Benefits of Long-Chain Omega-3 Fatty Acids EPA and DHA

An abundance of evidence strongly suggests that increased intakes of long-chain omega-3 fatty acids can markedly reduce the risk of heart disease. The omega-3 fatty acids believed to be largely responsible for these effects include EPA and DHA (eicosapentaenoic acid and docosahexaenoic acid). These are polyunsaturated fatty acids (PUFA) with numerous double bonds.

These "good fats" are naturally present in some types of fish and in other marine organisms such as algae, and they are also readily available in purified form in dietary supplements. Most Americans eat fish less than once a week or not at all, and average per capita consumption is only about five ounces per week. (National Oceanic and Atmospheric Administration, 2008; Smith, Barraj, et al., 2009) Consequently, Americans have very low intakes of the marine long-chain omega-3 fatty acids EPA and DHA (also referred to as n-3 fatty acids).

According to the late Dr. William E. Connor of the Oregon Health Sciences University, an internationally recognized expert on omega-3 fatty acids and health, hundreds of experimental and clinical studies have provided strong evidence that omega-3 fatty acids may help prevent heart disease through a number of different mechanisms. Several studies indicate that eating fish once or twice a week can reduce deaths from coronary artery disease by about 50 percent. "The most important finding is of a reduction in sudden death from ventricular fibrillation and tachycardia." Omega-3 fatty acids also reduce the tendency to thrombosis (formation of blood clots), and thus help prevent myocardial infarction (MI). EPA and DHA also have several actions that inhibit the development of atherosclerosis. While these fatty acids do not lower plasma cholesterol levels, they do have a substantial triglyceride-lowering effect and also raise levels of HDL ("good" cholesterol). Connor concluded that omega-3 fatty acids "are natural food substances that prevent coronary artery disease and sudden death." He emphasized that these fatty acids "have immense public health significance for the control of the current coronary epidemic." (Connor, 2001)

WHAT ARE OMEGA-3 AND OMEGA-6 FATTY ACIDS?

The term "omega-3" or "n-3" indicates that the first double bond is located at the third carbon from the end of the fatty acid chain. The long-chain omega-3s from marine sources are EPA and DHA, with 20 and 22 carbons and with five or six double bonds. These are the focus of this chapter. There are also plant sources of omega-3 fatty acids with 18 carbons and three double bonds.

Structure of Omega-3 Fatty Acids

Docosahexaenoic acid (DHA)
22 carbons and six double bonds

Eicosapentaenoic acid (EPA)
20 carbons and five double bonds

Alpha-linolenic acid (ALA)
18 carbons and three double bonds

Omega-6 fatty acids are polyunsaturated fatty acids that have the first double bond at the sixth carbon from the end of the fatty acid chain, like linoleic acid, which has 18 carbons and two double bonds. These are the types of fats present in some of the most commonly used vegetable oils such as corn oil, safflower oil, and sunflower oil.

In the U.S., intakes of omega-6 fatty acids are about 10 times as high as intakes of omega-3 fatty acids. The average intake for omega-6 fatty acids in adults is nine to 17 grams per day, while the average intake for omega-3 fatty acids is only one to two grams per day. Further, most of the omega-3 intake is in the form of ALA, not in the form of EPA and DHA. Average intake of EPA in adults is less than 0.01 gram per day, and average intake of DHA is also less than 0.1 gram per day. (Institute of Medicine, 2002)

RECOMMENDATIONS OF AN ILSI WORKSHOP

A workshop sponsored by the International Life Sciences Institute of North America (ILSI) in 2008 evaluated the evidence on the benefits of increased consumption of EPA and DHA and recommended a combined intake of 250 to 500 mg per day to reduce the risk of heart disease. (Harris, Mozaffarian, et al., 2009) Some of the key findings of the workshop are summarized below.

Heart disease is a complex condition that may develop over years but eventually results in an acute attack. The build-up of plaque in the arteries is a long, slow process that may begin in youth and continue to old age. The plaque may remain stable for years, but when it ruptures it may cause clots, blockage, and ventricular arrhythmia, which is usually fatal. Numerous studies have demonstrated that people with higher intakes or higher blood levels of EPA and DHA have a lower risk of death—including sudden death—from heart attacks. The impact of EPA and DHA may be primarily in preventing or alleviating the arrhythmia.

