National Institutes of Health
Office of Dietary Supplements

Omega-3 Fatty Acids

Fact Sheet for Health Professionals

Collapse All

Introduction

The two major classes of polyunsaturated fatty acids (PUFAs) are the omega-3 and omega-6 fatty acids. Like all fatty acids, PUFAs consist of long chains of carbon atoms with a carboxyl group at one end of the chain and a methyl group at the other. PUFAs are distinguished from saturated and monounsaturated fatty acids by the presence of two or more double bonds between carbons within the fatty acid chain.

Omega-3 fatty acids (omega-3s) have a carbon–carbon double bond located three carbons from the methyl end of the chain. Omega-3s, sometimes referred to as n-3s, are present in certain foods such as flaxseed and fish as well as dietary supplements such as fish oil. Several different omega-3s exist, but the majority of scientific research focuses on three: alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). ALA contains 18 carbon atoms, whereas EPA and DHA are considered long-chain (LC) omega-3s because EPA contains 20 carbons and DHA contains 22.

PUFAs are frequently designated by their number of carbon atoms and double bonds. ALA, for example, is known as C18:3n-3 because it has 18 carbons and 3 double bonds and is an n-3, or omega-3, fatty acid. Similarly, EPA is known as C20:5n-3 and DHA as C22:6n-3. Omega-6 fatty acids (omega-6s) have a carbon–carbon double bond that is six carbons away from the methyl end of the fatty acid chain. Linoleic acid (C18:2n-6) and arachidonic acid (C20:4n-6) are two of the major omega-6s.

The human body can only form carbon–carbon double bonds after the ninth carbon from the methyl end of a fatty acid [1]. Therefore, ALA and linoleic acid are considered essential fatty acids, meaning that they must be obtained from the diet [2]. ALA can be converted into EPA and then to DHA, but the conversion (which occurs primarily in the liver) is very limited, with reported rates of less than 15% [3]. Therefore, consuming EPA and DHA directly from foods and/or dietary supplements is the only practical way to increase levels of these fatty acids in the body.

ALA is present in plant oils, such as flaxseed, soybean, and canola oils [3]. DHA and EPA are present in fish, fish oils, and krill oils, but they are originally synthesized by microalgae at the base of the marine food chain, not by the fish. As microalgae move up the food chain, fish acquire the omega-3s and accumulate them in their tissues [3].

After ingestion, dietary lipids are hydrolyzed in the intestinal lumen [1]. The hydrolysis products—monoglycerides and free fatty acids—are then incorporated into bile-salt– containing micelles and absorbed into enterocytes, largely by passive diffusion. The process is efficient, with an absorption rate of about 95%, which is similar to that of other ingested fats [1]. Within intestinal cells, free fatty acids are primarily incorporated into chylomicrons and enter the circulation via the lymphatic system [1,4]. Once in the

bloodstream, lipoprotein particles circulate within the body, delivering lipids to various organs for subsequent oxidation, metabolism, or storage in adipose tissue [4,5].

Omega-3s play important roles in the body as components of the phospholipids that form the structures of cell membranes [5]. DHA, in particular, is especially high in the retina, brain, and sperm [3,5,6]. In addition to their structural role in cell membranes, omega-3s (along with omega-6s) provide energy for the body and are used to form eicosanoids. Eicosanoids are signaling molecules that have similar chemical structures to the fatty acids from which they are derived; they have wide-ranging functions in the body's cardiovascular, pulmonary, immune, and endocrine systems [1,2].

The eicosanoids made from omega-6s are generally more potent mediators of inflammation, vasoconstriction, and platelet aggregation than those made from omega-3s, although there are some exceptions [3,7]. Because both classes of fatty acids compete for the same desaturation enzymes, ALA is a competitive inhibitor of linoleic acid metabolism and vice versa [8]. Similarly, EPA and DHA can compete 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 important implications for the pathogenesis of many chronic diseases, such as cardiovascular disease (CVD) and cancer [8], but the optimal ratio—if any—has not been defined [10]. Others have concluded that such ratios are too nonspecific and are insensitive to individual fatty acid levels [11-13]. Most agree that raising EPA and DHA blood levels is far more important than lowering linoleic acid or arachidonic acid levels.

Currently, most clinicians do not assess omega-3 status, but it can be done by measuring individual omega-3s in plasma or serum phospholipids and expressing them as the percentage of total phospholipid fatty acids by weight [14-16]. Experts have not established normal ranges, but mean values for serum or plasma phospholipid EPA plus DHA among U.S. adults not taking omega-3 supplements are about 3%–4% [14-16]. Plasma and serum fatty acid values, however, can vary substantially based on an individual's most recent meal, so they do not reflect long-term dietary consumption [3,17].

It is also possible to assess omega-3 status via analysis of erythrocyte fatty acids, a measurement that reflects longer term intakes over approximately the previous 120 days [18,19]. The omega-3 index proposed by Harris and von Schacky reflects the content of EPA plus DHA in erythrocyte membranes expressed as a percentage of total erythrocyte fatty acids [20,21]. This index can be used as a surrogate for assessing tissue levels of EPA plus DHA [16,22,23]. EPA and DHA typically comprise about 3%–5% of erythrocyte fatty acids in Western populations with low fish intakes. In Japan, where fish consumption is high, erythrocyte EPA and DHA levels are about twice those of Western populations [3].

Recommended Intakes

Intake recommendations for fatty acids and other nutrients are provided in the Dietary Reference Intakes (DRIs) developed by the Food and Nutrition Board of the Institute of Medicine (IOM) (now called the National Academy of Medicine) [5]. DRI is the general term for a set of reference values used for planning and assessing nutrient intakes of healthy people. These values, which vary by age and sex, include the following:

- Recommended Dietary Allowance (RDA): Average daily level of intake sufficient to meet the nutrient requirements of nearly all (97%–98%) healthy individuals; often used to plan nutritionally adequate diets for individuals
- Adequate Intake (AI): Intake at this level is assumed to ensure nutritional adequacy; established when evidence is insufficient to develop an RDA
- Estimated Average Requirement (EAR): Average daily level of intake estimated to meet the requirements of 50% of healthy individuals; usually used to assess the nutrient intakes of groups of people and to plan nutritionally adequate diets for them; can also be used to assess the nutrient intakes of individuals
- Tolerable Upper Intake Level (UL): Maximum daily intake unlikely to cause adverse health effects

When the IOM last reviewed omega-3s, insufficient data were available to establish an EAR, so the IOM established AIs for all ages based on omega-3 intakes in healthy populations [5].

Table 1 lists the current AIs for omega-3s in grams per day. Human milk contains omega-3s as ALA, EPA, and DHA, so the IOM established an AI for infants from birth to 12 months that is equivalent to the mean intake of omega-3s in healthy, breastfed infants.

For infants, the AIs apply to total omega-3s. For age 1 and older, the AIs apply only to ALA because ALA is the only omega-3 that is essential. The IOM did not establish specific intake recommendations for EPA, DHA, or other LC omega-3s.

Table 1: Adequate Intakes (AIs) for Omega-3s [5]

Age	Male	Female	Pregnancy	Lactation
Birth to 6 months*	0.5 g	0.5 g		
7–12 months*	0.5 g	0.5 g		
1–3 years**	0.7 g	0.7 g		
4–8 years**	0.9 g	0.9 g		
9–13 years**	1.2 g	1.0 g		
14–18 years**	1.6 g	1.1 g	1.4 g	1.3 g
19–50 years**	1.6 g	1.1 g	1.4 g	1.3 g
51+ years**	1.6 g	1.1 g		

*As total omega-3s
**As ALA

Sources of Omega-3s

Food

Plant oils that contain ALA include flaxseed (linseed), soybean, and canola oils [2,3]. Chia seeds and walnuts also contain ALA.

The omega-3 content of fish varies widely. Cold-water fatty fish, such as salmon, mackerel, tuna, herring, and sardines, contain high amounts of LC omega-3s, whereas fish with a lower fat content—such as bass, tilapia,

and cod—as well as shellfish contain lower levels [3]. The omega-3 content of fish also depends on the composition of the food that the fish consumes [24]. Farmed fish usually have higher levels of EPA and DHA than wild-caught fish, but it depends on the food they are fed [24,25]. An analysis of the fatty acid composition of farm-raised Atlantic salmon from Scotland showed that the EPA and DHA content significantly decreased between 2006 and 2015 due to the replacement of traditional marine ingredients in fish feed with other ingredients [26].

Beef is very low in omega-3s, but beef from grass-fed cows contains somewhat higher levels of omega-3s, mainly as ALA, than that from grain-fed cows [27].

Some foods, such as certain brands of eggs, yogurt, juices, milk, and soy beverages, are fortified with DHA and other omega-3s. Since 2002, manufacturers have added DHA and arachidonic acid (the two most prevalent LC PUFAs in the brain) to most infant formulas available in the United States [28].

Several food sources of ALA, DHA, and/or EPA are listed in Table 2. The U.S. Food and Drug Administration (FDA) has established a Daily Value (DV) of 65 g for total fat but not for omega-3s. Thus, Table 2 presents the amounts of omega-3 fatty acids in grams per serving only and not the percent of the DV.

Table 2: ALA, EPA, and DHA Content of Selected Foods [29]

Food	Grams per serving		
	ALA	DHA	EPA
Flaxseed oil, 1 tbsp	7.26		
Chia seeds, 1 ounce	5.06		
English walnuts, 1 ounce	2.57		
Flaxseed, whole, 1 tbsp	2.35		
Salmon, Atlantic, farmed, cooked, 3 ounces		1.24	0.59
Salmon, Atlantic, wild, cooked, 3 ounces		1.22	0.35
Herring, Atlantic, cooked, 3 ounces*		0.94	0.77
Canola oil, 1 tbsp	1.28		
Sardines, canned in tomato sauce, drained, 3 ounces*		0.74	0.45
Mackerel, Atlantic, cooked, 3 ounces*		0.59	0.43
Salmon, pink, canned, drained, 3 ounces*	0.04	0.63	0.28
Soybean oil, 1 tbsp	0.92		
Trout, rainbow, wild, cooked, 3 ounces		0.44	0.40
Black walnuts, 1 ounce	0.76		
Mayonnaise, 1 tbsp	0.74		
Oysters, eastern, wild, cooked, 3 ounces	0.14	0.23	0.30
Sea bass, cooked, 3 ounces*		0.47	0.18
Edamame, frozen, prepared, ½ cup	0.28		
Shrimp, cooked, 3 ounces*		0.12	0.12
Refried beans, canned, vegetarian, ½ cup	0.21		
Lobster, cooked, 3 ounces*	0.04	0.07	0.10

Food	Grams per serving		
	ALA	DHA	EPA
Tuna, light, canned in water, drained, 3 ounces*		0.17	0.02
Tilapia, cooked, 3 ounces*	0.04	0.11	
Scallops, cooked, 3 ounces*		0.09	0.06
Cod, Pacific, cooked, 3 ounces*		0.10	0.04
Tuna, yellowfin, cooked 3 ounces*		0.09	0.01
Kidney beans, canned, ½ cup	0.10		
Baked beans, canned, vegetarian, ½ cup	0.07		
Ground beef, 85% lean, cooked, 3 ounces**	0.04		
Bread, whole wheat, 1 slice	0.04		
Egg, cooked, 1		0.03	
Chicken, breast, roasted, 3 ounces		0.02	0.01
Milk, low-fat (1%), 1 cup	0.01		

*Except as noted, the U.S. Department of Agriculture (USDA) database does not specify whether fish are farmed or wild caught.
**The USDA database does not specify whether beef is grass fed or grain fed.

