# Omega-3 Fatty Acids EPA and DHA: Health Benefits Throughout Life[1,2]

**Danielle Swanson,[3] Robert Block,[4] and Shaker A. Mousa[3,5*]**

*[3]The Pharmaceutical Research Institute, Albany College of Pharmacy and Health Sciences, Rensselaer, NY; [4]Department of Community and Preventive Medicine, and Division of Cardiology, Department of Medicine, University of Rochester School of Medicine and Dentistry, Rochester, NY; [5]College of Medicine, King Saud University, Riyadh, Saudi Arabia*

**ABSTRACT**

Omega-3 [(n-3)] fatty acids have been linked to healthy aging throughout life. Recently, fish-derived omega-3 fatty acids EPA and DHA have been associated with fetal development, cardiovascular function, and Alzheimer's disease. However, because our bodies do not efficiently produce some omega-3 fatty acids from marine sources, it is necessary to obtain adequate amounts through fish and fish-oil products. Studies have shown that EPA and DHA are important for proper fetal development, including neuronal, retinal, and immune function. EPA and DHA may affect many aspects of cardiovascular function including inflammation, peripheral artery disease, major coronary events, and anticoagulation. EPA and DHA have been linked to promising results in prevention, weight management, and cognitive function in those with very mild Alzheimer's disease. *Adv. Nutr. 3: 1–7, 2012.*

## Introduction

Omega-3 [(n-3)] long-chain PUFA, including EPA and DHA, are dietary fats with an array of health benefits (1). They are incorporated in many parts of the body including cell membranes (2) and play a role in antiinflammatory processes and in the viscosity of cell membranes (3,4). EPA and DHA are essential for proper fetal development and healthy aging (5). DHA is a key component of all cell membranes and is found in abundance in the brain and retina (6). EPA and DHA are also the precursors of several metabolites that are potent lipid mediators, considered by many investigators to be beneficial in the prevention or treatment of several diseases (7).

It can be challenging to get the appropriate intake of EPA and DHA through diet alone, even though EPA and DHA are produced by water plants such as algae and are prevalent in marine animals. A shorter chain omega-3 fatty acid, $\alpha$-linolenic acid (ALA),[6] is a prominent component of our diet as it is found in many land plants that are commonly eaten, but it does not provide the health benefits seen with EPA and DHA. Although it is possible for the body to convert ALA to EPA and DHA by enlongase and desaturase enzymes, research suggests that only a small amount can be synthesized in the body from this process (8). For example, 1 study suggested that only ~2 to 10% of ALA is converted to EPA or DHA (9), and other studies found even less: Goyens et al. (10) found an ALA conversion of ~7% for EPA, but only 0.013% for DHA; Hussein et al. (11) found an ALA conversion of only 0.3% for EPA and <0.01% for DHA.

The current American diet has changed over time to be high in SFA and low in omega-3 fatty acids (12). This change in eating habits is centered on fast food containing high amounts of saturated fat, which has small amounts of essential omega-3 PUFA compared with food prepared in the home (13). Seafood sources such as fish and fish-oil supplements are the primary contributors of the 2 biologically important dietary omega-3 fatty acids, EPA and DHA (14–16). This low intake of dietary EPA and DHA is thought to be associated with increased inflammatory processes as well as poor fetal development, general cardiovascular health, and risk of the development of Alzheimer's disease (AD).

This review focuses on the many benefits of EPA and DHA supplementation throughout life, including use during pregnancy for proper fetal development and full-term gestation, to reduce many cardiovascular issues, and potential uses in AD.

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[6] Abbreviations used: AD, Alzheimer's disease; ALA, $\alpha$-linolenic acid; CRP, C-reactive protein; MMSE, Mini-Mental State Examination; PAD, peripheral arterial disease.

* To whom correspondence should be addressed: E-mail: shaker.mosua@acphs.edu.

 

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## Omega-3 fatty acids and fetal development

Maternal nutrition guidelines have always stressed a diet including sufficient caloric and protein requirements, but recently fatty acids have also been deemed important (17). This is partially due to the fact that EPA and DHA supplementation during pregnancy has been associated with multiple benefits for the infant (**Table 1**). During pregnancy, the placenta transfers nutrients, including DHA, from the mother to the fetus (18). The amount of omega-3 fatty acid in the fetus is correlated with the amount ingested by the mother, so it is essential that the mother has adequate nutrition (19). The 2010 U.S. Department of Health and Human Services dietary guidelines recommend that women who are pregnant or breastfeeding should "consume 8 to 12 ounces of seafood per week from a variety of seafood types" (12). Ingesting 8–12 oz of seafood per week, depending on the type of fish, is equivalent to ~300–900 mg EPA+DHA per day. Unfortunately, this amount is not being met by most mothers in the United States and Canada, which means that infants many not be receiving adequate amounts of these vital nutrients in the womb (20).

