ANNUAL REVIEWS

Annual Review of Food Science and Technology

Omega-3 Polyunsaturated Fatty Acids and Their Health Benefits

Fereidoon Shahidi and Priyatharini Ambigaipalan

Department of Biochemistry, Memorial University of Newfoundland, St. John's, Newfoundland A1B 3X9, Canada; email: fshahidi@mun.ca

Annu. Rev. Food Sci. Technol. 2018. 9:345–81

The *Annual Review of Food Science and Technology* is online at food.annualreviews.org

https://doi.org/10.1146/annurev-food-111317-095850

Copyright © 2018 by Annual Reviews.
All rights reserved

ANNUAL REVIEWS Further

Click here to view this article's online features:

- Download figures as PPT slides
- Navigate linked references
- Download citations
- Explore related articles
- Search keywords

Keywords

omega-3, fish oil, health benefits, metabolism, bioavailability, cardiovascular disease

Abstract

Omega-3 polyunsaturated fatty acids (PUFAs) include α-linolenic acid (ALA; 18:3 ω-3), stearidonic acid (SDA; 18:4 ω-3), eicosapentaenoic acid (EPA; 20:5 ω-3), docosapentaenoic acid (DPA; 22:5 ω-3), and docosahexaenoic acid (DHA; 22:6 ω-3). In the past few decades, many epidemiological studies have been conducted on the myriad health benefits of omega-3 PUFAs. In this review, we summarized the structural features, properties, dietary sources, metabolism, and bioavailability of omega-3 PUFAs and their effects on cardiovascular disease, diabetes, cancer, Alzheimer's disease, dementia, depression, visual and neurological development, and maternal and child health. Even though many health benefits of omega-3 PUFAs have been reported in the literature, there are also some controversies about their efficacy and certain benefits to human health.

INTRODUCTION

Interest in omega-3 (ω-3) polyunsaturated fatty acids (PUFAs) has escalated in recent years because of their various roles in health promotion and disease risk reduction. ω-3 PUFAs include α-linolenic acid (ALA; 18:3 ω-3), stearidonic acid (SDA; 18:4 ω-3), eicosapentaenoic acid (EPA; 20:5 ω-3), docosapentaenoic acid (DPA; 22:5 ω-3), and docosahexaenoic acid (DHA; 22:6 ω-3). Oils containing these fatty acids (FAs), or some of these fatty acids, originate primarily from certain plant sources or are modified in plants, as well as marine, algal, and single-cell sources. Long-chain (LC) ω-3 FAs such as EPA and DHA occur in the body lipids of fatty fish, the liver of white lean fish, and the blubber of marine mammals. Fish oils are sold as ω-3 PUFA supplements or in a concentrated form as ethyl esters (EEs) or acylglycerols, whereas algal, fungal, and single-cell oils have recently become popular as novel and renewable sources of LC ω-3 FAs. In addition, krill oil containing both triacylglycerol (TAG) and phospholipid (PL) forms containing EPA and DHA has been successfully marketed. Researchers have also incorporated ω-3 PUFAs into different oils such as borage oil and evening primrose oil to provide a better balance of PUFA components (Hamam & Shahidi 2006, Senanayake & Shahidi 2002). Furthermore, soy and other plants have been genetically modified to contain higher levels of ω-3 PUFAs (FAO 2010). Although marine organisms are the major source of ω-3 PUFAs, some plant seeds also contain them. For example, flax, chia, and canola seeds are good sources of ALA, which serves as a precursor to the synthesis of LC PUFAs in the human body. However, production of LC ω-3 PUFAs from ALA in the body is limited to rates of less than 4% at best, hence incorporating LC ω-3 PUFAs into the daily diet is important. According to Dietitians of Canada (2013), the required ALA level varies between 1.1 and 1.6 g/day depending on the age and gender. In addition, they also recommend the intake of at least two servings of fish per week, thus providing nearly 0.3–0.45 g of EPA and DHA per day. The Food and Agricultural Organization (FAO 2010) of the United Nations recommends 0.5–0.6% ALA per day for the prevention of deficiency symptoms in adults, with a total ω-3 PUFA intake of 0.5–2%. In other studies, LC ω-3 PUFAs such as EPA and DHA have been incorporated into plants such as flax and *Brassica* species using genetic modification (Hixson et al. 2016). These novel and renewable sources of ω-3 offer oils without any fishy odor.

The earliest reports and epidemiological studies revealed that the traditional Greenlandic diet rich in marine mammals and fish reduced the incidence of cardiovascular disease in the Inuit population and Danish settlers significantly, albeit to different levels (Shahidi & Miraliakbari 2006). Several researchers have shown that ω-3 PUFAs play a major role in altering blood lipid profiles and membrane lipid composition and affect eicosanoid biosynthesis, cell signaling cascades, and gene expression, thereby influencing health (Shahidi & Ambigaipalan 2015, 2016). In addition, the beneficial effect of ω-3 PUFAs in patients with myriad health conditions and diseases, such as cardiovascular disease (atrial fibrillation, atherosclerosis, thrombosis, inflammation, and sudden cardiac death, among others), diabetes, cancer, depression and various mental illnesses, age-related cognitive decline, periodontal disease, and rheumatoid arthritis, has been investigated (Finley & Shahidi 2001, Lopez et al. 2011). The roles of ω-3 oils, particularly DHA oils, in the diet of pregnant and lactating women and in the developing fetus and infants for brain and eye function have been thoroughly studied.

The bioavailability of ω-3 PUFAs is influenced by the form in which they exist, e.g., EE, TAG, or PL (Beckermann et al. 1990). The superior bioavailability of TAGs compared to EEs has been confirmed in some recent findings, but this remains a controversial subject, as contrary findings have also been reported in recent years (Mozaffarian et al. 2013a). In addition, information on the relative bioavailability of PL forms of ω-3 PUFAs is limited and inconclusive (Laidlaw et al. 2014). This contribution summarizes the sources, structural features, metabolism, bioavailability, and health effects of ω-3 PUFAs.

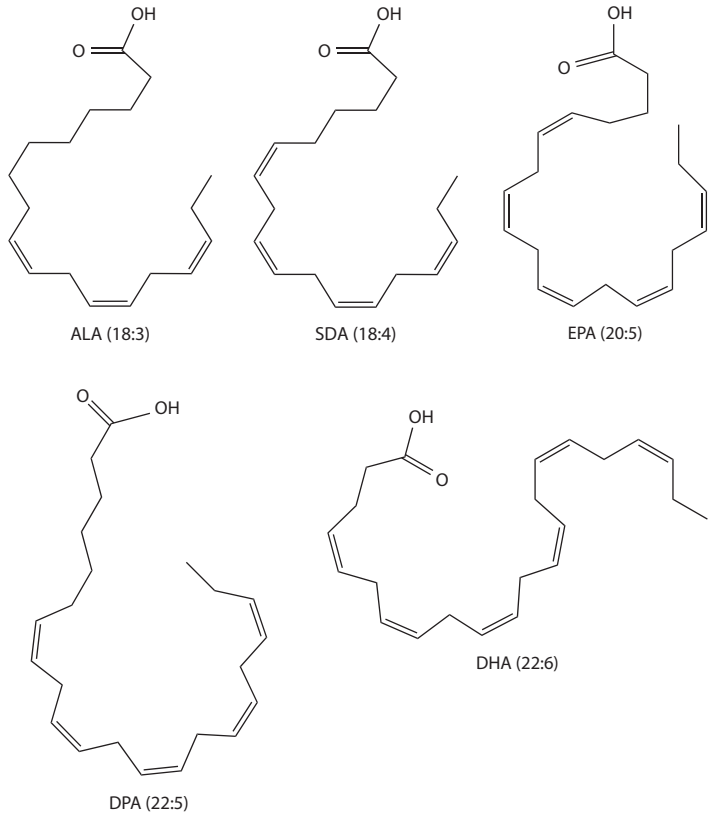


Figure 1

Chemical structures of omega-3 polyunsaturated fatty acids. Abbreviations: ALA, α-linolenic acid; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; EPA, eicosapentaenoic acid; SDA, stearidonic acid.

STRUCTURAL FEATURES AND PROPERTIES OF OMEGA-3 FATTY ACIDS

The first methylene interrupted double bond in ω-3 PUFAs is located on the third carbon atom from the methyl end of the FA chain, and hence named ω-3. ω-3 PUFAs include ALA (*cis*-9,*cis*-12,*cis*-15-octadecatrienoic acid, 18:3), SDA (*cis*-6,*cis*-9,*cis*-12,*cis*-15-octadecatetraenoic acid, 18:4), EPA (*cis*-5,*cis*-8,*cis*-11,*cis*-14,*cis*-17-eicosapentaenoic acid, 20:5), DPA (*cis*-7,*cis*-10,*cis*-13,*cis*-16,*cis*-19-docosapentaenoic acid, 22:5), and DHA (*cis*-4,*cis*-7,*cis*-10,*cis*-13,*cis*-16,*cis*-19-docosahexaenoic acid, 22:6) (**Figure 1**). ALA is the parent FA of ω-3 PUFAs and desaturates and elongates to form ω-3 PUFAs. The human body is incapable of synthesizing all these ω-3 PUFAs as a result of the limitation of the enzyme responsible for inserting *cis* double bonds. ALA is an 18-carbon essential unsaturated FA that is converted to EPA or DPA by chain elongation and desaturation. A detailed relevant pathway is explained in the section below titled Metabolism and Bioavailability of Omega-3 Fatty Acids.

ω-3 PUFAs exist mainly in an esterified form and are associated with PLs in the cellular membrane or with the TAG form in storage lipids. Although marine organisms are the richest source of ω-3 PUFAs, the spatial arrangement of TAG FAs in fish and marine mammal oils has been shown to vary. LC PUFAs of fish oils are distributed primarily in the *sn*-2 position of TAG, whereas marine mammal lipids contain LC PUFAs predominantly in the *sn*-1 and *sn*-3 positions

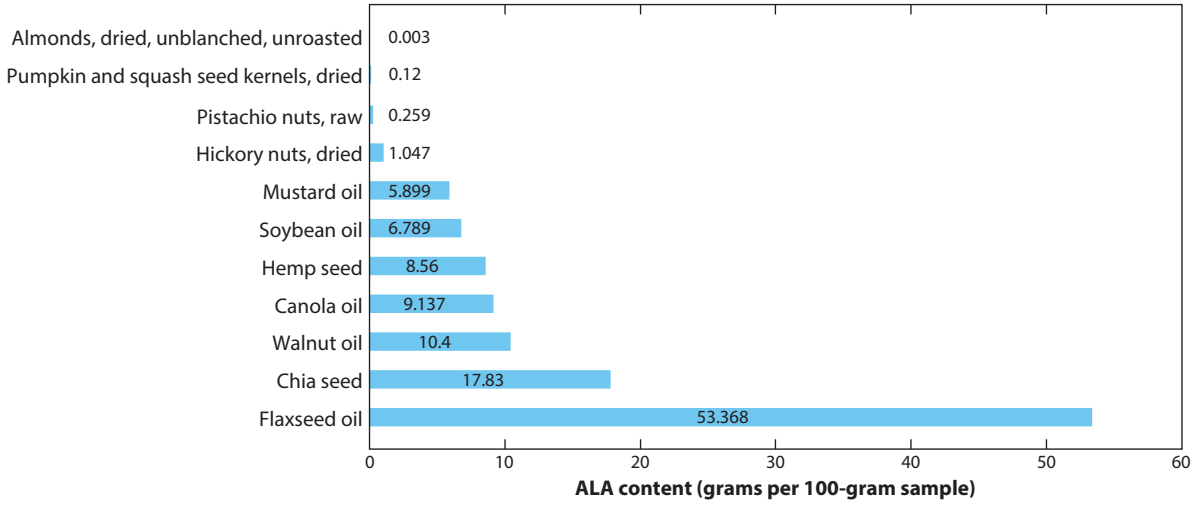


Figure 2

α-Linolenic acid (ALA) content of nuts and seeds (Health Can. 2016).

of TAG (Shahidi & Miraliakbari 2004, 2005). DHA has been shown to be the main component of brain gray matter, and PLs have been shown to be the main components of the retina, testes, and sperm (Senanayake & Fichtali 2006).

DIETARY SOURCES OF OMEGA-3 FATTY ACIDS

ω-3 PUFAs are exclusively found in aquatic organisms and mainly originate in the liver of lean white fish such as cod and halibut, the body of oily fish such as mackerel, menhaden, and salmon, and the blubber of marine mammals such as seals and whales (Shahidi 1998). The major ω-3 PUFAs from marine sources are EPA and DHA, and DPA is present in fairly low levels in most fish oils.

The primary source of ALA is plants, concentrated mainly in some seeds and nuts and in some vegetable oils (FAO 2010). Flaxseed, chia seeds, walnut, and echium seed oils are known to be good sources of ALA (**Figure 2**) (Dietit. Can. 2013), whereas safflower, sunflower, corn, and soybean oils are rich in linoleic acid (18:2 ω-6) (Shahidi & Miraliakbari 2004). Flaxseed oil contains a high amount of ALA (49.2 g/100 g) and other sources of ALA are walnut, canola, and soybean oils, whereas salmon, sardine, and herring oils contain relatively high amounts of EPA and DHA (Dietit. Can. 2013). EPA and DHA can be synthesized in the human body using ALA as a precursor. However, bioconversion of ALA to EPA and DHA is limited; thus, we require adequate dietary intake of LC ω-3s. Marine oils are also rich sources of fat-soluble vitamins. The livers of cod, haddock, halibut, shark, whales, and tuna are mainly used to produce vitamins A and D supplement oils (Bimbo 1990). Vitamins A and D contents of cod liver oil are 1,000 and 10 IU/g, respectively (Bimbo 1990). Among all fish oils, cod flesh, halibut, and skipjack tuna have been shown to contain the highest amounts of DHA (30% of total FAs), whereas cod flesh, flounder species, and haddock contain the highest amounts of EPA (15–19% of total FAs) (**Table 1**) (Shahidi & Miraliakbari 2006). In addition to fish and marine mammals, crustaceans, bivalves, and cephalopods also contain ω-3 PUFA (**Table 1**). Among tested seafood, salted mackerel contained a high amount of EPA and DHA (4.57 g/100 g of cooked sample) compared with other cooked fish (**Figure 3**).

Table 1 Omega-3 polyunsaturated fatty acid content of marine sources

Marine sources	EPA (%)	DHA (%)	DPA (%)	Reference
Fish				
Menhaden oil	18.3	9.6	1.8	Ackman 2005
Herring oil	7.5	6.8	0.75	
Cod liver oil	12.2	12.7	1.7	Copeman & Parrish 2004
Cod flesh oil	19.1	32.6	2	
Capelin oil	9.3	4.1	0.9	
Skipjack tuna oil	11.1	29.1	0	Tanabe et al. 1999
Butterfish oil	5.1	10.8	2.4	Budge et al. 2002
Yellowtail flounder oil	15	18.7	3.3	
Winter flounder oil	14.4	20.1	3.8	
Haddock oil	14.8	24.8	1.9	
Halibut oil	9.6	30.6	2.6	
Mackerel oil	8	19.3	1.6	
Salmon oil	6.2	9.1	1.8	Aursand et al. 1994
Marine mammals				
Bearded seal oil	9.27	13.38	4.76	Shahidi 1998
Grey seal oil	5.23	7.12	4.94	
Harbor seal oil	9.31	7.76	4.22	
Harp seal oil	6.41	7.58	4.66	
Hooded seal oil	4.29	7.47	3.48	
Ringed seal oil	10.57	26.19	14.55	
Crustaceans				
Shrimp	15.26	11.37	0.74	Budge et al. 2002
Red crab	12.13	11.93	2.25	
Rock crab	20.74	10.35	2.06	
Lobster	17.04	7.69	1.29	
Bivalves				
Surf clam	22.9	14.3	Trace	Copeman & Parrish 2004
Greenland cockle	22.6	16.5	0.1	
Blue mussel	19.6	13.2	0	
Icelandic scallop	26.9	25.9	0	
Cephalopods				
Common octopus	16.1	20.6	1.8	Arts et al. 2001
European squid	14.3	31.6	0.4	
Squid	13.9	16.9	1.3	

Microalgae and some microorganisms (fungi) also contain ω-3 PUFAs. Senanayake & Fichtali (2006) reported that marine algae are the predominant producers of LC ω-3 PUFAs (e.g., DHA) in the biosphere. Numerous algal species have been identified as sources of DHA. *Crypthecodinium cohnii* and *Schizochytrium* spp. are the two major algal sources of DHA at levels of 55% and 40% of total fatty acids, respectively (Senanayake & Fichtali 2006). ω-3 PUFAs, especially EPA and DHA, are synthesized by phytoplankton, and algae are eventually transferred via the food web and deposited into the lipids of fish and marine mammals (Alasalvar et al. 2002). Seeds from the

