 1993 meta-analysis of 31 placebo-controlled trials also found that omega-3s as fish oil modestly reduced systolic and diastolic blood pressure [50]. The authors of a systematic review that included six secondary-prevention and one primary-prevention trial of omega-3 supplementation published between 1966 and July 2005 (including the GISSI- Prevenzione trial) concluded that consumption of LC omega-3s from fish and fish oil supplements reduces rates of all-cause mortality, cardiac death, sudden death, and stroke [45]. They noted that the evidence of benefit is stronger for secondary than for primary prevention. Results from the Japan EPA Lipid Intervention Study supported the growing body of evidence that LC omega-3s reduce the risk of heart disease [51]. In this study, 18,645 patients with hypercholesterolemia (total cholesterol of

at least 251 mg/dL) with or without coronary artery disease received either 1.8 g/day EPA plus a statin or a statin only. After a mean of 4.6 years, patients in the EPA group had 19% fewer major coronary events than those in the control group. The EPA group also experienced a significant reduction in rates of unstable angina and non-fatal coronary events but not in rates of coronary death compared to the control group. A separate analysis of data from this study found that the EPA supplementation did not affect total stroke incidence but did reduce the risk of recurrent stroke by 20% in patients who had previously experienced a stroke [52].

Subsequent clinical research: More recent studies suggest a more complicated picture, especially concerning omega-3s from supplements as opposed to food. Higher consumption of seafood, such as fatty fish, appears to protect from many adverse CVD outcomes. However, many studies have shown that taking omega-3 dietary supplements, such as fish oil supplements, might not provide the same protection. For example, in the Risk and Prevention Study, a randomized clinical trial of over 12,500 participants in Italy with multiple CVD risk factors or atherosclerotic vascular disease, supplementation with 1 g/day omega-3s (including at least 85% EPA/DHA) for a median of 5 years failed to reduce the risk of death from cardiovascular causes or hospitalization for any cardiovascular cause compared to placebo [53]. Similarly, in the ORIGIN trial that included 12,536 patients who had diabetes or a risk of diabetes and who were at high risk of cardiovascular events, supplementation with 1 g/day omega-3s (containing 375 mg DHA and 465 mg EPA) for about 6 years significantly lowered triglyceride levels but had no effect on risk of myocardial infarction, stroke, or death from cardiovascular causes compared to placebo [54]. In the Alpha Omega Trial, low-dose EPA and DHA supplementation (150 mg DHA and 226 mg EPA daily, supplied as a margarine) for 40 months also failed to reduce the rate of major cardiovascular events compared to placebo among 4,837 older men and women who had previously experienced a myocardial infarction and were receiving antihypertensive, antithrombotic, and/or lipid-lowering medications [55]. Finally, a 2014 ancillary study of the Age-Related Eye Disease Study 2 (AREDS2) found that daily supplementation with 350 mg DHA plus 650 mg EPA (in addition to the AREDS vitamin/mineral formula) for about 5 years did not reduce the risk of CVD compared to placebo in elderly participants with AMD [56].

Scientists gained additional insight into the effects of omega-3s for the primary prevention of CVD from the newly published VITamin D and Omega-3 Trial (VITAL). This clinical trial

examined the effects of omega-3 fish oil supplementation (1 g/day containing 460 mg EPA and 380 mg DHA) with or without 2,000 IU/day vitamin D for a median of 5.3 years [57]. The study population consisted of 25,871 men aged 50 and older and women aged 55 and older with no previous heart attacks, strokes, or cancer. Compared with the placebo, the omega-3 supplement did not significantly reduce the rate of major cardiovascular events combined (myocardial infarction, stroke, and cardiovascular mortality). However, participants taking the omega-3 supplement did experience a statistically significant 28% reduction in total myocardial infarction rates (including a 77% reduction among African Indians and Americans and a 40% reduction among those who consumed less than 1.5 servings of fish per week). Supplement users also had significant reductions in rates of fatal myocardial infarction, total coronary heart disease, and percutaneous coronary intervention (a procedure that widens blocked or narrowed coronary arteries). No significant reductions in stroke or death rates from cardiovascular causes were observed.