Several studies confirmed the benefit of omega-3 supplementation during pregnancy in terms of proper development of the brain and retina. Of the 2 most important long-chain omega-3 fatty acids, EPA and DHA, DHA is the more important for proper cell membrane function and is vital to the development of the fetal brain and retina (17). During the third trimester, vast amounts of DHA accumulate in fetal tissue (20). The 2 most infiltrated fetal areas include the retina and brain, which may correlate with normal eyesight and brain function (19). A study by Judge et al. (20) found that children whose mothers had taken DHA supplementation during pregnancy ($n$ = 29) had significantly better problem-solving skills at 9 mo old ($P$ = 0.017) than those whose mothers had not taken DHA supplementation during pregnancy ($n$ = 15). Another study provided a cognitive assessment of children 2.5 y after maternal EPA+DHA supplementation during pregnancy from 20 wk of gestation until delivery ($n$ = 33) compared with children in a placebo group ($n$ = 39). Children in the EPA + DHA–supplemented group attained significantly higher scores for eye and hand coordination [mean score, 114

**TABLE 1.** Studies involving omega-3 fatty acid supplementation and pregnancy

| Study | Design | No. of pregnant patients who completed trial | Omega-3 fatty acids assessed and amounts | Major finding |
|---|---|---|---|---|
| Judge et al. (20) | Double-blind, placebo-controlled, randomized | 29 | DHA (average consumption 1500 mg/wk DHA ($n$ = 14, gestation week 24 until birth) vs. placebo ($n$ = 15) | Maternal DHA intake was associated with enhanced infant problem-solving skills but not recognition skills at 9 mo old |
| Dunstan et al. (19) | Double-blind, placebo-controlled, randomized | 98 | DHA (2.2 g/d) and EPA (1.1 g/d) (gestation week 20 until birth) vs. placebo ($n$ = 39) | At 2.5 y old, children ($n$ = 32) whose mothers were supplemented had significantly better scores of hand and eye coordination |
| Olsen et al. (23) | Randomized clinical intervention | $n$ = 435 supplemented, $n$ = 463 placebo | DHA+EPA (fish-oil capsules with 2.7 g/d PUFA) | Supplementation delayed onset of delivery in subjects who had experienced preterm delivery in previous pregnancies and were classified as low and medium fish consumers |
| Olsen et al. (21) | Placebo-controlled, randomized | Supplemented ($n$ = 263) vs. placebo ($n$ = 136) | DHA+EPA (fish-oil capsules daily, 2.7 g/d PUFA) | Supplementation during pregnancy was associated with a decreased incidence of asthma in the children at 16 y old |
| Makrides et al. (25) | Double-blind, placebo-controlled, randomized | 2399 ($n$ = 1197 supplemented, $n$ = 1202 placebo; 726 children were followed up with) | DHA (fish-oil capsules providing 800 mg/d DHA) | Supplementation did not result in lower levels of postpartum depression in mothers or improved cognitive and language development in offspring during early childhood |
| Krauss-Etschmann et al. (26) | Double-blind, placebo-controlled, randomized | 311 | DHA+EPA daily with either fish oil with DHA (0.5 g) and EPA (0.15 g) or with methyltetrahydrofolic acid (400 $\mu$g), both, or placebo, from gestation week 22 | Fish-oil supplementation was associated with decreased levels of maternal inflammatory/$T_H1$ cytokines and a decrease of fetal Th2-related cytokines |
| Furuhjelm et al. (27) | Placebo-controlled, randomized | 145 | DHA+EPA daily with either DHA (1.1 g) and EPA (1.6 g), or placebo, given from gestation week 25 to an average 3–4 mo of breastfeeding | At 1 y old, infants whose mothers were supplemented had a decreased risk of food allergy and IgE-associated eczema |

(SD 10.2] than those in the placebo group [mean score, 108 (SD 11.3)] ($P = 0.021$, adjusted $P = 0.008$) (19).

Of great clinical importance, EPA and DHA supplementation during pregnancy has been associated with longer gestation and increased concentrations of EPA and DHA in fetal tissues (21). In 2005, preterm births accounted for 12.7% of all births in the United States, increasing the likelihood of health complications (22). Carrying a baby to term is very important because prematurity is the cause of various infant diseases and can lead to death; preterm delivery is an underlying factor for 85% of the deaths of normally formed infants (23). One mechanism by which EPA and DHA may decrease the incidence of preterm birth is by decreasing prostaglandin $E_2$ and prostaglandin $F_{2\alpha}$ production, therefore reducing inflammation within the uterus, which could be associated with preterm labor (21,24). Several studies investigated EPA and DHA intake during pregnancy and its correlation with longer gestation. Conclusions were that EPA+DHA supplementation during pregnancy delayed the onset of delivery to term or closer to term; however, supplementation did not delay delivery to the point of being postterm (20,23,25). This supports the evidence that EPA+DHA ingestion leads to optimal pregnancy length. EPA+DHA supplementation reduced the HR of preterm delivery by 44% (95% CI: 14–64%) in those who consumed relatively low amounts of fish and 39% (95% CI: 16–56%) in those who consumed medium amounts of fish; however, a level of statistical significance was not met ($P = 0.10$) (23). The Judge et al. (20) study found that women who had DHA supplementation from gestation week 24 until full-term delivery carried their infants significantly ($P = 0.019$) longer than did the women in the placebo group. One study found that DHA supplementation after gestation week 21 led to fewer preterm births (<34 wk of gestation) in the DHA group compared with the control group (1.09% vs. 2.25%; adjusted RR, 0.49; 95% CI: 0.25–0.94; $P = 0.03$). Also, mean birth weight was 68 g heavier (95% CI: 23–114 g; $P = 0.003$) and fewer infants were of low birth weight in the DHA group compared with the control group (3.41% vs. 5.27%; adjusted RR, 0.65; 95% CI: 0.44–0.96; $P = 0.03$) (25).