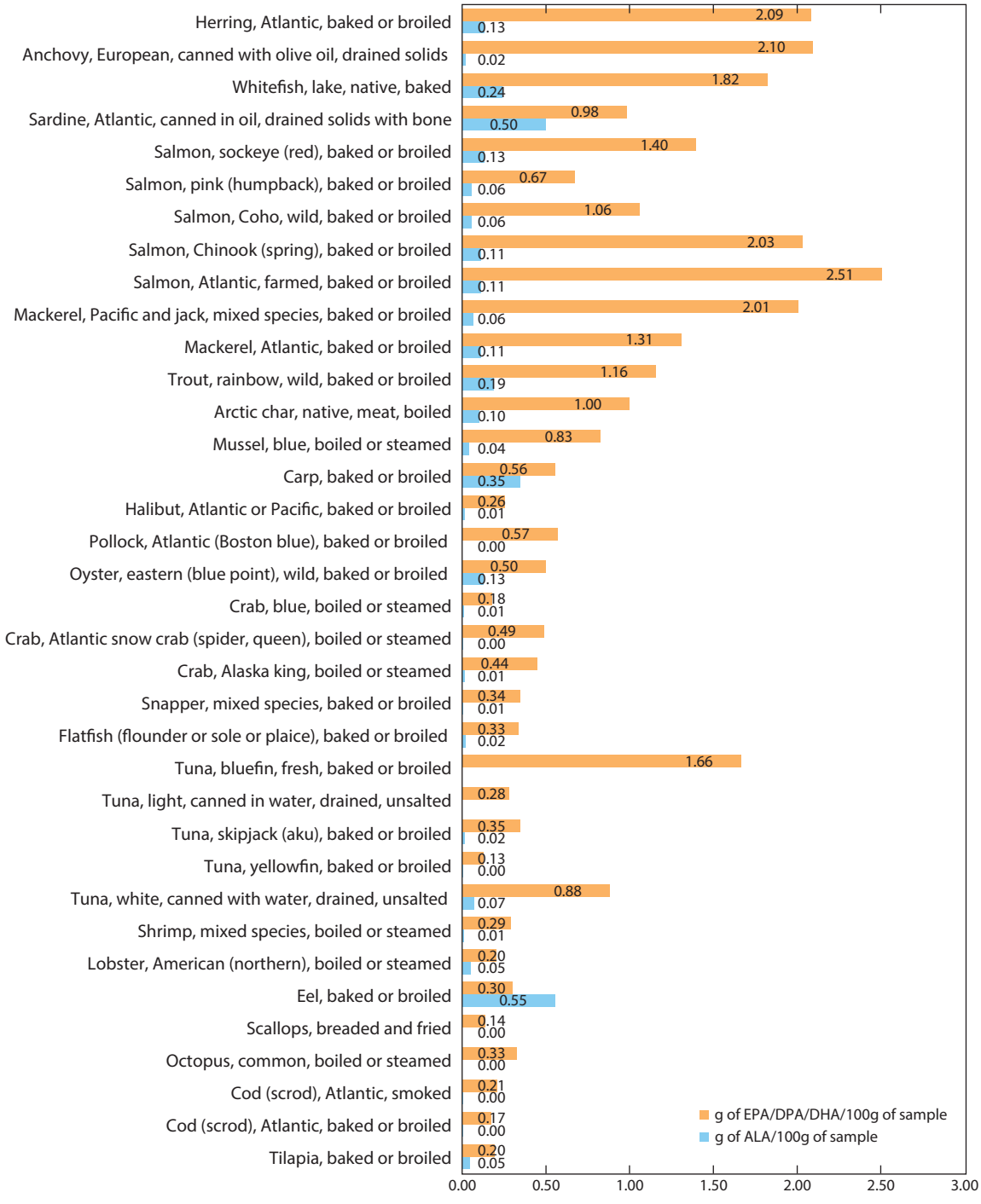


Figure 3

α-Linolenic acid (ALA), docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA) content of fish and seafood (Health Can. 2016).

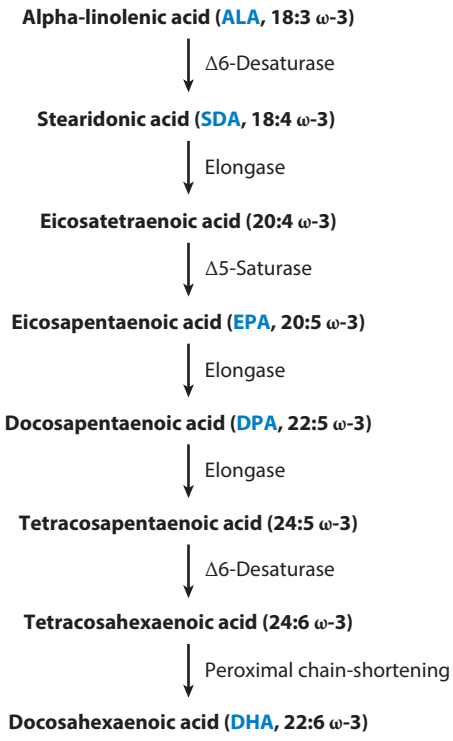


Figure 4

Metabolic pathway for the synthesis of omega-3 polyunsaturated fatty acids from α-linolenic acid.

Boraginaceae family, such as borage, *Echium vulgare* (viper's bugloss), and *Buglossoides arvensis* (corn gromwell), hemp oil, and fish are good sources of SDA. However, SDA is not a major component of the human diet. Recently, SDA has received much attention due to the fact that dietary supplementation with SDA increases the EPA level more than that of ALA supplementation (Guil-Guerrero 2007).

METABOLISM AND BIOAVAILABILITY OF OMEGA-3 FATTY ACIDS

The metabolic pathway of synthesis of ω-3 PUFAs from dietary ALA is shown in **Figure 4**. SDA is the first metabolite synthesized from ALA, which subsequently leads to the synthesis of EPA, DPA, and DHA. The conversion requires desaturases (Δ5 and Δ6), an elongase of the microsomal system, and oxidation in the peroxisomes for chain shortening. Another major pathway involves the synthesis of omega-6 (ω-6) PUFAs from linoleic acid (18:2 ω-6), where arachidonic acid (20:4 ω-6) is the major end product. The metabolic pathway of ω-6 PUFAs from linoleic acid also employs the same enzymes as the metabolic pathway of ω-3 PUFAs. Because the ALA levels are generally lower in the human diet than those of linoleic acid, plasma and cellular levels of ω-6 PUFAs tend to be higher than those of ω-3 PUFAs (FAO 2010). Burdge & Calder (2005) observed that intake of ALA significantly increased EPA and DPA levels in plasma fractions (platelets, white cells, and red blood cells) and breast milk, whereas only a minor increase of DHA was observed. Another study using a stable isotope showed the conversion efficiency of EPA, DPA, and DHA from ALA as 0.2%, 0.13%, and 0.05%, respectively (Pawlosky et al. 2001). Burdge & Wootton

(2002) showed that in healthy young women the conversion of ALA to EPA and DHA was 21% and 9%, respectively, whereas in young men the conversion was 8% EPA and 0–4% DHA. A report released by FAO (2010) revealed that low insulin levels as well as protein and mineral (iron, zinc, copper, and magnesium) deficiencies could decrease Δ6 desaturase activity and therefore inhibit the conversion of linoleic acid and ALA to ω-6 and ω-3 PUFAs, respectively. They also suggested that this topic has not been well studied, thus requiring further investigation.

ω-6 and ω-3 PUFAs are essential for the synthesis of eicosanoids such as prostaglandins (PGs), prostacyclin (PGI), thromboxane (TX), leukotrienes, hydroperoxytetraenoic acid, hydroxyeicosatetraenoic acid, and lipoxins, which play a crucial role in vascular physiology (Shahidi & Miraliakbari 2004). These eicosanoids are involved in several physiological actions, including pro/anti-inflammatory, pro/antiplatelet aggregatory, vasodilation, vasoconstriction, immune response, and cell growth and proliferation (FAO 2010). However, the function of PGs derived from arachidonic acid differs from those derived from EPA. PGE2 and TXA2 formed from arachidonic acid are produced in platelets and promote inflammation with potent chemo-activity and platelet aggregation and act as vasoconstrictors. However, EPA-derived PGE and TXA act only as vasodilators and antiaggregators (FAO 2010). Hence, the source of eicosanoids plays a major role in physiological function, and the imbalance could lead to several conditions, including thrombosis, inflammation, asthma, and inflammatory bowel disease (Calder 2006).

The ω-3 PUFAs may be present as EEs, TAGs, free fatty acids (FFAs), or PLs. ω-3 PUFAs from krill oil exist mainly in the form of TAGs and FFAs, and a substantial amount is bound with PLs (Schuchardt et al. 2011). Schuchardt et al. (2011) reported that products containing the EE form of ω-3s may have somewhat lower bioavailabilities than do the FFA forms. Presence of dietary fat has been shown to enhance the absorption of both EEs and FFAs (Davidson et al. 2012, Dyerberg et al. 2010). Laidlaw and coworkers (2014) reported that the position at which ω-3 PUFAs are attached to TAGs plays an important role in their absorption. ω-3 PUFAs attached to the *sn*-2 position are preferentially absorbed as monoacylglycerols (MAGs) by passive diffusion after the cleavage of the LC FAs from *sn*-1 and *sn*-3 positions, whereas the cleaved LC FAs are absorbed only when a protein mediator is present. Because ω-3 PUFAs of fish oil are in the *sn*-2 position, bioavailability is greater in fish oil than in marine mammal oils, where ω-3 PUFAs are located in *sn*-1 and *sn*-3 positions. In addition, Schulthess et al. (1994) reported that incorporation of LC FAs into plasma lipoprotein fractions is influenced by the distribution of these FAs between the inner and outer positions of intestinally resynthesized TAGs.

Digestion and absorption of ω-3 supplements containing EEs and FFAs are shown in **Figure 5**. Fat digestion starts in the stomach, where gastric lipases partially break down TAGs into diacylglycerol (DAG) and FAs and form large emulsions of fat globules. The complete digestion of fat emulsion then occurs in the intestinal lumen with the aid of bile salt and pancreatic lipases, which yield FAs and MAGs, followed by passive diffusion into enterocytes (Shi & Burn 2004). However, EEs of ω-3s (EPA + DHA) are principally hydrolyzed by pancreatic carboxylic acid ester lipase and release FFAs for absorption (**Figure 5**). Researchers have shown that digestion and absorption of various forms of ω-3s (EEs, TAGs, or PLs) are highly dependent on the fat content of the meal, which enhances the activity of pancreatic enzymes (Beckermann et al. 1990, Lawson & Hughes 1988, Schuchardt et al. 2011). In contrast, FFA forms of ω-3s have been shown to be independent of pancreatic enzymes and meal fat content (Beckermann et al. 1990, Davidson et al. 2012, Lawson & Hughes 1988). The superior bioavailability of TAGs compared to EEs has been confirmed in some recent findings, but this remains a controversial subject, as some contrary findings have also been reported (Dyerberg et al. 2010, Mozaffarian et al. 2013a, Wakil et al. 2010). In addition, the relative bioavailability of the PL forms of ω-3 PUFAs is limited and inconclusive. Laidlaw et al. (2014) reported that re-esterified TAGs obtained from a fish oil supplement (650 mg of EPA and

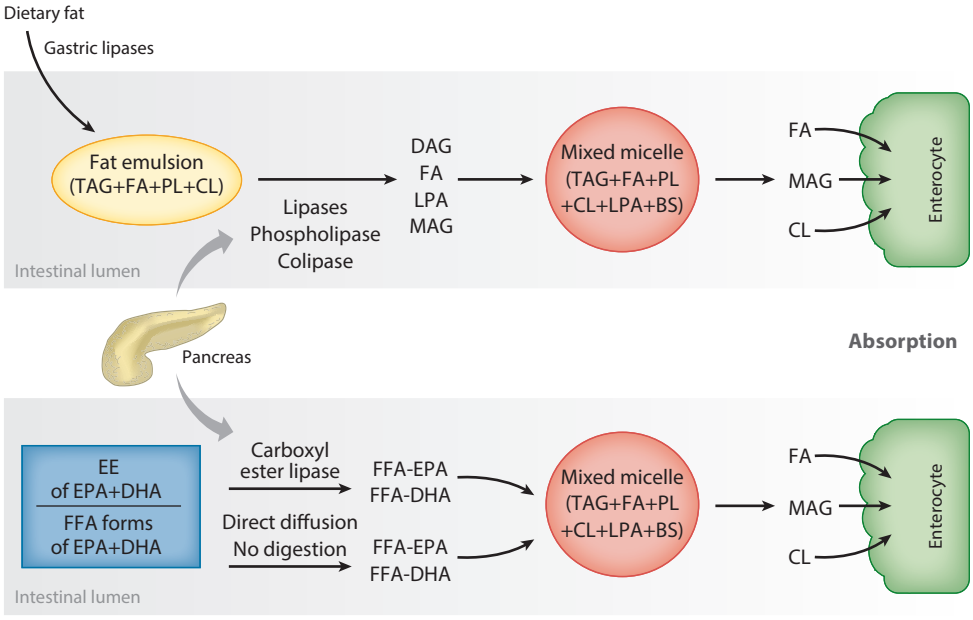


Figure 5

A schematic representation of dietary fat digestion and absorption of ethyl ester (EE) and free fatty acid (FFA) forms of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Permission obtained from Springer Nature and Elsevier, respectively, for Shi & Burn (2004) and Davidson et al. (2012). Abbreviations: BS, bile salt; CL, cholesterol; DAG, diacylglycerol; FA, fatty acid; LPA, lysophosphatidic acid; MAG, monoacylglycerol; PL, phospholipid; TAG, triacylglycerol.

450 mg of DHA) showed greater cardiovascular risk reduction than did any other supplement [e.g., EEs from fish oil (EPA, 756 mg; DHA, 228 mg), PLs from krill oil (EPA, 150 mg; DHA, 90 mg), and TAGs from salmon oil (EPA, 180 mg; DHA, 220 mg)] in a randomized controlled trial (RCT). However, Schuchardt et al. (2011) found that the bioavailability of EPA + DHA from krill oil (mainly PLs) was higher than that of re-esterified TAG and EE forms of EPA + DHA from fish oil and suggested that the observed effect might be due to the high content of free EPA and DHA in krill oil. In vivo studies on the bioavailability of ω-3 PUFAs in different forms are presented in **Table 2**.

Zhong & Shahidi (2011) prepared esters of DHA with the major green tea polyphenol [epigallocatechin gallate (EGCG)], which exhibited a high stability and antioxidant properties (Shahidi & Zhong 2015). In addition, in vivo studies have shown that these esters protected ICR (Institute of Cancer Research) mice from colon tumorigenesis (Zhong et al. 2012). Furthermore, DHA was esterified with phytosterols to lower both cholesterol and TAG via the action of their constituent moieties (Tan et al. 2012a). Bioavailability of these esters needs to be addressed to find out whether the DHA conjugate remains as it is after passing through the phospholipid bilayer or dissociates. In addition, further studies are required to reveal the mechanism of action of these esters.

HEALTH EFFECTS OF OMEGA-3 FATTY ACIDS

Cardiovascular Disease

Cardiovascular diseases and related mortality rates are high in the Western world because of the consumption of a high-fat diet. Numerous studies have been conducted on the effects of ω-3

Table 2 Bioavailability of omega-3 (ω-3) PUFAs in different forms: in vivo studies

EPA + DHA: dose (g/day)	Time of study	Results	Reference
FFA/TAG/EE = ~1.7	8–16 h	FFA > TAG > EE	Lawson & Hughes 1988
Natural TAG/re-esterified TAG/enzymatic synthesized TAG/enzymatic synthesized DAG/ Enzymatic synthesized MAG = 0.9	24 h	Re-esterified TAG > natural TAG > enzymatic synthesized TAG/DAG/MAG	Wakil et al. 2010
Fish oil FFA/EE = 4.0	24 h	FFA > EE	Kling et al. 2011
TAG = 2.4 EE = 3.3	32 h	TAG > EE	Beckermann et al. 1990
Fish oil re-esterified TAG/fish oil EE/Krill oil = 1.7	72 h	Krill oil > fish oil re-esterified TAG > fish oil EE	Schuchardt et al. 2011
Fish oil re-esterified TAG/FFA/EE/cod liver oil = ~3.3	2 weeks	Re-esterified TAG > fish oil + cod liver = FFA > EE	Dyerberg et al. 2010
PL-rich herring roe oil (Romega® 30): 628 mg/day EPA; 1,810 mg/day DHA; 137 mg/day DPA TAG-rich fish oil: 575 mg/day EPA; 1,843 mg/day DHA; 259 mg/day DPA	2 weeks	PL-rich herring roe = TAG-rich fish oil	Cook et al. 2016
Concentrated rTG fish oil: 650 mg EPA, 450 mg DHA EE fish oil: 756 mg EPA, 228 mg DHA PL krill oil: 150 mg EPA, 90 mg DHA TG salmon oil: 180 mg EPA, 220 mg DHA	4 weeks	rTG fish oil > EE fish oil > TAG salmon > PL krill oil	Laidlaw et al. 2014
Krill oil = 0.3 Fish oil = 0.4	4 weeks	Krill oil > fish oil	Maki et al. 2009
Fish = 0.9 Fish oil EE = 0.3–0.8	6 weeks	Fish > fish oil EE	Visioli et al. 2003
Krill oil = 0.5 Fish oil = 0.9	7 weeks	No difference	Ulven et al. 2011
Fish oil TAG/fish oil EE = 3.4	7 weeks	TAG > EE	Hansen et al. 1993
Fish oil = 2.2 Linseed oil = 4.4	2 months	Fish oil > linseed oil	Cao et al. 2006
Fish/fish oil = 0.5	4 months	Fish = fish oil	Harris et al. 2007
Fish oil TAG = 5.0 Fish oil EE = 6.0	6 months	TAG > EE	Reis et al. 1990
Fish oil re-esterified TAG/EE = ~1.7	6 months	Re-esterified TAG > EE	Neubronner et al. 2011

Abbreviations: DAG, diacylglycerol; DHA, docosahexaenoic acid; EE, ethyl ester; EPA, eicosapentaenoic acid; FFA, free fatty acid; MAG, monoacylglycerol; PL, phospholipid; rTG, re-esterified triglyceride; TAG, triacylglycerol; TG, triglyceride.

PUFAs on major cardiovascular conditions, such as myocardial infarction, stroke, congenital heart disease, rhythm disorders, atrial fibrillation, subclinical atherosclerosis, coronary heart disease, heart failure, sudden cardiac death, valvular disease, and peripheral arterial disease (Mozaffarian et al. 2016). According to the American Heart Association, coronary heart disease (CHD) represents multiple physiological processes, such as chronic stable atherosclerotic plaque progression (happens over years, leads to angina), instability of plaque (happens over weeks to months), acute plaque rupture (happens over seconds, leads to acute coronary syndrome), thrombosis and coagulation (happens over minutes to hours, leads to acute myocardial infarction), and ischemia-induced cardiac arrhythmia (happens over seconds, leads to CHD death) (Siscovick et al. 2017).