The USDA's FoodData Central (https://fdc.nal.usda.gov/) website [29] lists the nutrient content of many foods and provides a comprehensive list of foods containing ALA arranged by nutrient content and by food name, foods containing DHA arranged by nutrient content and by food name, and foods containing EPA arranged by nutrient content and by food name.

Dietary Supplements

LC omega-3s are present in several dietary supplement formulations, including fish oil, krill oil, cod liver oil, and vegetarian products that contain algal oil. A typical fish oil supplement provides about 1,000 mg fish oil, containing 180 mg EPA and 120 mg DHA, but doses vary widely [30]. Cod liver oil supplements provide vitamin A and vitamin D in addition to LC omega-3s. Although seafood contains varying levels of methyl mercury (a toxic heavy metal) [31], omega-3 supplements have not been found to contain this contaminant because it is removed during processing and purification [32].

Dietary supplements can contain several different forms of omega-3s, including natural triglycerides, free fatty acids, ethyl esters, re-esterified triglycerides, and phospholipids [32-34]. Natural triglycerides are the form that occur naturally in fish oil, whereas ethyl esters are synthesized from natural triglycerides by replacement of the glycerol molecule of the triglyceride with ethanol. Re-esterified triglycerides are formed by the conversion of ethyl esters back to triglycerides. Omega-3s as re-esterified triglycerides, natural triglycerides, and free fatty acids have somewhat higher bioavailability than ethyl esters, but consumption of all forms significantly increases plasma EPA and DHA levels [33,35].

Krill oil contains omega-3s primarily as phospholipids. Some studies suggest that these phospholipids have somewhat higher bioavailability than the omega-3s in fish oil, whereas other studies do not [34,36,37,38,39,40,41,42].

Plant-based sources of omega-3s from algal oil usually provide around 100–300 mg DHA; some contain EPA as well. These supplements typically contain omega-3s in the triglyceride form [32]. According to a small study, the bioavailability of DHA from algal oil is equivalent to that from cooked salmon [43].

Formulations of omega-3 dietary supplements vary widely, so it is important to check product labels to determine the types and amounts of omega-3s in these products. The Dietary Supplement Label Database (http://www.dsld.nlm.nih.gov/dsld/) from the National Institutes of Health contains label information from many dietary supplements on the market that contain omega-3s.

Omega-3 Intakes and Status

According to data from the 2011–2012 National Health and Nutrition Examination Survey (NHANES), most children and adults in the United States consume recommended amounts of omega-3s as ALA [44]. Among children and teens age 2–19 the average daily ALA intake from foods is 1.32 g for females and 1.55 g for males. In adults age 20 and over, the average daily ALA intake from foods is 1.59 g in females and 2.06 g in males.

Consumption of DHA and EPA from foods contributes a very small amount to total daily omega-3 intakes (about 40 mg in children and teens and about 90 mg in adults) [44]. Use of dietary supplements containing omega-3s also contributes to total omega-3 intakes. Fish oil is one of the most commonly used nonvitamin/nonmineral dietary supplements by U.S. adults and children [45,46]. Data from the 2012 National Health Interview Survey indicate that 7.8% of U.S. adults and 1.1% of U.S. children use supplements containing fish oil, omega-3s, and/or DHA or EPA [45,46]. According to an analysis of 2003–2008 NHANES data, use of these supplements adds about 100 mg to mean daily ALA intakes, 10 mg to mean DHA intakes, and 20 mg to mean EPA intakes in adults [47].

Omega-3 Deficiency

A deficiency of essential fatty acids—either omega-3s or omega-6s—can cause rough, scaly skin and dermatitis [5]. Plasma and tissue concentrations of DHA decrease when an omega-3 fatty acid deficiency is present. However, there are no known cut-off concentrations of DHA or EPA below which functional endpoints, such as those for visual or neural function or for immune response, are impaired.

Groups at Risk of Omega-3 Inadequacy

Evidence that higher LC omega-3 levels are associated with a reduced risk of several chronic diseases, including coronary heart disease, suggests that many Americans could benefit from slightly higher intakes. However, classical essential fatty acid deficiency in healthy individuals in the United States is virtually nonexistent [5]. During periods of dietary-fat restriction or malabsorption accompanied by an energy deficit, the body releases essential fatty acids from adipose-tissue reserves. For this reason, clinical signs of essential fatty-acid deficiency are usually only found in patients receiving parenteral nutrition that lacks PUFAs. This was documented in case reports during the 1970s and 1980s [5], but all current enteral and parenteral feeding solutions contain adequate levels of PUFAs.

Omega-3s and Health

The potential health benefits of consuming omega-3s are the focus of a great deal of scientific research. By far, the majority of research has focused on EPA and DHA from foods (e.g., fish) and/or dietary supplements (e.g., fish oil) as opposed to ALA from plant-based foods.

Many observational studies link higher intakes of fish and other seafood with improved health outcomes. However, it is difficult to ascertain whether the benefits are due to the omega-3 content of the seafood (which varies among species), other components in the seafood, the substitution of seafood for other less healthful foods, other healthful behaviors, or a combination of these factors. Data from randomized clinical trials are needed to shed light on these questions.

This section focuses on areas of health in which omega-3s might be involved: CVD and its risk factors; infant health and neurodevelopment; cancer prevention; Alzheimer's disease, dementia, and cognitive function; age-related macular degeneration; dry eye disease; rheumatoid arthritis; and other conditions.

Cardiovascular disease and cardiovascular disease 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 those in Japan [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, coronary disease, and fatal coronary heart disease [48,49].

Initial clinical research

Clinical trial data from the 1989 Diet and Reinfarction Trial, the 1999 open-label GISSI-Prevenzione trial, and others 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 [50-55]. The authors of a systematic review that included six secondary-prevention trials and one primary-prevention trial of omega-3 supplementation published between 1966 and 2005 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 [50]. They noted that the evidence of benefit is stronger for secondary than for primary prevention.

Results from the Japan EPA Lipid Intervention Study in 2007 supported the growing body of evidence that LC omega-3s reduce the risk of heart disease, especially in people with a history of coronary artery disease [56]. In this study, 18,645 people 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, the EPA group had 19% fewer major coronary events than the control group. The EPA group also experienced a significant reduction in rates of unstable angina and nonfatal coronary events but not in rates of sudden cardiac death or coronary death in comparison with the control group.

In an analysis of the primary prevention subgroup from this study (participants with no history of coronary artery disease), EPA supplementation had no significant effects on any outcome. However, for the secondary prevention subgroup (those with a history of coronary artery disease), the EPA group had a 28% reduction in the rate of unstable angina and a 19% reduction in that of major coronary events. 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 [57].

Several subsequent clinical trials, however, had largely null findings [58-60]. For example, the 2012 Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial included 12,536 patients who had diabetes or a high risk of diabetes and a high risk of cardiovascular events. Supplementation with 1 g/day omega-3s (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 in comparison with placebo [59]. Similarly, in the 2010 Alpha Omega Trial, low-dose EPA and DHA supplementation (150 mg DHA and 226 mg EPA daily, supplied in a margarine) for 40 months also failed to reduce the rate of major cardiovascular events in comparison with 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 [60].

Recent clinical trials

Scientists gained additional insight into the effects of omega-3s for the primary prevention of CVD, including in patients with diabetes, from two 2018 trials: VITamin D and OmegA-3 TriaL (VITAL) and A Study of Cardiovascular Events in Diabetes (ASCEND) [61,62]. Both trials compared the same 1 g/day omega-3 formulation (460 mg EPA and 380 mg DHA) with placebo, but in different populations. VITAL included 25,871 men age 50 and older and women age 55 and older with no previous heart attacks, strokes, or cancer, whereas ASCEND included 15,480 adults age 40 or older with diabetes but no evidence of CVD. VITAL also tested the omega-3 supplement with and without 2,000 International Units (IU)/day vitamin D.

In VITAL, the omega-3 supplement did not significantly reduce the rate of major cardiovascular events combined (myocardial infarction, stroke, and cardiovascular mortality) after a median of 5.3 years [62]. 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 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.

ASCEND had similar findings [61]. After a mean follow-up of 7.4 years, the omega-3 supplement did not significantly affect the risk of a serious vascular event (composite of nonfatal myocardial infarction or stroke, transient ischemic attack, and cardiovascular death, excluding intracranial hemorrhage) or revascularization. However, omega-3 supplementation did significantly reduce the risk of cardiovascular death by 19% in comparison with placebo.

The 2019 Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT) found significant CVD benefits with Vascepa, a high-dose, prescription form of omega-3s containing EPA in the form of icosapent ethyl (IPE), an ethyl ester [63]. REDUCE-IT included 8,179 participants with CVD age 45

years or older or with diabetes and at least one other risk factor age 50 years or older. All participants had a fasting triglyceride level of 135 to 499 mg/dL even though they were receiving statin therapy, and an LDL cholesterol level of 41 to 100 mg/dL. Participants received either 4 g/day IPE or a placebo of mineral oil for a median of 4.9 years. IPE significantly reduced rates of cardiovascular events (a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, and unstable angina) by 25%. IPE also significantly reduced rates of other outcomes, including cardiovascular death by 20%, fatal or nonfatal stroke by 28%, and fatal or nonfatal myocardial infarction by 31%.

A subsequent 2020 clinical trial known as STRENGTH (Long-Term Outcomes Study to Assess Statin Residual Risk with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia) found no significant CVD benefits with Epanova, a high-dose, prescription form of omega-3s containing EPA and DHA in a carboxylic acid form (omega-3 CA) [64]. STRENGTH included 13,078 participants from 22 countries (mean age 62.5 years) at high cardiovascular risk, including hypertriglyceridemia, low HDL cholesterol, diabetes, and established CVD. Participants received either 4 g/day omega-3 CA or a placebo of corn oil in addition to their usual therapies, including statins, for a projected trial duration of 4.5 years. However, the trial was stopped after participants were treated for a median of about 3.5 years when the probability of benefit from omega-3 CA appeared low and the supplemented group had a higher incidence of atrial fibrillation. Omega-3 CA did not significantly reduce the composite end point of cardiovascular death, myocardial infarction, stroke, coronary revascularization, or hospitalization for unstable angina.

