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A Systemic Review of the Roles of n-3 Fatty Acids in Health and Disease

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ABSTRACT

Attention to the role of n-3 long-chain fatty acids in human health and disease has been continuously increased during recent decades. Many clinical and epidemiologic studies have shown positive roles for n-3 fatty acids in infant development; cancer; cardiovascular diseases; and more recently, in various mental illnesses, including depression, attention-deficit hyperactivity disorder, and dementia. These fatty acids are known to have pleiotropic effects, including effects against inflammation, platelet aggregation, hypertension, and hyperlipidemia. These beneficial effects may be mediated through several distinct mechanisms, including alterations in cell membrane composition and function, gene expression, or eicosanoid production. A number of authorities have recently recommended increases in intakes of n-3 fatty acids by the general population. To comply with this recommendation a variety of food products, most notably eggs, yogurt, milk, and spreads have been enriched with these fatty acids. Ongoing research will further determine the tissue distribution, biological effects, cost-effectiveness, and consumer acceptability of such enriched products. Furthermore, additional controlled clinical trials are needed to document whether long-term consumption or supplementation with eicosapentaenoic acid/docosahexaenoic acid or the plant-derived counterpart (α-linolenic acid) results in better quality of life.
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Interest in the potential health benefits of fish oil has emerged since the 1950s (1-4). Early studies have reported benefits of cod liver oil on atopic eczema (1), hypercholesterolemia (2), and arthritis (3). An early finding was that the Eskimo of northern populations had a low incidence of heart disease despite high fat intake. It was found that the deepwater fish the Eskimo consumed are abundant with n-3 long-chain fatty acids (5). These early observations led to an increase in research examining the beneficial and/or preventative effects of n-3 fatty acids on numerous debilitating and common conditions, including cardiovascular disease (CVD), rheumatoid arthritis, and asthma, among others (6-23). The findings from these studies led health professionals to encourage the general population to consume more n-3 fatty acids. The food industry subsequently marketed a number of food products such as milk, eggs, cheeses, and spreads enriched with n-3 fatty acids (24,25).

There are three major dietary n-3 fatty acids: α-linolenic acid (ALA) (C18:3), eicosapentaenoic acid (EPA) (C20:5) and docosahexaenoic acid (DHA) (C22:6). Beneficial effects of these dietary fats, particularly DHA, have been extensively studied in both human beings and animals. The proposed mechanisms for health benefits of n-3 fatty acids appear to be related to the incorporation of the fatty acids into membrane phospholipids (26). This results in increasing the production of series 3 eicosanoids, prostaglandin I_3, thromboxane A_3, and series 5 leukotriene B_5 via the cyclooxygenase and lipoxygenase pathways (27-30). Eicosanoids, produced by both n-6 and n-3 fatty acids, are involved in the regulation of inflammation, platelet aggregation, and vasoconstriction/dilation. Both EPA and n-6 arachidonic acid (ARA) (C20:4) compete for the common cyclooxygenase and lipoxygenase enzymes; thus the n-6:n-3 fatty acid ratio seems to be a determining factor for the outcome of the enzymatic pathways. Compared to EPA, ARA produces more potent inflammatory and pro-aggregatory eicosanoids. This is par-

ticularly important when considering the abundance of n-6 fatty acids and the scarcity of n-3 fatty acids in our diets (27). The aim of this review article was to review critically available literature on the role of n-3 fatty acids on human health and disease and also to highlight the influence of increased consumption of n-3 fatty acids on improving quality of life.

METHODS

PubMed search was performed to locate pertinent literature published in English during the past 50 years, with particular attention paid to recent clinical trials published within the past 5 years. Animal studies were included to establish etiology in some cases. Key words used to locate articles included, but were not limited to, n-3 fatty acid, EPA, DHA, ALA, fish oil, flaxseed oil, infant development, cardiovascular disease, cancer, tumor, dementia, depression, and functional foods. Many more articles were retrieved than could be included in this article; thus, as mentioned, the focus was on recent well-performed clinical trials.