Albert et al. (1998) reported that regular consumption of fish containing ω-3 PUFAs lowers the risk of death from cardiovascular diseases. The "Eskimo paradox" is the phenomenon that despite high intake of dietary fat and cholesterol (40% of caloric intake), Greenland Inuits showed a lower incidence of cardiovascular diseases than did Danish settlers (Bang et al. 1980). In addition, epidemiological studies from coastal Japanese and Alaskan populations also showed an inverse relationship between heart diseases and intake of ω-3 PUFA (Davidson et al. 1993). However, Fodor et al. (2014) reported that this was not correct and in fact there was a higher rate of death for Eskimos from myocardial infarction than the Danes living there. However, this tunnel vision approach did not consider genetic differences, different lifestyles, and other relevant factors, as noted by Shahidi (2015), and shoddy bookkeeping and incomplete/inaccurate data were also possible concerns.

Jones et al. (2014) found that a novel, DHA-rich canola oil improved high-density lipoprotein (HDL) cholesterol, TAG, and blood pressure, thus reducing the risk of coronary heart disease in multicenter RCT. Several studies and reviews based on clinical trials have shown that the ω-3 PUFAs could provide a survival benefit to cardiovascular disease by preventing sudden cardiac death (Burr et al. 1989, Harris et al. 2007, Hu et al. 2002, Macchia et al. 2013, Mozaffarian et al. 2011, Mozaffarian & Wu 2011, O'Connell et al. 2016, Shahidi & Miraliakbari 2004, Siscovick et al. 2017) and improve the outcomes from heart failure (Tavazzi et al. 2008). However, recently, O'Connell et al. (2016) reported that the role of ω-3 PUFAs in cardiovascular diseases remains controversial. Rizos et al. (2012) reported from a meta-analysis study that intake of ω-3 PUFAs was not related to a lower risk of cardiovascular mortality from, e.g., cardiac death, sudden cardiac death, myocardial infarction, or stroke. However, this study placed too much emphasis on statistics and significance rather than considering dose and duration effects, and it included groups with defibrillators or on statin drugs, which would definitely overwhelm the dietary effects (Shahidi 2015). Lewis (2013) suggested that the source of ω-3 PUFAs (fish oil or marine mammal oil) could influence the beneficial effects on cardiovascular disease. **Table 3** summarizes the physiological effect of ω-3 PUFAs on cardiovascular health.

Table 3 Physiological effect of omega-3 (ω-3) PUFA on cardiovascular health (Mozaffarian & Wu 2011)

Tissue	Effect	Dose-response relationship
Liver	Reduce triacylglycerol production	Linear up to 7 g/day
	Increase gluconeogenesis to a small extent	Not established
Artery	Decrease blood pressure	Linear with typical dietary intake up to 750 mg/day
	Decrease systemic vascular resistance	Not established
	Increase vasodilatory response	Not established
	Increase arterial wall compliance	Not established
	Decrease endothelial dysfunction	Not established
Heart	Decrease arrhythmia	Linear with typical dietary intake up to 750 mg/day
	Decrease heart rate	Linear with typical dietary intake up to 750 mg/day
	Increase myocardial efficiency	Not established
	Increase left-ventricular diastolic filling	Not established
	Increase autonomic function/vagal tone	Not established
Blood	Decrease thrombosis	Effect only at high supplement level > 4 g/day
	Decrease production of arachidonic acid–derived eicosanoids	Not established
	Increase production of ω-3-derived metabolites	Not established

Uauy & Valenzuela (2000) reported that the LC ω-3 PUFAs, especially DHA and EPA, reduce the clinical risk of cardiovascular disease by altering lipid and hemostatic factors such as platelet aggregation and bleeding time. DHA has been shown to exert antiplatelet aggregation, TAG lowering effect, and an antiarrhythmic effect (Kang & Leaf 1996). In addition, Simon et al. (1995) found that higher serum levels of the saturated FA palmitic acid (16:0) were associated with increased CHD risk, whereas ω-3 PUFAs DHA and DPA were inversely associated with CHD risk in a multivariate male model that controlled for the effects of the HDL-to-LDL (low-density lipoprotein) cholesterol ratio. Mori et al. (2000) reported that supplementation with DHA (>1.2 g per day) for six weeks resulted in a significant drop of TAG (~20%) and increased HDL levels in a placebo-controlled trial of subjects with abnormal lipid levels. In addition, Engler et al. (2004) suggested that DHA could improve the vascular health of hyperlipidemic children who are at high risk for early heart disease due to inherited high cholesterol levels.

The cardiovascular effects of ω-3 PUFAs have been linked to substrate competition between ω-3 PUFAs and arachidonic acid for cyclooxygenase (COX) enzymes, which produce PGs and TX (Shahidi & Miraliakbari 2006). This competition could result in vasodilation and decreased platelet aggregation because of the following: (*a*) Substrate competition by ω-3 PUFAs for the Δ6-desaturase enzyme could inhibit the production of arachidonic acid; (*b*) competition of ω-3 PUFA with arachidonic acid (AA) for the sn-2 position of membrane PLs, thus decreasing the level of membrane AA levels; and (*c*) increasing the ratio of membrane EPA/AA could shift eicosanoid production from the proaggregatory eicosanoids PGI2 and TXA2 toward the anti-aggregatory TXA3 in platelets and PGI3 in endothelial cells, hence anti-inflammatory and antiaggregatory effects (Garg et al. 1988). Kris-Etherton et al. (2002) reported that ω-3 PUFAs can reduce susceptibility of the heart to ventricular arrhythmia, retard growth of atherosclerotic plaque (by reducing adhesion molecule expression and platelet-derived growth factor and being anti-inflammatory), promote nitric oxide–induced endothelial relaxation, are mildly hypotensive, and exert antithrombogenic and hypotriglyceridemic (fasting and postprandial) effects, and are, therefore, cardioprotective.

The effect of ω-3 PUFAs on heart rate and blood pressure has been attributed to an increased production rate of nitric oxide (Harris et al. 2007), alleviation of vasoconstriction responses to norepinephrine and angiotensin II (Chin et al. 1993), enhancement of vasodilatory responses, and improvement of arterial compliance (Mori et al. 2000). Even though ω-3 PUFAs have been shown to exhibit an antithrombotic effect, their influence on coronary thrombosis at practical doses of ω-3 PUFAs is found to be very mild (Kristensen et al. 2001). In addition, some studies have revealed that consumption of ω-3 PUFAs has no consistent effect on coagulation or platelet aggregation in human trials (Mozaffarian & Wu 2011). A summary of research findings on ω-3s and cardiovascular health clinical trials is shown in **Table 4**. Recently, Schwab et al. (2014) conducted a systematic review analysis from the articles published between the years 2000 and 2012 for the effect of ω-3s on cardiovascular health. They found convincing evidence for decreasing fasting serum or plasma total and LDL cholesterol levels when the saturated fat was partially replaced with polyunsaturated or monounsaturated fats. In addition, the ratio of ω-6 (linoleic acid and arachidonic acid) to ω-3 (EPA, DHA, and linolenic acid) is considered as an important biomarker for analyzing the risk of cardiovascular diseases (Simopoulos 2002). However, Harris and coworkers (2007) reported that ω-3 PUFA levels in tissues may have better prognostic and diagnostic utility in cardiovascular risk assessment than either ω-6 PUFAs or the AA/EPA ratio. For patients with cardiovascular disease and congestive heart failure, DeFilippis et al. (2010) recommended one daily serving of fatty fish (200–400 g) or fish oil (900 mg of EPA + DHA) and an ALA-rich diet for health improvement. ω-3 PUFAs have been associated with improving vascular function and lowering blood pressure (Colussi et al. 2017). However, neither DHA nor

Table 4 Summary of research findings on omega-3s (ω-3s) and cardiovascular health

Findings	Number of persons	Number of cardiovascular disease incidents	Reference
Intake of tuna and dark fish, ALA, and marine ω-3 PUFAs were not associated with risk of major CVD in women without history of CVD	713,559 women (>45 years)	1,941 cases of incident major CVD (MI, stroke, and cardiovascular death)	Rhee et al. 2017
Supplementation with DHA decreased liver and visceral fat and enhanced metabolic abnormalities in children with nonalcoholic fatty liver disease	51	ND	Pacifico et al. 2015
Supplementation with ω-3 PUFA (1 g/d) for 1 year did not reduce recurrent AF in participants with confirmed symptomatic paroxysmal AF	586	125 recurrent symptomatic AF	Macchia et al. 2013
Short-term supplementation with fish oil (1.7–4.5 g/d EPA + DHA) did not appreciably reduce postoperative AF	2,687	ND	Mozaffarian et al. 2013b
No significant benefit of ω-3 PUFAs was detected in reducing the risk of death from CVD in a large population of patients with multiple CVD risk factors and no history of MI	12,513	1,478 death, nonfatal MI, and nonfatal stroke	Risk Prev. Study Collab. Group 2013
Intake of ω-3 PUFAs (1-g capsule: 900 mg of EE of ω-3s) for 6 years did not reduce the rate of death from CVD or other outcomes in patients with dysglycemia and a history of MI, stroke, revascularization, or angina with documented ischemia	12,536 (≥50 years)	1,055 CVD death	ORIGIN Trial Investig. 2012
Consumption of ω-3 PUFAs did not lower the risk of all-cause mortality, cardiac death, sudden death, MI, or stroke	68,680	7,044 deaths [3,993 cardiac deaths, 1,150 sudden deaths, 1,837 MI and 1,490 strokes]	Rizos et al. 2012
The risk of heart failure was lowered with increased intake of baked/broiled fish in postmenopausal women	84,493 aged 50–79 years	1,858 with heart failure	Belin et al. 2011
Marine ω-3 PUFAs lowered the risk of heart failure	176,441	5,480	Djoussé et al. 2011
Consumption of EPA + DHA and fish lowered fatal CHD and MI risk (dose-responsive manner) in Dutch populations with no history of MI or stroke and low fish consumption	21,342 aged 20–65 years	647 participants (3%) died, of which 82 died of CHD	de Goede et al. 2010
In patients with a history of MI who were receiving good clinical care, low doses of ω-3 fatty acids did not significantly reduce the rates of cardiovascular endpoints	4,837	Major cardiovascular events 671; CHD deaths 138	Kromhout et al. 2010
Treatment of acute MI with ω-3 resulted in a low rate of sudden cardiac death and other clinical events within 1 year of follow-up	3,851	Major cardiovascular events 331; sudden deaths 57	Rauch et al. 2010
A treatment with ω-3 provided a small beneficial advantage in terms of mortality and admission to hospital for cardiovascular reasons in patients with heart failure	6,975	Total mortality 1,969 (sudden death 632); cardiovascular death 1,477	Tavazzi et al. 2008
Long-term intake of fatty fish lowered CHD death in men	1,373 men aged 40–60 years	348 (66 sudden death)	Streppel et al. 2008

(*Continued*)

Table 4 (*Continued*)

Findings	Number of persons	Number of cardiovascular disease incidents	Reference
Dietary intake of fish and ω-3 PUFAs inversely correlated with cardiovascular mortality, especially for heart failure, suggesting a protective effect of fish intake on cardiovascular diseases Japanese men and women	57,972	2,045 total CVD deaths and 7,008 total deaths [IHD (419, including 329 MI), cardiac arrest (107), heart failure (307); stroke (972), intraparenchymal hemorrhages (223), subarachnoid hemorrhages (153), ischemic strokes (319)]	Yamagishi et al. 2008
ω-3 PUFAs, especially EPA, exhibited an effective treatment for prevention of major coronary events, including nonfatal coronary events, in Japanese hypercholesterolemic patients	18,645	586 major coronary events [coronary deaths (60); sudden deaths (35)]	Yokoyama et al. 2007
A higher fish intake (8 times/week, or 180 g/d) reduced risk of coronary heart disease, primarily nonfatal cardiac events, among middle-aged Japanese persons free of prior diagnoses of CVD and cancer	477,325 (40–59 years)	258 incident cases of coronary heart disease [definite (198); MI (23); sudden cardiac deaths (37)]	Iso et al. 2006
High consumption of fish was associated with a decreased risk of CHD among women, whereas no significant association was seen among men who were free of CHD	2,775 men and 2,445 women aged 30–79 years	335 men and 163 women died of CHD during a follow-up	Järvinen et al. 2006
High consumption of fish might or might not be one of the contributing factors for Japanese longevity	8,879 subjects (3,945 men and 4,934 women)	1,745 deaths [Stroke death (28); cerebral hemorrhage death (63); cerebral infarction death (165); CHD death (142)]	Nakamura et al. 2005
High consumption of fish and ω-3 PUFAs was associated with a lower risk of CHD, especially CHD deaths in women	84,688 women	1,513 incident cases of CHD [CHD death (484); nonfatal MI (1,029)]	Hu et al. 2002
Weekly consumption of fish and shellfish reduced the risk of fatal MI in middle-aged and older men in China	18,244 men	113 deaths from acute MI	Yuan et al. 2001
Intake of fish and marine ω-3 PUFAs had health benefits in postmenopausal women free of cancer and CVD	442,965 women aged 55–69 years	4,653 deaths	Folsom & Demissie 2004
High concentration of ω-3 PUFAs in serum lipids associated with a significantly lower risk of death in both men and women with CHD	285 men and 130 women aged 33–74 years	36 patients died, 21 had myocardial infarctions, and 12 had strokes	Erkkilä et al. 2003
Higher intake of DHA and EPA and possibly ALA might lower the risk of fatal IHD in older adults aged ≥65 years	5,201 men and women	54 cases of fatal IHD, 125 cases of nonfatal MI	Lemaitre et al. 2003
Dietary supplementation with ω-3 PUFAs exerted significant benefit in patients surviving recent (≤3 months) MI	11,324 men	520 cardiac deaths; 286 sudden deaths	GISSI-Prevenzione Investig. 1999
Consumption of fish at least once per week reduced the risk of sudden cardiac death in men free of MI, cerebrovascular disease, and cancer	20,551 men 40 to 84 years of age	133 sudden deaths	Albert et al. 1998

(*Continued*)

Table 4 (*Continued*)

Findings	Number of persons	Number of cardiovascular disease incidents	Reference
An inverse relationship was observed between fish consumption and the 30-year risk of fatal MI, particularly nonsudden death from MI, in Chicago men	1,882 men aged 40–55 years	293 deaths from MI (196 sudden deaths, 94 nonsudden deaths), 430 deaths from any type of CHD, 573 from any type of CVD and 1,042 from any cause	Daviglus et al. 1997
Consumption of fatty fish (2–3 portions per week) reduced the mortality in men who have recovered from MI	2,033 men	IHD events 276; IHD deaths 194	Burr et al. 1989

Abbreviations: AF, atrial fibrillation; ALA, α-linolenic acid; CHD, coronary heart disease; CVD, cardiovascular disease; DHA, docosahexaenoic acid; EE, ethyl ester; EPA, eicosapentaenoic acid; IHD, ischemic heart disease; LDL, low-density lipoprotein; MI, myocardial infarction; ND, no data; PUFAs, polyunsaturated fatty acids; TAG, triacylglycerol.

EPA in fish oil influenced platelet monocyte aggregation or several markers of vascular function in healthy young men after supplementation for six weeks (Cottin et al. 2016).

A recent report from the American Heart Association, based on the current evidence from RCTs (Siscovick et al. 2017), suggested that ω-3 PUFA supplementation did not provide any benefits toward preventing cardiovascular disease among patients with or at risk for diabetes mellitus and did not lower the risk of stroke among patients without a history of stroke. They also reported that the ω-3 PUFA supplements may reduce death from coronary heart disease among patients with prior coronary heart disease, possibly via reducing ischemia-induced sudden cardiac death, but the treatment did not reduce the incidence of recurrent nonfatal myocardial infarction (Siscovick et al. 2017). The National Heart, Lung, and Blood Institute (NHLBI) recommended increasing the intake of seafood as a source of ω-3 PUFAs (O'Connell et al. 2016). In addition, the American Heart Association recommends an ω-3 supplement of 1 g/day for patients with cardiovascular disease, claiming benefits from this supplementation such as lowering TAG level as well as prevention of arrhythmias and atherosclerosis. No recommendation was provided to prevent incident stroke among patients at high cardiovascular disease risk and recurrent atrial fibrillation because of the lack of reported RCTs related to the primary prevention of CHD, heart failure, and atrial fibrillation (Siscovick et al. 2017).

Diabetes

Some controversies exist with respect to the role of ω-3 PUFAs in the control of diabetes. Djoussé et al. (2011) reported that there is an increased risk of type 2 diabetes with higher intake of ω-3 PUFAs (≥0.20 g ω-3/day or ≥2 servings of fish/day). However, several studies have shown that ω-3 PUFAs or fish oil supplementation exert beneficial effects against type 2 diabetes (Wang et al. 2003). Tsitouras et al. (2008) found that consumption of an ω-3 PUFA diet increased insulin sensitivity in older people after eight weeks and significantly decreased serum C reactive protein.