Possible reasons for conflicting findings

The omega-3 form, study population, background dietary omega-3 intakes, and use of statins and other cardioprotective therapies might explain some conflicting findings among studies [17,59,60,65-72]. In addition, dose probably plays a major role in the ability of omega-3 supplementation to confer significant benefits [65]. The REDUCE-IT findings suggest that a high daily dose of IPE, 4 g, is an effective adjunct to statin therapy in people with CVD or a high risk of CVD [63]. The daily dose of 1 g used in many studies of omega-3 dietary supplements might affect some CVD pathways [65] but has had no significant effect on the primary outcomes in several trials [59,61,62].

However, both the REDUCE-IT and STRENGTH studies used similar doses of omega-3s (4 g/day) but reported significant CVD benefit in the former and none in the latter. The reasons for the different results are not clear, but a partial explanation—beyond differences in the omega-3 formulation (ethyl ester EPA vs. carboxylic acid EPA and DHA) and the baseline health of the study population—may lie with the different placebo comparators used, mineral oil in REDUCE-IT and corn oil in STRENGTH [64,73,74]. Mineral oil is not a neutral placebo; it affects lipid levels and inflammatory markers and may inhibit the absorption of statin drugs. Therefore, in REDUCE-IT, differences in CVD events between the treatment and placebo groups would likely be smaller if a more neutral placebo oil had been used.

Furthermore, in the clinical trials mentioned above, the effects of LC omega-3s are not uniform across CVD outcomes. Therefore, use of primary composite endpoints that combine multiple outcomes might dilute significant effects on individual components of those endpoints [67].

Recent reviews and meta-analyses

A 2019 systematic review and meta-analysis of 13 trials included ASCEND, VITAL, and REDUCE-IT (but not STRENGTH) and a total of 127,477 participants [67]. LC omega-3 doses ranged from 0.376 to 4 g/day, and

the mean treatment duration was 5 years. The authors concluded that LC-omega-3 supplementation reduces the risk of myocardial infarction, coronary heart disease death, total coronary heart disease, CVD death, and total CVD and the effects appear to be dose related. However, the findings showed no significant associations for risk of fatal and nonfatal stroke. The authors noted that REDUCE-IT reduced risk of stroke significantly [63], suggesting that a higher dose of omega-3s (4 g/day) might be needed to affect this outcome.

A 2020 Cochrane Review of 86 randomized controlled trials published between 1968 and 2019 found that 0.5 g/day to more than 5 g/day LC omega-3s for 12 to 88 months in a total of 162,796 participants reduced serum triglyceride levels by about 15% and slightly decreased rates of cardiovascular mortality and coronary heart disease events [75]. However, the supplements did not affect all-cause mortality, cardiovascular events, stroke, or arrhythmia. The authors of several earlier meta-analyses and systematic reviews, as well as a 2016 report from the Agency for Healthcare Research and Quality (AHRQ), concluded that omega-3 supplements do not appear to significantly reduce the risk of most cardiovascular events [68-70,76-87]. Many of these analyses [68-70,81-86], however, but not all [80,87], did find that omega-3s reduce the risk of cardiac death.

Recommendations from the American Heart Association and the Dietary Guidelines for Americans

Between 2017 and 2019, the American Heart Association (AHA) released three science advisories on omega-3s [66,88,89]. All three advisories recommend one to two servings of seafood per week to reduce the risk of congestive heart failure, coronary heart disease, ischemic stroke, and sudden cardiac death, especially when the seafood replaces less healthy foods [66]. For people with existing coronary heart disease, such as a recent myocardial infarction, the AHA recommends approximately 1 g/day EPA plus DHA, preferably from oily fish; however, supplements could also be considered under the direction of a physician [88]. The AHA does not recommend omega-3 supplements for people who do not have a high CVD risk.

To manage high triglyceride levels, the AHA concludes that 4 g/day prescription omega-3s (containing EPA plus DHA or EPA only) lower triglyceride levels when used alone or as adjuncts to other lipid-lowering medications [89]. Although this finding pertains to high-dose prescription omega-3s, an earlier analysis of 58 trials also revealed a dose-response relationship between lower-dose dietary and supplemental omega-3 intakes and triglyceride levels [90]. Each increase of 1 g/day of LC omega-3 reduced triglyceride levels by 5.9 mg/dL, and the effect was stronger in people with higher baseline triglyceride levels.

The 2015–2020 *Dietary Guidelines for Americans* states that strong evidence from mostly prospective cohort studies but also some randomized controlled trials shows that eating patterns that include seafood are associated with a reduced risk of CVD [91]. In addition, 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, especially when the seafood is consumed in place of less healthy foods. Fish oil and other LC omega-3 supplements lower triglyceride levels and might reduce the risk of some cardiovascular endpoints, especially among people with low dietary omega-3 intakes. Evidence of a protective effect for

omega-3 supplementation is stronger for people with existing coronary heart disease than for healthy individuals.

In 2004, FDA approved a qualified health claim for conventional foods and dietary supplements that contain EPA and DHA [92]. This health claim 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.” FDA also specifies that the labels of dietary supplements should not recommend a daily intake of EPA and DHA higher than 2 g [92].

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 [91]. 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 [93]. 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 [94]. It is not possible to establish causality, however, because all of these studies were observational.

Seafood contains varying levels of methyl mercury [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 [94-97].

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 [98]. 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 [99]. 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 [100]. 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 [101]. 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 [103]. 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 [103]. Omega-3 supplementation did, however, increase latency (time from randomization to birth) by about 2 days and mean birth weight by about 103 g.

Agency for Healthcare Research and Quality report

In 2016, AHRQ published a review on the effects of omega-3 fatty acids on child and maternal health [104]. 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 Americans

The 2015–2020 *Dietary Guidelines for Americans* 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 [91], 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 [97].

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 of 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 [105-107].

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 potential to inhibit cell growth factors [68]. 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 [102,103]. 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 [14,15,108]. 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 [62]. The study included 25,871 men age 50 and older and women age 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 age 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 [109]. Similarly, among 35,016 female participants age 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 [110].

According to a systematic review of three case-control studies and five prospective studies published in 2007–2011, evidence is increasing that higher intakes of dietary and supplemental LC omega-3s are associated with a lower risk of breast cancer [111]. 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 [112]. 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 of 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 is associated with a reduced risk of colorectal cancer [111].

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 [113]. 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 [114].

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 age 50–76 [115]. 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, 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 (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 age 55–84 years participating in the Prostate Cancer Prevention Trial, serum phospholipid levels of DHA were positively associated with risk of high-grade, but not low-grade, prostate cancer [14]. Serum EPA levels, however, were not associated with 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 [116]. 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 for the population as a whole [117].

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 [118]. 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 [119]. 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 [120]. In the Health Professionals Follow-up Study, a prospective cohort of more than 47,000 men age 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 [121]. However, men who used fish oil supplements did not have a decreased risk of prostate cancer.

A number of 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 [122]. 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 [123]. In other analyses, dietary intakes of LC omega-3s had no effect on prostate cancer risk [125], whereas fish consumption decreased prostate cancer mortality but had no effect on prostate cancer incidence [125]. A 2015 meta-analysis found no significant associations between dietary intakes or blood levels of LC omega-3s and total prostate cancer risk [126]. 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 a role of omega-3s in the prevention of cancers at other sites. For example, evidence is insufficient to determine whether omega-3s affect the risk of skin cancers, including basal-cell carcinoma, squamous-cell carcinoma, and melanoma [127,128]. 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 [129].

Associations between omega-3 intakes and endometrial cancer have been mixed. Some evidence indicates that dietary intakes of EPA and DHA may provide protection from the development of endometrial cancer [130]. Other evidence indicates that they decrease risk in women who are normal weight but have no effect or even increase risk in women with overweight or obesity [131,132].

A systematic review and meta-analysis of nine prospective cohort and 10 case-control studies did not find an association between fish or LC-omega-3 intakes and risk of pancreatic cancer [133]. Similarly, systematic reviews and meta-analyses have not found significant associations between fish consumption and risk of gastric or esophageal cancers [134,135].

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.

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 [136,137]. 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 [137]. 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 [138,139]. 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 preservation of brain volume [140].

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 age 70–89, fish consumption was associated with less cognitive decline at follow-up 5 years later [141]. In addition, 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 age 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 [142]. Subsequent follow-up 6 years after baseline, however, found no associations between omega-3 intakes and incidence of dementia or Alzheimer's disease [143]. 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 [144] and with a larger brain volume and improved cognitive test scores in the Framingham Offspring cohort [145]. 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 [146]. 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 age 70–79 years received either 500 mg DHA and 200 mg EPA or placebo daily for 24 months [147]. Cognitive function did not differ significantly between the two groups, although cognitive function did not decline in either group. In the Age-Related Eye Disease Study 2 (AREDS2) clinical trial, 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 age-related macular degeneration (AMD) [138].

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 [148]. 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 [149]. 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 [150].

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 [136,151-153]. Overall, the findings indicate that LC omega-3 supplementation does not affect cognitive function in healthy older adults or in 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 [153]. However, these findings need to be confirmed in additional clinical trials.

Age-Related Macular Degeneration

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) [154]. 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 age 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 [155]. Results were similar in a study in 681 elderly male twins [156] and an analysis of 38,022 healthy female health professionals [154]. 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 [157].

In the AREDS clinical trial, 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 [158]. 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 [159].

These findings, combined with other epidemiological evidence, formed the basis for the AREDS2 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 [160]. 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 [161] that included the results from AREDS2 and the Nutritional AMD Treatment 2 study [162], 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 have 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 [163,164]. 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 [165]. 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 age 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) [166]. 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 no significant associations for EPA. However, in another cross-sectional study of 322 postmenopausal women, total dietary omega-3 intakes were not correlated with the prevalence of dry eye disease [165].

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 [167].

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 India reduced symptoms and some signs of dry eye disease compared with placebo [168]. 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 [169]. In addition, 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 found that EPA and DHA from fish oil supplements are no better than placebo at relieving symptoms or signs of dry eye disease [164]. This 12-month trial included 535 participants (about 81% female) age 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 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 conjunctive and cornea integrity as well as tear volume and quality.