There is also evidence that mothers who use EPA and DHA supplementation during pregnancy and breastfeeding may protect their children against allergies. This may be due to the fact that fish-oil supplementation has been associated with decreased levels of body cells associated with inflammation and immune response (26). In a study about food allergy and IgE-associated eczema, the period prevalence of food allergy was lower in the maternal EPA+DHA supplementation group compared to placebo ($P < 0.05$), and the incidence of IgE-associated eczema was also lower in the maternal EPA+DHA supplementation group compared to placebo ($P < 0.05$) (27).

## Omega-3 fatty acids and cardiovascular disease

Cardiovascular disease is the cause of 38% of all deaths in the United States, many of which are preventable (28). Chronic inflammation is thought to be the cause of many chronic diseases, including cardiovascular disease (29). EPA and DHA are thought to have antiinflammatory effects and a role in oxidative stress (30) and to improve cellular function through changes in gene expression (31). In a study that used human blood samples, EPA+DHA intake changed the expression of 1040 genes and resulted in a decreased expression of genes involved in inflammatory and atherogenesis-related pathways, such as nuclear transcription factor $\kappa$B signaling, eicosanoid synthesis, scavenger receptor activity, adipogenesis, and hypoxia signaling (31). Circulating markers of inflammation, such as C-reactive protein (CRP), TNF $\alpha$, and some ILs (IL-6, IL-1), correlate with an increased probability of experiencing a cardiovascular event (32). Inflammatory markers such as IL-6 trigger CRP to be synthesized by the liver, and elevated levels of CRP are associated with an increased risk of the development of cardiovascular disease (33). A study of 89 patients showed that those treated with EPA+DHA had a significant reduction in high-sensitivity CRP (66.7%, $P < 0.01$) (33). The same study also showed a significant reduction in heat shock protein 27 antibody titers (57.69%, $P < 0.05$), which have been shown to be overexpressed in heart muscle cells after a return of blood flow after a period of ischemia (ischemia-reperfusion injury) and may potentially have a cardioprotective effect (33).

There have been conflicting results reported about EPA and DHA and their use with regard to major coronary events and their use after myocardial infarction. EPA+DHA has been associated with a reduced risk of recurrent coronary artery events and sudden cardiac death after an acute myocardial infarction (RR, 0.47; 95% CI: 0.219–0.995) and a reduction in heart failure events (adjusted HR: 0.92; 99% CI: 0.849–0.999) (34–36). A study using EPA supplementation in combination with a statin, compared with statin therapy alone, found that, after 5 y, the patients in the EPA group ($n = 262$) who had a history of coronary artery disease had a 19% relative reduction in major coronary events ($P = 0.011$). However, in patients with no history of coronary artery disease ($n = 104$), major coronary events were reduced by 18%, but this finding was not significant (37). This Japanese population already has a high relative intake of fish compared with other nations, and, thus, these data suggest that supplementation has cardiovascular benefits in those who already have sufficient baseline EPA+DHA levels. Another study compared patients with impaired glucose metabolism ($n = 4565$) with normoglycemic patients ($n = 14{,}080$). Impaired glucose metabolism patients had a significantly higher coronary artery disease HR (1.71 in the non-EPA group and 1.63 in the EPA group). The primary endpoint was any major coronary event including sudden cardiac death, myocardial infarction, and other nonfatal events. Treatment of impaired glucose metabolism patients with EPA showed a significantly lower major coronary event HR of 0.78 compared with the non–EPA-treated impaired glucose metabolism patients (95% CI: 0.60–0.998; $P = 0.048$), which demonstrates that EPA significantly suppresses major coronary events (38). When looking at the use of EPA+DHA and cardiovascular events after myocardial

infarction, of 4837 patients, a major cardiovascular event occurred in 671 patients (13.9%) (39). A post hoc analysis of the data from these diabetic patients showed that rates of fatal coronary heart disease and arrhythmia-related events were lower among patients in the EPA+DHA group than among the placebo group (HR for fatal coronary heart disease: 0.51; 95% CI: 0.27–0.97; HR for arrhythmia-related events: 0.51; 95% CI: 0.24–1.11, not statistically significant) (39). Another study found that there was no significant difference in sudden cardiac death or total mortality between an EPA +DHA supplementation group and a control group in those patients treated after myocardial infarction (40). Although these last 2 studies appear to be negative in their results, it is possible that the more aggressive treatment with medications in these more recent studies could attribute to this.