n-3 Fatty Acids and Infant Development

n-3 fatty acids are required for normal conception, growth, and development of an embryo. During the third trimester, approximately 50 to 60 mg/day of maternal DHA stores are transferred to a fetus via the placenta (31,32). DHA is particularly highly concentrated in the brain and retinal membranes, especially in photoreceptors, and is therefore assumed to play a critical role in both vision and cognitive function (17). A positive association has been observed between red blood cell DHA content and improved visual acuity as well as other indexes of brain development in human infants (33-35). Interestingly, folic acid supplementation may further enhance DHA content in maternal plasma (36,37), potentially offering added benefits to infants. Several clinical studies have also reported improved visual acuity (37-39) and hand-eye coordination (40) in infants receiving greater DHA in the womb and/or during lactation. On the other hand, Auestad and colleagues (41) found formula-fed infants supplemented with DHA for 12 months did not show improved visual acuity at 39 months of age compared to controls. This apparent discrepancy may be related to the experimental design (42). When n-3 fatty acid–deficient rhesus monkeys were treated with dietary DHA, plasma, erythrocytes, and cerebral cortex DHA levels increased but no improvement in visual function occurred (43). This implies that provision of DHA at the early stages of development is critical and subsequent deficiency could result in irreversible functional limitations.

Cognitive function has also shown to be improved in formula-fed term infants supplemented with DHA and ARA for 17 weeks (39). However, as summarized in Table 1, supplementation with n-3 fatty acids during pregnancy or lactation and infancy does not appear to consistently generate additional benefits on the brain function of the infants (17,39,44-46). This lack of consistency may be due to methodologic approaches comparing breast milk and enriched infant formulas. Furthermore, the benefits in infant development have mainly been attributed to DHA. Supplementation with ALA by lactating women has shown to significantly increase breast milk ALA and EPA, but not DHA (47). Future well-designed placebo-controlled clinical trials will help clarify if various n-3 fatty acid supplementations to mothers or infants will improve the brain function of infants (44).

Based on the results of several studies, the 1999 International Society for the Study of Fatty Acids and Lipids and World Association of Perinatal Medicine Dietary Guidelines Working Group recommended the inclusion of EPA/DHA in infant formulas when breastfeeding was not possible (48,49). Many such enriched formulas have been marketed since. This is an important step to improving infant health; however, pregnancy and lactation still remain as critical stages of infant development. Breastfeeding is the optimal nutrition, thus efforts should be made to improve n-3 fatty acid intake by lactating women because quality of breast milk fat is directly related to maternal diet (50). Furthermore, women seem to have low n-3 fatty acid intakes (51,52), including some that may be at risk of n-3 fatty acid deficiency during pregnancy (53). Consequently, increased n-3 fatty acid intake should be particularly encouraged for the pregnant and lactating women to ensure the optimal health of their infants, especially during the third trimester when n-3 fatty acid intake may be most effective in achieving optimal infant development (54). This recommendation, although in place (49), is not currently promoted sufficiently.

n-3 Fatty Acid and CVD

One of the leading causes of morbidity and mortality in the world is CVD (55). Cardiovascular benefits from n-3 fatty acids may be mediated through beneficial modifications in lipoprotein profile. For example, supplementation with 4 g/day EPA decreased triglyceride levels by 23% in subjects with mild hyperlipidemia (56), and by 12% in healthy subjects (57). Supplementation with as little as 1 g/day DHA alone or in combination with EPA (1,252 mg total) in subjects with hypertriglyceridemia resulted in similar reductions in plasma triglyceride levels (21.8%) (58). In addition, Kris-Etherton and colleagues (59) reported that supplementation with 2 to 4 g/day EPA+DHA can lower plasma triglyceride levels by approximately 25% to 30% in patients with hypertriglyceridemia. Possible mechanisms by which EPA/DHA may reduce plasma triglyceride concentrations have been reviewed by Davidson (60). Other clinical trials (61,62) did not report significant triglyceride-lowering effects.

Cholesterol-lowering effects of n-3 fatty acids have also been studied, but the results are controversial. Contacos and colleagues (63) observed a 1 nm increase in the diameter of low-density lipoprotein (LDL) particles after consumption of 3 g/day fish oil for 6 weeks. Kelley and associates (64) also observed a significant 21% reduction in the number of small, dense LDL particles and a 0.6 nm increase in LDL particle size in men with hypertriglyceridemia receiving 3 g/day DHA. This may explain, in part, the increased LDL cholesterol levels observed in some clinical trials (62,65). An increase in apolipoprotein B concentrations following n-3 fatty acid supplementation has been observed in healthy elderly subjects (66). n-3 fatty acid intake was also associated with small increases in high-density lipoprotein cholesterol concentrations in

Table 1. Summary of key clinical trials assessing the effects of eicosapentaenoic acid (EPA)/docosahexaenoic acid (DHA) during pregnancy and/or lactation/formula feeding on indexes of infant development