Insulin resistance leads to postprandial hyperglycemia, elevated FFA levels, hyperinsulinemia, and pancreatic β-cell dysfunction and results in obesity, metabolic syndrome, and type 2 diabetes (Lalia & Lanza 2016). A recent in vivo study on mice fed a high-fat diet suggested that the mechanism of ω-3 on insulin resistance was initiated by its active metabolites, called specialized

Table 5 Summary of research findings of omega-3 (ω-3) PUFAs and diabetes

Findings	Number of participants	Reference
Dietary ω-3 (EPA + DHA; 3.9 g/day) supplementation did not improve disposal of peripheral glucose, secretion of insulin, or skeletal muscle mitochondrial function in insulin-resistant nondiabetic humans	31	Lalia & Lanza 2016
Insulin sensitivity was improved in type 2 diabetic patients supplemented with ω-3 PUFAs due to decreased levels of nonesterified FFA	44	Farsi et al. 2014
ω-3 PUFAs exerted a positive effect on glucose storage and oxidation in insulin-stimulated skeletal muscle that was not affected by total acylcarnitine accumulation in healthy men	6	Stephens et al. 2014
Fish oil supplementation reduced adipose macrophages and MCP-1 expression and increased capillary size in insulin-resistant humans but did not show any measurable effect on insulin sensitivity	34	Spencer et al. 2013
ω-3 PUFA supplementation lowered levels of fasting plasma glucose, plasma lipids, metalloproteinases, and inflammatory parameters	167 (82 males and 85 females)	Derosa et al. 2012
DHA supplementation (3 g/day, 90 days) increased fasting plasma glucose concentration but did not affect other indices of insulin resistance based on fasting, such as postprandial insulin and glucose concentrations	14–17	Kelley et al. 2012
Administration of ω-3 PUFAs (3.5 g/d, 8.9 weeks) lowered TAG and VLDL cholesterol levels but increased LDL level in type 2 diabetic individuals	1,075	Hartweg et al. 2008
Diets varying in the ratio of ω-6/ω-3 did not influence insulin sensitivity or lipase activity in women aged 45–70	258	Griffin et al. 2006
Moderate supplementation with EPA and DHA decreased the insulin resistance in patients with chronic renal failure on maintenance hemodialysis	35	Rasic-Milutinovic et al. 2007
Treating type 2 diabetes patients with ω-3 PUFAs caused a rapid and reversible metabolic deterioration, with increased basal hepatic glucose output and impaired insulin secretion, but glucose disposal rates remained unchanged	6	Glauber et al. 1988

Abbreviations: DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FFA, free fatty acid; LDL, low-density lipoprotein; PUFAs, polyunsaturated fatty acids; TAG, triacylglycerol; VLDL, very-low-density lipoprotein.

proresolving mediators [SPMs: resolvins (Rv), protectins (PD), and maresins (MaR)] (White et al. 2010). MacLean et al. (2004) reviewed several articles and suggested that ω-3 PUFAs have a favorable effect on plasma TAG levels and no direct effect on total cholesterol, HDLs, LDLs, fasting blood sugar, or glycosylated hemoglobin levels in type 2 diabetic or metabolic syndrome patients. In addition, they also suggested that ω-3 PUFAs did not affect plasma insulin or insulin resistance in type 2 diabetics or metabolic syndrome patients. However, Schwab et al. (2014) reported that there was limited suggestive evidence for effects of ω-3 PUFAs on diabetes 2 mellitus. The summary of research findings (**Table 5**) reveals that controversies still exist with respect to the effect of ω-3 PUFAs in diabetes and insulin resistance. Therefore, further clinical investigation is necessary to determine whether ω-3 PUFAs are influencing diabetes and insulin resistance in humans.

Cancer

Over the past decade several experimental and epidemiological studies have shown that the ω-3 PUFAs reduce the risk of cancer. These effects are supported by several clinical studies. A summary

Table 6 Summary of research findings on omega-3s (ω-3s) and cancer

Type of cancer	Number of participants and time	Number of incidents	Findings	Reference
Skin	1,516 melanoma, 3,927 squamous cell cancer, and 30,312 basal cell carcinomas cases Observation time: 26–28 years	ND	No significant association was found between ω-3 PUFA intake and risk of melanoma. However, intake of ω-3 increased the risk of basal cell carcinoma	Park et al. 2017
Colon	1,011 stage III colon cancer patients Observation time: 7 years	343 colon cancer recurrences and 305 deaths	Intake of long-chain ω-3 PUFAs and dark-meat fish improved disease-free survival in patients with high COX2 expression tumors after diagnosis of colon cancer	Van Blarigan et al. 2017
Lung	5,885 Japanese residents Observation time: 14 years	51	Frequent consumption of fresh fish reduced the risk of lung cancer regardless of the cooking method used	Takezaki et al. 2003
Breast	121,700 female nurses Observation time: 18 years	4,107 cases of breast cancer	No evidence was found for intake of fish and breast cancer risk	Holmes et al. 2003
Prostate	6,272 Swedish men Observation time: 30 years	466 (340 were fatal)	Consumption of ω-3 lowered the risk of prostate cancer via inhibiting biosynthesis of arachidonic acid–derived eicosanoid	Terry et al. 2001
Colorectal	14,727 women aged 34–65 years Observation time: 7.1 years	100	Continuous clinical observation showed a progressive decline in risk of colorectal cancer with increasing intake of fish and shellfish	Kato et al. 1997

Abbreviations: PUFA, polyunsaturated fatty acid; ND, no data.

of clinical studies on the effect of ω-3s and cancer is provided in **Table 6**. Prener et al. (1996) reported that ω-3 PUFAs exert an anticarcinogenic effect, whereas saturated and ω-6 PUFAs may promote cancer development. Based on cross-cultural studies among people from Canada, Alaska, and Greenland between 1969 and 1988, Prener et al. (1996) reported that the incidence rate of prostate cancer among the Inuit population was 70–80% less than that of non-Inuit population and attributed this to the traditional seafood diet, which is rich in ω-3 PUFAs, of the Inuit population. However, some systematic reviews report that there is insufficient evidence to suggest a significant association between ω-3 PUFAs and cancer incidence (MacLean et al. 2006). Therefore, more thorough studies are required to prove or refute this view.

ω-3 PUFAs have been shown to affect various types of cancer, including prostate, colon, breast, lung, colorectal, ovarian, pancreatic, skin, and stomach (Kato et al. 1997, Takezaki et al. 2003). In addition, ω-3 PUFAs have been shown to improve the efficacy and tolerability of chemotherapy (Mocellin et al. 2017). Several reviews have been published on this topic (Chen et al. 2007, Larsson et al. 2004, MacLean et al. 2006, Simopoulos 2002, Terry et al. 2001, Zheng et al. 2013). In addition, several molecular mechanisms have been proposed for the anticarcinogenic effect of ω-3s. Larsson et al. (2004) reported the following possible mechanisms: (*a*) decreasing the biosynthesis of arachidonic acid–derived eicosanoids, which leads to altered immune responses to

cancer cells, inflammatory modulation, cell proliferation, apoptosis, metastasis, and angiogenesis; (*b*) impacting the activity of a transcription factor that causes changes in metabolism, cell growth, and differentiation; (*c*) changing the metabolic activity of estrogen followed by a decrease in estrogen-stimulated cell growth; (*d*) alteration of free radicals and reactive oxygen production; and (*e*) modulation of insulin sensitivity and membrane fluidity. Kobayashi et al. (2006) reported that ω-3 PUFAs invade and inhibit tumor cell growth by decreasing cyclooxygenase COX-2 and PGE_2 levels and hence could serve as a natural COX inhibitor. Berquin et al. (2007) showed that a ratio of ω-6 to ω-3 lower than five was effective in slowing cancer progression. Meanwhile, increased intake of ω-6 PUFAs was shown to promote breast, prostate, and colon cancer in both animals and humans (Sakai et al. 2012). The mechanisms behind the protumor effect of ω-6 include lipid peroxidation, generation of carcinogens after 17-β-estradiol (E2) epoxidation, and a cocarcinogenic effect via enhancement of the genotoxic effects of other compounds (e.g., chromatin) (Yu et al. 2004).

A recent study showed that combining ω-3 with 1α,25-dihydroxy-vitamin D_3 significantly increased cell apoptosis in breast cancer cell lines (Yang et al. 2017). Dietary supplementation with ω-3s, α-tocopherol, linolenic acid, fiber, and phytoestrogen exerts a positive effect in breast cancer patients (Chen et al. 2002, Flower et al. 2014). Shahverdi & Niknam (2017) suggested that flaxseed exerts an antiproliferative activity in breast cancer patients and recommended 25 g per day of flax for premenopausal women. A recent systematic meta-analysis study showed a positive correlation between intake of ω-3s and breast cancer risk, which had 527,392 participants and 16,178 breast cancer patients (Zheng et al. 2013). Pedrazzoli et al. (2017) found that using ω-3 as a nutritional supplement for head and neck cancer patients undergoing radiotherapy helped them maintain body weight through increased protein-caloric intake and tolerate the anticancer treatment, improving their quality of life. ω-3 PUFAs also suppressed polycyclic aromatic hydrocarbon-mediated lung cancers in mice (Moorthy et al. 2017). Meanwhile, Yu et al. (2004) reported that increasing PUFAs (5 g/day) had no significant influence on lung cancer risk, whereas increased intake (5–15 g/day) increased the risk of lung cancer based on a meta-analysis study consisting of 1,268,442 individuals. In another study, 33 patients undergoing chemotherapy for advanced inoperable non-small-cell lung cancer were given 4 capsules/day (510 mg of EPA and 340 mg of DHA) for 66 days (Finocchiaro et al. 2012). Finocchiaro et al. (2012) observed a significant increase in body weight as well as effective antioxidative and anti-inflammatory effects of ω-3 PUFAs.

Caygill and coworkers (1996) reported an inverse correlation between colon cancer mortality and fish/fish oil consumption based on mortality data collected from 24 European countries. Dichwalkar et al. (2017) found that treatment of upper gastrointestinal cancers (UGCs) with DHA-Paclitaxel conjugate inhibited cellular proliferation, induced cell death, and suppressed long-term survival in UGC cells. ω-3 PUFAs have been shown to be effective in enhancing the nutritional status and immune function of gastrointestinal patients who underwent surgery (Yu et al. 2017). In addition, substitution of dietary fat with ω-3-rich menhaden oil inhibited 40–70% of neuroblastoma tumor growth in humans (Barnés et al. 2011). Therefore, So et al. (2015) suggested that inhibition of neuroblastoma tumor growth by ω-3 PUFAs was mainly due to inhibition of cell proliferation and induction of apoptosis. Because prolonged administration of ω-3s is considered safe for children, studies recommend the use of ω-3 PUFAs (DHA and EPA) for cancer therapy for neuroblastoma (So et al. 2015). Recently, de Aguiar Pastore Silva et al. (2015) suggested that supplementation with ω-3 PUFAs (600 mg to 3.6 g) alongside conventional cancer therapies such as radiotherapy, chemotherapy, and chemo-radiotherapy could possibly prevent toxicity and improve the survival rate of cancer patients. Furthermore, ω-3 supplementation could also prevent neurotoxicity in addition to cancer treatment (Vilar-González et al. 2017). Furthermore,

prolonged intake of ω-3 PUFAs (1.5 g/day) enhanced clinical, biological, and functional parameters of cancer cachexia (advanced cancer patients with weight loss) and improved quality of life (Werner et al. 2017). Recently, Sorensen et al. (2014) found that supplementation with ω-3 PUFAs (3 g for 7 days) in the diets of colorectal cancer patients just before the surgery showed rapid incorporation of EPA into the colonic mucosa and colonic muscle layer compared to DHA. In another study, plasma EPA levels increased in advanced lung and pancreatic cancer patients supplemented with ω-3 (2 g EPA + 1 g DHA per day), whereas there was no change in plasma DHA levels (Balstad et al. 2015).

Certain factors may influence the inconsistent results of ω-3s on cancer: (*a*) differences in the source, type (ALA, DHA, or EPA), form (TAG or alkyl ester), and amount of ω-3 PUFAs; (*b*) the ratio of ω-6 to ω-3 PUFAs; and (*c*) genetic factors, such as polymorphism in the modifier genes of COX and lipoxygenase enzymes (Berquin et al. 2007). More clinical trials are needed to find out the effective dose and formulas of ω-3s for specific cancer pathologies. Several cancer therapeutic drugs developed recently lacked proper clinical trials because of funding constraints; these should be considered more seriously and further evaluated.

Alzheimer's Disease and Dementia

Several epidemiological studies have shown that lower intakes of ω-3 PUFAs are associated with an increased risk of cognitive decline or dementia, especially for Alzheimer's disease (Cole et al. 2009). MacLean et al. (2004) reported that sufficient clinical evidence exists for ω-3s and prevention of Alzheimer's disease. DHA is the primary component of membrane PLs in the brain, especially in the cerebral cortex, mitochondria, synaptosomes, and synaptic vesicles (Connor 2000). Several reviews have also analyzed the effects of ω-3s on dementia (Cole et al. 2009, Cunnane et al. 2009).

The action mechanism of PUFAs on brain function includes modifications to (*a*) membrane fluidity, (*b*) the activity of membrane-bound enzymes, (*c*) the number and affinity of receptors, (*d*) the function of ion channels, (*e*) the production and activity of neurotransmitters, and (*f*) signal transduction, which controls the activity of neurotransmitters and neuronal growth factors (Yehuda et al. 2005). ω-3 PUFAs could induce a decrease in lymphocyte proliferation, TNF_{α} production, natural killer cell activity, and interleukin IL-1 and interleukin IL-2 production in humans (Boudrault et al. 2009, Singer & Richter-Heinrich 1991). Dijck-Brouwer et al. (2005) investigated umbilical artery and umbilical vein FA compositions as well as early neonatal neurological conditions in 317 term infants and reported that lower fetal DHA, AA, and essential FA levels negatively influence the neurological condition of early postnatal neurological condition. In addition, early neonatal PUFA deficiency could lead to Huntington's disease, schizophrenia, high blood pressure, and increased appetite signaling during adult life (Mathai et al. 2004). Several studies have shown that deficiency in essential FAs, especially ω-3 PUFAs, contributes to attention deficit hyperactivity disorder (ADHD) (Farooqui & Horrocks 2001, Ross et al. 2003). Yehuda and coworkers (2011) found that administration of ω-3 PUFAs significantly improved quality of life, ability to concentrate, sleep quality, and hemoglobin levels in iron-deficient and sleep-disturbed attention deficit hyperactivity disorder (ADHD) children. Overall, the intake of fish and ω-3 PUFAs has been shown to exert a positive cognitive health effect in older healthy adults, whereas consumption of ω-3 PUFAs appears to be controversial when considering patients with Alzheimer's disease (Cederholm 2017). Cederholm (2017) reported that ω-3 supplementation could also benefit older adults with memory complaints/mild cognitive impairment and Alzheimer's disease based on studies published during 2015–2016. A summary of clinical studies on the effects of ω-3s in Alzheimer's disease dementia is provided in **Table 7**.

Table 7 Summary of research findings on omega-3s (ω-3) and dementia/Alzheimer's disease

Findings	Number of persons	Number of incidents	Reference
Intake of phosphatidylserine enriched with DHA (100 mg/day) could improve or maintain cognitive status in elderly subjects with memory complaints	122 elderly individuals	ND	Vakhapova et al. 2014
Low levels of red-blood-cell DHA were associated with smaller brain volumes and a vascular pattern of cognitive impairment even in persons free of clinical dementia	1,575 participants (854 women) aged 67 ± 9 years	ND	Tan et al. 2012b
Increased DHA intake from marine sources reduced the risk of dementia	266 participants	42 dementia and 30 AD	Lopez et al. 2011
Supplementation with algal DHA (2 g/day) did not slow down the rate of cognitive and functional decline in patients with mild to moderate AD	295 individuals with mild to moderate AD	ND	Quinn et al. 2010
The cognitive function did not decline over 2 years of study in healthy adults with administration of 200 mg EPA plus 500 mg DHA	748 cognitively healthy adults (55% men), aged 70–79 years	ND	Dangour et al. 2010
Intake of ω-3 PUFAs was not associated with dementia or AD in the Canadian Study of Health and Aging	663 nondemented subjects aged more than 65 years	149 were incident cases of dementia, including 105 with AD	Kröger et al. 2009
Supplementation with DHA (800 mg/day) and lutein (12 mg/day) significantly improved verbal fluency scores, memory scores, and rate of learning in elderly women	49 women (aged 60–80 years)	ND	Johnson et al. 2008
High consumption of fish (nonprocessed lean fish and fatty fish) and fish products (>10 g/day) was associated with better cognitive performance in a dose-dependent manner in elderly people	2,031 subjects (55% women) aged 70–74 years	80 poor cognitive performance who had low fish consumption (<10 g/day)	Nurk et al. 2007
Intake of fatty fish and marine ω-3 PUFAs reduced the risk of impaired cognitive function in this middle-aged population, whereas intake of cholesterol and saturated fat showed an increased risk	1,613 subjects ranging from 45 to 70 years	ND	Kalmijn et al. 2004
Intake of dietary ω-3 (DHA) PUFAs and fish reduced the risk of incident AD, but EPA did not show any significant effect	815 residents (65 to 94 years), who were initially unaffected by AD	131 participants developed AD	Morris et al. 2003
Consumption of fish (weekly) reduced the risk of AD	8,085 nondemented participants aged 65	281 incident cases of dementia, including 183 AD	Barberger-Gateau et al. 2002

Abbreviations: AD, Alzheimer's disease; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; ND, no data; PUFAs, polyunsaturated fatty acids.