Findings from the ILSI workshop included the estimate that "cardiac mortality is reduced about 35 percent by modest EPA+DHA consumption (about 250-500 mg/d), an effect at least as great, for example, as that of statin therapy." (Harris, Mozaffarian, et al., 2009) Several European groups have published recommendations for EPA+DHA intake, and these tend to be at the upper end of this range—around 500 mg per day.

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Higher intakes of EPA and DHA have favorable effects on other factors related to cardiovascular risk, including blood pressure, heart rate, and triglyceride levels. The potential benefit of ALA on cardiovascular risk is less well established. According to the ILSI workshop, ALA "should not be considered as a replacement for EPA+DHA in reducing risk of cardiac death or other CVD [cardiovascular disease]."

The participants in the ILSI workshop concluded that the evidence "indicates that modest EPA+DHA consumption markedly reduces the risk of cardiac death. The quality, strength, and concordance of this evidence are remarkable, meeting and indeed generally exceeding those for any other dietary factor" implicated in reducing heart disease risk, including the evidence relating to saturated fat, dietary cholesterol, salt, and dietary fiber. (Harris, Mozaffarian, et al., 2009)

In infancy, the brain and retina contain large amounts of DHA and of arachidonic acid (AA). These fatty acids accumulate in the central nervous system during fetal development and throughout infancy and early childhood. Adequate levels of omega-3 fatty acids have been shown to be related to visual function, possibly cognitive development, and language or communication ability. Regulations currently permit DHA to be added to infant formula in the U.S. at a level up to 0.35 percent. The ILSI workshop suggested that this maximum permitted level may actually be the minimum level necessary for a benefit.

Cognitive decline is widespread in the aging population and can lead to dementia, defined as loss of cognitive function that is sufficiently severe to interfere with everyday function. DHA is concentrated in some of the most metabolically active areas of the brain, and animal studies have shown that DHA levels in the brain decrease with aging. The decrease is associated with decreases in antioxidant enzymes, fluidity of synaptic membranes, oxidation of lipid membranes, and ischemic damage. Some epidemiologic studies have shown a decreased risk of dementia in people who ate fish once or twice a week, and more studies are underway. The evidence regarding cognitive decline is described as "promising but limited."

An Omega-3 Index has been developed, which is a measure of the amounts of EPA+DHA in red cell membranes as a percentage of total red cell fatty acids. EPA and DHA affect basic cellular function through their effects on and in membranes. "This marker has been validated against dietary intake and has been shown to correlate strongly with reduced risk for mortality from CHD." An Omega-3 Index of less than 4 percent is associated with a high risk of sudden cardiac death, while an Omega-3 Index of 8 percent indicates a strong cardioprotective effect. (Harris, Mozaffarian, et al., 2009)

EPIDEMIOLOGY SHOWS BENEFITS OF FISH AND OMEGA-3 CONSUMPTION

For many years, scientists were puzzled by the fact that heart disease among Greenland Eskimos was extremely rare despite their consumption of a high-fat, high-cholesterol diet. Research revealed that the Eskimos were protected by diets largely based on seals, whales, and fish, all of which provide high intakes of omega-3 polyunsaturated fatty acids, especially EPA and DHA. (Bang & Dyerberg, 1973)

Later epidemiological studies in many countries, including the United States, demonstrated that even people who eat moderate amounts of fish get some degree of protection against heart disease.