Study	Subjects (n)[a]	Dose[b] (g)	Duration	Outcomes
Dunstan and colleagues, 2008 (40)	Pregnant Australian women (n=98)	2.2 DHA g/d+1.1 EPA g/d	20 wks gestation until delivery	• Increased score for eye-hand coordination at 2½ y (P=0.008) • No change in growth between groups at age 2½ y
Helland and colleagues, 2006 (46)	Pregnant Norwegian women who later breastfed their infants (n=75)	1,183 mg DHA+ 803 mg EPA/d	18 wks gestation until 3 mo after delivery	• Increased plasma DHA in mother and n-3/n-6 ratio in cord plasma phospholipids (P<0.001) • Cord plasma DHA increased correlation with pregnancy length (P=0.001) • Increased levels of EPA and DHA in breast milk (P<0.001)
Decsi and colleagues, 2005 (37)	Pregnant women from Germany, Hungary, and Spain (n=77)	500 mg/d of DHA or 500 mg/d DHA+400 mg/d folate	20 wks gestation until term	• Increase in the contribution of DHA to maternal, placental, and venous cord blood lipids (P<0.05) • Infants in the DHA+5-MTHF[d] combined group displayed increased scores in one subsection of visual acuity (P<0.05)
Montgomery and colleagues, 2003 (45)	Pregnant Scottish women (n=50)	200 mg/d DHA	15 wks gestation until term	• Increased maternal plasma and erythrocyte status (P<0.03) • Appears to limit the last trimester decrease in maternal DHA status (P<0.05) • No change in fetal cord DHA
Auestad and colleagues, 2003 (41)	Formula-fed infants (n=35-50)	0.23% DHA enriched formula or combination 0.43% ARA[c]+ 0.12% DHA	Within 1 wk after birth until 12 mo	• DHA supplemented infants showed no change in visual acuity, visual motor index scores, expressive vocabulary, receptive vocabulary, and Intelligence Quotient at 39 mo
Hoffman and colleagues, 2003 (38)	Healthy term infants (n=30)	0.36% DHA+ 0.72% ARA enriched formula	Time of weaning (4-6 mo)-1 y	• Red blood cell DHA levels increased (P<0.05) • Red blood cell DHA levels show increased association with VEP[e] acuity (P<0.0005) • No change in stereoacuity
O'Connor and colleagues, 2001 (42)	Premature infants with birth weights 750 to 1,800 g (n=138-140)	0.42% ARA+ 0.26% DHA formula to term and then 0.16% DHA to 12 mo	3-4 d after birth until 1 y	• No change in visual acuity at 2, 4, and 6 mo via acuity cards • Visual acuity significantly increased in supplemented groups at 6 mo according to swept-parameter VEPs (P<0.01) • No change in Bayley Mental Development Index at 12 mo between groups, only significant between treatment and control in infants ≤1,250 g (P=0.007) • Vocabulary comprehension increased in treated infants (excluding infants from Spanish-speaking families and twins) compared to control (P=0.01)
Birch and colleagues, 2000 (39)	Healthy term infants (n=17-20)	0.35% DHA formula and another group fed 0.36% DHA+0.72% ARA formula	Up to 4 d after birth until 17 wks	• MDI[f] scores were significantly increased in the DHA+ARA group compared to both control and DHA (P<0.05) • MDI was positively correlated with both plasma and red blood cell DHA at 4 mo and VEP acuity (P=0.016) • No change between groups in Behavioral Rating Scale • No change in Psychomotor Developmental Index between groups and did not correlate with plasma or red blood cell DHA at 4 mo

[a]Value given is n per treatment group; a range is given when there are multiple treatment groups (two or more) with differing number of participants in each group.
[b]"+" symbol indicates multiple active ingredients within a treatment dose; "or" indicates multiple treatment groups.
[c]ARA=arachidonic acid.
[d]MTHF=methyl tetryhydrofolate.
[e]VEP=Visually Evoked Potential.
[f]MDI=Mental Development Index.

healthy volunteers and patients with familial hyperlipidemia (67-70). Overall, benefits of fish oil on LDL and/or high-density lipoprotein cholesterol metabolism appear inconsistent, whereas influences of particle size seem to be key.