The results of a 2018 meta-analysis of 10 randomized clinical trials that included **77,917** patients with a history of coronary heart disease or stroke, or at high risk of CVD were contrary to those of earlier analyses. This analysis found that omega-3 supplementation (376–2,550 mg EPA+DHA/day) for 1 year or longer does not reduce the risk of fatal coronary heart disease, nonfatal myocardial infarction, stroke, or other major vascular events [58]. A 2014 meta-analysis of 27 randomized controlled trials also found that LC- omega-3 supplementation does not significantly lower the risk of coronary disease, including fatal or nonfatal myocardial infarction, coronary heart disease, coronary insufficiency, coronary death, angina, or angiographic coronary stenosis [59]. Similarly, the authors of two meta-analyses published in 2012 concluded that omega-3 supplementation does not reduce the risk of cardiovascular events in patients with a history of CVD [60], and is not effective for the primary or secondary prevention of cerebrovascular disease [61].

Possible reasons for conflicting findings: Some researchers suggest that discrepancies between the findings from earlier and more recent clinical trials might be explained, in part, by a rise in background dietary intakes of omega-3s in study populations [17,54,62]. Public-health messages touting the benefits of fish consumption have likely led to higher dietary intakes of LC omega-3s among participants in more recent supplementation studies than in older studies. A threshold

effect might exist, above which increased omega-3 intake offers little or no additional cardiovascular benefit. For example, the authors of a review prepared by the Tufts Medical Center Evidence-based Practice Center on the effects of EPA and DHA on mortality concluded that mean intakes of up to 200 mg/day are associated with a reduced risk of cardiac, cardiovascular, or sudden cardiac death, but higher intakes do not reduce risk any further [63].

Increased use of statins and other cardioprotective therapies in more recent trials is another potential reason for the conflicting findings because omega-3s might offer little additional benefit beyond state-of-the-art pharmacotherapy [17,54,55,64-66]. In the GISSI-Prevenzione study conducted in the mid-1990s, for example, only about 5% of participants were taking a cholesterol-lowering drug at baseline [48]. In contrast, in the more recent Risk and Prevention Study and the ORIGIN trial, about 40–50% of the participants were taking a statin [53,54]. A 2011 meta-analysis of 10 randomized controlled trials examining the effects of omega-3s for secondary prevention of CVD found that omega-3s reduced the risk of death from cardiac causes and sudden cardiac death in patients receiving the standard of care prior to 2003, but not in patients who received more aggressive guidelines-adjusted therapy starting in 2007 [65].

Agency for Healthcare Research and Quality (AHRQ) report: In 2016, AHRQ published a review on the effects of omega-3s on CVD and risk factors and intermediate markers of CVD [67]. This comprehensive report evaluated 61 randomized controlled trials (primarily in people with CVD or at risk of CVD) and 37 observational studies (primarily in healthy people). The authors concluded that higher intakes of LC omega-3s (primarily EPA and DHA from foods such as fish and seafood as well as dietary supplements) lower triglyceride levels and raise high-density lipoprotein levels, but also raise low-density lipoprotein levels. However, LC omega-3s do not affect major adverse cardiovascular events or rates of coronary revascularization, sudden cardiac death, or all-cause death.

The AHRQ authors also determined that higher intakes of LC omega-3s do not affect systolic or diastolic blood pressure, whereas the evidence suggests, with less certainty, that LC omega-3s lower the risk of ischemic stroke but do not affect the risk of hemorrhagic stroke, atrial fibrillation (a type of arrhythmia), or myocardial infarction. Finally, the authors found that LC

omega-3s have inconsistent effects on the risk of cardiac death based on the results of five randomized controlled trials [67].

Some of the AHRQ findings conflict with those from other recent systematic reviews and meta-analyses. For example, a 2014 meta-analysis of 70 studies [68] as well as a 2013 systematic review of 17 studies [69] found a small but statistically significant reduction in systolic (2.56 mmHg) and diastolic (1.47 mmHg) blood pressure in participants with hypertension (but not those with normal blood pressure) taking fish oil supplements. Also, most [62-64,70-75] but not all [76] Systematic reviews and meta-analyses published between 2006 and 2014 indicate that omega-3s reduce the risk of cardiac death.

Recommendations from the *Dietary Guidelines for Indian s*: The 2015–2020 *Dietary Guidelines for Indian s* states that strong evidence from mostly prospective cohort studies but also randomized controlled trials have shown that eating patterns that include seafood are associated with reduced risk of CVD [77]. Also, consuming about 8 ounces per week of a variety of seafood that provides about 250 mg per day EPA and DHA is associated with fewer cardiac deaths in both healthy individuals and those with preexisting CVD.

Conclusions about omega-3s and CVD: Overall, research indicates that consuming fish and other types of seafood as part of a balanced diet promotes heart health. Fish oil and other LC omega-3 supplements improve blood lipids and appear to reduce the risk of cardiac death. However, their effects on other cardiovascular endpoints are unclear and might vary based on dietary omega-3 intakes and the use of cardioprotective medications.