Omega-3 fatty acids have been found to play a role in atherosclerosis and peripheral arterial disease (PAD). It is thought that both EPA and DHA improve plaque stability, decrease endothelial activation, and improve vascular permeability, thereby decreasing the chance of experiencing a cardiovascular event (41). It was found that EPA supplementation is associated with significantly higher amounts of EPA in the carotid plaque than placebo ($P < 0.0001$), which may lead to decreased plaque inflammation and increased stability (42). PAD, a manifestation of atherosclerosis, is characterized by buildup of plaque in the arteries of the leg and can eventually lead to complete blockage of the arteries. EPA+DHA supplementation has been shown to improve endothelial function in patients with PAD by decreasing plasma levels of soluble thrombomodulin from a median value of 33.0 $\mu$g/L to 17.0 $\mu$g/L ($P = 0.04$) and improve brachial artery flow–mediated dilation from 6.7% to 10.0% ($P = 0.02$) (43). Patients who had PAD and were supplemented with EPA experienced a significantly lower major coronary event HR than those who did not take EPA (HR: 0.44; 95% CI: 0.19–0.97; $P = 0.041$) (44).

Omega-3 fatty acids have been shown to increase platelet responsiveness to subtherapeutic anticoagulation therapies, including aspirin. Recently, it was noted that patient response to aspirin for anticoagulation therapy is widely variable (45), and, thus, the number of patients with a low response to aspirin or aspirin resistance is estimated to range from <1% to 45%, depending on many variables. However, in patients with stable coronary artery disease taking low-dose aspirin, EPA+DHA supplementation has been proven to be as effective as aspirin dose escalation to 325 mg/d for anticoagulation benefits (45). The antiplatelet drug clopidogrel has also been associated with hyporesponsiveness in some patients. This could be attributed to poor patient compliance, differences in genes and platelet reactivity, variability of drug metabolism, and drug interactions. More importantly, in 1 study, patients receiving standard dual antiplatelet therapy (aspirin 75 mg/d and clopidogrel 600-mg loading dose followed by 75 mg/d) were assigned to either EPA+DHA supplementation or placebo. After 1 mo of treatment, the $P2Y_{12}$ receptor reactivity index (an indicator of clopidogrel resistance) was significantly lower, by 22%, for patients taking EPA+DHA compared with patients taking placebo ($P = 0.020$) (46).

## Omega-3 fatty acids and AD

AD is a devastating disease for which there are limited treatment options and no cure. Memory loss is an early indicator of the disease, which is progressive, and leads to the inability of the patient to care for him- or herself and eventually to death (47). Currently, the number of individuals with AD is estimated to be 26.6 million and is expected to increase to 106.2 million by 2050 (48). There have been many studies conducted regarding the use of omega-3 fatty acid supplementation and AD (**Table 2**). DHA is present in large amounts in neuron membrane phospholipids, where it is involved in proper function of the nervous system, which is why it is thought to play a role in AD (49). A case-control study consisting of 148 patients with cognitive impairment [Mini-Mental State Examination (MMSE) score <24] and 45 control patients (MMSE score ≥24) showed that serum cholesteryl ester-EPA and -DHA levels were significantly lower ($P < 0.05$ and $P < 0.001$, respectively) in all MMSE score quartiles of patients with AD compared with control values (49). Another study found that a diet characterized by higher intakes of foods high in omega-3 fatty acids (salad dressing, nuts, fish, tomatoes, poultry, cruciferous vegetables, fruits, dark and green leafy vegetables), and a lower intake of foods low in omega-3 fatty acids (high-fat dairy products, red meat, organ meat, butter) was strongly associated with a lower AD risk (50). Image analysis of brain sections of an aged AD mouse model showed that overall plaque burden was significantly reduced by 40.3% in mice with a diet enriched with DHA ($P < 0.05$) compared with placebo. The largest reductions (40–50%) were seen in brain regions that are thought to be involved with AD, the hippocampus and parietal cortex (51). A central event in AD is thought to be the activation of multiple inflammatory cells in the brain. Release of IL-1B, IL-6, and TNF $\alpha$ from microglia cells may lead to dysfunction of the neurons in the brain (52). In 1 study, AD patients treated with EPA +DHA supplementation increased their plasma concentrations of EPA and DHA, which were associated with reduced release of inflammatory factors IL-1B, IL-6, and granulocyte colony–stimulating factor from peripheral blood mononuclear cells (53).

Unintended weight loss is a problem that many patients with AD may face, and EPA+DHA supplementation has had a positive effect on weight gain in patients with AD. In a study using EPA+DHA supplementation, patients' weight significantly increased by 0.7 kg in the EPA+DHA treatment group at 6 mo ($P = 0.02$) and by 1.4 kg at 12 mo ($P < 0.001$) and was observed mainly in patients with a BMI <23 at the study start (54). This means that those patients with a lower BMI preferentially gained weight compared with those patients already with a higher BMI.