Inflammation is now recognized to be a major contributor to the underlying mechanism of atherosclerosis (71-73). Treatment with n-3 fatty acids was associated with reductions in plasma levels of tumor necrosis factor-α and interleukin-1β in healthy subjects (74,75). Conversely, Mori and colleagues (76) showed that neither purified EPA nor DHA given at 4 g/day for 6 weeks to subjects with type 2 diabetes significantly decreased interleukin-6 or C-reactive protein levels. However, both fatty acids remarkably reduced the levels of tumor necrosis factor-α by 25%. Philips and associates (77) have found that dietary DHA supplementation decreased exercise-induced inflammation by reducing C-reactive protein and interleukin-6 in healthy subjects. Most of the above-mentioned immune-modulatory effects of n-3 fatty acids may suggest prevention of atherosclerosis. Some of the anti-atherosclerotic associations of n-3 fatty acids (78,79) may be the result of their beneficial affects on platelet activities. In light of this, a 35% decline in platelet-monocyte aggregates was reported after supplementing diets of 14 healthy subjects with 500 g/week fish oil for 4 weeks (80).

n-3 fatty acids may also play a role in regulation of blood pressure (81); this effect may be mediated through an alteration in the balance between vasoconstrictive prostaglandins and increasing production of vasodilatory prostacyclin. In this regard, DHA seems to be more potent than EPA (82). A study by Mori and colleagues (83) reported a significant reduction in systolic and diastolic blood pressure in subjects with overweight by feeding 4 g/day purified DHA. Several factors, including the dose of fish oil, concurrent use of medications, an inadequate sample size, population type, the choice of placebo oil, and inadequate statistical power may be the reasons for a lack of antihypertensive effects of these oils observed in other studies (64,84,85).

Anti-arrhythmic properties of n-3 fatty acids are another area of interest associated with CVD. These effects may be direct consequences of the incorporation of n-3 fatty acids, especially DHA and EPA, into cell membranes (28). Both EPA and DHA are readily incorporated into cell membranes following supplementation (86). The membrane enrichment with EPA/DHA may result in increasing membrane fluidity in cardiac cells, thereby preventing atrial fibrillation (87,88) and reducing the binding of inflammatory cytokines to their receptors (89). This may explain benefits of EPA/DHA in preventing cardiac events. Consuming 3 g/day encapsulated fish oil for 6 weeks reduced inducible ventricular tachycardia and risk of sudden cardiac death among patients with coronary artery disease (90). This could be the result of an attenuation in intracellular calcium and in the response to noradrenalin (91). Moreover, habitual consumption of fish and marine n-3 fatty acids was linked with particular heart rate variability constituents, including indexes of vagal activity, baroreceptor responses, and sinoatrial node function among American adults (92). Such enhancement of vagal control by tuna and other fish consumption could explain, in part, improved endothelial function and reduced resting heart rate after fish oil supplements in a randomized study in healthy men and women (93). Studies pertaining to the effects of EPA/DHA on cardiovascular risks are summarized in Table 2.

n-3 Fatty Acid and Cancer

Dietary fats have been known to play a significant role in the etiology of cancer (94). A positive association between high intake of fat and the incidence of breast, colon, pancreatic, and prostate cancers has been shown (94). However, such an association may be independent of the energy contents of the fats (94). Further studies revealed that diets rich in monounsaturated fats (94), n-3 fatty acid (eg, fish oil and flaxseed oil), or high n-3 fatty acid content in erythrocyte membranes were inversely correlated with the development of colorectal cancer (22,95-98) and breast cancer (99). On the other hand, diets high in animal fat or n-6 fatty acid intake contributed to an increased risk of colorectal cancer (100,101) and breast cancer (102).

The mechanisms by which dietary n-3 fatty acids contribute to the prevention of cancers have not been fully established. Nonetheless, the n-6:n-3 ratio of eicosanoid production seems to play a major role. ARA has been shown to stimulate pancreatic cancer cell growth in vitro, whereas EPA had suppressed such growth (103). Other mechanisms may include modifications in the hormonal status, cell membrane structure and function, cell signaling transduction pathways and gene expression, and immune function (104). For example, daily consumption of EPA (2 g/day) by patients with colorectal adenomas led to the production of 3-series prostaglandins such as PGE3, the suppression of crypt cell proliferation, and increased apoptosis in colonic mucosa (105). In addition, n-3 fatty acid supplementation of 0.2 g/kg body weight through total parenteral nutrition in patients who had undergone colorectal cancer resection was associated with a significant reduction in interleukin-6 levels and a trend toward reduced postoperative hospitalization period compared to controls (106).