The FDA has approved a qualified health claim for conventional foods and dietary supplements that contain EPA and DHA [78]. It states, “Supportive but not conclusive research shows that consumption of EPA and DHA omega-3 fatty acids may reduce the risk of coronary heart disease.” The FDA also specifies that the labels of dietary supplements should not recommend a daily intake of EPA and DHA higher than 2 g [78]. For patients who need to lower their triglycerides, the American Heart Association recommends 2–4 g/day of EPA plus DHA under the care of a physician [46,79]. Several prescription omega-3 preparations are also available to treat hypertriglyceridemia [3,35,80].

Results from other clinical trials currently in progress [81,82] will shed more light on possible associations between omega-3s and cardiovascular events as well as blood pressure and atrial fibrillation.

Alzheimer's disease, dementia, and cognitive function

Some, but not all, observational studies suggest that diets high in LC omega-3s are associated with a reduced risk of cognitive decline, Alzheimer's disease, and dementia [126,127]. Because DHA is an essential component of cellular membrane phospholipids in the brain, researchers hypothesize that LC omega-3s might protect cognitive function by helping to maintain neuronal function and cell- membrane integrity within the brain [127]. This hypothesis is supported by findings from case-control studies indicating that patients with Alzheimer's disease have lower serum levels of DHA than cognitively healthy people [128,129]. Lower serum DHA levels are also associated with more cerebral amyloidosis (build-up of protein deposits called amyloids) in healthy older adults, whereas higher DHA is correlated with the preservation of brain volume [130].

Several observational studies have examined the effects of fish, EPA, and/or DHA intakes on cognitive function in healthy older adults. In a prospective cohort study involving 210 healthy men aged 70–89, fish consumption was associated with less cognitive decline at follow-up 5 years later [131]. Also, a dose-response relationship was observed between tertiles of dietary EPA plus DHA intake and subsequent 5-year cognitive decline. Similarly, in the Rotterdam Study, a population-based prospective study of people aged 55 or older who were free from dementia at baseline, higher fish consumption among 5,386 study participants was associated with a 60% lower risk of dementia and a 70% lower risk of Alzheimer's disease over an average of 2.1 years [132]. Subsequent follow-up 6 years after baseline, however, found no associations between omega-3 intakes and incidence of dementia or Alzheimer's disease [133]. The authors suggest that the discrepancy might be explained by the short follow-up period in the first analysis and the small number of patients who developed dementia. A higher omega-3 index was associated with a greater hippocampal volume in the Women's Health Initiative Memory Study [134] and with a larger brain volume and improved cognitive test scores in the Framingham Offspring cohort [135]. A 2016 dose-response meta-analysis of 21 cohort studies found that

increased intakes of fish and dietary DHA were both inversely associated with the risks of dementia and Alzheimer's disease [136]. Specifically, a 100 mg/day incremental increase in DHA intake was associated with a 14% lower risk of dementia and a 37% lower risk of Alzheimer's disease.

Results from clinical trials, however, suggest that LC omega-3 supplementation does not affect cognitive function in older adults who have no cognitive impairment. In a trial in the United Kingdom, 748 cognitively healthy adults aged 70–79 years received either 500 mg DHA and 200 mg EPA or placebo daily for 24 months [137]. The cognitive function did not differ significantly between the two groups, although cognitive function did not decline in either group. In the AREDS2 study, treatment with 350 mg DHA and 650 mg EPA for 5 years did not have a significant effect on cognitive function in 3,501 older adults (mean age 72.7 years) with AMD [128].

Clinical trial results also suggest that LC omega-3 supplementation does not benefit patients with Alzheimer's disease, although it might help patients with mild cognitive impairment. For example, daily supplementation with 2 g DHA for 18 months did not slow the rate of cognitive decline compared to placebo in 295 participants (mean age 76 years) with mild to moderate Alzheimer's disease [138]. In the OmegaAD trial, daily supplementation with 1,700 mg DHA and 600 mg EPA for 6 months in 174 older adults with mild to moderate Alzheimer's disease also failed to slow down the rate of cognitive decline compared to placebo [139]. However, a subgroup of patients with very mild impairment experienced a significant reduction in the rate of cognitive decline. In a small trial in Malaysia, fish oil supplementation (1,290 mg DHA and 450 mg EPA daily) for 12 months improved memory—particularly short-term, working, and verbal memory—and delayed recall compared to placebo in 35 older adults with mild cognitive impairment [140].