Although results from studies regarding the disease processes of AD seem to be promising, there are conflicting data regarding the use of omega-3 fatty acids in terms of cognitive

**TABLE 2.** Studies involving omega-3 fatty acid supplementation and Alzheimer's disease[1]

| Study | Design | No. of patients | Omega-3 fatty acids assessed and amounts | Major finding |
|---|---|---|---|---|
| Omega AD study, Freund-Levi et al. (47) | Double-blind, placebo-controlled, randomized | 174[1] | DHA (1.7 g/d) and EPA (0.6 g/d) | Decline in cognitive function did not differ between supplemented group and placebo group at 6 mo. However, patients with very mild cognitive dysfunction ($n$ = 32, MMSE score >27) in the EPA+DHA-supplemented group had a significant reduction in MMSE score decline rate at 6 mo |
| Omega AD study, Vedin et al. (53) | Double-blind, placebo-controlled, randomized | 25,[1] first subjects to be randomized in the Omega AD Study | DHA (1.7 g/d) and EPA (0.6 g/d) | Supplementation was associated with decreased levels of IL-1$\beta$, IL-6, and granulocyte colony–stimulating factor from peripheral blood mononuclear cells at 6 mo |
| Omega AD study, Irving et al. (54) | Double-blind, placebo-controlled, randomized | 174[1] | DHA (1.7 g/d) and EPA (0.6 g/d) for 6 mo, then for all subjects (supplementation group and placebo group) | Supplementation was associated with positive weight gain and appetite in supplementation group at 6 mo, but not in the placebo group, and for both groups at 12 mo |
| Omega AD study, Quinn et al. (56) | Double-blind, placebo-controlled, randomized | 295; mild to moderate AD (MMSE score 14–26) supplementation group ($n$ = 171), placebo group ($n$ = 124) | DHA (2 g/d for 18 mo) | DHA supplementation led to no beneficial effect on rate of cognitive and functional decline |

[1] Subjects in the Omega AD study were patients with mild to moderate AD ($n$ = 89) with acetylcholine esterase inhibitor use and an MMSE score between 15 and 30 and a placebo group ($n$ = 85). Supplementation was for 12 mo; the placebo group was started on supplementation after 6 mo. AD, Alzheimer's disease; MMSE, Mini-Mental State Examination.

function. Neuropsychiatric symptoms accompany AD from early stages and tend to increase with the progression of the disease (55). An analysis of 174 patients randomized to a placebo group or to a group with mild to moderate AD (MMSE score ≥15) treated with daily DHA (1.7 g) and EPA (0.6 g) found that at 6 mo, the decline in cognitive function did not differ between the groups. Yet, in a subgroup with very mild cognitive dysfunction ($n$ = 32, MMSE score >27), they observed a significant reduction in the MMSE decline rate in the DHA+EPA-supplemented group compared with the placebo group (47). Another study that looked at DHA supplementation in individuals with mild to moderate AD used the Alzheimer's Disease Assessment Scale–Cognitive subscale, which evaluates cognitive function on a 70-point scale in terms of memory, attention, language, orientation, and praxis. This study found that DHA supplementation had no beneficial effect on cognition during the 18-mo trial period for the DHA group vs. placebo (56).

## Conclusion

The omega-3 PUFA EPA and DHA are important throughout life and are a dietary necessity found predominantly in fish and fish-oil supplements. The omega-3 fatty acids EPA and DHA are essential for proper fetal development, and supplementation during pregnancy has also been linked to decreased immune responses in infants including decreased incidence of allergies in infants. Omega-3 fatty acid consumption has been associated with improved cardiovascular function in terms of antiinflammatory properties, PAD, reduced major coronary events, and improved antiplatelet effects in the face of aspirin resistance or clopidogrel hyporesponsiveness. Patients with AD have been shown to be deficient in DHA, and supplementing them with EPA +DHA not only reverses this deficiency, but may also improve cognitive functioning in patients with very mild AD. With increasing rates of pediatric allergies, cardiovascular disease, and AD in the United States, EPA and DHA may be a safe and inexpensive link to a healthier life. Further research should be conducted in humans to assess a variety of clinical outcomes including quality of life and mental status. In addition, because potent lipid mediator metabolites of EPA and DHA are of great interest currently, their influence on these important outcomes should be assessed because current evidence suggests that their antiinflammatory and tissue-protective effects are nearly 1000 times greater than those of EPA and DHA (7).

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## Literature Cited

1. Su KP, Huang SY, Chiu TH, Huang KC, Huang CL, Chang HC, Pariante CM. Omega-3 fatty acids for major depressive disorder during pregnancy: results from a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry. 2008;69:644–51.
2. Lazzarin N, Vaquero E, Exacoustos C, Bertonotti E, Romanini ME, Arduini D. Low-dose aspirin and omega-3 fatty acids improve uterine artery blood flow velocity in women with recurrent miscarriage due to impaired uterine perfusion. Fertil Steril. 2009;92:296–300.
3. Smith GI, Atherton P, Reeds DN, Mohammed BS, Rankin D, Rennie MJ, Mittendorfer B. Dietary omega-3 fatty acid supplementation