Nonconclusive evidence for effectiveness of n-3 fatty acids against cancer has mainly come from epidemiologic studies and animal experimentation (107-110). Well-designed, large-scale clinical trials are required to document potential anticancer effects of dietary n-3 fatty acid.

n-3 Fatty Acids and Mental Illness

The brain is a lipid-rich organ; phospholipids compose nearly 25% of the dry weight of the brain (111). n-3 fatty acids likely have similar functions in the brain as in other tissues, namely production of less inflammatory and less aggregatory eicosanoids, which may preserve or enhance brain function (111). Incorporation of DHA into brain cell membranes also improves membrane fluidity, which may contribute to brain function via their ability to bind ligands and initiate a series of signal transduction processes (112-115). DHA and EPA may also influence brain function by affecting production and function of neurotransmitters such as serotonin and dopamine (116,117), inhibition of phospholipase A_2 (118), and inhibition of protein kinase C

Table 2. Summary of key clinical trials assessing the effects of eicosapentaenoic acid (EPA)/docosahexaenoic acid (DHA) on indexes of cardiovascular risk

Study	Subjects (n)[a]	Dose[b] (g)	Duration	Outcomes
Kelley and colleagues, 2007 (64)	Hypertriglyceridemic men aged 39-66 y (n=34)	3 g DHA/d	90 d	• Decrease in plasma TG[c] (P=0.03), large VLDL[d] particles (P<0.05), and small HDL[e] particles (P=0.0003) • Increase in plasma small VLDL particles (P=0.02), large HDL particles (P=0.0002) • No change in heart rate, systolic, and diastolic blood pressures
Schwellenbach and colleagues, 2006 (58)	Hypertriglyceridemic (200-750 mg/dL) men and women (n=57-59)	Either 1,000 mg/day DHA or 1,252 mg/day DHA+EPA	8 wks	• 21.8% and 18.3% decrease in plasma TG in DHA alone (P<0.001) and DHA + EPA group (P<0.001), respectively • No change in TG lowering between DHA only and DHA + EPA combined • DHA alone showed greater (P<0.05) increase in HDL cholesterol
Goyens and Mensink, 2006 (66)	Mildly hyper-cholesterolemic elderly men and women (n=14)	1.05 g/d EPA+0.55 g/d DHA	6 wks	• No change in plasma lipid levels between groups or compared to baseline • EPA/DHA-induced subjects had an increase in apoliporotein B (P=0.0031)
Sanders and colleagues, 2006 (62)	Healthy men and women (n=40)	1.5 g DHA/d+0.6 g DPA[f]/d	4 wks	• Serum total, LDL[g], and HDL cholesterol increased (P=0.001) • Factor VII coagulant activity increased (P=0.006) • No changes in blood pressure, serum C-reactive protein, plasma factor VII antigen, or fibrinogen
Wilkinson and colleagues, 2005 (86)	Healthy men (n=17-21)	3 g EPA+DHA/d	12 wks	• EPA and DHA increased in erythrocyte membranes (P<0.001) • Plasma total cholesterol, HDL, TG, and small dense LDL decreased (P<0.05)
Engler and colleagues, 2004 (70)	Children (9-19 y old) with familial hypercholeserolemia or familial combined hyperlipidemia (n=20)	1.2 g DHA/d	6 mo	• Endothelium-dependent flow-mediated dilation of brachial artery increased with DHA supplementation (P<0.012) compared to placebo • Total cholesterol (P<0.01), LDL, and HDL increased (P<0.001)

[a]Value given is n per treatment group; a range is given when there are multiple treatment groups (two or more) with differing number of participants in each group.
[b]"+" symbol indicates multiple active ingredients within a treatment group; "or" indicates multiple treatment groups.
[c]TG=triglyceride.
[d]VLDL=very–low-density lipoprotein.
[e]HDL=high-density lipoprotein.
[f]DPA=docosapentaenoic acid.
[g]LDL=low-density lipoprotein.

(119). Altogether, available evidence from a few clinical studies strongly suggests that this area needs to be further investigated through well-designed placebo-controlled clinical investigations (120).

Several epidemiologic studies have reported low plasma DHA status in individuals with schizophrenia, attention-deficit hyperactivity disorder (ADHD), dyslexia, personality disorder, depression, and bipolar disorder (120-124). The decline in n-3 fatty acid intake in the past few decades may be correlated with an increased prevalence of several of these mental disorders (125). The worldwide prevalence of ADHD in children and adolescents aged 18 years and younger is approximately 5%, with slightly higher rates found in North America (126). Furthermore, an estimated 4.4% of American adults are afflicted with ADHD (127). The World Health Organization predicts that in <15 years, depression will become the second highest cause of disability worldwide (128).

ADHD. ADHD is associated with low red blood cell DHA and high n-6 fatty acid levels (129). Stevens and colleagues (130) found that EPA levels of red blood cells were positively associated with reduced disruptive behavior in children with ADHD receiving 480 mg/day DHA and 80 mg/day EPA for 4 months. Conversely, Hirayama and colleagues (131) reported no improvement in performance or behavior in children with ADHD given 3.6

g/week DHA for 2 months. Voigt and colleagues (132) also found no improvement in ADHD symptoms in children receiving 345 mg/day DHA for 4 months, despite the fact that DHA in plasma phospholipids was significantly increased.