A subsequent clinical trial, an ancillary study of the VITAL trial described earlier, evaluated whether long-term daily supplementation with omega-3s prevents the development of dry eye disease in participants without the disease or not experiencing severe dry eye symptoms [170]. A total of 23,523 men and women (50 and 55 years of age or older, respectively) received either a daily supplement of 1,000 mg omega-3s (460 mg EPA and 380 mg DHA) or a placebo for a median of 5.3 years. The supplement had no significant effects on the incidence of diagnosed dry eye disease or severe disease symptoms.

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 [171].

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 [172,173]. 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 [9,173-176]. For example, fish oil supplementation significantly reduced NSAID use in a controlled trial in Sweden [177]. 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 [172]. 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 post-hoc analysis, the researchers found that the supplements reduced the amount 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 [178]. 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 have had inconsistent findings [9,173-176]. 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 [174,175]. Others indicate that LC omega-3s reduce joint swelling and pain, morning stiffness, and number of painful joints in addition to reducing NSAID use [9,173,176]. 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 [9,176]. 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 [179]. 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 [180]. 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 [181]. 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 [182].

Attention-deficit/hyperactivity disorder

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 [183]. 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 five randomized clinical trials on omega-3 intakes during pregnancy and outcomes of childhood allergic disease (eczema, rhino-conjunctivitis, and asthma) found inconsistent results [184]. 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 [185].

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 [186]. However, the authors concluded that there is not enough evidence to recommend routine use of omega-3 supplements by people with cystic fibrosis.

Summary

The potential benefits of omega-3s for these and other conditions require further study.

Safety of Omega-3s

For most macronutrients, the IOM has established an acceptable macronutrient distribution range (AMDR) that suggests an acceptable range of intake. The AMDR for total fat intake, for example, is based on adverse effects from either very low fat or very high fat diets. The IOM established an AMDR for omega-3s (as ALA) of 0.6% to 1.2% of energy for children and adults age 1 year and older [5]. The IOM also noted that about 10% of the AMDR can be consumed as EPA and/or DHA.

The IOM did not establish a UL for any omega-3s, although it noted that high doses of DHA and/or EPA (900 mg/day of EPA plus 600 mg/day DHA or more for several weeks) might reduce immune function due to suppression of inflammatory responses. Doses of 2–15 g/day EPA and/or DHA might also increase bleeding time by reducing platelet aggregation [5]. However, according to the European Food Safety Authority, long-term consumption of EPA and DHA supplements at combined doses of up to about 5 g/day appears to be safe [187]. It noted that these doses have not been shown to cause bleeding problems or affect immune function, glucose homeostasis, or lipid peroxidation. Similarly, FDA has concluded that dietary supplements providing no more than 5 g/day EPA and DHA are safe when used as recommended [188]. Two large clinical trials completed after these assessments found that taking 4 g/day of omega-3 supplements for several years slightly increased the risk of atrial fibrillation in people with CVD or at high risk of CVD [63,64].

Commonly reported side effects of omega-3 supplements are usually mild. These include unpleasant taste, bad breath, heartburn, nausea, gastrointestinal discomfort, diarrhea, headache, and odoriferous sweat [153,182].

Interactions with Medications

Omega-3 dietary supplements, such as fish oil, have the potential to interact with medications. One example is provided below. People taking these and other medications on a regular basis should discuss possible interactions with their health care providers.

Warfarin (Coumadin) and similar anticoagulants

Fish oil can have antiplatelet effects at high doses, although it appears to be less potent than aspirin [189,190]. Fish oil might prolong clotting times, as indicated by an elevated international normalized ratio (INR), when it is taken with warfarin [191], but most research indicates that doses of 3–6 g/day fish oil do not significantly affect the anticoagulant status of patients taking warfarin [192]. The authors of a 2014 review concluded that omega-3s do not affect the risk of clinically significant bleeding [193], and the FDA-approved package inserts for omega-3 pharmaceuticals state that studies with omega-3s have not produced "clinically significant bleeding episodes" [194]. However, these package inserts also state that patients taking these products with anticoagulants should be monitored periodically for changes in INR.

Omega-3s and Healthful Diets

The federal government's 2020–2025 *Dietary Guidelines for Americans* notes that "Because foods provide an array of nutrients and other components that have benefits for health, nutritional needs should be met primarily through foods. … In some cases, fortified foods and dietary supplements are useful when it is not possible otherwise to meet needs for one or more nutrients (e.g., during specific life stages such as pregnancy)"[91].

With respect to seafood and omega-3s, the *Dietary Guidelines for Americans* state that

- A healthy dietary pattern that consists of nutrient-dense forms of foods and beverages, including seafood, in recommended amounts and within calorie limits, supports health and helps minimize the risk of diet-related chronic diseases, such as cardiovascular disease, type 2 diabetes, and obesity.
- Seafood intake during pregnancy is recommended, as it is associated with favorable measures of cognitive development in young children.
- Women who might become or are pregnant or breastfeeding should consume at least 8 and up to 12 ounces of a variety of seafood per week, from choices that are lower in methyl mercury. Women who are pregnant or breastfeeding and young children should not eat certain types of fish that are high in methyl mercury.
- The recommendation to consume 8 or more ounces per week (less for young children) of seafood is for the total package of nutrients that seafood provides, including its EPA and DHA content. Some seafood choices with higher amounts of EPA and DHA should be included.
- Seafood varieties commonly consumed in the United States that are higher in EPA and DHA and lower in methyl mercury include salmon, anchovies, sardines, Pacific oysters, and trout.
- Tilapia, shrimp, catfish, crab, and flounder are commonly consumed varieties that also are lower in methyl mercury.
- For more information about building a healthy diet, refer to the *Dietary Guidelines for Americans* (https://www.dietaryguidelines.gov) and the USDA's MyPlate (http://www.choosemyplate.gov).

References

1. Jones PJH, Rideout T. Lipids, sterols, and their metabolites. In: Ross AC, Caballero B, Cousins RJ, Tucker KL, Ziegler TR, eds. Modern Nutrition in Health and Disease. 11th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2014.
2. Jones PJH, Papamandjaris AA. Lipids: cellular metabolism. In: Erdman JW, Macdonald IA, Zeisel SH, eds. Present Knowledge in Nutrition. 10th ed. Washington, DC: Wiley-Blackwell; 2012:132-48.
3. Harris WS. Omega-3 fatty acids. In: Coates PM, Betz JM, Blackman MR, et al., eds. Encyclopedia of Dietary Supplements. 2nd ed. London and New York: Informa Healthcare; 2010:577-86.
4. Lichtenstein AH, Jones PJH. Lipids: absorption and transport. In: Erdman JW, Macdonald IA, Zeisel SH, eds. Present Knowledge in Nutrition. 10th ed. Washington, DC: Wiley-Blackwell; 2012:118-31.
5. Institute 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.
6. 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;24:87-138. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/15555528/)]
7. Gabbs M, Leng S, Devassy JG, Monirujjaman M, Aukema HM. Advances in our understanding of oxylipins derived from dietary PUFAs. Adv Nutr 2015;6:513-40. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/26374175/)]
8. Simopoulos AP. The importance of the omega-6/omega-3 fatty acid ratio in cardiovascular disease and other chronic diseases. Exp Biol Med 2008;233:674-88. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/18408140/)]
9. James M, Proudman S, Cleland L. Fish oil and rheumatoid arthritis: past, present and future. Proc Nutr Soc 2010;69:316-23. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/20509981/)]
10. Wang C, Chung M, Lichtenstein A, Balk E, Kupelnick B, DeVine D, et al. Effects of omega-3 fatty acids on cardiovascular disease. (https://archive.ahrq.gov/downloads/pub/evidence/pdf/o3cardio/o3cardio.pdf) Summary, evidence report/technology assessment no. 94. (Prepared by the Tufts New England Medical Center Evidence-based Practice Center, Boston, MA.) AHRQ Publication No. 04-E009-1. Agency for Healthcare Research and Quality, 2004.
11. Stanley JC, Elsom RL, Calder PC, Griffin BA, Harris WS, Jebb SA, et al. UK Food Standards Agency workshop report: the effects of the dietary n-6:n-3 fatty acid ratio on cardiovascular health. Br J Nutr 2007;98:1305-10. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/18039412/)]
12. Harris WS, Davidson MH. RE: Plasma phospholipid fatty acids and prostate cancer risk in the SELECT trial. J Natl Cancer Inst 2014;106:dju019. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/24685928/)]
13. Fritsche KL. Too much linoleic acid promotes inflammation-doesn't it? Prostaglandins Leukot Essent Fatty Acids 2008;79:173-5. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/18990555/)]
14. Brasky TM, Till C, White E, Neuhouser ML, Song X, Goodman P, et al. Serum phospholipid fatty acids and prostate cancer risk: results from the prostate cancer prevention trial. Am J Epidemiol 2011;173:1429-39. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/21518693/)]
15. Brasky TM, Darke AK, Song X, Tangen CM, Goodman PJ, Thompson IM, et al. Plasma phospholipid fatty acids and prostate cancer risk in the SELECT trial. J Natl Cancer Inst 2013;105:1132-41. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/23843441/)]
16. Harris WS, Sands SA, Windsor SL, Ali HA, Stevens TL, Magalski A, et al. Omega-3 fatty acids in cardiac biopsies from heart transplantation patients: correlation with erythrocytes and response to