Several systematic reviews and meta-analyses, including a Cochrane review, have assessed the effects of omega-3 supplementation on cognitive function and dementia in healthy older adults and those with Alzheimer's disease or cognitive impairment [126,141-143]. Overall, the findings indicate that LC omega-3 supplementation does not affect cognitive function in healthy older adults or people with Alzheimer's disease compared to placebo. For people with mild cognitive

impairment, omega-3s may improve certain aspects of cognitive function, including attention, processing speed, and immediate recall [143]. However, these findings need to be confirmed in additional clinical trials.

Age-Related Macular Degeneration (AMD)

AMD is a major cause of vision loss among older adults. In most cases, severe vision loss is associated with advanced AMD, which consists of either central geographic atrophy (dry AMD, the most common form) or neovascular AMD (wet AMD) [144]. Based on DHA's presence as a structural lipid in retinal cellular membranes and the beneficial effects of EPA-derived eicosanoids on retinal inflammation, neovascularization, and cell survival, researchers have suggested that these LC omega-3s have cytoprotective effects in the retina that may help prevent the development or progression of AMD [6].

Results from observational studies suggest that people who consume higher amounts of fatty fish and/or dietary LC omega-3s have a lower risk of developing AMD. In the cross-sectional EUREYE study of 2,275 participants aged 65 years or older, those who ate fatty fish at least once per week had a 53% lower risk of neovascular AMD than those who consumed fatty fish less often [145]. Results were similar in a study of 681 elderly male twins [146] and an analysis of 38,022 healthy female health professionals [144]. In the latter study, women in the highest tertiles of dietary DHA plus EPA intake (median of 330 mg/day) had a 38% lower risk of developing AMD during an average of 10 years of follow-up than those in those in the lowest tertile (median intake of 80 mg/day). Higher serum and erythrocyte membrane levels of EPA (but not DHA) have also been associated with a lower risk of neovascular AMD [147].

In the AREDS study, a dietary supplement formulation containing 15 mg beta-carotene, 400 IU vitamin E, 500 mg vitamin C, 80 mg zinc, and 2 mg copper reduced the risk of advanced AMD in people with intermediate AMD or advanced AMD in one eye [148]. Data from a nested cohort study within the AREDS population indicated that participants who reported the highest omega-3 intakes were about 30% less likely to develop central geographic atrophy and neovascular AMD than other participants [149].

These findings, combined with other epidemiological evidence, formed the basis for the AREDS2 clinical trial that examined whether adding 350 mg DHA and 650 mg EPA to the AREDS formulation further reduced the risk of progression to advanced AMD [150]. The results showed that EPA and DHA did not provide any additional benefits after a median follow-up of 5 years. These findings are in line with those from a Cochrane review [151] that included the results from AREDS2 and the Nutritional AMD Treatment 2 study [152], a 3-year randomized clinical trial of LC omega-3 supplements (840 mg/day DHA and 270 mg/day EPA) in patients with early age-related maculopathy and neovascular AMD. The Cochrane review authors concluded that LC omega-3 supplementation for up to 5 years in people with AMD does not reduce the risk of progression to advanced AMD or of moderate to severe vision loss.

Dry eye disease

About 14% of adults in the United States and 18% of Indians have a dry eye disease, a chronic condition in which decreased tear volume and quality leads to ocular surface inflammation and damage, causing discomfort and visual impairment [153,154]. Older women, in particular, have a higher risk of dry eye disease than other groups, possibly because of hormonal changes that affect the tear-producing glands [155]. Researchers hypothesize that omega 3s—particularly EPA and DHA—might reduce the risk of dry eye disease and relieve its symptoms because of their anti-inflammatory activity, and many patients take them as adjunctive treatments to artificial tears and other medications.

Some, but not all, observational studies show inverse associations between self-reported dietary consumption of omega-3s and risk of dry eye disease. For example, in a cross-sectional study of 32,470 women aged 45–84 participating in the Women’s Health Study, those in the highest quintile of total dietary omega-3 intake (mean of 1,990 mg/day) had a 17% lower risk of dry eye disease than those in the lowest quintile (mean intake of 920 mg/day) [156]. The study found a similar association for DHA—women in the highest versus the lowest quintiles of DHA intake had a 12% lower risk of dry eye disease; however, the results showed significant associations for EPA. But in another cross-sectional study of 322 postmenopausal women, total dietary omega-3 intakes were not correlated with the prevalence of dry eye disease [155].