Depression. After adjusting for several confounding factors, Kamphuis and associates (133) reported that every 50 mg/day increase in n-3 fatty acid intake was correlated with a 7% risk reduction of depressive symptoms in elderly men. Furthermore, Su and colleagues (134) found that following four weeks of intervention, subjects treated with EPA/DHA displayed significantly lower depression scores as compared to controls. DHA and EPA supplementation of 1.2 and 0.9 g/day in subjects following an act of self-harm for 12 weeks also reduced depressive and suicidal scores (135). Nemets and colleagues (136) reported improvements in depression score in children with major depressive disorder receiving 400 mg/day and 200 mg/day EPA and DHA, respectively, for 4 months. On the other hand, 6 g/day EPA for 4 months in patients with bipolar depression resulted in no difference in depressive symptoms compared to controls (137). Beneficial effects of n-3 fatty acids on prevention or improvement of perinatal depression were not observed in recent clinical trials (138,139).

Dementia and Alzheimer's Disease. Dementia, including both vascular dementia and Alzheimer's disease, afflicts >30% of elderly persons older than age 85 years (140). This burden is increasing as the elderly population continues to grow (141). Epidemiologic studies have shown that dementia and CVD may share several common risk factors, including high intakes of dietary total fat, high saturated fat, high n-6:n-3 fatty acid ratio, and low fish intake (142). Because n-3 fatty acids possess anti-inflammatory properties and inflammatory markers have been located in the brain of patients with Alzheimer's disease, it seems reasonable to suggest that n-3 fatty acids may delay the onset of Alzheimer's disease by reducing brain inflammatory state (143). This may be one of the reasons behind prevention of Alzheimer's disease/dementia by adequate DHA/EPA intake suggested by the Framingham heart study (142,144,145). Conversely, such an association was not observed in the Rotterdam Study (146).

Results from a randomized double-blind placebo controlled study (19) showed that patients with very mild Alzheimer's disease, n-3 fatty acid supplementation was associated with a significantly higher mean Mini Mental State Examination scores (ie, less severe Alzheimer's disease symptoms) at 6 months compared to placebo-treated group. Effects of treatment were not significantly different in patients with severe cases of Alzheimer's disease. These results indicate that supplementation with n-3 fatty acids may be more effective in the treatment of early stage Alzheimer's disease. Patients with cognitive impairment given 240 mg/day DHA and ARA for 90 days displayed improved short-term memory; however, visuospatial/construction and language scores did not improve (147). Boston and colleagues (148) reported no improvement in Alzheimer's symptoms in patients with Alzheimer's disease receiving 1 g/day EPA for 12 weeks. These studies continue to support the notion of varying efficacy depending on Alzheimer's severity. An additional factor to consider when interpreting data on Alzheimer's disease is the allele already identified to influence development of Alzheimer's disease, apolipoprotein E epsilon4, regardless of diet (149,150). Key clinical studies investigating n-3 fatty acid intake on brain function are described in Table 3.

The above-mentioned evidence opens opportunities for future research in the area of n-3 fatty acids and brain function. Specifically, additional large-scale clinical studies are needed to ascertain whether treatment with n-3 fatty acids offers significant benefits to individuals with various mental illnesses. As a result of the relationship between dementia and CVD risks, EPA/DHA supplements may be recommended to these patient populations. Further studies investigating the synergistic effects of n-3 fatty acids with common psychiatric drugs are also needed.

Other Benefits

Evidence for effectiveness of n-3 fatty acids in improving functions of a number of other systems, including immune system, reproductive system, skin, and others, is accumulating. Rheumatoid arthritis is one of the most common inflammatory illnesses that has shown improvement by n-3 fatty acid supplementation. In a recent meta-analysis conducted by Goldberg and Katz (151), it was found that n-3 fatty acid supplementation may improve pain intensity, morning stiffness, number of affected joints, and amount of medication needed to alleviate symptoms of this disorder. Supplementation with n-3 fatty acid during infancy with cod liver oil may also prevent type 1 diabetes, another autoimmune condition (152). The role of n-3 fatty acids in the reproductive system appears to benefit both sexes; decreased DHA in spermatozoa may be associated with infertility (153). It has been shown that maternal supplementation with DHA is associated with increases in birth weight, length, and head circumference of infants (154,155). Kim and colleagues (156) have shown that topical agents containing n-3 fatty acids may possess antiaging effects by increasing gene expression of collagen and elastic fibers in both young and aged human skin. Finally, the pleiotropic effects of n-3 fatty acids may be the reasons behind their effectiveness in reducing post-transplant complications and improving the graft function observed in human cases (157).