increases the rate of muscle protein synthesis in older adults: a randomized controlled trial. Am J Clin Nutr. 2011;93:402–12.
4. Conquer JA, Tierney MC, Zecevic J, Bettger WJ, Fisher RH. Fatty acid analysis of blood plasma of patients with Alzheimer's disease, other types of dementia, and cognitive impairment. Lipids. 2000;35:1305–12.
5. Dunstan JA, Mitoulas LR, Dixon G, Doherty DA, Hartmann PE, Simmer K, Prescott SL. The effects of fish oil supplementation in pregnancy on breast milk fatty acid composition over the course of lactation: a randomized controlled trial. Pediatr Res. 2007;62:689–94.
6. Krauss-Etschmann S, Shadid R, Campoy C, Hoster E, Demmelmair H, Jimenez M, Gil A, Rivero M, Veszpremi B, Decsi T, et al. Effects of fish-oil and folate supplementation of pregnant women on maternal and fetal plasma concentrations of docosahexaenoic acid and eicosapentaenoic acid: a European randomized multicenter trial. Am J Clin Nutr. 2007;85:1392–400.
7. Serhan CN, Chiang N, Van Dyke TE. Resolving inflammation: dual anti-inflammatory and pro-resolution lipid mediators. Nat Rev Immunol. 2008;8:349–61.
8. Neff LM, Culiner J, Cunningham-Rundles S, Seidman C, Meehan D, Maturi J, Wittkowski KM, Levine B, Breslow JL. Algal docosahexaenoic acid affects plasma lipoprotein particle size distribution in overweight and obese adults. J Nutr. 2011;141:207–13.
9. Chiu CC, Su KP, Cheng TC, Liu HC, Chang CJ, Dewey ME, Stewart R, Huang SY. The effects of omega-3 fatty acids monotherapy in Alzheimer's disease and mild cognitive impairment: a preliminary randomized double-blind placebo-controlled study. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32:1538–44.
10. Goyens PL, Spilker ME, Zock PL, Katan MB, Mensink RP. Compartmental modeling to quantify alpha-linolenic acid conversion after longer term intake of multiple tracer boluses. J Lipid Res. 2005;46:1474–83.
11. Hussein N, Ah-Sing E, Wilkinson P, Leach C, Griffin BA, Millward DJ. Long-chain conversion of [13C]linoleic acid and alpha-linolenic acid in response to marked changes in their dietary intake in men. J Lipid Res. 2005;46:269–80.
12. Dietary Guidelines for Americans. 2010. Washington, DC: U.S. Government Printing Office.
13. Dangardt F, Osika W, Chen Y, Nilsson U, Gan LM, Gronowitz E, Strandvik B, Friberg P. Omega-3 fatty acid supplementation improves vascular function and reduces inflammation in obese adolescents. Atherosclerosis. 2010;212:580–5.
14. Leaf DA, Hatcher L. The effect of lean fish consumption on triglyceride levels. Phys Sportsmed. 2009;37:37–43.
15. Mann NJ, O'Connell SL, Baldwin KM, Singh I, Meyer BJ. Effects of seal oil and tuna-fish oil on platelet parameters and plasma lipid levels in healthy subjects. Lipids. 2010;45:669–81.
16. Saito Y, Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Ishikawa Y, Oikawa S, Sasaki J, Hishida H, Itakura H, et al. Effects of EPA on coronary artery disease in hypercholesterolemic patients with multiple risk factors: sub-analysis of primary prevention cases from the Japan EPA Lipid Intervention Study (JELIS). Atherosclerosis. 2008;200:135–40.
17. Ramakrishnan U, Stein AD, Parra-Cabrera S, Wang M, Imhoff-Kunsch B, Juarez-Marquez S, Rivera J, Martorell R. Effects of docosahexaenoic acid supplementation during pregnancy on gestational age and size at birth: randomized, double-blind, placebo-controlled trial in Mexico. Food Nutr Bull. 2010;31:S108–16.
18. Helland IB, Smith L, Blomen B, Saarem K, Saugstad OD, Drevon CA. Effect of supplementing pregnant and lactating mothers with n-3 very-long-chain fatty acids on children's IQ and body mass index at 7 years of age. Pediatrics. 2008;122:e472–9.
19. Dunstan JA, Simmer K, Dixon G, Prescott SL. 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. 2008;93:F45–50.
20. Judge MP, Harel O, Lammi-Keefe CJ. Maternal consumption of a docosahexaenoic acid-containing functional food during pregnancy: benefit for infant performance on problem-solving but not on recognition memory tasks at age 9 mo. Am J Clin Nutr. 2007;85:1572–7.