supplementation. Circulation 2004;110:1645-9. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/15353491/)]
17. Harris WS. Are n-3 fatty acids still cardioprotective? Curr Opin Clin Nutr Metab Care 2013;16:141-9. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/23196817/)]
18. Sun Q, Ma J, Campos H, Hankinson SE, Hu FB. Comparison between plasma and erythrocyte fatty acid content as biomarkers of fatty acid intake in US women. Am J Clin Nutr 2007;86:74-81. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/17616765/)]
19. Agency for Healthcare Research and Quality. Omega-3 fatty acids and cardiovascular disease - update. (https://effectivehealthcare.ahrq.gov/products/fatty-acids-cardiovascular-disease/research-protocol) 2015.
20. Harris WS, Von Schacky C. The Omega-3 Index: a new risk factor for death from coronary heart disease? Prev Med 2004;39:212-20. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/15208005/)]
21. Harris WS. The omega-3 index as a risk factor for coronary heart disease. Am J Clin Nutr 2008;87:1997S-2002S. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/18541601/)]
22. Metcalf RG, Cleland LG, Gibson RA, Roberts-Thomson KC, Edwards JR, Sanders P, et al. Relation between blood and atrial fatty acids in patients undergoing cardiac bypass surgery. Am J Clin Nutr 2010;91:528-34. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/20089730/)]
23. von Schacky C. Use of red blood cell fatty-acid profiles as biomarkers in cardiac disease. Biomark Med 2009;3:25-32. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/20477493/)]
24. Miller MR, Nichols PD, Carter CG. n-3 Oil sources for use in aquaculture--alternatives to the unsustainable harvest of wild fish. Nutr Res Rev 2008;21:85-96. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/19087364/)]
25. Cladis DP, Kleiner AC, Freiser HH, Santerre CR. Fatty acid profiles of commercially available finfish fillets in the United States. Lipids 2014;49:1005-18. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/25108414/)]
26. Sprague M, Dick JR, Tocher DR. Impact of sustainable feeds on omega-3 long-chain fatty acid levels in farmed Atlantic salmon, 2006-2015. Sci Rep 2016;6:21892. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/26899924/)]
27. Van Elswyk ME, McNeill SH. Impact of grass/forage feeding versus grain finishing on beef nutrients and sensory quality: the U.S. experience. Meat Sci 2014;96:535-40. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/24018274/)]
28. U.S. Food and Drug Administration. Questions & answers for consumers concerning infant formula. (http://www.fda.gov/food/foodborneillnesscontaminants/peopleatrisk/ucm108079.htm) 2015.
29. U.S. Department of Agriculture, Agricultural Research Service. FoodData Central (https://fdc.nal.usda.gov/), 2019.
30. National Institutes of Health. Dietary Supplement Label Database. (http://www.dsld.nlm.nih.gov/dsld) 2015.
31. U.S. Food and Drug Administration. Fish: what pregnant women and parents should know. (http://www.fda.gov/Food/FoodborneIllnessContaminants/Metals/ucm393070.htm) 2014.
32. ConsumerLab.com. Product review: fish oil and omega-3 fatty acid supplements review (including krill, algae, calamari, green-lipped mussel oil). (https://www.consumerlab.com/reviews/fish_oil_supplements_review/omega3) 2016.

33. Dyerberg J, Madsen P, Moller JM, Aardestrup I, Schmidt EB. Bioavailability of marine n-3 fatty acid formulations. Prostaglandins Leukot Essent Fatty Acids 2010;83:137-41. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/20638827/)]
34. Cunningham E. Are krill oil supplements a better source of n-3 fatty acids than fish oil supplements? J Acad Nutr Diet 2012;112:344. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/22459227/)]
35. Davidson MH, Kling D, Maki KC. Novel developments in omega-3 fatty acid-based strategies. Curr Opin Lipidol 2011;22:437-44. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/21986642/)]
36. Schuchardt JP, Schneider I, Meyer H, Neubronner J, von Schacky C, Hahn A. Incorporation of EPA and DHA into plasma phospholipids in response to different omega-3 fatty acid formulations--a comparative bioavailability study of fish oil vs. krill oil. Lipids Health Dis 2011;10:145. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/21854650/)]
37. Ulven SM, Holven KB. Comparison of bioavailability of krill oil versus fish oil and health effect. Vasc Health Risk Manag 2015;11:511-24. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/26357480/)]
38. Ramprasath VR, Eyal I, Zchut S, Jones PJ. Enhanced increase of omega-3 index in healthy individuals with response to 4-week n-3 fatty acid supplementation from krill oil versus fish oil. Lipids Health Dis 2013;12:178. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/24304605/)]
39. Ulven SM, Kirkhus B, Lamglait A, Basu S, Elind E, et al. 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;46(1):37-46. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/21042875/)]
40. Salem N Jr, Kuratko CN. A reexamination of krill oil bioavailability studies. Lipids Health Dis 2014;13:137. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/25156381/)]
41. Yurko-Mauro K, Kralovec J, Bailey-Hall E, Smeberg V, Stark JG, et al. Similar eicosapentaenoic acid and docosahexaenoic acid plasma levels achieved with fish oil or krill oil in a randomized double-blind four-week bioavailability study. Lipids Health Dis 2015;14:99. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/26328782/)]
42. 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;14:19. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/25884846/)]
43. Arterburn LM, Oken HA, Bailey Hall E, Hamersley J, Kuratko CN, Hoffman JP. Algal-oil capsules and cooked salmon: nutritionally equivalent sources of docosahexaenoic acid. J Am Diet Assoc 2008;108:1204-9. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/18589030/)]
44. U.S. Department of Agriculture, Agricultural Research Service. What we eat in America, 2011-2012. (http://www.ars.usda.gov/Services/docs.htm?docid=18349) 2015.
45. Clarke TC, Black LI, Stussman BJ, Barnes PM, Nahin RL. Trends in the use of complementary health approaches among adults: United States, 2002-2012. Natl Health Stat Report 2015:1-16. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/25671660/)]
46. Black LI, Clarke TC, Barnes PM, Stussman BJ, Nahin RL. Use of complementary health approaches among children aged 4-17 years in the United States: National Health Interview Survey, 2007-2012. Natl Health Stat Report 2015:1-19. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/25671583/)]
47. Papanikolaou Y, Brooks J, Reider C, Fulgoni VL, 3rd. U.S. adults are not meeting recommended levels for fish and omega-3 fatty acid intake: results of an analysis using observational data from NHANES 2003-2008. Nutr J 2014;13:31. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/24694001/)]

48. Djousse L, Akinkuolie AO, Wu JH, Ding EL, Gaziano JM. Fish consumption, omega-3 fatty acids and risk of heart failure: a meta-analysis. Clin Nutr 2012;31:846-53. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/22682084/)]
49. Del Gobbo LC, Imamura F, Aslibekyan S, Marklund M, Virtanen JK, Wennberg M, et al. Omega-3 polyunsaturated fatty acid biomarkers and coronary heart disease: pooling project of 19 cohort studies. JAMA Intern Med 2016;176:1155-66. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/27357102/)]
50. Wang C, Harris WS, Chung M, Lichtenstein AH, Balk EM, Kupelnick B, et al. n-3 Fatty acids from fish or fish-oil supplements, but not alpha-linolenic acid, benefit cardiovascular disease outcomes in primary- and secondary-prevention studies: a systematic review. Am J Clin Nutr 2006;84:5-17. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/16825676/)]
51. Kris-Etherton PM, Harris WS, Appel LJ, American Heart Association. Nutrition C. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. Circulation 2002;106:2747-57. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/12438303/)]
52. Burr ML, Fehily AM, Gilbert JF, Rogers S, Holliday RM, Sweetnam PM, et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: Diet and Reinfarction Trial (DART). Lancet 1989;2:757-61. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/2571009/)]
53. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. Lancet 1999;354:447-55. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/10465168/)]
54. Marchioli R, Barzi F, Bomba E, Chieffo C, Di Gregorio D, Di Mascio R, et al. Early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction: time-course analysis of the results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione. Circulation 2002;105:1897-903. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/11997274/)]
55. Morris MC, Sacks F, Rosner B. Does fish oil lower blood pressure? A meta-analysis of controlled trials. Circulation 1993;88:523-33. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/8339414/)]
56. Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y, et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. Lancet 2007;369:1090-8. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/17398308/)]
57. Tanaka K, Ishikawa Y, Yokoyama M, Origasa H, Matsuzaki M, Saito Y, et al. Reduction in the recurrence of stroke by eicosapentaenoic acid for hypercholesterolemic patients: subanalysis of the JELIS trial. Stroke 2008;39:2052-8. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/18451347/)]
58. Risk and Prevention Study Collaborative Group, Roncaglioni MC, Tombesi M, Avanzini F, Barlera S, Caimi V, Longoni P, Marzona I, Milani V, Silletta MG, Tognoni G, Marchioli R. n-3 fatty acids in patients with multiple cardiovascular risk factors. N Engl J Med. 2013 May 9;368(19):1800-8. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/23656645/)]
59. ORIGIN Trial Investigators, Bosch J, Gerstein HC, Dagenais GR, Diaz R, Dyal L, et al. n-3 fatty acids and cardiovascular outcomes in patients with dysglycemia. N Engl J Med 2012;367:309-18. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/22686415/)]
60. Kromhout D, Giltay EJ, Geleijnse JM, Alpha Omega Trial Group. n-3 fatty acids and cardiovascular events after myocardial infarction. N Engl J Med 2010;363:2015-26. [PubMed abstract

(https://pubmed.ncbi.nlm.nih.gov/20929341/)]
61. Bowman L, Mafham M, Wallendszus K, Stevens W, Buck G, et al.; ASCEND Study Collaborative Group. Effects of n-3 Fatty Acid Supplements in Diabetes Mellitus.N Engl J Med 2018;379:1540-50. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/30146932/)]
62. Manson JE, Cook NR, Lee I-M, Christen W, Bassuk SS, Mora S, et al. Marine n-3 fatty acids and prevention of cardiovascular disease and cancer. N Engl J Med. 2018 Nov 10. doi: 10.1056/NEJMoa1811403. [Epub ahead of print] [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/30415637/)]
63. Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, et al; REDUCE-IT Investigators. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. N Engl J Med 2019;380:11-22. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/30415628/)]
64. Nicholls SJ, Lincoff M, Garcia M, Dash D, Ballantyne CM, Barter PJ, et al. 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;324:2268-80. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/33190147/)]
65. Kris-Etherton PM, Richter CK, Bowen KJ, Skulas-Ray AC, Jackson KH, et al. Recent clinical trials shed new light on the cardiovascular benefits of omega-3 fatty acids. Methodist Debakey Cardiovasc J 2019;15:171-8. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/31687095/)]
66. Rimm EB, Appel LJ, Chiuve SE, Djoussé L, Engler MB, et al.; 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. Seafood long-chain n-3 polyunsaturated fatty acids and cardiovascular disease: a science advisory from the American Heart Association. Circulation 2018;138:e35-e47. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/29773586/)]
67. Hu Y, Hu FB, Manson JE. Marine omega-3 supplementation and cardiovascular disease: an updated meta-analysis of 13 randomized controlled trials involving 127 477 participants. J Am Heart Assoc 2019;8:e013543. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/31567003/)]
68. Weylandt KH, Serini S, Chen YQ, Su HM, Lim K, Cittadini A, et al. Omega-3 polyunsaturated fatty acids: the way forward in times of mixed evidence. Biomed Res Int 2015;2015:143109. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/26301240/)]
69. Trikalinos TA, Lee J, Moorthy D, Yu WW, Lau J, Lichtenstein AH, et al. Effects of eicosapentanoic acid and docosahexanoic acid on mortality across diverse settings: systematic review and meta-analysis of randomized trials and prospective cohorts. Nutritional Resaerch Series vol. 4. In. Rockville (MD): Agency for Healthcare Research and Quality (US); 2012. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/22479722/)]
70. Wen YT, Dai JH, Gao Q. Effects of omega-3 fatty acid on major cardiovascular events and mortality in patients with coronary heart disease: a meta-analysis of randomized controlled trials. Nutr Metab Cardiovasc Dis 2014;24:470-5. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/24472636/)]
71. Chen Q, Cheng LQ, Xiao TH, Zhang YX, Zhu M, Zhang R, et al. Effects of omega-3 fatty acid for sudden cardiac death prevention in patients with cardiovascular disease: a contemporary meta-analysis of randomized, controlled trials. Cardiovasc Drugs Ther 2011;25:259-65. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/21626218/)]