Depression

According to the World Health Organization (WHO), depression will be the second leading disability worldwide by 2020 (Lin & Su 2007). Several epidemiological studies have shown that consumption of fish is associated with lower risk of depression (Hibbeln 1998, Nemets et al. 2006). Su et al. (2001) found that supplementation with ω-3 PUFAs (a mixture of EPA + DHA) exerted a positive effect in pregnant schizophrenic women. EPA has been shown to act as an antidepressive

Table 8 Summary of research findings of omega-3 (ω-3) PUFAs and depression

Findings	Number of participants	Reference
Supplementation with ω-3 for 12 weeks (1.4 g EPA, 0.2 g DHA, and 0.27 g other ω-3 per day) increased blood levels substantially, more so in smaller children	95 7–14-year-old patients (depression $n = 72$; bipolar $n = 23$)	Arnold et al. 2017
Low intake of ω-3 PUFAs and moderate-dose supplementation (300 mg/day; 18 weeks) did not alter impulsive behaviors nor corticolimbic and corticostriatal brain functionality in healthy midlife adults	272 healthy volunteers	Ginty et al. 2017
Supplementation with ω-3 PUFAs (1.9 g/day) for 12 weeks improved depressive symptoms in CAD patients with pretreatment evidence of oxidative stress	79 patients with CAD	Mazereeuw et al. 2017
Supplementation with ω-3 (930 mg EPA/750 mg DHA/day) could be an effective treatment for depression; the required dosage and duration of treatment may depend on the patient's ω-3 baseline level	122 participants with major depressive disorder	Carney et al. 2016
Supplementation with fish oil (1,000 mg/day) from 16–20 weeks of gestation to one month after giving birth significantly decreased the mean score on the EPDS at weeks 35 to 37	150 pregnant women with EPDS score less than 20, aged 18 to 35 years	Farshbaf-Khalili et al. 2016
Supplementation with fish oil (1.4 g/day) to young depressive disorder patients revealed ω-3 PUFAs as a first-line therapy for major depressive disorder	400 participants aged between 15 and 25 years	Rice et al. 2016
Neither EPA-enriched (1,000 mg/day) nor DHA-enriched (1,000 mg/day) ω-3 was superior to placebo for the treatment of major depressive disorder	154 patients	Mischoulon et al. 2015
EPA effectively prevented depression in hepatitis C virus patients who received interferon (IFN)-α therapy	152 patients	Su et al. 2014
Supplementation with EPA or DHA (1 g/day) or placebo (coconut oil) for 12 weeks showed a greater efficacy of EPA compared to DHA or placebo	81 mild-to-moderately depressed outpatients	Mozaffari-Khosravi et al. 2013
Consumption of ω-3 PUFAs (2.5 g/day, 1.67 g EPA + 0.83 g DHA) efficiently ameliorated depressive symptoms and quality of life of depressed elderly female patients	46 depressed women, aged 66–95 years	Rondanelli et al. 2010
Intake of DHA (220 mg/day) or DHA + AA (220 mg/day each) from week 16 of pregnancy until 3 months postpartum did not prevent peripartum depressive symptoms in women with low DHA intake	119 pregnant women	Doornbos et al. 2009
Intake of fish oil, with or without antidepressants, improved depressive symptoms in patients with Parkinson's disease with mean age of 64.4 years old	29 patients with Parkinson's disease and major depression	da Silva et al. 2008
Treatment with EPA (1,000 mg/day) and fluoxetine (20 mg/day) for 8 weeks had equal therapeutic effects in major depressive disorder and the combination showed superior results to either of them alone	60 outpatients with major depressive disorder	Jazayeri et al. 2008
Findings did not support the beneficiary effect of ω-3 when tuna fish oil was used in addition to conventional treatment for major depression	183 outpatients with major depression	Grenyer et al. 2007
ω-3 PUFAs significantly improved depression in patients with clearly defined depression or with bipolar disorder	329	Lin & Su 2007

(*Continued*)

Table 8 (*Continued*)

Findings	Number of participants	Reference
Intake of ω-3 PUFAs significantly improved the condition of women regardless of dose	16 women with postpartum depression	Freeman et al. 2006
Dietary supplementation with long-chain ω-3 PUFAs showed beneficial effect in patients with CAD and depression	803 patients (54 depressed)	Frasure-Smith et al. 2004
Supplementation with ω-3 PUFAs improved the short-term course of depression and was well tolerated in patients with major depressive disorder	28 patients with major depressive disorder	Su et al. 2001
Supplementation with fish oil and ω-3 PUFAs inhibited synthesis of cytokines that cause depression	247 healthy adults (146 males, 101 females)	Mamalakis et al. 2002

Abbreviations: CAD, coronary artery disease; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; EPDS; Edinburgh postnatal depression scale; PUFAs, polyunsaturated fatty acids.

agent that causes structural brain changes, including a reduction in the lateral ventricular volume of the brain and reduced neuronal PL turnover (Puri et al. 2002). A meta-analysis study based on 28 clinical trials provided evidence that EPA may be more efficacious than DHA in treating depression (Martins 2009). In addition, deficiency in DHA during early development may affect the central nervous system and could increase vulnerability to depression during adult life (Farquharson et al. 1995, Hibbeln 1998). Furthermore, intake of or supplementation with fish oil/ω-3 PUFAs has been shown to protect youth (15–25 years) from major depressive disorder (Nemets et al. 2006, Rice et al. 2016). A summary of research findings on the effect of ω-3s and depression is shown in **Table 8**.

The possible mechanisms of action for the use of ω-3 PUFAs as antidepressants include (*a*) secretion of inflammatory cytokines, which can provoke signs and symptoms as in major depressive disorder (Mischoulon & Fava 2000); (*b*) an increase in membrane fluidity, which causes an increase in serotonin 5-HT (hydroxytryptamine) transport by endothelial cells (Block & Edwards 1987); (*c*) an increase in DHA concentration in the frontal cortex, which can increase dopamine concentration and D (dopamine) 2 receptor binding (Hibbeln 1998); and (*d*) interaction with neuronal cell membrane receptors and second messengers, which leads to mood alteration (Mischoulon & Fava 2000). However, some of these findings on the potential antidepressant ability of ω-3 PUFAs are contradictory in nature with respect to positive or negative effects; hence, larger clinical RCTs are needed. A recent meta-analysis from 1980 to 2014 using 35 RCTs showed that further RCTs are needed to study populations with diagnosed or clinically significant depression of adequate duration using EPA-predominant ω-3 PUFA formulations (Hallahan et al. 2016).

Visual and Neurological/Brain Development

Several studies have reported the important role of dietary ω-3 PUFAs on the development of the brain (**Table 9**). Low intake of dietary ω-3 PUFAs increases the ratio of brain AA/DHA during pre- or postnatal development (Clandinin et al. 1981, McNamara et al. 2017). The ratio change reduces delays in neuronal migration, neurogenesis, embryonic cortical plate expansion, synaptic pruning, brain glucose uptake, and metabolism and causes impaired glutamate and monoamine synaptic function (McNamara et al. 2017).

Table 9 Summary of research findings of omega-3 (ω-3) PUFAs and visual and neurological development clinical trials

Findings	Number of participants	Reference
Pregnant women supplemented with 800 mg of DHA daily followed up after 7 years showed strong evidence for the lack of benefit of prenatal DHA supplementation on IQ at 7 years and cognition at 18 months and 4 years	543 children born to mothers supplemented with DHA (800 mg/day) at 7 years of age	Gould et al. 2017
Prenatal folate supplementation during pregnancy, rather than fish oil or fish oil + 5-MTHF supplementation, improved children's ability to solve response conflicts after 8 years of follow up	136 children born to mothers who had prenatal supplementation with fish oil, 5-MTHF, or fish oil + 5-MTHF	Catena et al. 2016
Supplementation with fish oil (1.5:1 EPA:DHA; 2200 mg/day), aerobic exercise, and cognitive stimulation attenuated frontal, parietal, and cingulate cortex gray matter volume reductions	22 patients with mild cognitive impairment (8 females; 60–80 years)	Köbe et al. 2016
Supplementation with human milk with DHA (~1% of total fatty acids) given in the first months of life to preterm infants did not confer any long-term benefit for visual processing at school age	104 children at 7 years of age	Molloy et al. 2016
Supplementation with fish oil reduced ventricular enlargement, cognitive decline, and atrophy in cerebral cortex gray matter and hippocampus	Older adults (229 cognitively normal individuals, 397 mild cognitive impairment, and 193 patients with AD)	Daiello et al. 2015
The protective effect of ω-3 PUFAs on brain atrophy could be confined to humans with good B vitamin status	168 elderly people (≥70 years) with mild cognitive impairment	Jernerén et al. 2015
High ω-3 levels were associated with larger total normal brain volume and hippocampal volume in postmenopausal women measured 8 years later	1,111 postmenopausal women	Pottala et al. 2014
Dietary consumption of baked or broiled fish (weekly) was associated with larger gray matter volumes (hippocampus, precuneus, posterior cingulate, and orbital frontal cortex gray matter volumes) independent of ω-3 PUFA content	260 cognitively normal individuals	Raji et al. 2014
High blood DHA level was associated with less baseline-endpoint cortical thinning in the left, middle, and superior temporal gyrus and similar trends were also observed in the right hemisphere	92 healthy persons aged 23–87 years	Walhovd et al. 2014
Dietary intake of EPA and DHA positively associated with global gray matter volume (not global white matter or total/regional brain volume) and increased global cognitive performance 5 years later in elderly humans	252 cognitively health elderly aged 70 years (122 females)	Titova et al. 2013
High baseline level of plasma EPA associated with slower right hippocampus and amygdala gray matter atrophy over 4 years	281 participants aged 65 years or older with plasma fatty acid measurements at baseline	Samieri et al. 2012
Modest DHA supplementation [high-DHA algal oil (~200 mg/d of DHA)] from delivery until 4 months postpartum performed better on a test of sustained attention	Children at 5 years of age	Jensen et al. 2010
Supplementation with DHA (~1% total fatty acids) in early life did not increase Bayley Mental Development Index (MDI) scores of preterm infants overall but improved the MDI scores of girls after 18-month follow-up	657 infants born after gestation for fewer than 33 weeks	Makrides et al. 2009

(*Continued*)

Table 9 (*Continued*)

Findings	Number of participants	Reference
Supplementation with DHA (400-mg/day) capsules for 4 months increased blood DHA level and increased scores on the Peabody Picture Vocabulary Test (a test of listening comprehension and vocabulary acquisition)	93 healthy 4-year-old children	Ryan & Nelson 2008
Modest intake of tuna/other fish (not fried fish) was associated with better white matter grade but not better sulcal and ventricular grades or markers of brain atrophy or lower prevalence of subclinical infarcts and white matter abnormalities among older adults	3,660 participants aged >65	Virtanen et al. 2008
Supplementation with DHA during pregnancy played a vital role in the maturation of the visual system	30 pregnant women 18–35 years of age and <20 weeks gestation	Judge et al. 2007
Supplementation with fish oil capsules rich in DHA from week 15 of pregnancy until delivery was associated with the status of DHA in infants at term and early postnatal development and suggested that DHA status itself may influence maturation of the central visual pathways	100 pregnant women	Malcolm et al. 2003

Abbreviations: 5-MTHF, 5-methyltetrahydrofolate; AD, Alzheimer's disease; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; PUFAs, polyunsaturated fatty acids.

DHA is an important structural component for retinal photoreceptors and cortical gray matter within the visual system; hence, supplementation with DHA during pregnancy assists in the maturation of the visual system (Judge et al. 2007). DHA accumulated rapidly in neural cortex tissues and retinal membrane synapses during the second half of a pregnancy (Clandinin et al. 1981, Fleith & Clandinin 2005, Gould et al. 2013). Supplementation with ω-3 PUFAs during pregnancy has been shown to positively associate with high-grade stereo-acuity, vocabulary comprehension, receptive vocabulary, verbal intelligence quotient, and higher cognitive scores from infancy to nine years of age (Hibbeln et al. 2007). Meanwhile, a recent review by Gould et al. (2013) suggests that there is no conclusive evidence that supplementation with ω-3 PUFAs during pregnancy improves cognitive or visual development. They suggested that there is a need for further evidence from high-quality clinical trials to establish a conclusion about whether ω-3 PUFA supplementation in pregnancy influences developmental progression and the prevalence of neurologic deficits in the offspring (Gould et al. 2013). More recently, Simmer (2016) reported that controversies continue with respect to maternal supplementation with ω-3s and brain development and thus recommended further research.

Maternal and Child Health

Plenty of epidemiological studies have shown the association of ω-3 PUFAs with maternal health during pregnancy and child health. ω-3 PUFAs affect length of gestation, preterm birth, birth weight, peripartum depression, gestational hypertension/preeclampsia, postnatal growth patterns, visual acuity, neurological development, cognitive development, autism spectrum disorder, ADHD, learning disorders, atopic dermatitis, allergies, and respiratory disorders (Newberry et al. 2016). A recent meta-analysis based on clinical studies suggests the benefits of increased ω-3 PUFAs in the maternal diet and for outcomes of childhood allergic disease (Best et al. 2016). A summary of research outcomes is shown in **Table 10**.

Table 10 Summary of research findings of omega-3 (ω-3) PUFAs and maternal and child health

Findings	Number of participants	Reference
Prenatal supplementation with ω-3 PUFAs (400 mg DHA/day) did not affect nonfasting serum lipid and glucose concentrations of offspring at 4 years of age.	524 offspring	Gutierrez-Gomez et al. 2017
Supplementation with DHA (600 mg/day) from the first trimester until delivery effectively ameliorated the red cell membrane DHA anomaly in pregnant women with type 2 diabetes and neonates and prevented the decline of maternal DHA during pregnancy	88 women with type 2 diabetes and 85 healthy women	Min et al. 2014
Supplementation with ω-3s (600 mg DHA/day) in the last half of gestation resulted in overall greater gestation duration and infant size	301 healthy pregnant women consumed capsules (placebo, DHA) from <20 week of gestation to birth	Carlson et al. 2013
Supplementation with EPA-rich fish oil (1,060 mg EPA plus 274 mg DHA) and DHA-rich fish oil (900 mg DHA plus 180 mg EPA) did not prevent depressive symptoms during pregnancy or postpartum	118 pregnant women at risk for depression (EPDS score of 9–19 or a history of depression) in early pregnancy	Mozurkewich et al. 2013
Supplementation with ω-3s (1,200 mg/day) did not show any evidence for reduction in arachidonic acid intake during pregnancy; lactation relevantly affected fat mass in offspring during the first year of life	170 healthy pregnant women before the fifteenth week of gestation, between 18 to 43 years of age	Hauner et al. 2012
Consumption of DHA containing functional food during pregnancy could be beneficial with respect to infant body composition at birth and insulin sensitivity	37 healthy pregnant women, mid-pregnancy (20–24 weeks)	Courville et al. 2011
Modest intake of fish (up to 3 meals/week) prior to 22 weeks of gestation reduced the risk of repeat preterm birth	852 randomized women	Klebanoff et al. 2011
ω-3 PUFA supplementation offered no benefit in reducing preterm birth among women received 17α-hydroxyprogesterone caproate	852 women with a history of at least one prior singleton preterm delivery between 20 and 36 6/7 weeks of gestation after spontaneous preterm labor or premature rupture of the membranes, and a current singleton pregnancy between 16 and 21 6/7 weeks of gestation	Harper et al. 2010
Maternal fish oil (2.2 g DHA + 1.1 g EPA/day) supplementation from 20 weeks gestation until delivery could have potentially beneficial effects on the child's eye and hand coordination and is safe for the fetus and infant	33 healthy term infants of pregnant women	Dunstan et al. 2008
Intake of long-chain ω-3 PUFAs and seafood was not correlated with length of gestation or risk of preterm birth	2,109 pregnant women	Oken et al. 2004

Abbreviations: DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; EPDS; Edinburgh postnatal depression scale; PUFAs, polyunsaturated fatty acids.

CONCLUSION

ω-3 PUFAs exert myriad health benefits on cardiovascular disease (atrial fibrillation, atherosclerosis, thrombosis, inflammation, and sudden cardiac death), diabetes, cancer, depression and various mental illnesses, age-related cognitive decline, periodontal disease, and rheumatoid arthritis. However, research findings reveal that controversies continue with respect to the effect of ω-3 PUFAs in several health issues such as stroke, diabetes, cancer, and visual and neurological/brain

development. In addition, several therapeutic drugs that use ω-3 PUFAs have been developed but some lack proper clinical trials because of funding constraints. Therefore, further clinical investigation is necessary. The beneficial effect of ω-3 PUFAs cannot always be unequivocally confirmed or rejected. Furthermore, our patented process of combining DHA esters with EGCG showed that the EGCG-DHA derivative efficiently arrested colon tumorigenesis in ICR mice; this finding requires further clinical trials (Shahidi & Zhong 2015, Zhong et al. 2012).