In the Physicians Health Study, researchers identified 94 men "in whom sudden death was the first manifestation of cardiovascular disease." These men were matched with 184 controls, and blood levels of long chain omega-3 fatty acids (also called n-3 fatty acids) were assessed. Men with low blood levels of omega-3 fatty acids were three to five times more likely to suffer sudden death from heart disease than men with higher blood levels of omega-3 fatty acids. The researchers suggest that omega-3 fatty acids may protect against death from heart disease by decreasing the heart's tendency to arrhythmia. (Albert, Campos, et al., 2002)

In the Nurses Health Study, fish consumption was found to be associated with a lower risk of coronary heart disease (CHD) and a lower rate of all-cause mortality during 16 years of follow-up. The protective effect was stronger for fatal CHD than for nonfatal myocardial infarction (MI). The protective association with omega-3 fatty acid intake was similar to that for fish intake. "This finding is consistent with the hypothesis that omega-3 fatty acids are the active agent primarily responsible for the apparent protective effect of fish." (Hu, Bronner, et al., 2002)

An earlier report from the Nurses Health Study found that fish consumption lowered the risk of stroke. The researchers found that the "risk of thrombotic infarction [stroke] was significantly reduced by 48 percent among women who ate fish 2 to 4 times per week." (Iso, Rexrode, et al., 2001)

Among the Inuit of northern Quebec, the traditional diet is very high in long-chain omega-3 fatty acids from fish, whales, and seals, and the Inuit have traditionally had low rates of heart disease. In modern times, the Inuit diet may be shifting away from traditional patterns, but the Inuit still have a very low rate of heart disease, and the researchers attribute this protective effect to a diet rich in omega-3 fatty acids. Average consumption of marine products in this population was 131 grams per day (about 4.8 ounces). This corresponds to an intake of about 2 grams of EPA and DHA per day. (Dewailly, Blanchet, et al., 2001)

In the Netherlands, people over the age of 65 were followed for 17 years and the relationship between fish consumption and heart disease was evaluated. About 60 percent of this elderly cohort ate fish and 40 percent did not. Those who ate fish had a significantly lower rate of mortality from heart disease. (Kromhout, Feskens, et al., 1995)

In a case-control study of 334 people with primary cardiac arrest and 493 controls, researchers in the Cardiovascular Health Research Unit at the University of Washington found seafood consumption to be protective. People who ate even one fatty fish or seafood meal per week had a 50 percent reduced risk of cardiac arrest compared to people who ate none. People with higher levels of omega-3 fatty acids in their red blood cell membranes (five percent compared to three percent) had a 70 percent lower risk of cardiac arrest. The researchers suggested that an increase in membrane levels of omega-3 fatty acids in some way lowers the subjects' vulnerability to arrhythmia or ventricular fibrillation. (Siscovick, Raghunathan, et al., 1995)

In the Physicians Health Study, researchers from Brigham and Women's Hospital and Harvard Medical School found that doctors who consumed fish at least once a week had half the risk of sudden cardiac death compared to doctors who ate fish less than once a month. The researchers noted that there are about 250,000 sudden cardiac deaths every year in the United States, and over half of these occur in people with no history of heart disease. Therefore, the public health impact of any intervention that could reduce that risk would be substantial. (Albert, Hennekens, et al., 1998)

In the Cardiovascular Health Study, plasma omega-3 levels were measured in 179 adults who had a fatal or nonfatal MI compared to 179 controls. The plasma samples were drawn about two years before the events. Higher plasma levels of EPA+DHA were associated with a lower risk of fatal MI. "The association of n-3 polyunsaturated fatty acids with fatal ischemic heart disease, but not with nonfatal myocardial infarction, is consistent with possible antiarrhythmic effects of these fatty acids." (Lemaitre, King, et al., 2003)

KEY CLINICAL TRIALS

Numerous studies have specifically investigated the benefits of long-chain omega-3 fatty acids given as nutritional supplements. One large intervention trial studied more than 11,000 men who had survived an MI. It examined the effects of supplements of omega-3 fatty acids or vitamin E in protecting against later events, including nonfatal MI, stroke, or death. The patients followed Mediterranean dietary habits (considered beneficial for heart health) and continued to receive appropriate medical treatment with pharmaceutical preparations during the study. The omega-3 group was given one gram of combined EPA and DHA per day, and the vitamin E group was given 300 mg per day. No effect of supplemental vitamin E was observed, but the omega-3 supplement "significantly decreased, over 3.5 years, the rate of death, non-fatal myocardial infarction, and stroke." The decrease in risk was 10 to 15 percent. This study is known as the GISSI trial (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico). (GISSI, 1999)