72. Eussen SR, Geleijnse JM, Giltay EJ, Rompelberg CJ, Klungel OH, Kromhout D. Effects of n-3 fatty acids on major cardiovascular events in statin users and non-users with a history of myocardial infarction. Eur Heart J 2012;33:1582-8. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/22301766/)]
73. Doi T, Langsted A, Nordestgaard BG. A possible explanation for the contrasting results of REDUCE-IT vs. STRENGTH: Cohort study mimicking trial designs. European Heart Journal 2021;42:4807-17. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/34455435/)]
74. Bostrom JA, Beckman JA, Berger JS. Summoning STRENGTH to question the placebo in REDUCE-IT. Circulation 2021;144:407-9. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/34370544/)]
75. Abdelhamid AS, Brown TJ, Brainard JS, Biswas P, Thorpe GC, et al. Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2020;3:CD003177. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/32114706/)]
76. Aung T, Halsey J, Kromhout D, Gerstein HC, Marchioli R, Tavazzi L, Geleijnse JM, Rauch B, Ness A, Galan P, Chew EY, Bosch J, Collins R, Lewington S, Armitage J, Clarke R; Omega-3 Treatment Trialists' Collaboration. Associations of omega-3 fatty acid supplement use with cardiovascular disease risks: Meta-analysis of 10 trials involving 77 917 individuals. JAMA Cardiol 2018;3:225-34. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/29387889/)]
77. Chowdhury R, Warnakula S, Kunutsor S, Crowe F, Ward HA, Johnson L, et al. Association of dietary, circulating, and supplement fatty acids with coronary risk: a systematic review and meta-analysis. Ann Intern Med 2014;160:398-406. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/24723079/)]
78. Kwak SM, Myung SK, Lee YJ, Seo HG, Korean Meta-analysis Study G. Efficacy of omega-3 fatty acid supplements (eicosapentaenoic acid and docosahexaenoic acid) in the secondary prevention of cardiovascular disease: a meta-analysis of randomized, double-blind, placebo-controlled trials. Arch Intern Med 2012;172:686-94. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/22493407/)]
79. Chowdhury R, Stevens S, Gorman D, Pan A, Warnakula S, Chowdhury S, et al. Association between fish consumption, long chain omega 3 fatty acids, and risk of cerebrovascular disease: systematic review and meta-analysis. BMJ 2012;345:e6698. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/23112118/)]
80. Agency for Healthcare Research and Quality. Omega-3 fatty acids and cardiovascular disease: an updated systematic review. (https://effectivehealthcare.ahrq.gov/products/fatty-acids-cardiovascular-disease/research) 2016.
81. Casula M, Soranna D, Catapano AL, Corrao G. Long-term effect of high dose omega-3 fatty acid supplementation for secondary prevention of cardiovascular outcomes: A meta-analysis of randomized, placebo controlled trials [corrected]. Atheroscler Suppl 2013;14:243-51. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/23958480/)]
82. Delgado-Lista J, Perez-Martinez P, Lopez-Miranda J, Perez-Jimenez F. Long chain omega-3 fatty acids and cardiovascular disease: a systematic review. Br J Nutr 2012;107 Suppl 2:S201-13. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/22591894/)]
83. Kotwal S, Jun M, Sullivan D, Perkovic V, Neal B. Omega 3 fatty acids and cardiovascular outcomes: systematic review and meta-analysis. Circ Cardiovasc Qual Outcomes 2012;5:808-18. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/23110790/)]
84. Leon H, Shibata MC, Sivakumaran S, Dorgan M, Chatterley T, Tsuyuki RT. Effect of fish oil on arrhythmias and mortality: systematic review. BMJ 2008;337:a2931. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/19106137/)]

85. Marik PE, Varon J. Omega-3 dietary supplements and the risk of cardiovascular events: a systematic review. Clin Cardiol 2009;32:365-72. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/19609891/)]
86. Rizos EC, Ntzani EE, Bika E, Kostapanos MS, Elisaf MS. Association between omega-3 fatty acid supplementation and risk of major cardiovascular disease events: a systematic review and meta-analysis. JAMA 2012;308:1024-33. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/22968891/)]
87. Zhao YT, Chen Q, Sun YX, Li XB, Zhang P, Xu Y, et al. Prevention of sudden cardiac death with omega-3 fatty acids in patients with coronary heart disease: a meta-analysis of randomized controlled trials. Ann Med 2009;41:301-10. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/19148838/)]
88. Siscovick DS, Barringer TA, Fretts AM, Wu JH, Lichtenstein AH, et al.; 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;135:e867-84. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/28289069/)]
89. Skulas-Ray AC, Wilson PWF, Harris WS, Brinton EA, Kris-Etherton PM, et al.; 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;140:e673-91. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/31422671/)]
90. Mozaffarian D, Wu JH. Omega-3 fatty acids and cardiovascular disease: effects on risk factors, molecular pathways, and clinical events. J Am Coll Cardiol 2011;58:2047-67. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/22051327/)]
91. U.S. Department of Agriculture. Dietary Guidelines for Americans, 2020-2025. (https://www.dietaryguidelines.gov) 9th ed. 2020.
92. U.S. Food and Drug Administration. Summary of qualified health claims subject to enforcement discretion. (http://www.fda.gov/Food/FoodborneIllnessContaminants/Metals/ucm393070.htm) 2014.
93. Oken E, Radesky JS, Wright RO, Bellinger DC, Amarasiriwardena CJ, Kleinman KP, et al. Maternal fish intake during pregnancy, blood mercury levels, and child cognition at age 3 years in a US cohort. Am J Epidemiol 2008;167:1171-81. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/18353804/)]
94. Hibbeln JR, Davis JM, Steer C, Emmett P, Rogers I, Williams C, et al. Maternal seafood consumption in pregnancy and neurodevelopmental outcomes in childhood (ALSPAC study): an observational cohort study. Lancet 2007;369:578-85. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/17307104/)]
95. Starling P, Charlton K, McMahon AT, Lucas C. Fish intake during pregnancy and foetal neurodevelopment--a systematic review of the evidence. Nutrients 2015;7:2001-14. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/25793632/)]
96. van Wijngaarden E, Thurston SW, Myers GJ, Strain JJ, Weiss B, Zarcone T, et al. Prenatal methyl mercury exposure in relation to neurodevelopment and behavior at 19 years of age in the Seychelles Child Development Study. Neurotoxicol Teratol 2013;39:19-25. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/23770126/)]
97. Section on Breastfeeding. Breastfeeding and the use of human milk. Pediatrics 2012;129:2011-3552. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/22371471/)]

98. Makrides M, Gibson RA, McPhee AJ, Yelland L, Quinlivan J, Ryan P, et al. Effect of DHA supplementation during pregnancy on maternal depression and neurodevelopment of young children: a randomized controlled trial. JAMA 2010;304:1675-83. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/20959577/)]
99. Makrides M, Gould JF, Gawlik NR, Yelland LN, Smithers LG, Anderson PJ, et al. Four-year follow-up of children born to women in a randomized trial of prenatal DHA supplementation. JAMA 2014;311:1802-4. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/24794375/)]
100. Molloy CS, Stokes S, Makrides M, Collins CT, Anderson PJ, Doyle LW. Long-term effect of high-dose supplementation with DHA on visual function at school age in children born at <33 wk gestational age: results from a follow-up of a randomized controlled trial. Am J Clin Nutr 2016;103:268-75. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/26537943/)]
101. Meldrum SJ, D'Vaz N, Simmer K, Dunstan JA, Hird K, Prescott SL. Effects of high-dose fish oil supplementation during early infancy on neurodevelopment and language: a randomised controlled trial. Br J Nutr 2012;108:1443-54. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/22348468/)]
102. Gould JF, Smithers LG, Makrides M. The effect of maternal omega-3 (n-3) LCPUFA supplementation during pregnancy on early childhood cognitive and visual development: a systematic review and meta-analysis of randomized controlled trials. Am J Clin Nutr 2013;97:531-44. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/23364006/)]
103. Saccone G, Berghella V. Omega-3 long chain polyunsaturated fatty acids to prevent preterm birth: a systematic review and meta-analysis. Obstet Gynecol 2015;125:663-72. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/25730231/)]
104. Newberry SJ, Chung M, Booth M, Maglione M, Tang AM, C.E. OH, et al. Omega-3 fatty acids and maternal and child health: an updated systematic review. Evidence Report/Technology Assessment No. 224. (Prepared by the RAND Southern California Evidence-based Practice Center under Contract No. 290-2012-00006-I.) AHRQ Publication No. 16-E003-EF. Rockville, MD: Agency for Healthcare Research and Quality; 2016.
105. O'Connor NR. Infant formula. Am Fam Physician 2009;79:565-70. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/19378873/)]
106. Simmer K, Patole SK, Rao SC. Long-chain polyunsaturated fatty acid supplementation in infants born at term. Cochrane Database Syst Rev 2011:CD000376. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/22161363/)]
107. Schulzke SM, Patole SK, Simmer K. Long-chain polyunsaturated fatty acid supplementation in preterm infants. Cochrane Database Syst Rev 2011:CD000375. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/21328248/)]
108. MacLean CH, Newberry SJ, Mojica WA, Khanna P, Issa AM, Suttorp MJ, et al. Effects of omega-3 fatty acids on cancer risk: a systematic review. JAMA 2006;295:403-15. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/16434631/)]
109. Gago-Dominguez M, Yuan JM, Sun CL, Lee HP, Yu MC. Opposing effects of dietary n-3 and n-6 fatty acids on mammary carcinogenesis: The Singapore Chinese Health Study. Br J Cancer 2003;89:1686-92. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/14583770/)]
110. Brasky TM, Lampe JW, Potter JD, Patterson RE, White E. Specialty supplements and breast cancer risk in the VITamins And Lifestyle (VITAL) Cohort. Cancer Epidemiol Biomarkers Prev 2010;19:1696-708. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/20615886/)]