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

LITERATURE CITED

Ackman RG. 2005. Fish oils. In *Bailey's Industrial Oil and Fat Products*, Vol. 3, ed. F Shahidi, pp. 279–317. Hoboken, NJ: Wiley

Alasalvar C, Shahidi F, Quantick P. 2002. Food and health applications of marine nutraceuticals: a review. In *Seafoods: Quality, Technology and Nutraceutical Applications*, ed. C Alasalvar, T Taylor, pp. 175–204. Heidelberg, Ger.: Springer

Albert CM, Hennekens CH, O'Donnell CJ, Ajani UA, Carey VJ, et al. 1998. Fish consumption and risk of sudden cardiac death. *J. Am. Med. Assoc.* 279:23–28

Arnold LE, Young AS, Belury MA, Cole RM, Gracious B, et al. 2017. Omega-3 fatty acid plasma levels before and after supplementation: correlations with mood and clinical outcomes in the omega-3 and therapy studies. *J. Child Adolesc. Psychopharmacol.* 27:223–33

Arts MT, Ackman RG, Holub BJ. 2001. Essential fatty acids in aquatic ecosystems: a crucial link between diet and human health and evolution. *Can. J. Fish. Aquat. Sci.* 58:122–37

Aursand M, Bleivik B, Rainuzzo JR, Leif J, Mohr V. 1994. Lipid distribution and composition of commercially farmed Atlantic salmon (*Salmo salar*). *J. Sci. Food Agric.* 64:239–48

Balstad TR, Pettersen CH, Laird B, Fearon K, Schønberg SMA, et al. 2015. MON-PP096: changes in plasma levels of omega-3 PUFAs in response to supplementation with omega-3 PUFA-enriched oral nutritional supplements in advanced cancer patients. *Clin. Nutr.* 34:S163

Bang HO, Dyerberg J, Sinclair HM. 1980. The composition of the Eskimo food in north western Greenland. *Am. J. Clin. Nutr.* 33:2657–61

Barberger-Gateau P, Letenneur L, Deschamps V, Pérès K, Dartigues JF, Renaud S. 2002. Fish, meat, and risk of dementia: cohort study. *BMJ* 325:932–33

Barnés CM, Prox D, Christison-Lagay EA, Le HD, Short S, et al. 2011. Inhibition of neuroblastoma cell proliferation with omega-3 fatty acids and treatment of a murine model of human neuroblastoma using a diet enriched with omega-3 fatty acids in combination with sunitinib. *Pediatr. Res.* 71:168–78

Beckermann B, Beneke M, Seitz I. 1990. Comparative bioavailability of eicosapentaenoic acid and docasahexaenoic acid from triglycerides, free fatty acids and ethyl esters in volunteers. *Arzneimittel-Forschung* 40:700–4

Belin RJ, Greenland P, Martin L, Oberman A, Tinker L, et al. 2011. Fish intake and the risk of incident heart failure: the women's health initiative. *Circ. Heart Fail.* 4:404–13

Berquin IM, Min Y, Wu R, Wu J, Perry D, et al. 2007. Modulation of prostate cancer genetic risk by omega-3 and omega-6 fatty acids. *J. Clin. Investig.* 117:1866–75

Best KP, Gold M, Kennedy D, Martin J, Makrides M. 2016. 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.* 103:128–43

Bimbo AP. 1990. Production of fish oil. In *Fish Oils in Nutrition*, ed. ME Stansby, pp. 141–80. New York: Van Nostrand Reinhold

Block ER, Edwards D. 1987. Effect of plasma membrane fluidity on serotonin transport by endothelial cells. *Am. J. Physiol. Cell Physiol.* 253:C672–78

Boudrault C, Bazinet RP, Ma DW. 2009. Experimental models and mechanisms underlying the protective effects of n-3 polyunsaturated fatty acids in Alzheimer's disease. *J. Nutr. Biochem.* 20:1–10

Budge SM, Iverson SJ, Bowen WD, Ackman RG. 2002. Among- and within-species variability in fatty acid signatures of marine fish and invertebrates on the Scotian Shelf, Georges Bank, and southern Gulf of St. Lawrence. *Can. J. Fish. Aquat. Sci.* 59:886–98

Burdge GC, Wootton SA. 2002. Conversion of α-linolenic acid to eicosapentaenoic, docosapentaenoic and docosahexaenoic acids in young women. *Br. J. Nutr.* 88:411–20

Burdge GC, Calder PC. 2005. Conversion of α-linolenic acid to longer-chain polyunsaturated fatty acids in human adults. *Reprod. Nutr. Dev.* 45:581–97

Burr ML, Gilbert JF, Holliday RA, Elwood PC, Fehily AM, et al. 1989. Effects of changes in fat, fish, and fiber intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). *Lancet* 334:757–61

Calder PC. 2006. Polyunsaturated fatty acids and inflammation. *Prostaglandin Leukot. Essent. Fatty Acids* 75:197–202

Cao J, Schwichtenberg KA, Hanson NQ, Tsai MY. 2006. Incorporation and clearance of omega-3 fatty acids in erythrocyte membranes and plasma phospholipids. *Clin. Chem.* 52:2265–72

Carlson SE, Colombo J, Gajewski BJ, Gustafson KM, Mundy D, et al. 2013. DHA supplementation and pregnancy outcomes. *Am. J. Clin. Nutr.* 97:808–15

Carney RM, Steinmeyer BC, Freedland KE, Rubin EH, Rich MW, Harris WS. 2016. Baseline blood levels of omega-3 and depression remission: a secondary analysis of data from a placebo-controlled trial of omega-3 supplements. *J. Clin. Psychiatry* 77:e138–43

Catena A, Muñoz-Machicao JA, Torres-Espínola FJ, Martínez-Zaldívar C, Diaz-Piedra C, et al. 2016. Folate and long-chain polyunsaturated fatty acid supplementation during pregnancy has long-term effects on the attention system of 8.5-y-old offspring: a randomized controlled trial. *Am. J. Clin. Nutr.* 103(1):115–27

Caygill CPJ, Charlett A, Hill MJ. 1996. Fat, fish, fish oil and cancer. *Br. J. Cancer* 74:159–64

Cederholm T. 2017. Fish consumption and omega-3 fatty acid supplementation for prevention or treatment of cognitive decline, dementia or Alzheimer's disease in older adults: any news? *Curr. Opin. Clin. Nutr. Metab. Care* 20:104–9

Chen J, Stavro PM, Thompson LU. 2002. Dietary flaxseed inhibits human breast cancer growth and metastasis and downregulates expression of insulin-like growth factor and epidermal growth factor receptor. *Nutr. Cancer* 43:187–92

Chen YQ, Edwards IJ, Kridel SJ, Thornburg T, Berquin IM. 2007. Dietary fat-gene interactions in cancer. *Cancer Metastasis Rev.* 26:535–51

Chin JP, Gust AP, Nestel PJ, Dart AM. 1993. Marine oils dose-dependently inhibit vasoconstriction of forearm resistance vessels in humans. *Hypertension* 21:22–28

Clandinin MT, Chappell JE, Heim T, Swyer PR, Chance GW. 1981. Fatty acid utilization in perinatal de novo synthesis of tissues. *Early Hum. Dev.* 5:355–66

Cole GM, Ma QL, Frautschy SA. 2009. Omega-3 fatty acids and dementia. *Prostaglandin Leukot. Essent. Fatty Acids* 81:213–21

Colussi G, Catena C, Novello M, Bertin N, Sechi LA. 2017. Impact of omega-3 polyunsaturated fatty acids on vascular function and blood pressure: relevance for cardiovascular outcomes. *Nutr. Metab. Cardiovasc. Dis.* 27:191–200

Connor WE. 2000. Importance of n-3 fatty acids in health and disease. *Am. J. Clin. Nutr.* 71:171S–75

Cook CM, Hallaråker H, Sæbø PC, Innis SM, Kelley KM, et al. 2016. Bioavailability of long chain omega-3 polyunsaturated fatty acids from phospholipid-rich herring roe oil in men and women with mildly elevated triacylglycerols. *Prostaglandin Leukot. Essent. Fatty Acids* 111:17–24

Copeman LA, Parrish CC. 2004. Lipids classes, fatty acids, and sterols in seafood from Gilbert Bay, Southern Labrador. *J. Agric. Food Chem.* 52:4872–81

Cottin SC, Alsaleh A, Sanders TAB, Hall WL. 2016. Lack of effect of supplementation with EPA or DHA on platelet-monocyte aggregates and vascular function in healthy men. *Nutr. Metab. Cardiovasc. Dis.* 26:743–51

Courville AB, Harel O, Lammi-Keefe CJ. 2011. Consumption of a DHA-containing functional food during pregnancy is associated with lower infant ponderal index and cord plasma insulin concentration. *Br. J. Nutr.* 106:208–12

Cunnane SC, Plourde M, Pifferi F, Bégin M, Féart C, Barberger-Gateau P. 2009. Fish, docosahexaenoic acid and Alzheimer's disease. *Prog. Lipid Res.* 48:239–56

Daiello LA, Gongvatana A, Dunsiger S, Cohen RA, Ott BR, Alzheimer's Dis. Neuroimaging Initiat. 2015. Association of fish oil supplement use with preservation of brain volume and cognitive function. *Alzheimer's Dement.* 11:226–35

Dangour AD, Allen E, Elbourne D, Fasey N, Fletcher AE, et al. 2010. 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.* 91:1725–32

da Silva TM, Munhoz RP, Alvarez C, Naliwaiko K, Kiss Á, et al. 2008. Depression in Parkinson's disease: a double-blind, randomized, placebo-controlled pilot study of omega-3 fatty-acid supplementation. *J. Affect. Disord.* 111:351–59

Davidson M, Bulkow LR, Gellin BG. 1993. Cardiac mortality in Alaska's indigenous and non-native residents. *Int. J. Epidemiol.* 22:62–71

Davidson MH, Johnson J, Rooney MW, Kyle ML, Kling DF. 2012. A novel omega-3 free fatty acid formulation has dramatically improved bioavailability during a low-fat diet compared with omega-3-acid ethyl esters: the ECLIPSE (Epanova® compared to Lovaza® in a pharmacokinetic single-dose evaluation) study. *J. Clin. Lipidol.* 6:573–84

Daviglus ML, Stamler J, Orencia AJ, Dyer AR, Liu K, et al. 1997. Fish consumption and the 30-year risk of fatal myocardial infarction. *N. Engl. J. Med.* 336:1046–53

de Aguiar Pastore Silva J, de Souza Fabre ME, Waitzberg DL. 2015. Omega-3 supplements for patients in chemotherapy and/or radiotherapy: a systematic review. *Clin. Nutr.* 34:359–66

de Goede J, Geleijnse JM, Boer JM, Kromhout D, Verschuren WM. 2010. Marine (n-3) fatty acids, fish consumption, and the 10-year risk of fatal and nonfatal coronary heart disease in a large population of Dutch adults with low fish intake. *J. Nutr.* 140:1023–28

DeFilippis AP, Blaha MJ, Jacobson TA. 2010. Omega-3 fatty acids for cardiovascular disease prevention. *Curr. Treat. Options Cardiovasc. Med.* 12:365–80

Derosa G, Cicero AF, Fogari E, D'Angelo A, Bonaventura A, et al. 2012. Effects of n-3 PUFAs on postprandial variation of metalloproteinases, and inflammatory and insulin resistance parameters in dyslipidemic patients: evaluation with euglycemic clamp and oral fat load. *J. Clin. Lipidol.* 6:553–64

Dichwalkar T, Patel S, Bapat S, Pancholi P, Jasani N, et al. 2017. Omega-3 fatty acid grafted PAMAM-Paclitaxel conjugate exhibits enhanced anticancer activity in upper gastrointestinal cancer cells. *Macromol. Biosci.* 17:1600457

Dietit. Can. 2013. *Food Sources of Omega-3 Fats*. Toronto, Ont.: Dietit. Can. **http://www.dietitians.ca/getattachment/de95e92c-3fb3-40db-b457-173de89bdc3a/FACTSHEET-Food-Sources-of-Omega-3-Fats.pdf.aspx**

Dijck-Brouwer DJ, Hadders-Algra M, Bouwstra H, Decsi T, Boehm G, et al. 2005. Lower fetal status of docosahexaenoic acid, arachidonic acid and essential fatty acids is associated with less favorable neonatal neurological condition. *Prostaglandin Leukot. Essent. Fatty Acids* 72:21–28

Djoussé L, Gaziano JM, Buring JE, Lee IM. 2011. Dietary omega-3 fatty acids and fish consumption and risk of type 2 diabetes. *Am. J. Clin. Nutr.* 93:143–50

Doornbos B, Van Goor SA, Dijck-Brouwer DAJ, Schaafsma A, Korf J, Muskiet FAJ. 2009. Supplementation of a low dose of DHA or DHA+AA does not prevent peripartum depressive symptoms in a small population based sample. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* 33:49–52

Dunstan JA, Simmer K, Dixon G, Prescott SL. 2008. Cognitive assessment of children at age $2^1/_2$ years after maternal fish oil supplementation in pregnancy: a randomised controlled trial. *Arch. Dis. Child. Fetal Neonatal Ed.* 93:F45–50

Dyerberg J, Madsen P, Møller JM, Aardestrup I, Schmidt EB. 2010. Bioavailability of marine n-3 fatty acid formulations. *Prostaglandin Leukot. Essent. Fatty Acids* 83:137–41

Engler MM, Engler MB, Malloy M, Chiu E, Besio D, et al. 2004. Docosahexaenoic acid restores endothelial function in children with hyperlipidemia: results from the EARLY study. *Int. J. Clin. Pharmacol. Ther.* 42:672–79

Erkkilä AT, Lehto S, Pyörälä K, Uusitupa MI. 2003. n-3 fatty acids and 5-y risks of death and cardiovascular disease events in patients with coronary artery disease. *Am. J. Clin. Nutr.* 78:65–71

FAO. 2010. Fats and fatty acids in human nutrition: report of an expert consultation. Rome: FAO

Farooqui AA, Horrocks LA. 2001. Plasmalogens, phospholipase A_2, and docosahexaenoic acid turnover in brain tissue. *J. Mol. Neurosci.* 16:263–72

Farquharson J, Jamieson EC, Abbasi KA, Patrick WJ, Logan RW, Cockburn F. 1995. Effect of diet on the fatty acid composition of the major phospholipids of infant cerebral cortex. *Arch. Dis. Child.* 72:198–203

Farshbaf-Khalili A, Mohammad-Alizadeh S, Farshbaf-Khalili A, Mohammadi F, Ostadrahimi A. 2016. Fish-oil supplementation and maternal mental health: a triple-blind, randomized controlled trial. *Iran Red Crescent Med. J.* 19:e36327

Farsi PF, Djazayery A, Eshraghian MR, Koohdani F, Saboor-Yaraghi AA, et al. 2014. Effects of supplementation with omega-3 on insulin sensitivity and non-esterified free fatty acid (NEFA) in type 2 diabetic patients. *Arq. Bras. Endocrinol. Metabol.* 58:335–40

Finley JW, Shahidi F. 2001. The chemistry, processing, and health benefits of highly unsaturated fatty acids: an overview. In *Omega-3 Fatty Acids*, ed. F Shahidi, JW Finely, pp. 2–11. Washington, DC: ACS

Finocchiaro C, Segre O, Fadda M, Monge T, Scigliano M, et al. 2012. Effect of n-3 fatty acids on patients with advanced lung cancer: a double-blind, placebo-controlled study. *Br. J. Nutr.* 108:327–33

Fleith M, Clandinin MT. 2005. Dietary PUFA for preterm and term infants: review of clinical studies. *Crit. Rev. Food Sci. Nutr.* 45:205–29

Flower G, Fritz H, Balneaves LG, Verma S, Skidmore B, et al. 2014. Flax and breast cancer: a systematic review. *Integr. Cancer Ther.* 13:181–92

Fodor JG, Helis E, Yazdekhasti N, Vohnout B. 2014. "Fishing" for the origins of the "Eskimos and heart disease" story: facts or wishful thinking? *Can. J Cardiol.* 30:864–68

Folsom AR, Demissie Z. 2004. Fish intake, marine omega-3 fatty acids, and mortality in a cohort of postmenopausal women. *Am. J. Epidemiol.* 160:1005–10

Frasure-Smith N, Lespérance F, Julien P. 2004. Major depression is associated with lower omega-3 fatty acid levels in patients with recent acute coronary syndromes. *Biol. Psychiatry* 55:891–96

Freeman M, Hibbeln JR, Wisner KL, Brumbach BH, Watchman M, Gelenberg AJ. 2006. Randomized dose-ranging pilot trial of omega-3 fatty acids for postpartum depression. *Acta Psychiatr. Scand.* 113:31–35

Garg ML, Sebokova E, Thomson AB, Clandinin MT. 1988. Δ6-Desaturase activity in liver microsomes of rats fed diets enriched with cholesterol and/or ω3 fatty acids. *Biochem. J.* 249:351–56

Ginty AT, Muldoon MF, Kuan DC, Schirda B, Kamarck TW, et al. 2017. Omega-3 supplementation and the neural correlates of negative affect and impulsivity: a double-blind, randomized, placebo-controlled trial in midlife adults. *Psychosom. Med.* 79:549–56

GISSI-Prevenzione Investig. 1999. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. *Lancet* 354:447–55

Glauber H, Wallace P, Griver K, Brechtel G. 1988. Adverse metabolic effect of omega-3 fatty acids in non-insulin-dependent diabetes mellitus. *Ann. Int. Med.* 108:663–68

Gould JF, Smithers LG, Makrides M. 2013. 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.* 97:531–44

Gould JF, Treyvaud K, Yelland LN, Anderson PJ, Smithers LG, et al. 2017. Seven-year follow-up of children born to women in a randomized trial of prenatal DHA supplementation. *J. Am. Med. Assoc.* 317:1173–75

Grenyer BF, Crowe T, Meyer B, Owen AJ, Grigonis-Deane EM, et al. 2007. Fish oil supplementation in the treatment of major depression: a randomised double-blind placebo-controlled trial. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* 31:1393–96

Griffin MD, Sanders TA, Davies IG, Morgan LM, Millward DJ, et al. 2006. Effects of altering the ratio of dietary n-6 to n-3 fatty acids on insulin sensitivity, lipoprotein size, and postprandial lipemia in men and postmenopausal women aged 45–70 y: the OPTILIP Study. *Am. J. Clin. Nutr.* 84:1290–98

Guil-Guerrero JL. 2007. Stearidonic acid (18:4n-3): metabolism, nutritional importance, medical uses and natural sources. *Eur. J. Lipid Sci. Technol.* 109:1226–36

Gutierrez-Gomez Y, Stein AD, Ramakrishnan U, Barraza-Villarreal A, Moreno-Macias H, et al. 2017. Prenatal docosahexaenoic acid supplementation does not affect non-fasting serum lipid and glucose concentrations of offspring at 4 years of age in a follow-up of a randomized controlled clinical trial in Mexico. *J. Nutr.* 147:242–47

Hallahan B, Ryan T, Hibbeln JR, Murray IT, Glynn S, et al. 2016. Efficacy of omega-3 highly unsaturated fatty acids in the treatment of depression. *Br. J. Psychiatry* 209:192–201

Hamam F, Shahidi F. 2006. Synthesis of structured lipids containing medium-chain and omega-3 fatty acids. *J. Agric. Food Chem.* 54:4390–96

Hansen JB, Olsen JO, Wilsgård L, Lyngmo V, Svensson B. 1993. Comparative effects of prolonged intake of highly purified fish oils as ethyl ester or triglyceride on lipids, haemostasis and platelet function in normolipaemic men. *Eur. J. Clin. Nutr.* 47:497–507