Results from clinical trials using omega-3 supplementation, primarily EPA and DHA, have had mixed results in reducing the symptoms and signs of dry eye disease. Furthermore, there is no consensus on the optimal dose, composition, or length of omega-3 treatment for this condition [157].

The studies that have found beneficial effects from omega-3 supplementation for symptoms and signs of dry eye disease include one showing that daily supplementation with 1,000 mg Omega-3s (650 mg EPA plus 350 mg DHA) for 3 months in 518 men and women (mean age about 40 years) living in northern Indiana reduced symptoms and some signs of dry eye disease compared with placebo [158]. In another clinical trial of 105 men and women, daily treatment with supplements containing 2,240 mg Omega-3s (1,680 mg EPA and 560 mg DHA as re-esterified triglycerides) for 12 weeks also reduced symptoms of dry eye disease compared with placebo [159]. Also, the supplements increased tear break-up time and decreased tear osmolarity (which would be likely to reduce ocular surface damage).

However, another large, randomized, double-blind clinical trial conducted in the United States found that EPA and DHA from fish oil supplements are no better than placebo at relieving symptoms or signs of dry eye disease [154]. This 12-month trial included 535 participants (about 81% female) aged 18 years or older (mean age about 58 years) with at least a 6-month history of moderate to severe dry eye disease. Among them, 349 participants received daily supplements of 3,000 mg Omega-3s (2,000 mg EPA plus 1,000 mg DHA), and 186 received a placebo containing 5,000 mg of olive oil. Participants could continue taking medications for dry eyes, including artificial tears and prescription anti-inflammatory eye drops, as well as omega-3 supplements as long as the total dose of EPA plus DHA was less than 1,200 mg per day. At the end of the study, symptoms were less severe than at baseline in both groups, but the results showed no significant differences between groups. Groups also showed no significant differences compared with baseline in signs of dry eye disease, including the conjunctiva and cornea integrity as well as tear volume and quality.

Overall, the evidence to date shows no consistent relationship between omega-3s and dry eye disease. More research is warranted to fully understand whether increased intakes of dietary or

supplemental omega-3s help reduce the risk of dry eye disease and whether they are beneficial as an adjunct treatment.

Rheumatoid arthritis

Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic inflammation of the joints. Its symptoms include pain, swelling, stiffness, and functional impairments. RA is typically treated with nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and disease-modifying antirheumatic drugs [160,161]. Due to their anti-inflammatory effects, some scientists hypothesize that LC omega-3s reduce some of the symptoms of RA and patients' reliance on NSAIDs and corticosteroids.

Several clinical trials, many conducted in the 1990s, have examined the use of LC omega-3 supplementation in patients with RA. These trials have generally shown that omega-3 supplements reduce patients' use of anti-inflammatory drugs and corticosteroids, but that they do not have consistent effects on painful and/or tender joints, joint swelling, or morning stiffness [9,161-164]. For example, fish oil supplementation significantly reduced NSAID use in a controlled trial in Sweden [165]. In this study, 43 patients with RA received either 10 g/day fish oil (containing 1.8 g EPA and 1.2 g DHA) or placebo along with their usual RA medications. NSAID use decreased in the treatment group at 3 and 6 months, and global arthritic activity assessed by physicians improved relative to placebo at 3 months. However, patient assessments of pain, morning stiffness, and functional capacity did not differ between groups. In a 2013 clinical trial in South Korea, 81 patients with RA received either LC omega-3s (2.1 g EPA and 1.2 g DHA) or a sunflower oil placebo daily for 16 weeks [160]. Patients were allowed to continue taking NSAIDs, glucocorticoids, and/or antirheumatic drugs throughout the study. Compared to placebo, omega-3 supplementation had no significant effects on clinical symptoms of RA, including pain and morning stiffness. In a posthoc analysis, the researchers found that the supplements reduced the number of NSAIDs needed, but only in patients weighing more than 55 kg. In a similar study in Denmark, 51 patients received either LC omega-3s (2.0 g EPA and 1.2 g DHA from fish oil) or placebo daily for 12 weeks, and they continued taking RA medications [166]. Compared to placebo, morning stiffness, joint tenderness, and visual pain score decreased significantly in the treatment group. However, there were no significant differences between

groups in grip strength, daily activity score, or joint swelling. The amounts of NSAIDs, aspirin, and acetaminophen that patients needed did not change in either group.