Potential Adverse Effects of n-3 Fatty Acids

Fish or fish oil is the main source of EPA and DHA. However, nausea and fishy burps may accompany regular use of fish oil supplements. Certain types of fish are known to be high in methyl-mercury. Thus, mercury poisoning may be a reasonable danger with regular consumption of certain fish (158,159). Fish particularly high in mercury include shark, swordfish, king mackerel, and tilefish (160). Less mercury is found in fish oil alone compared to fish meat (161). Therefore, frequent intakes of the above-named fish should be cautioned and avoided particularly in young children and pregnant/breastfeeding women (162,163). Pregnant and lactating women can still safely eat 12 oz/week of fish that are not high in mercury, including shellfish, canned fish, smaller ocean fish, and farm-bred fish (163). There is speculation re-

Table 3. Summary of key clinical trials assessing the effects of eicosapentaenoic acid (EPA)/docosahexaenoic acid (DHA) treatment in depression, dementia/Alzheimer's disease, and attention-deficit hyperactivity disorder (ADHD)

Study	Subjects (n)[a]	Dose[b] (g)	Duration	Outcomes
Depression				
Hallahan and colleagues, 2007 (135)	Patients presenting after act of repeated self-harm (n=22-27)	1.2 EPA g/d+ 0.9 DHA g/d	12 wks	• EPA and DHA group had decreased scores for depression (P=0.004), suicidality (P=0.018), and perception of daily stresses (P=0.021)
Keck and colleagues, 2006 (137)	Men and women with bipolar depression (n=57-59)	6 g EPA/d	4 mo	• No change in depressive symptoms or manic symptoms between EPA and control groups
Nemets and colleagues, 2006 (136)	Children aged 6-12 y with major depressive disorder (n=10)	400 mg EPA/d+ 200 mg DHA/d	4 mo	• Childhood Depression Rating Scale (P<0.003), Childhood Depression Inventory (P<0.005), and Clinical Global Impression scores (P<0.0001) all improved with EPA and DHA supplementation
Dementia and Alzheimer's disease				
Whalley and colleagues, 2008 (149)	Men and women with cognitive aging at age 64, 66, and 68 y and *APOE*[c] allele status (n=20)	N/A[d]	N/A[d]	• Cognitive benefits were associated with increased erythrocyte n-3 polyunsaturated fatty acid content but were significant only in the absence of the *APOE* 4 allele (P<0.05)
Kotani and colleagues, 2006 (147)	Men and women with cognitive impairment (n=12)	240 mg each ARA+DHA/d	90 d	• Improved immediate memory score (P<0.01) • No significant improvement in visuospatial/construction and language scores
Boston and colleagues, 2004 (148)	Patients diagnosed with Alzheimer's (n=19)	500 mg EPA 2x/d	12 wks	• No significant improvement in Alzheimer's symptoms
Attention Deficit Hyperactivity Disorder				
Hirayama and colleagues, 2004 (131)	Children aged 6-12 y with ADHD (n=20)	3.6 g DHA/wk	2 mo	• Performance of the subjects in the DHA group did not improve compared to the control group
Stevens and colleagues, 2003 (130)	Children with ADHD symptoms (n=5-6)	480 mg DHA+ 80 mg EPA/d	4 mo	• Increase in EPA and DHA in plasma phospholipids and red blood cell total lipids (P<0.05) • Increase of EPA in red blood cells associated with decrease in disruptive behavior (P<0.05) • Decreased conduct problems rated by parents (P=0.05) and increased attention symptoms rated by teachers (P=0.03) compared to control
Voigt and colleagues, 2001 (132)	Children 6-12 y of age diagnosed with ADHD (n=31-32)	345 mg DHA/d	4 mo	• Plasma phospholipid DHA concentration increased with DHA supplementation (P<0.001) • No improvement in ADHD symptoms

[a]Value given is n per treatment group; a range is given when there are multiple treatment groups (two or more) with differing number of participants in each group.
[b]"+" symbol indicates multiple active ingredients within a treatment dose; "or" indicates multiple treatment groups.
[c]APOE=apolipoprotein E.
[d]N/A=not applicable; study duration follows an observational follow-up study timeline.

garding the role of n-3 fatty acids on excessive bleeding, although the literature reviewed by Harris (164) indicates that with moderate n-3 fatty acid intake there is little risk of excessive bleeding, which is additionally outweighed by the benefits. Other environmental pollutants such as dioxins may be present in fish oil products, suggesting discouragement of frequent consumption (165). The other major n-3 fatty acid, ALA, and its main sources do not possess many of the limitations of EPA/DHA and fish. There are little or no concerns with allergy, dietary restriction (eg, vegetarianism), environmental pollutants, global supply, and methyl mercury with regard to food sources of ALA. Therefore, ALA may be a viable alternative to EPA/DHA. Conversely, its potency is mild in comparison to EPA/DHA, and its conversion to EPA/DHA is limited in human beings (166).