Harper M, Thom E, Klebanoff MA, Thorp J Jr., Sorokin Y, et al. 2010. Omega-3 fatty acid supplementation to prevent recurrent preterm birth: a randomized controlled trial. *Obstet. Gynecol.* 115:232–42

Harris WS, Pottala JV, Sands SA, Jones PG. 2007. Comparison of the effects of fish and fish-oil capsules on the n-3 fatty acid content of blood cells and plasma phospholipids. *Am. J. Clin. Nutr.* 86:1621–25

Hartweg J, Perera R, Montori VM, Dinneen SF, Neil AH, Farmer AJ. 2008. Omega-3 polyunsaturated fatty acids (PUFA) for type 2 diabetes mellitus. *Cochrane Database Syst. Rev.* 1:CD003205

Hauner H, Much D, Vollhardt C, Brunner S, Schmid D, et al. 2012. Effect of reducing the n-6:n-3 long-chain PUFA ratio during pregnancy and lactation on infant adipose tissue growth within the first year of life: an open-label randomized controlled trial. *Am. J. Clin. Nutr.* 95:383–94

Health Can. 2016. *The Canadian Nutrient File*. Ottawa, Ont.: Health Can. **https://www.canada.ca/en/health-canada/services/food-nutrition/healthy-eating/nutrient-data/canadian-nutrient-file-2015-download-files.html**

Hibbeln JR. 1998. Fish consumption and major depression. *Lancet* 351:1213

Hibbeln JR, Davis JM, Steer C, Emmett P, Rogers I, et al. 2007. Maternal seafood consumption in pregnancy and neurodevelopmental outcomes in childhood (ALSPAC study): an observational cohort study. *Lancet* 369:578–85

Hixson SM, Shukla K, Campbell LG, Hallett RH, Smith SM, et al. 2016. Long-chain omega-3 polyunsaturated fatty acids have developmental effects on the crop pest, the cabbage white butterfly *Pieris rapae*. *PLOS ONE* 11:e0152264

Holmes MD, Colditz GA, Hunter DJ, Hankinson SE, Rosner B, et al. 2003. Meat, fish and egg intake and risk of breast cancer. *Int. J. Cancer* 104:221–27

Hu FB, Bronner L, Willett WC, Stampfer MJ, Rexrode KM, et al. 2002. Fish and omega-3 fatty acid intake and risk of coronary heart disease in women. *J. Am. Med. Assoc.* 287:1815–21

Iso H, Kobayashi M, Ishihara J, Sasaki S, Okada K, et al. 2006. Intake of fish and n3 fatty acids and risk of coronary heart disease among Japanese. *Circulation* 113:195–202

Järvinen R, Knekt P, Rissanen H, Reunanen A. 2006. Intake of fish and long-chain n-3 fatty acids and the risk of coronary heart mortality in men and women. *Br. J. Nutr.* 95(4):824–29

Jazayeri S, Tehrani-Doost M, Keshavarz SA, Hosseini M, Djazayery A, 2008. Comparison of therapeutic effects of omega-3 fatty acid eicosapentaenoic acid and fluoxetine, separately and in combination, in major depressive disorder. *Aust. N. Z. J. Psychiatry* 42:192–98

Jensen CL, Voigt RG, Llorente AM, Peters SU, Prager TC, et al. 2010. Effects of early maternal docosahexaenoic acid intake on neuropsychological status and visual acuity at five years of age of breast-fed term infants. *J. Pediatr.* 157(6):900–5

Jernerén F, Elshorbagy AK, Oulhaj A, Smith SM, Refsum H, Smith AD. 2015. Brain atrophy in cognitively impaired elderly: the importance of long-chain ω-3 fatty acids and B vitamin status in a randomized controlled trial. *Am. J. Clin. Nutr.* 102:215–21

Johnson EJ, McDonald K, Caldarella SM, Chung HY, Troen AM, Snodderly DM. 2008. Cognitive findings of an exploratory trial of docosahexaenoic acid and lutein supplementation in older women. *Nutr. Neurosci.* 11:75–83

Jones PJ, Senanayake VK, Pu S, Jenkins DJ, Connelly PW, et al. 2014. DHA-enriched high–oleic acid canola oil improves lipid profile and lowers predicted cardiovascular disease risk in the canola oil multicenter randomized controlled trial. *Am. J. Clin. Nutr.* 100:88–97

Judge MP, Harel O, Lammi-Keefe CJ. 2007. A docosahexaenoic acid–functional food during pregnancy benefits infant visual acuity at four but not six months of age. *Lipids* 42:117–22

Kalmijn SV, Van Boxtel MPJ, Ocke M, Verschuren WMM, Kromhout D, Launer LJ. 2004. Dietary intake of fatty acids and fish in relation to cognitive performance at middle age. *Neurol.* 62:275–80

Kang JX, Leaf A. 1996. The cardiac antiarrhythmic effects of polyunsaturated fatty acid. *Lipids* 31:S41–44

Kato I, Akhmedkhanov A, Koenig K, Toniolo PG, Shore RE, Riboli E. 1997. Prospective study of diet and female colorectal cancer: the New York University Women's Health Study. *Nutr. Cancer* 28:276–81

Kelley DS, Adkins Y, Woodhouse LR, Swislocki A, Mackey BE, Siegel D. 2012. Docosahexaenoic acid supplementation improved lipocentric but not glucocentric markers of insulin sensitivity in hypertriglyceridemic men. *Metab. Syndr. Relat. Disord.* 10:32–38

Klebanoff MA, Harper M, Lai Y, Thorp J Jr., Sorokin Y, et al. 2011. Fish consumption, erythrocyte fatty acids, and preterm birth. *Obstetr. Gynecol.* 117:1071–77

Kling DF, Johnson J, Rooney M, Davidson M. 2011. Omega-3 free fatty acids demonstrate more than 4-fold greater bioavailability for EPA and DHA compared with omega-3-acid ethyl esters in conjunction with a low-fat diet: the ECLIPSE Study. *J. Clin. Lipidol.* 5:231

Kobayashi N, Barnard RJ, Henning SM, Elashoff D, Reddy ST, et al. 2006. Effect of altering dietary ω-6/ω-3 fatty acid ratios on prostate cancer membrane composition, cyclooxygenase-2, and prostaglandin E2. *Clin. Cancer Res.* 12:4662–70

Köbe T, Witte AV, Schnelle A, Lesemann A, Fabian S, et al. 2016. Combined omega-3 fatty acids, aerobic exercise and cognitive stimulation prevents decline in gray matter volume of the frontal, parietal and cingulate cortex in patients with mild cognitive impairment. *Neuroimage* 131:226–38

Kris-Etherton PM, Harris WS, Appel LJ. 2002. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. *Circulation* 106:2747–57

Kristensen SD, Iversen AB, Schmidt EB. 2001. n-3 polyunsaturated fatty acids and coronary thrombosis. *Lipids* 36:S79–82

Kröger E, Verreault R, Carmichael PH, Lindsay J, Julien P, et al. 2009. Omega-3 fatty acids and risk of dementia: the Canadian Study of Health and Aging. *Am. J. Clin. Nutr.* 90:184–92

Kromhout D, Giltay EJ, Geleijnse JM. 2010. n–3 fatty acids and cardiovascular events after myocardial infarction. *N. Engl. J. Med.* 2010:2015–26

Laidlaw M, Cockerline CA, Rowe WJ. 2014. A randomized clinical trial to determine the efficacy of manufacturers' recommended doses of omega-3 fatty acids from different sources in facilitating cardiovascular disease risk reduction. *Lipids Health Dis.* 13:99

Lalia AZ, Lanza IR. 2016. Insulin-sensitizing effects of omega-3 fatty acids: lost in translation? *Nutrients* 8:329

Larsson SC, Kumlin M, Ingelman-Sundberg M, Wolk A. 2004. Dietary long-chain n-3 fatty acids for the prevention of cancer: a review of potential mechanisms. *Am. J. Clin. Nutr.* 79:935–45

Lawson LD, Hughes BG. 1988. Human absorption of fish oil fatty acids as triacylglycerols, free acids, or ethyl esters. *Biochem. Biophys. Res. Commun.* 152:328–35

Lemaitre RN, King IB, Mozaffarian D, Kuller LH, Tracy RP, Siscovick DS. 2003. n-3 polyunsaturated fatty acids, fatal ischemic heart disease, and nonfatal myocardial infarction in older adults: the Cardiovascular Health Study. *Am. J. Clin. Nutr.* 77:319–25

Lewis EJH. 2013. Omega-3 fatty acid supplementation and cardiovascular disease events. *J. Am. Med. Assoc.* 309:27

Lin PY, Su KP. 2007. A meta-analytic review of double-blind, placebo-controlled trials of antidepressant efficacy of omega-3 fatty acids. *J. Clin. Psychiatry* 68:1056–61

Lopez LB, Kritz-Silverstein D, Barrett-Connor E. 2011. High dietary and plasma levels of the omega-3 fatty acid docosahexaenoic acid are associated with decreased dementia risk: the Rancho Bernardo study. *J. Nutr. Health Aging* 15:25–31

Macchia A, Grancelli H, Varini S, Nul D, Laffaye N, et al. 2013. Omega-3 fatty acids for the prevention of recurrent symptomatic atrial fibrillation: results of the FORWARD (Randomized Trial to Assess Efficacy of PUFA for the Maintenance of Sinus Rhythm in Persistent Atrial Fibrillation) trial. *J. Am. Coll. Cardiol.* 61:463–68

MacLean CH, Mojica WA, Morton SC, Pencharz J, Garland RH, et al. 2004. 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: summary. *Evid. Rep. Technol. Assess.* (*Summ.*) 89:1–4

MacLean CH, Newberry SJ, Mojica WA, Khanna P, Issa AM, et al. 2006. Effects of omega-3 fatty acids on cancer risk: a systematic review. *J. Am. Med. Assoc.* 295:403–15

Maki KC, Reeves MS, Farmer M, Griinari M, Berge K, et al. 2009. Krill oil supplementation increases plasma concentrations of eicosapentaenoic and docosahexaenoic acids in overweight and obese men and women. *Nutr. Res.* 29:609–15

Makrides M, Gibson RA, McPhee AJ, Collins CT, Davis PG, et al. 2009. Neurodevelopmental outcomes of preterm infants fed high-dose docosahexaenoic acid: a randomized controlled trial. *J. Am. Med. Assoc.* 301:175–82

Malcolm CA, McCulloch DL, Montgomery C, Shepherd A, Weaver LT. 2003. Maternal docosahexaenoic acid supplementation during pregnancy and visual evoked potential development in term infants: a double blind, prospective, randomised trial. *Arch. Dis. Child. Fetal Neonatal Ed.* 88:F383–90

Mamalakis G, Tornaritis M, Kafatos A. 2002. Depression and adipose essential polyunsaturated fatty acids. *Prostaglandin Leukot. Essent. Fatty Acids* 67:311–18

Martins JG. 2009. EPA but not DHA appears to be responsible for the efficacy of omega-3 long chain polyunsaturated fatty acid supplementation in depression: evidence from a meta-analysis of randomized controlled trials. *J. Am. Coll. Nutr.* 28:525–42

Mathai ML, Soueid M, Chen N, Jayasooriya AP, Sinclair AJ, et al. 2004. Does perinatal ω-3 polyunsaturated fatty acid deficiency increase appetite signaling? *Obesity* 12:1886–94

Mazereeuw G, Herrmann N, Andreazza AC, Scola G, Ma DW, Oh PI, Lanctôt KL. 2017. Oxidative stress predicts depressive symptom changes with omega-3 fatty acid treatment in coronary artery disease patients. *Brain Behav. Immun.* 60:136–41

McNamara RK, Asch RH, Lindquist DM, Krikorian R. 2017. Role of polyunsaturated fatty acids in human brain structure and function across the lifespan: an update on neuroimaging findings. *Prostaglandin Leukot. Essent. Fatty Acids.* In press. **https://doi.org/10.1016/j.plefa.2017.05.001**

Min Y, Djahanbakhch O, Hutchinson J, Bhullar AS, Raveendran M, et al. 2014. Effect of docosahexaenoic acid–enriched fish oil supplementation in pregnant women with type 2 diabetes on membrane fatty acids and fetal body composition: double-blinded randomized placebo-controlled trial. *Diabetic Med.* 31:1331–40

Mischoulon D, Fava M. 2000. Docosahexanoic acid and ω-3 fatty acids in depression. *Psychiatr. Clin. N. Am.* 23:785–94

Mischoulon D, Nierenberg AA, Schettler PJ, Kinkead BL, Fehling K, et al. 2015. A double-blind, randomized controlled clinical trial comparing eicosapentaenoic acid versus docosahexaenoic acid for depression. *J. Clin. Psychiatry* 76:54–61

Mocellin MC, de Quadros Camarg C, de Souza Fabre ME, de Moraes Trindade EBS. 2017. Fish oil effects on quality of life, body weight and free fat mass change in gastrointestinal cancer patients undergoing chemotherapy: a triple blind, randomized clinical trial. *J. Funct. Foods.* 31:113–22

Molloy CS, Stokes S, Makrides M, Collins CT, Anderson PJ, Doyle LW. 2016. 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.* 103:268–75

Moorthy B, Jiang W, Zhou G. 2017. Attenuation of polycyclic aromatic hydrocarbon (PAH)-mediated pulmonary carcinogenesis in mice by omega-3-fatty acids. *FASEB J.* 31(Suppl. 1):1067–64

Mori TA, Burke V, Puddey IB, Watts GF, O'Neal DN, et al. 2000. Purified eicosapentaenoic and docosahexaenoic acids have differential effects on serum lipids and lipoproteins, LDL particle size, glucose, and insulin in mildly hyperlipidemic men. *Am. J. Clin. Nutr.* 71:1085–94

Morris MC, Evans DA, Bienias JL, Tangney CC, Bennett DA, et al. 2003. Consumption of fish and n-3 fatty acids and risk of incident Alzheimer disease. *Arch. Neurol.* 60:940–46

Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, et al. 2016. Executive summary: heart disease and stroke statistics-2016 update: a report from the American Heart Association. *Circulation* 133:447–54

Mozaffarian D, Lemaitre RN, King IB, Song X, Huang H, et al. 2013a. Plasma phospholipid long-chain ω-3 fatty acids and total and cause-specific mortality in older adults: a cohort study. *Ann. Intern. Med.* 158:515–25

Mozaffarian D, Lemaitre RN, King IB, Song X, Spiegelman D, et al. 2011. Circulating long-chain ω-3 fatty acids and incidence of congestive heart failure in older adults: the cardiovascular health study: a cohort study. *Ann. Intern. Med.* 155:160–70

Mozaffarian D, Wu JH. 2011. Omega-3 fatty acids and cardiovascular disease: effects on risk factors, molecular pathways, and clinical events. *J. Am. Coll. Cardiol.* 58:2047–67

Mozaffarian D, Wu JH, de Oliveira Otto MC, Sandesara CM, Metcalf RG, et al. 2013b. Fish oil and post-operative atrial fibrillation. *J. Am. Coll. Cardiol.* 61:2194–96

Mozaffari-Khosravi H, Yassini-Ardakani M, Karamati M, Shariati-Bafghi SE. 2013. Eicosapentaenoic acid versus docosahexaenoic acid in mild-to-moderate depression: a randomized, double-blind, placebo-controlled trial. *Eur. Neuropsychopharmacol.* 23:636–44

Mozurkewich EL, Clinton CM, Chilimigras JL, Hamilton SE, Allbaugh LJ, et al. 2013. The Mothers, Omega-3, and Mental Health Study: a double-blind, randomized controlled trial. *Am. J. Obstetr. Gynecol.* 208:313-e1

Nakamura Y, Ueshima H, Okamura T, Kadowaki T, Hayakawa T, et al. 2005. Association between fish consumption and all-cause and cause-specific mortality in Japan: NIPPON DATA80, 1980–99. *Am. J. Med.* 118:239–45

Nemets H, Nemets B, Apter A, Bracha Z, Belmaker RH. 2006. Omega-3 treatment of childhood depression: a controlled, double-blind pilot study. *Am. J. Psychiatry* 163(6):1098–100

Neubronner J, Schuchardt JP, Kressel G, Merkel M, Von Schacky C, Hahn A. 2011. Enhanced increase of omega-3 index in response to long-term n-3 fatty acid supplementation from triacylglycerides versus ethyl esters. *Eur. J. Clin. Nutr.* 65:247–54

Newberry SJ, Chung M, Booth M, Maglione MA, Tang AM, et al. 2016. *Omega-3 fatty acids and maternal and child health: an updated systematic review*. Evid. Rep./Technol. Assess. Number 224 Rep. 16(17)-E003-EF, Agency Healthc. Res. Qual., Rockville, MD

Nurk E, Drevon CA, Refsum H, Solvoll K, Vollset SE, et al. 2007. Cognitive performance among the elderly and dietary fish intake: the Hordaland Health Study. *Am. J. Clin. Nutr.* 86:1470–78

O'Connell TD, Block RC, Huang SP, Shearer GC. 2016. ω3-Polyunsaturated fatty acids for heart failure: effects of dose on efficacy and novel signaling through free fatty acid receptor 4. *J. Mol. Cell. Cardiol.* 103:74–92

Oken E, Kleinman KP, Olsen SF, Rich-Edwards JW, Gillman MW. 2004. Associations of seafood and elongated n-3 fatty acid intake with fetal growth and length of gestation: results from a US pregnancy cohort. *Am. J. Epidemiol.* 160:774–83

ORIGIN Trial Investig., Bosch J, Gerstein HC, Dagenais GR, Díaz R, et al. 2012. n-3 fatty acids and cardiovascular outcomes in patients with dysglycemia. *N. Engl. J. Med.* 367:309–18