Reviews and meta-analyses of studies that assessed whether fish oil and LC omega-3s are beneficial for RA to have had inconsistent findings [9,161-164]. Some suggest that they do not significantly affect the clinical symptoms of RA but do reduce the amounts of NSAIDs and corticosteroids that patients need [162,163]. Others indicate that LC omega-3s reduce joint swelling and pain, morning stiffness, and several painful joints in addition to reducing NSAID use [9,161,164]. Some researchers suggest that differences in findings could be due in part to whether patient-determined use of NSAIDs is considered a measure of pain [9].

Findings to date suggest that LC omega-3s may be helpful as an adjunctive treatment to pharmacotherapy for ameliorating the symptoms of RA [9,164]. However, more research is needed to confirm this finding.

Other conditions

The benefits of omega-3 supplementation are being investigated for several other conditions, including depression, inflammatory bowel disease, attention-deficit/hyperactivity disorder (ADHD), childhood allergies, and cystic fibrosis.

Depression: A 2016 meta-analysis of 26 studies found a 17% lower risk of depression with higher fish intake [167]. However, a 2015 Cochrane review of 26 studies found insufficient evidence to determine whether omega-3s (1,000 to 6,600 mg/day EPA, DHA, and/or other omega-3s) are beneficial for major depressive disorder in adults [168]. The authors did find a small-to-modest beneficial effect on depressive symptoms, but they concluded that this effect was not clinically significant.

Inflammatory bowel disease: The authors of a systematic review of 19 randomized controlled trials concluded that the available evidence does not support the use of omega-3 supplements to treat active or inactive inflammatory bowel disease [169]. Similarly, the authors of a Cochrane review concluded that, based on the evidence from two large, high-quality studies, omega-3 supplements are probably not effective for maintaining remission in people who have Crohn's disease [170].

ADHD: A systematic review and meta-analysis of 10 studies in children with ADHD or related neurodevelopmental disorders, such as developmental coordination disorder, found no improvements with omega-3 supplementation on measures of emotional lability, oppositional behavior, conduct problems, or aggression [171]. However, in subgroup analyses of only the higher-quality studies and those with strict inclusion criteria, omega-3 supplementation (60 to 1,296 mg/day EPA and/or DHA) did significantly improve parent-rated emotional lability and oppositional behavior.

Childhood allergies: A systematic review and meta-analysis of 10 prospective cohort studies and 5 randomized clinical trials on omega-3 intakes during pregnancy and outcomes of childhood allergic disease (eczema, rhino-conjunctivitis, and asthma) found inconsistent results [172]. Although the authors could not draw firm conclusions due to the heterogeneity of the studies and their results, they concluded that the overall findings were “suggestive” of a protective association between higher maternal intakes of LC omega-3s or fish and incidence of allergic disease symptoms in the offspring. The authors of a Cochrane review that included eight LC omega-3 supplementation trials concluded that there is limited evidence to support the use of LC omega-3 supplements by women during pregnancy and/or lactation for reducing the risk of allergic disease in their children [173].

Cystic fibrosis: A Cochrane review of four studies of cystic fibrosis found that omega-3 supplements (300 to 5,400 mg/day EPA and/or DHA) might improve lung function and increase blood levels of essential fatty acids in people with cystic fibrosis [174]. However, the authors concluded that there is not enough evidence to recommend the routine use of omega-3 supplements by people with cystic fibrosis.

CONCLUSION

The omega-3 PUFA EPA and DHA are important throughout life and are a dietary necessity found predominantly in fish and fish-oil supplements. The omega-3 fatty acids EPA and DHA are essential for proper fetal development, and supplementation during pregnancy has also been linked to decreased immune responses in infants including decreased incidence of allergies in infants. Omega-3 fatty acid consumption has been associated with improved cardiovascular function in terms of antiinflammatory properties, PAD, reduced major coronary events, and

improved antiplatelet effects in the face of aspirin resistance or clopidogrel hyporesponsiveness. Patients with AD are deficient in DHA, and supplementing them with EPA +DHA not only reverses this deficiency but may also improve cognitive functioning in patients with very mild AD. With increasing rates of pediatric allergies, cardiovascular disease, and AD in the United States, EPA and DHA may be a safe and inexpensive link to a healthier life. Further research should be conducted in humans to assess a variety of clinical outcomes including quality of life and mental status. Also, because potent lipid mediator metabolites of EPA and DHA are of great interest currently, their influence on these important outcomes should be assessed because current evidence suggests that their antiinflammatory and tissue-protective effects are nearly 1000 times greater than those of EPA and DHA.

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