111. Gerber M. Omega-3 fatty acids and cancers: a systematic update review of epidemiological studies. Br J Nutr 2012;107 Suppl 2:S228-39. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/22591896/)]
112. Zheng JS, Hu XJ, Zhao YM, Yang J, Li D. Intake of fish and marine n-3 polyunsaturated fatty acids and risk of breast cancer: meta-analysis of data from 21 independent prospective cohort studies. BMJ 2013;346:f3706. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/23814120/)]
113. Geelen A, Schouten JM, Kamphuis C, Stam BE, Burema J, Renkema JM, et al. Fish consumption, n-3 fatty acids, and colorectal cancer: a meta-analysis of prospective cohort studies. Am J Epidemiol 2007;166:1116-25. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/17823383/)]
114. Wu S, Feng B, Li K, Zhu X, Liang S, Liu X, et al. Fish consumption and colorectal cancer risk in humans: a systematic review and meta-analysis. Am J Med 2012;125:551-9 e5. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/22513196/)]
115. Kantor ED, Lampe JW, Peters U, Vaughan TL, White E. Long-chain omega-3 polyunsaturated fatty acid intake and risk of colorectal cancer. Nutr Cancer 2014;66:716-27. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/24053119/)]
116. Dahm CC, Gorst-Rasmussen A, Crowe FL, Roswall N, Tjonneland A, Drogan D, et al. Fatty acid patterns and risk of prostate cancer in a case-control study nested within the European Prospective Investigation into Cancer and Nutrition. Am J Clin Nutr 2012;96:1354-61. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/23134890/)]
117. Park SY, Wilkens LR, Henning SM, Le Marchand L, Gao K, Goodman MT, et al. Circulating fatty acids and prostate cancer risk in a nested case-control study: the Multiethnic Cohort. Cancer Causes Control 2009;20:211-23. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/18821021/)]
118. Alexander W. Prostate cancer risk and omega-3 Fatty Acid intake from fish oil: a closer look at media messages versus research findings. P T 2013;38:561-4. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/24273402/)]
119. Torfadottir JE, Stampfer MJ, Mucci LA, Giovannucci EL. RE: Plasma phospholipid fatty acids and prostate cancer risk in the SELECT trial. J Natl Cancer Inst 2014;106:dju018. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/24685929/)]
120. Bosire C, Stampfer MJ, Subar AF, Park Y, Kirkpatrick SI, Chiuve SE, et al. Index-based dietary patterns and the risk of prostate cancer in the NIH-AARP diet and health study. Am J Epidemiol 2013;177:504-13. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/23408548/)]
121. Augustsson K, Michaud DS, Rimm EB, Leitzmann MF, Stampfer MJ, Willett WC, et al. A prospective study of intake of fish and marine fatty acids and prostate cancer. Cancer Epidemiol Biomarkers Prev 2003;12:64-7. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/12540506/)]
122. Crowe FL, Appleby PN, Travis RC, Barnett M, Brasky TM, Bueno-de-Mesquita HB, et al. Circulating fatty acids and prostate cancer risk: individual participant meta-analysis of prospective studies. J Natl Cancer Inst 2014;106. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/25210201/)]
123. Chua ME, Sio MC, Sorongon MC, Morales ML, Jr. The relevance of serum levels of long chain omega-3 polyunsaturated fatty acids and prostate cancer risk: A meta-analysis. Can Urol Assoc J 2013;7:E333-43. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/23766835/)]
124. Chua ME, Sio MC, Sorongon MC, Dy JS. Relationship of dietary intake of omega-3 and omega-6 Fatty acids with risk of prostate cancer development: a meta-analysis of prospective studies and review of literature. Prostate Cancer 2012;2012:826254. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/23193480/)]

125. Szymanski KM, Wheeler DC, Mucci LA. Fish consumption and prostate cancer risk: a review and meta-analysis. Am J Clin Nutr 2010;92:1223-33. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/20844069/)]
126. Alexander DD, Bassett JK, Weed DL, Barrett EC, Watson H, Harris W. Meta-analysis of long-chain omega-3 polyunsaturated fatty acids (LC omega-3PUFA) and prostate cancer. Nutr Cancer 2015;67:543-54. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/25826711/)]
127. Noel SE, Stoneham AC, Olsen CM, Rhodes LE, Green AC. Consumption of omega-3 fatty acids and the risk of skin cancers: a systematic review and meta-analysis. Int J Cancer 2014;135:149-56. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/24265065/)]
128. Serini S, Fasano E, Celleno L, Cittadini A, Calviello G. Potential of long-chain n-3 polyunsaturated fatty acids in melanoma prevention. Nutr Rev 2014;72:255-66. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/24665956/)]
129. Ibiebele TI, Nagle CM, Bain CJ, Webb PM. Intake of omega-3 and omega-6 fatty acids and risk of ovarian cancer. Cancer Causes Control 2012;23:1775-83. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/22933054/)]
130. Arem H, Neuhouser ML, Irwin ML, Cartmel B, Lu L, Risch H, et al. Omega-3 and omega-6 fatty acid intakes and endometrial cancer risk in a population-based case-control study. Eur J Nutr 2013;52:1251-60. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/22915050/)]
131. Brasky TM, Neuhouser ML, Cohn DE, White E. Associations of long-chain omega-3 fatty acids and fish intake with endometrial cancer risk in the VITamins And Lifestyle cohort. Am J Clin Nutr 2014;99:599-608. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/24500149/)]
132. Brasky TM, Rodabough RJ, Liu J, Kurta ML, Wise LA, Orchard TS, et al. Long-chain omega-3 fatty acid intake and endometrial cancer risk in the Women's Health Initiative. Am J Clin Nutr 2015;101:824-34. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/25739930/)]
133. Qin B, Xun P, He K. Fish or long-chain (n-3) PUFA intake is not associated with pancreatic cancer risk in a meta-analysis and systematic review. J Nutr 2012;142:1067-73. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/22535760/)]
134. Han YJ, Li J, Huang W, Fang Y, Xiao LN, Liao ZE. Fish consumption and risk of esophageal cancer and its subtypes: a systematic review and meta-analysis of observational studies. Eur J Clin Nutr 2013;67:147-54. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/23321574/)]
135. Wu S, Liang J, Zhang L, Zhu X, Liu X, Miao D. Fish consumption and the risk of gastric cancer: systematic review and meta-analysis. BMC Cancer 2011;11:26. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/21247502/)]
136. Dangour AD, Whitehouse PJ, Rafferty K, Mitchell SA, Smith L, Hawkesworth S, et al. B-vitamins and fatty acids in the prevention and treatment of Alzheimer's disease and dementia: a systematic review. J Alzheimers Dis 2010;22:205-24. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/20847412/)]
137. Sydenham E, Dangour AD, Lim WS. Omega 3 fatty acid for the prevention of cognitive decline and dementia. Cochrane Database Syst Rev 2012;6:CD005379. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/22696350/)]
138. Chew EY, Clemons TE, Agron E, Launer LJ, Grodstein F, Bernstein PS, et al. Effect of omega-3 fatty acids, lutein/zeaxanthin, or other nutrient supplementation on cognitive function: the AREDS2 randomized clinical trial. JAMA 2015;314:791-801. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/26305649/)]

139. Tully AM, Roche HM, Doyle R, Fallon C, Bruce I, Lawlor B, et al. Low serum cholesteryl ester-docosahexaenoic acid levels in Alzheimer's disease: a case-control study. Br J Nutr 2003;89:483-9. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/12654166/)]
140. Yassine HN, Feng Q, Azizkhanian I, Rawat V, Castor K, Fonteh AN, et al. Association of serum docosahexaenoic acid with cerebral amyloidosis. JAMA Neurol 2016. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/27532692/)]
141. van Gelder BM, Tijhuis M, Kalmijn S, Kromhout D. Fish consumption, n-3 fatty acids, and subsequent 5-y cognitive decline in elderly men: the Zutphen Elderly Study. Am J Clin Nutr 2007;85:1142-7. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/17413117/)]
142. Kalmijn S, Launer LJ, Ott A, Witteman JC, Hofman A, Breteler MM. Dietary fat intake and the risk of incident dementia in the Rotterdam Study. Ann Neurol 1997;42:776-82. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/9392577/)]
143. Engelhart MJ, Geerlings MI, Ruitenberg A, Van Swieten JC, Hofman A, Witteman JC, et al. Diet and risk of dementia: Does fat matter? The Rotterdam Study. Neurology 2002;59:1915-21. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/12499483/)]
144. Pottala JV, Yaffe K, Robinson JG, Espeland MA, Wallace R, Harris WS. Higher RBC EPA + DHA corresponds with larger total brain and hippocampal volumes: WHIMS-MRI study. Neurology 2014;82:435-42. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/24453077/)]
145. Tan ZS, Harris WS, Beiser AS, Au R, Himali JJ, Debette S, et al. Red blood cell omega-3 fatty acid levels and markers of accelerated brain aging. Neurology 2012;78:658-64. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/22371413/)]
146. Zhang Y, Chen J, Qiu J, Li Y, Wang J, Jiao J. Intakes of fish and polyunsaturated fatty acids and mild-to-severe cognitive impairment risks: a dose-response meta-analysis of 21 cohort studies. Am J Clin Nutr 2016;103:330-40. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/26718417/)]
147. Dangour AD, Allen E, Elbourne D, Fasey N, Fletcher AE, Hardy P, et al. Effect of 2-y n-3 long-chain polyunsaturated fatty acid supplementation on cognitive function in older people: a randomized, double-blind, controlled trial. Am J Clin Nutr 2010;91:1725-32. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/20410089/)]
148. Quinn JF, Raman R, Thomas RG, Yurko-Mauro K, Nelson EB, Van Dyck C, et al. Docosahexaenoic acid supplementation and cognitive decline in Alzheimer disease: a randomized trial. JAMA 2010;304:1903-11. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/21045096/)]
149. Freund-Levi Y, Eriksdotter-Jonhagen M, Cederholm T, Basun H, Faxen-Irving G, Garlind A, et al. Omega-3 fatty acid treatment in 174 patients with mild to moderate Alzheimer disease: OmegAD study: a randomized double-blind trial. Arch Neurol 2006;63:1402-8. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/17030655/)]
150. Lee LK, Shahar S, Chin AV, Yusoff NA. Docosahexaenoic acid-concentrated fish oil supplementation in subjects with mild cognitive impairment (MCI): a 12-month randomised, double-blind, placebo-controlled trial. Psychopharmacology (Berl) 2013;225:605-12. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/22932777/)]
151. Jiao J, Li Q, Chu J, Zeng W, Yang M, Zhu S. Effect of n-3 PUFA supplementation on cognitive function throughout the life span from infancy to old age: a systematic review and meta-analysis of randomized controlled trials. Am J Clin Nutr 2014;100:1422-36. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/25411277/)]