Pacifico L, Bonci E, Di Martino M, Versacci P, Andreoli G, et al. 2015. A double-blind, placebo-controlled randomized trial to evaluate the efficacy of docosahexaenoic acid supplementation on hepatic fat and associated cardiovascular risk factors in overweight children with nonalcoholic fatty liver disease. *Nutr. Metab. Cardiovasc. Dis.* 25:734–41

Park MK, Li WQK, Li T, Qureshi AA, Cho E. 2017. Prospective evaluation of fat intake and risk of skin cancer. *FASEB J.* 31(1 Suppl.):168–73

Pawlosky RJ, Hibbein JR, Novotny JA. Salem N Jr. 2001. Physiological compartmental analysis of α-linolenic acid metabolism in adult humans. *J. Lipid Res.* 42:1257–65

Pedrazzoli P, Cereda E, Cappello S, Colombo S, Klersy C, et al. 2017. Nutritional counseling with or without systematic use of oral nutritional supplements in head and neck cancer patients undergoing radiotherapy. *J. Clin. Oncol.* 35(15 Suppl.):10098

Pottala JV, Yaffe K, Robinson JG, Espeland MA, Wallace R, Harris WS. 2014. Higher RBC EPA + DHA corresponds with larger total brain and hippocampal volumes: WHIMS-MRI Study. *Neurol.* 82:435–42

Prener A, Storm HH, Nielsen NH. 1996. Cancer of the male genital tract in circumpolar Inuit. *Acta Oncol.* 35:589–93

Puri BK, Counsell SJ, Richardson AJ, Horrobin DF. 2002. Eicosapentaenoic acid in treatment-resistant depression. *Arch. Gen. Psychiatry* 59:91–92

Quinn JF, Raman R, Thomas RG, Yurko-Mauro K, Nelson EB, et al. 2010. Docosahexaenoic acid supplementation and cognitive decline in Alzheimer disease: a randomized trial. *J. Am. Med. Assoc.* 304:1903–11

Raji CA, Erickson KI, Lopez OL, Kuller LH, Gach HM, et al. 2014. Regular fish consumption and age-related brain gray matter loss. *Am. J. Prev. Med.* 47:444–51

Rasic-Milutinovic Z, Perunicic G, Pljesa S, Gluvic Z, Sobajic S, et al. 2007. Effects of n-3 PUFAs supplementation on insulin resistance and inflammatory biomarkers in hemodialysis patients. *Ren. Fail.* 29:321–29

Rauch B, Schiele R, Schneider S, Diller F, Victor N, et al. 2010. OMEGA, a randomized, placebo-controlled trial to test the effect of highly purified omega-3 fatty acids on top of modern guideline-adjusted therapy after myocardial infarction clinical perspective. *Circulation* 122:2152–59

Reis GJ, Silverman DI, Boucher TM, Sipperly ME, Horowitz GL, et al. 1990. Effects of two types of fish oil supplements on serum lipids and plasma phospholipid fatty acids in coronary artery disease. *Am. J. Cardiol.* 66:1171–75

Rhee JJ, Kim E, Buring JE, Kurth T. 2017. Fish consumption, omega-3 fatty acids, and risk of cardiovascular disease. *Am. J. Prev. Med.* 52:10–19

Rice SM, Hickie IB, Yung AR, Mackinnon A, Berk M, et al. 2016. Youth depression alleviation: the Fish Oil Youth Depression Study (YoDA-F): a randomized, double-blind, placebo-controlled treatment trial. *Early Interv. Psychiatry* 10:290–99

Risk Prev. Study Collab. Group. 2013. n-3 fatty acids in patients with multiple cardiovascular risk factors. *N. Engl. J. Med.* 368:1800–8

Rizos EC, Ntzani EE, Bika E, Kostapanos MS, Elisaf MS. 2012. Association between omega-3 fatty acid supplementation and risk of major cardiovascular disease events: a systematic review and meta-analysis. *J. Am. Med. Assoc.* 308:1024–33

Rondanelli M, Giacosa A, Opizzi A, Pelucchi C, La Vecchia C, et al. 2010. Effect of omega-3 fatty acids supplementation on depressive symptoms and on health-related quality of life in the treatment of elderly women with depression: a double-blind, placebo-controlled, randomized clinical trial. *J. Am. Coll. Nutr.* 29:55–64

Ross BM, McKenzie I, Glen I, Bennett CPW. 2003. Increased levels of ethane, a non-invasive marker of n-3 fatty acid oxidation, in breath of children with attention deficit hyperactivity disorder. *Nutr. Neurosci.* 6:277–81

Ryan AS, Nelson EB. 2008. Assessing the effect of docosahexaenoic acid on cognitive functions in healthy, preschool children: a randomized, placebo-controlled, double-blind study. *Clin. Pediatr.* 47:355–62

Sakai M, Kakutani S, Horikawa C, Tokuda H, Kawashima H, et al. 2012. Arachidonic acid and cancer risk: a systematic review of observational studies. *BMC Cancer* 12:606

Samieri C, Maillard P, Crivello F, Proust-Lima C, Peuchant E, et al. 2012. Plasma long-chain omega-3 fatty acids and atrophy of the medial temporal lobe. *Neurology* 79:642–50

Schuchardt JP, Schneider I, Meyer H, Neubronner J, von Schacky C, Hahn A. 2011. 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.* 10:145

Schulthess G, Lipka G, Compassi S, Boffelli D, Weber FE, et al. 1994. Absorption of monoacylglycerols by small intestinal brush border membrane. *Biochemistry* 33:4500–8

Schwab U, Lauritzen L, Tholstrup T, Haldorsson TI, Riserus U, et al. 2014. Effect of the amount and type of dietary fat on cardiometabolic risk factors and risk of developing type 2 diabetes, cardiovascular diseases, and cancer: a systematic review. *Food Nutr. Res.* 58:25145

Senanayake SPJN, Shahidi F. 2002. Lipase-catalyzed incorporation of docosahexaenoic acid (DHA) into borage oil: optimization using response surface methodology. *Food Chem.* 77:115–23

Senanayake SPJN, Fichtali J. 2006. Marine oils: single cell oil as a sources of nutraceuticals and speciality lipids: processing technologies and application. In *Nutraceutical and Speciality Lipids and their Co-Products*, ed. F Shahidi, pp. 251–80. Boca Raton, FL: CRC Press

Shahidi F. 1998. Functional seafood lipids and proteins. In *Functional Foods: Biochemical and Processing Aspects*, ed. G Mazza, pp. 381–401. Lancaster, UK: Technomic Publ.

Shahidi F. 2015. Omega-3 fatty acids and marine oils in cardiovascular and general health: a critical overview of controversies and realities. *J. Funct. Foods* 19:797–800

Shahidi F, Ambigaipalan P. 2015. Novel functional food ingredients from marine sources. *Curr. Opin. Food Sci.* 2:123–29

Shahidi F, Ambigaipalan P. 2016. Beverages fortified with omega 3 fatty acids, dietary fiber, minerals and vitamins. In *Handbook of Functional Beverages and Human Health*, ed. F Shahidi, C Alsalvar, pp. 801–13. Boca Raton, FL: CRC Press

Shahidi F, Miraliakbari H. 2004. Omega-3 (*n*-3) fatty acids in health and disease: part 1—cardiovascular disease and cancer. *J. Med. Food* 7:387–401

Shahidi F, Miraliakbari H. 2005. Omega-3 (*n*-3) fatty acids in health and disease: part 2—health effects of omega-3 fatty acids in autoimmune diseases, mental health, and gene expression. *J. Med. Food* 8:133–48

Shahidi F, Miraliakbari H. 2006. Marine oils: compositional characteristics and health effects. In *Nutraceutical and Specialty Lipids and their Co-Products*, ed. F Shahidi, pp. 227–50. Boca Raton, FL: CRC Press

Shahidi F, Zhong Y. 2015. Fatty acid derivatives of catechins and methods of their use. *US Patent No. 9018248*

Shahverdi E, Niknam R. 2017. Flaxseed: a good idea for reduction of mastalgia (breast pain) and risk of breast cancer. *Focus Sci.* 3(2):1–7

Shi Y, Burn P. 2004. Lipid metabolic enzymes: emerging drug targets for the treatment of obesity. *Nat. Rev. Drug Discov.* 3:695–710

Simmer K. 2016. Fish-oil supplementation: the controversy continues. *Am. J. Clin. Nutr.* 103:1–2

Simon JA, Hodgkins ML, Browner WS, Neuhaus JM, Bernert JT Jr., Hulley SB. 1995. Serum fatty acids and the risk of coronary heart disease. *Am. J. Epidemiol.* 142:469–76

Simopoulos AP. 2002. The importance of the ratio of omega-6/omega-3 essential fatty acids. *Biomed. Pharmacother.* 56:365–79

Singer P, Richter-Heinrich E. 1991. Stress and fatty liver: possible indications for dietary long-chain n-3 fatty acids. *Med. Hypotheses* 36:90–94

Siscovick DS, Barringer TA, Fretts AM, Wu JH, Lichtenstein AH, et al. 2017. Omega-3 polyunsaturated fatty acid (fish oil) supplementation and the prevention of clinical cardiovascular disease: a science advisory from the American Heart Association. *Circulation* 137:e867–84

So WW, Liu WN, Leung KN. 2015. Omega-3 polyunsaturated fatty acids trigger cell cycle arrest and induce apoptosis in human neuroblastoma LA-N-1 cells. *Nutrients* 7:6956–73

Sorensen LS, Rasmussen HH, Aardestrup IV, Thorlacius-Ussing O, Lindorff-Larsen K, et al. 2014. Rapid incorporation of ω-3 fatty acids into colonic tissue after oral supplementation in patients with colorectal cancer: a randomized, placebo-controlled intervention trial. *J. Parenter. Enter. Nutr.* 38:617–24

Spencer M, Finlin BS, Unal R, Zhu B, Morris AJ, et al. 2013. Omega-3 fatty acids reduce adipose tissue macrophages in human subjects with insulin resistance. *Diabetes* 62:1709–17

Stephens FB, Mendis B, Shannon CE, Cooper S, Ortori CA, et al. 2014. Fish oil omega-3 fatty acids partially prevent lipid-induced insulin resistance in human skeletal muscle without limiting acylcarnitine accumulation. *Clin. Sci.* 127:315–22

Streppel MT, Ocké MC, Boshuizen HC, Kok FJ, Kromhout D. 2008. Long-term fish consumption and n-3 fatty acid intake in relation to (sudden) coronary heart disease death: the Zutphen study. *Eur. Heart J.* 29:2024–30

Su KP, Lai HC, Yang HT, Su WP, Peng CY, et al. 2014. Omega-3 fatty acids in the prevention of interferon-α-induced depression: results from a randomized, controlled trial. *Biol. Psychiatry* 76:559–66

Su KP, Shen WW, Huang SY. 2001. Omega-3 fatty acids as a psychotherapeutic agent for a pregnant schizophrenic patient. *Eur. Neuropsychopharmacol.* 11:295–99

Tan Z, Le K, Moghadasian M, Shahidi F. 2012a. Enzymatic synthesis of phytosteryl docosahexaneates and evaluation of their anti-atherogenic effects in apo-E deficient mice. *Food Chem*. 134:2097–104

Tan ZS, Harris WS, Beiser AS, Au R, Himali JJ, et al. 2012b. Red blood cell omega-3 fatty acid levels and markers of accelerated brain aging. *Neurology* 78:658–64

Tanabe T, Suzuki T, Ogura M, Watanabe Y. 1999. High proportion of docosahexaenoic acid in the lipid of juvenile and young skipjack tuna, *Katsuwonus pelamis* from the tropical western Pacific. *Fish. Sci.* 65:806–7

Takezaki T, Inoue M, Kataoka H, Ikeda S, Yoshida M, et al. 2003. Diet and lung cancer risk from a 14-year population-based prospective study in Japan: with special reference to fish consumption. *Nutr. Cancer* 45:160–67

Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, et al. 2008. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. *Lancet* 372:1223–30

Terry P, Lichtenstein P, Feychting M, Ahlbom A, Wolk A. 2001. Fatty fish consumption and risk of prostate cancer. *Lancet* 357:1764–66

Titova OE, Sjögren P, Brooks SJ, Kullberg J, Ax E, et al. 2013. Dietary intake of eicosapentaenoic and docosahexaenoic acids is linked to gray matter volume and cognitive function in elderly. *Age* 35:1495–505

Tsitouras PD, Gucciardo F, Salbe AD, Heward C, Harman SM. 2008. High omega-3 fat intake improves insulin sensitivity and reduces CRP and IL6, but does not affect other endocrine axes in healthy older adults. *Horm. Metab. Res.* 40:199–205

Uauy R, Valenzuela A. 2000. Marine oils: the health benefits of n-3 fatty acids. *Nutrients* 16:680–84

Ulven SM, Kirkhus B, Lamglait A, Basu S, Elind E, et al. 2011. 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* 46:37–46

Vakhapova V, Cohen T, Richter Y, Herzog Y, Kam Y, Korczyn AD. 2014. Phosphatidylserine containing omega-3 fatty acids may improve memory abilities in nondemented elderly individuals with memory complaints: results from an open-label extension study. *Dement. Geriatr. Cogn. Dis.* 38:39–45

Van Blarigan E, Fuchs CS, Niedzwiecki D, Ye X, Zhang S, et al. 2017. Long-chain omega-3 fatty acid and fish intake after colon cancer diagnosis and disease-free, recurrence-free, and overall survival in CALGB 89803 (Alliance). *J. Clin. Oncol.* 35:585

Vilar-González S, Bloomfield D, Noble M. 2017. Could omega 3 supplements play a role in the prevention of neurocognitive impairment in cancer patients? *Clin. Oncol.* 29:e48

Virtanen JK, Siscovick DS, Longstreth WT, Kuller LH, Mozaffarian D. 2008. Fish consumption and risk of subclinical brain abnormalities on MRI in older adults. *Neurology* 71:439–46

Visioli F, Risé P, Barassi MC, Marangoni F, Galli C. 2003. Dietary intake of fish vs. formulations leads to higher plasma concentrations of n-3 fatty acids. *Lipids* 38:415–18

Wakil A, Mir M, Mellor DD, Mellor SF, Atkin SL. 2010. The bioavailability of eicosapentaenoic acid from reconstituted triglyceride fish oil is higher than that obtained from the triglyceride and monoglyceride forms. *Asia Pac. J. Clin. Nutr.* 19:499–505

Walhovd KB, Storsve AB, Westlye LT, Drevon CA, Fjell AM. 2014. Blood markers of fatty acids and vitamin D, cardiovascular measures, body mass index, and physical activity relate to longitudinal cortical thinning in normal aging. *Neurobiol. Aging* 35:1055–64

Wang L, Folsom AR, Zheng ZJ, Pankow JS, Eckfeldt JH, ARIC Study Investig. 2003. Plasma fatty acid composition and incidence of diabetes in middle-aged adults: the Atherosclerosis Risk in Communities (ARIC) Study. *Am. J. Clin. Nutr.* 78:91–98

Werner K, de Gaudry DK, Taylor LA, Keck T, Unger C, et al. 2017. Dietary supplementation with n-3-fatty acids in patients with pancreatic cancer and cachexia: marine phospholipids versus fish oil—a randomized controlled double-blind trial. *Lipids Health Dis.* 16:104

White PJ, Arita M, Taguchi R, Kang JX, Marette A. 2010. Transgenic restoration of long-chain n-3 fatty acids in insulin target tissues improves resolution capacity and alleviates obesity-linked inflammation and insulin resistance in high-fat-fed mice. *Diabetes* 59:3066–73

Yamagishi K, Iso H, Date C, Fukui M, Wakai K, et al. 2008. Fish, ω-3 polyunsaturated fatty acids, and mortality from cardiovascular diseases in a nationwide community-based cohort of Japanese men and women: the JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk) study. *J. Am. Coll. Cardiol.* 52:988–96

Yang J, Zhu S, Lin G, Song C, He Z. 2017. Vitamin D enhances omega-3 polyunsaturated fatty acids–induced apoptosis in breast cancer cells. *Cell Biol. Int.* 41:890–97

Yehuda S, Rabinovitz S, Mostofsky DI. 2005. Essential fatty acids and the brain: from infancy to aging. *Neurobiol. Aging* 26:98–102

Yehuda S, Rabinovitz-Shenkar S, Carasso RL. 2011. Effects of essential fatty acids in iron deficient and sleep-disturbed attention deficit hyperactivity disorder (ADHD) children. *Eur. J. Clin. Nutr.* 65:1167–69

Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, et al. 2007. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. *Lancet* 369:1090–98

Yu FL, Greenlaw R, Fang Q, Bender W, Yamaguchi K, et al. 2004. Studies on the chemopreventive potentials of vegetable oils and unsaturated fatty acids against breast cancer carcinogenesis at initiation. *Eur. J. Cancer Prev.* 13:239–48

Yu J, Liu L, Zhang Y, Wei J, Yang F. 2017. Effects of omega-3 fatty acids on patients undergoing surgery for gastrointestinal malignancy: a systematic review and meta-analysis. *BMC Cancer* 17:271

Yuan JM, Ross RK, Gao YT, Mimi CY. 2001. Fish and shellfish consumption in relation to death from myocardial infarction among men in Shanghai, China. *Am. J. Epidemiol.* 154:809–16

Zheng JS, Hu XJ, Zhao YM, Yang J, Li D. 2013. 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* 346:f3706

Zhong Y, Chiou YS, Pan MH, Ho CT, Shahidi F. 2012. Protective effects of epigallocatechin gallate (EGCG) derivatives on azoxymethane-induced colonic carcinogenesis in mice. *J. Funct. Foods* 4:323–30

Zhong Y, Shahidi F. 2011. Lipophilized epigallocatechin gallate (EGCG) derivatives as novel antioxidants. *J. Agric. Food Chem.* 59:6526–33