Alternative Sources of n-3 Fatty Acids

Food products are currently being manufactured and marketed to increase n-3 fatty acid intake. One of the first marketed foods was n-3 fatty acid–enriched eggs produced from chickens fed high n-3 fatty acid diets (167). The DHA content of these enriched eggs is approximately 150 mg/egg (168). Clinical studies have shown cardiovascular benefits from these eggs in men and women with mild hypertriglyceridemia (169) and healthy adult males (170). This suggests that absorption, distribution, and

metabolism of n-3 fatty acids probably remain unchanged in enriched eggs. Despite noticeable biological properties, the n-3 fatty acid–enriched eggs may suffer from poor consumer acceptability due to fishy taste and short shelf-life. Addition of antioxidant vitamins has been considered to improve quality and shelf life of these eggs (171).

The success in production of n-3 fatty acid–enriched eggs led to the generation of other n-3 fatty acid–enriched foods, including dairy and meat products. Daily intake of milk enriched with n-3 fatty acid, folic acid, and vitamin E was shown to significantly reduce serum triglyceride, total cholesterol, LDL cholesterol, apolioprotein B, glucose, and homocysteine levels in patients with metabolic syndrome (172,173). Several farm animals, including cattle, goats, ostriches, and pigs have been fed with n-3 fatty acid–enriched feed (174,175). Sources of n-3 fatty acid included flaxseed, fish products, and algae. Regardless of the n-3 fatty acid source, these diets resulted in n-3 fatty acid–enriched milk or meat products. However, these products also suffered from poor organoleptic properties, particularly if the source of n-3 fatty acid was fish or marine products. To combat this disadvantage, applications of antioxidant vitamins and microencapsulation techniques have been employed. Because these activities are in their early stage, the evidence for consumer acceptability and more importantly, biological properties of these food products, is being accumulated.

Overall, these products may help increase dietary intake of n-3 fatty acids in the North American population. Many of these products may be used as a substitute for fish to obtain the recommended amounts of dietary EPA/DHA. However, the n-3 fatty acid–enriched foods are sold at a higher cost than their nonenriched counterparts. Also, these products vary in their n-3 fatty acid contents, making it difficult to regulate the net daily n-3 fatty acid intake.

Perhaps the most recent advance in production of food products with high n-3 fatty acid contents is the generation of transgenic animals. *Fat-1* gene has been identified in the conversion of n-6 fatty acid to n-3 fatty acid (176). Expression of this gene in pigs and mice has resulted in high DHA contents in the animals' products, including milk, fat, and meat. Although early results from this technology are promising, generation of such products is still in the laboratory stage; abnormalities in these animals may exist (177). Time will identify whether or not the products from transgenic animals will be able to appear and survive in the marketplace with potential sensory and safety issues yet to be addressed. Several products have already been marketed, although the long-term health effects of consuming such products along with their cost-effectiveness and consumer acceptability remain to be documented. More information on this promising food technology has been reviewed elsewhere (178).

CONCLUSIONS

From all of the studies discussed in this review, it is evident that n-3 fatty acid, especially EPA and DHA, play important roles in human health through various mechanisms. n-3 fatty acids serve as a structural component for providing the optimal function of cellular membranes in health or disease states. n-3 fatty acid may generate changes in membrane fluidity, enzyme activity, balanced n-6:n-3 eicosanoid production, and gene expressions. This suggests that strategies to increase the amount of n-3 fatty acid consumed at the population level should be considered to obtain the potential health benefits observed in animal and human studies. Should increased intakes of n-3 fatty acid result in prevention of chronic diseases, a significant reduction in the burden of the health care industry can be achieved with minimal investment. The development of n-3 fatty acid supplements and several enriched food products is an initial step for promoting n-3 fatty acid consumption. Several stakeholders, including the government, industry, and health professionals should contemplate campaigning for availability and affordability of n-3 fatty acid food products. Encouragement of consumption of such products by the general population, specifically by people at higher risk for relevant chronic diseases, should also be addressed.

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