152. Yurko-Mauro K, Alexander DD, Van Elswyk ME. Docosahexaenoic acid and adult memory: a systematic review and meta-analysis. PLoS One 2015;10:e0120391. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/25786262/)]
153. Mazereeuw G, Lanctot KL, Chau SA, Swardfager W, Herrmann N. Effects of omega-3 fatty acids on cognitive performance: a meta-analysis. Neurobiol Aging 2012;33:1482 e17-29. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/22305186/)]
154. Christen WG, Schaumberg DA, Glynn RJ, Buring JE. Dietary omega-3 fatty acid and fish intake and incident age-related macular degeneration in women. Arch Ophthalmol 2011;129:921-9. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/21402976/)]
155. Augood C, Chakravarthy U, Young I, Vioque J, de Jong PT, Bentham G, et al. Oily fish consumption, dietary docosahexaenoic acid and eicosapentaenoic acid intakes, and associations with neovascular age-related macular degeneration. Am J Clin Nutr 2008;88:398-406. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/18689376/)]
156. Seddon JM, George S, Rosner B. Cigarette smoking, fish consumption, omega-3 fatty acid intake, and associations with age-related macular degeneration: the US Twin Study of Age-Related Macular Degeneration. Arch Ophthalmol 2006;124:995-1001. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/16832023/)]
157. Merle BM, Benlian P, Puche N, Bassols A, Delcourt C, Souied EH, et al. Circulating omega-3 Fatty acids and neovascular age-related macular degeneration. Invest Ophthalmol Vis Sci 2014;55:2010-9. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/24557349/)]
158. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. Arch Ophthalmol 2001;119:1417-36. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/11594942/)]
159. 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. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/19812176/)]
160. Age-Related Eye Disease Study 2 Research G. Lutein + zeaxanthin and omega-3 fatty acids for age-related macular degeneration: the Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial. JAMA 2013;309:2005-15. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/23644932/)]
161. Lawrenson JG, Evans JR. Omega 3 fatty acids for preventing or slowing the progression of age-related macular degeneration. Cochrane Database Syst Rev 2015;4:CD010015. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/25856365/)]
162. Souied EH, Delcourt C, Querques G, Bassols A, Merle B, Zourdani A, et al. Oral docosahexaenoic acid in the prevention of exudative age-related macular degeneration: the Nutritional AMD Treatment 2 study. Ophthalmology 2013;120:1619-31. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/23395546/)]
163. Craig JP, Nelson JD, Azar DT, Belmonte C, Bron AJ, Chauhan SK, de Paiva CS, Gomes JAP, Hammitt KM, Jones L, Nichols JJ, Nichols KK, Novack GD, Stapleton FJ, Willcox MDP, Wolffsohn JS, Sullivan DA. TFOS DEWS II report executive summary. Ocul Surf 2017;15:802-12. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/28797892/)]
164. The Dry Eye Assessment and Management Study Research Group. Omega-3 fatty acid supplementation for treatment of dry eye disease. N Engl J Med 2018;378:1681-90. [PubMed abstract

(https://pubmed.ncbi.nlm.nih.gov/29652551/)]
165. Ziemanski JF, Wolters LR, Jones-Jordan L, Nichols JJ, Nichols KK. Relation between dietary essential fatty acid intake and dry eye disease and meibomian gland dysfunction in postmenopausal women. Am J Ophthalmol 2018;189:29-40. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/29337006/)]
166. Miljanović B, Trivedi KA, Dana MR, Gilbard JP, Buring JE, Schaumberg DA. Relation between dietary n-3 and n-6 fatty acids and clinically diagnosed dry eye syndrome in women. Am J Clin Nutr 2005;82:887-93. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/16210721/)]
167. Hom MM, Asbell P, Barry B. Omegas and dry eye: more knowledge, more questions. Optom Vis Sci 2015;92:948-56. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/26164311/)]
168. Bhargava R, Kumar P, Kumar M, Mehra N, Mishra A. A randomized controlled trial of omega-3 fatty acids in dry eye syndrome. Int J Ophthalmol 2013;18;6:811-6. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/24392330/)]
169. Epitropoulos AT, Donnenfeld ED, Shah ZA, Holland EJ, Gross M, Faulkner WJ, Matossian C, Lane SS, Toyos M, Bucci FA Jr, Perry HD. Effect of oral re-esterified omega-3 nutritional supplementation on dry eyes. Cornea 2016;35:1185-91. PMID: [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/27442314/)]
170. Christian WG, Cook NR, Manson JE, Buring JE, Lee I-M, Bubes V, 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. Published online June 9, 2022. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/35679030/)]
171. Asbell PA, Maguire MG. Another disappointment for ω-3 fatty acid and dry eye disease. JAMA Ophthalmol. Published online June 9, 2022. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/35679039/)]
172. Park Y, Lee A, Shim SC, Lee JH, Choe JY, Ahn H, et al. Effect of n-3 polyunsaturated fatty acid supplementation in patients with rheumatoid arthritis: a 16-week randomized, double-blind, placebo-controlled, parallel-design multicenter study in Korea. J Nutr Biochem 2013;24:1367-72. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/23333088/)]
173. Miles EA, Calder PC. Influence of marine n-3 polyunsaturated fatty acids on immune function and a systematic review of their effects on clinical outcomes in rheumatoid arthritis. Br J Nutr 2012;107 Suppl 2:S171-84. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/22591891/)]
174. MacLean CH, Mojica WA, Morton SC, Pencharz J, Hasenfeld Garland R, Tu W, et al. Effects of omega-3 fatty acids on lipids and glycemic control in type ii diabetes and the metabolic syndrome and on inflammatory bowel disease, rheumatoid arthritis, renal disease, systemic lupus erythematosus, and osteoporosis. Evidence Report/Technology Assessment no. 89 (prepared by Southern California/RAND Evidence-based Practice Center, under contract no. 290-02- 0003). Rockville, MD: Agency for Healthcare Research and Quality; 2004.
175. Lee YH, Bae SC, Song GG. Omega-3 polyunsaturated fatty acids and the treatment of rheumatoid arthritis: a meta-analysis. Arch Med Res 2012;43:356-62. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/22835600/)]
176. Goldberg RJ, Katz J. A meta-analysis of the analgesic effects of omega-3 polyunsaturated fatty acid supplementation for inflammatory joint pain. Pain 2007;129:210-23. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/17335973/)]
177. Skoldstam L, Borjesson O, Kjallman A, Seiving B, Akesson B. Effect of six months of fish oil supplementation in stable rheumatoid arthritis. A double-blind, controlled study. Scand J Rheumatol

1992;21:178-85. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/1529284/)]
178. Nielsen GL, Faarvang KL, Thomsen BS, Teglbjaerg KL, Jensen LT, Hansen TM, et al. The effects of dietary supplementation with n-3 polyunsaturated fatty acids in patients with rheumatoid arthritis: a randomized, double blind trial. Eur J Clin Invest 1992;22:687-91. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/1459173/)]
179. Li F, Liu X, Zhang D. Fish consumption and risk of depression: a meta-analysis. J Epidemiol Community Health 2016;70:299-304. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/26359502/)]
180. Appleton KM, Sallis HM, Perry R, Ness AR, Churchill R. Omega-3 fatty acids for depression in adults. Cochrane Database Syst Rev 2015;11:CD004692. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/26537796/)]
181. Cabre E, Manosa M, Gassull MA. Omega-3 fatty acids and inflammatory bowel diseases - a systematic review. Br J Nutr 2012;107 Suppl 2:S240-52. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/22591898/)]
182. Lev-Tzion R, Griffiths AM, Leder O, Turner D. Omega 3 fatty acids (fish oil) for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev 2014;2:CD006320. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/24585498/)]
183. Cooper RE, Tye C, Kuntsi J, Vassos E, Asherson P. The effect of omega-3 polyunsaturated fatty acid supplementation on emotional dysregulation, oppositional behaviour and conduct problems in ADHD: A systematic review and meta-analysis. J Affect Disord 2016;190:474-82. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/26551407/)]
184. Best KP, Gold M, Kennedy D, Martin J, Makrides M. Omega-3 long-chain PUFA intake during pregnancy and allergic disease outcomes in the offspring: a systematic review and meta-analysis of observational studies and randomized controlled trials. Am J Clin Nutr 2016;103:128-43. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/26675770/)]
185. Gunaratne AW, Makrides M, Collins CT. Maternal prenatal and/or postnatal n-3 long chain polyunsaturated fatty acids (LCPUFA) supplementation for preventing allergies in early childhood. Cochrane Database Syst Rev 2015;7:CD010085. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/26197477/)]
186. Oliver C, Watson H. Omega-3 fatty acids for cystic fibrosis. Cochrane Database Syst Rev 2016;1:CD002201. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/26730723/)]
187. EFSA Panel on Dietetic Products NaA. Scientific opinion on the tolerable upper intake level of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and docosapentaenoic acid (DPA). EFSA Journal 2012;10:2815.
188. U.S. Food and Drug Administration. Qualified health claims: letters of enforcement discretion (https://www.fda.gov/media/128043/download). 2019.
189. Natural Medicines Comprehensive Database. Fish Oil. (http://www.NaturalDatabase.com) 2015.
190. Svaneborg N, Kristensen SD, Hansen LM, Bullow I, Husted SE, Schmidt EB. The acute and short-time effect of supplementation with the combination of n-3 fatty acids and acetylsalicylic acid on platelet function and plasma lipids. Thromb Res 2002;105:311-6. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/12031825/)]
191. Buckley MS, Goff AD, Knapp WE. Fish oil interaction with warfarin. Ann Pharmacother 2004;38:50-2 [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/14742793/)]

192. Bender NK, Kraynak MA, Chiquette E, Linn WD, Clark GM, Bussey HI. Effects of marine fsh oils on the anticoagulation status of patients receiving chronic warfarin therapy. J Thromb Thrombolysis 1998;5:257-61. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/10767122/)]
193. Wachira JK, Larson MK, Harris WS. n-3 fatty acids affect haemostasis but do not increase the risk of bleeding: clinical observations and mechanistic insights. Br J Nutr 2014;111:1652-62. [PubMed abstract (https://pubmed.ncbi.nlm.nih.gov/24472372/)]
194. GlaxoSmithKline. LOVAZA® (omega-3 acid ethyl esters) capsules, prescribing information. (http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021654s023lbl.pdf) 2008.

Disclaimer

This fact sheet by the National Institutes of Health (NIH) Office of Dietary Supplements (ODS) provides information that should not take the place of medical advice. We encourage you to talk to your health care providers (doctor, registered dietitian, pharmacist, etc.) about your interest in, questions about, or use of dietary supplements and what may be best for your overall health. Any mention in this publication of a specific product or service, or recommendation from an organization or professional society, does not represent an endorsement by ODS of that product, service, or expert advice.

Updated: December 17, 2024 History of changes to this fact sheet