21. Olsen SF, Osterdal ML, Salvig JD, Mortensen LM, Rytter D, Secher NJ, Henriksen TB. Fish oil intake compared with olive oil intake in late pregnancy and asthma in the offspring: 16 y of registry-based follow-up from a randomized controlled trial. Am J Clin Nutr. 2008;88:167–75.
22. Harper M, Thom E, Klebanoff MA, Thorp J, Jr., Sorokin Y, Varner MW, Wapner RJ, Caritis SN, Iams JD, Carpenter MW, et al. Omega-3 fatty acid supplementation to prevent recurrent preterm birth: a randomized controlled trial. Obstet Gynecol. 2010;115:234–42.
23. Olsen SF, Osterdal ML, Salvig JD, Weber T, Tabor A, Secher NJ. Duration of pregnancy in relation to fish oil supplementation and habitual fish intake: a randomised clinical trial with fish oil. Eur J Clin Nutr. 2007;61:976–85.
24. Roman AS, Schreher J, Mackenzie AP, Nathanielsz PW. Omega-3 fatty acids and decidual cell prostaglandin production in response to the inflammatory cytokine IL-1beta. Am J Obstet Gynecol. 2006;195:1693–9.
25. Makrides M, Gibson RA, McPhee AJ, Yelland L, Quinlivan J, Ryan P. Effect of DHA supplementation during pregnancy on maternal depression and neurodevelopment of young children: a randomized controlled trial. JAMA. 2010;304:1675–83.
26. Krauss-Etschmann S, Hartl D, Rzehak P, Heinrich J, Shadid R, Del Carmen Ramirez-Tortosa M, Campoy C, Pardillo S, Schendel DJ, Decsi T, et al. Decreased cord blood IL-4, IL-13, and CCR4 and increased TGF-beta levels after fish oil supplementation of pregnant women. J Allergy Clin Immunol. 2008;121:464–70 e6.
27. Furuhjelm C, Warstedt K, Larsson J, Fredriksson M, Bottcher MF, Falth-Magnusson K, Duchen K. Fish oil supplementation in pregnancy and lactation may decrease the risk of infant allergy. Acta Paediatr. 2009;98:1461–7.
28. Kelley DS, Siegel D, Fedor DM, Adkins Y, Mackey BE. DHA supplementation decreases serum C-reactive protein and other markers of inflammation in hypertriglyceridemic men. J Nutr. 2009;139:495–501.
29. Schubert R, Kitz R, Beermann C, Rose MA, Baer PC, Zielen S, Boehles H. Influence of low-dose polyunsaturated fatty acids supplementation on the inflammatory response of healthy adults. Nutrition. 2007;23:724–30.
30. Bloomer RJ, Larson DE, Fisher-Wellman KH, Galpin AJ, Schilling BK. Effect of eicosapentaenoic and docosahexaenoic acid on resting and exercise-induced inflammatory and oxidative stress biomarkers: a randomized, placebo controlled, cross-over study. Lipids Health Dis. 2009;8:36.
31. Bouwens M, van de Rest O, Dellschaft N, Bromhaar MG, de Groot LC, Geleijnse JM, Muller M, Afman LA. Fish-oil supplementation induces antiinflammatory gene expression profiles in human blood mononuclear cells. Am J Clin Nutr. 2009;90:415–24.
32. Micallef MA, Garg ML. Anti-inflammatory and cardioprotective effects of n-3 polyunsaturated fatty acids and plant sterols in hyperlipidemic individuals. Atherosclerosis. 2009;204:476–82.
33. Ebrahimi M, Ghayour-Mobarhan M, Rezaiean S, Hoseini M, Parizade SM, Farhoudi F, Hosseininezhad SJ, Tavallaei S, Vejdani A, Azimi-Nezhad M, et al. Omega-3 fatty acid supplements improve the cardiovascular risk profile of subjects with metabolic syndrome, including markers of inflammation and auto-immunity. Acta Cardiol. 2009;64:321–7.
34. Kris-Etherton PM, Harris WS, Appel LJ. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. Circulation. 2002;106:2747–57.
35. Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, Latini R, Lucci D, Nicolosi GL, Porcu M, Tognoni G. 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. 2008;372:1223–30.
36. Marchioli R, Barzi F, Bomba E, Chieffo C, Di Gregorio D, Di Mascio R, Franzosi MG, Geraci E, Levantesi G, Maggioni AP, et al. Early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction: time-course analysis of the results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione. Circulation. 2002;105:1897–903.

37. Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y, Oikawa S, Sasaki J, Hishida H, Itakura H, et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. Lancet. 2007;369:1090–8.
38. Oikawa S, Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y, Sasaki J, Hishida H, Itakura H, et al. Suppressive effect of EPA on the incidence of coronary events in hypercholesterolemia with impaired glucose metabolism: Sub-analysis of the Japan EPA Lipid Intervention Study (JELIS). Atherosclerosis. 2009;206:535–9.
39. Kromhout D, Giltay EJ, Geleijnse JM. n-3 fatty acids and cardiovascular events after myocardial infarction. N Engl J Med. 2010;363:2015–26.
40. Rauch B, Schiele R, Schneider S, Diller F, Victor N, Gohlke H, Gottwik M, Steinbeck G, Del Castillo U, Sack R, et al. 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. Circulation. 2010;122:2152–9.
41. Dawczynski C, Martin L, Wagner A, Jahreis G. n-3 LC-PUFA-enriched dairy products are able to reduce cardiovascular risk factors: a double-blind, cross-over study. Clin Nutr. 2010;29:592–9.
42. Cawood AL, Ding R, Napper FL, Young RH, Williams JA, Ward MJ, Gudmundsen O, Vige R, Payne SP, Ye S, et al. Eicosapentaenoic acid (EPA) from highly concentrated n-3 fatty acid ethyl esters is incorporated into advanced atherosclerotic plaques and higher plaque EPA is associated with decreased plaque inflammation and increased stability. Atherosclerosis. 2010;212:252–9.
43. Schiano V, Laurenzano E, Brevetti G, De Maio JI, Lanero S, Scopacasa F, Chiariello M. Omega-3 polyunsaturated fatty acid in peripheral arterial disease: effect on lipid pattern, disease severity, inflammation profile, and endothelial function. Clin Nutr. 2008;27:241–7.
44. Ishikawa Y, Yokoyama M, Saito Y, Matsuzaki M, Origasa H, Oikawa S, Sasaki J, Hishida H, Itakura H, Kita T, et al. Preventive effects of eicosapentaenoic acid on coronary artery disease in patients with peripheral artery disease. Circ J. 2010;74:1451–7.
45. Lev EI, Solodky A, Harel N, Mager A, Brosh D, Assali A, Roller M, Battler A, Kleiman NS, Kornowski R. Treatment of aspirin-resistant patients with omega-3 fatty acids versus aspirin dose escalation. J Am Coll Cardiol. 2010;55:114–21.
46. Gajos G, Rostoff P, Undas A, Piwowarska W. Effects of polyunsaturated omega-3 fatty acids on responsiveness to dual antiplatelet therapy in patients undergoing percutaneous coronary intervention: the OMEGA-PCI (OMEGA-3 fatty acids after pci to modify responsiveness to dual antiplatelet therapy) study. J Am Coll Cardiol. 2010;55:1671–8.
47. Freund-Levi Y, Eriksdotter-Jonhagen M, Cederholm T, Basun H, Faxen-Irving G, Garlind A, Vedin I, Vessby B, Wahlund LO, Palmblad J. Omega-3 fatty acid treatment in 174 patients with mild to moderate Alzheimer disease: OmegAD study: a randomized double-blind trial. Arch Neurol. 2006;63:1402–8.
48. Gillette-Guyonnet S, Andrieu S, Dantoine T, Dartigues JF, Touchon J, Vellas B. Commentary on "A roadmap for the prevention of dementia II. Leon Thal Symposium 2008." The Multidomain Alzheimer Preventive Trial (MAPT): a new approach to the prevention of Alzheimer's disease. Alzheimers Dement. 2009;5:114–21.
49. Tully AM, Roche HM, Doyle R, Fallon C, Bruce I, Lawlor B, Coakley D, Gibney MJ. Low serum cholesteryl ester-docosahexaenoic acid levels in Alzheimer's disease: a case-control study. Br J Nutr. 2003;89:483–9.
50. Gu Y, Nieves JW, Stern Y, Luchsinger JA, Scarmeas N. Food combination and Alzheimer disease risk: a protective diet. Arch Neurol. 2010; 67:699–706.
51. Lim GP, Calon F, Morihara T, Yang F, Teter B, Ubeda O, Salem N, Jr., Frautschy SA, Cole GM. A diet enriched with the omega-3 fatty acid docosahexaenoic acid reduces amyloid burden in an aged Alzheimer mouse model. J Neurosci. 2005;25:3032–40.
52. Freund-Levi Y, Hjorth E, Lindberg C, Cederholm T, Faxen-Irving G, Vedin I, Palmblad J, Wahlund LO, Schultzberg M, Basun H, et al. Effects of omega-3 fatty acids on inflammatory markers in cerebrospinal fluid and plasma in Alzheimer's disease: the OmegAD study. Dement Geriatr Cogn Disord. 2009;27:481–90.
53. Vedin I, Cederholm T, Freund Levi Y, Basun H, Garlind A, Faxen Irving G, Jonhagen ME, Vessby B, Wahlund LO, Palmblad J. Effects of docosahexaenoic acid-rich n-3 fatty acid supplementation on cytokine release from blood mononuclear leukocytes: the OmegAD study. Am J Clin Nutr. 2008;87:1616–22.
54. Irving GF, Freund-Levi Y, Eriksdotter-Jonhagen M, Basun H, Brismar K, Hjorth E, Palmblad J, Vessby B, Vedin I, Wahlund LO, et al. Omega-3 fatty acid supplementation effects on weight and appetite in patients with Alzheimer's disease: the omega-3 Alzheimer's disease study. J Am Geriatr Soc. 2009;57:11–7.
55. Freund-Levi Y, Basun H, Cederholm T, Faxen-Irving G, Garlind A, Grut M, Vedin I, Palmblad J, Wahlund LO, Eriksdotter-Jonhagen M. Omega-3 supplementation in mild to moderate Alzheimer's disease: effects on neuropsychiatric symptoms. Int J Geriatr Psychiatry. 2008;23:161–9.
56. Quinn JF, Raman R, Thomas RG, Yurko-Mauro K, Nelson EB, Van Dyck C, Galvin JE, Emond J, Jack CR, Jr., Weiner M, et al. Docosahexaenoic acid supplementation and cognitive decline in Alzheimer disease: a randomized trial. JAMA. 2010;304:1903–11.