In a later variation of the GISSI trial—the GISSI-HF trial—almost 3,500 patients with chronic heart failure and an equal number of controls were recruited and were given one gram daily of EPA+DHA or a placebo for about four years. In the treatment group, there was a small but significant decrease in the number of patients who died or were admitted to the hospital. The authors conclude, "A simple and safe treatment with n-3 PUFA can provide a small beneficial advantage in terms of mortality and admission to hospital for cardiovascular reasons in patients with heart failure in a context of usual care." (Tavazzi, Maggioni, et al., 2008)

In a Japanese trial (JELIS), more than 18,000 patients with high cholesterol levels were recruited and were given 1800 mg of EPA daily along with a statin, or the statin only (controls), for a period of five years. The endpoint was any major coronary events, including sudden cardiac death, fatal and non-fatal MI, unstable angina, angioplasty, stenting, or bypass. The EPA group had 19 percent fewer coronary events than the controls. Angina and non-fatal coronary events were also lower in the EPA group. There was no difference in the rates of sudden cardiac death. (Yokoyama, Origasa, et al., 2007)

In a study of 2,033 men who had recovered from heart attacks, researchers advised one group of men to eat more fish, but allowed them to take fish oil supplements instead of fish if they preferred. Two other groups were advised to decrease total fat consumption or to increase fiber intake. Over a two-year period, the fish and fish oil group had a 29 percent reduction in risk of death compared with the groups not advised to eat fish. The authors indicated that the fish and fish oils may have reduced mortality through their favorable effects on clotting mechanisms, platelet aggregation, and ventricular fibrillation. (Burr, Fehily, et al., 1989).

In postmenopausal women, supplementation with four g of EPA and DHA (2.4 g EPA plus 1.6 g DHA) reduced triglyceride levels by 26 percent. Reductions were similar in women using hormone replace therapy (HRT) and in those not using HRT. The researchers suggest that "this approach could potentially reduce the risk of coronary heart disease by 27 percent in postmenopausal women." (Stark, Park, et al., 2000)

COST-EFFECTIVENESS OF OMEGA-3 SUPPLEMENTATION

An analysis of the cost-effectiveness of omega-3 supplementation for secondary prevention, based on the results of clinical trials in subjects who had already experienced an MI or had otherwise been diagnosed with cardiovascular disease, concluded that "omega-3 supplements are likely to improve health and lower total costs." The authors suggest that "omega-3 supplementation should be considered an important and cost-effective option for prevention of secondary cardiovascular events." (Schmier, Rachman, et al., 2006)

HOW DO OMEGA-3 FATTY ACIDS PROTECT AGAINST CARDIOVASCULAR DISEASE?

Omega-3 fatty acids have been shown to impact several key risk factors related to heart disease. Dr. Alexander Leaf and coworkers at the Harvard Medical School and Massachusetts General Hospital in Boston have examined the effects of omega-3 fatty acids in preventing arrhythmia in heart cells and have suggested that omega-3s may prevent sudden cardiac death through this mechanism. (Leaf, 2007)

Long-chain omega-3 fatty acids can have an impact on the risk of atherosclerosis through numerous mechanisms. They not only lower triglycerides, but also decrease platelet aggregation, favor dilation of the blood vessels, and decrease the tendency to thrombosis. In a review article, Dr. Artemis Simopoulos of the Center for Genetics, Nutrition and Health lists 17 separate mechanisms by which omega-3 fatty acids may have these physiological effects. In clinical trials, beneficial effects have been attributed primarily to reducing arrhythmias and reducing thrombosis in the vessels. (Simopoulos, 1999)

WHAT OTHER BENEFITS DO OMEGA-3 FATTY ACIDS HAVE?

While there is an abundance of research on the cardiovascular benefits of omega-3 fatty acids, it should also be recalled that these substances are critical to many physiological functions. Maternal levels of omega-3 fatty acids during pregnancy determine the levels present in the developing infant. The long-chain omega-3 fatty acid DHA is particularly critical in supporting infant growth and development, and DHA levels in newborns are correlated with birth weight, birth length, and head circumference. It has been suggested that women and their infants may benefit if the mother is supplemented with DHA during pregnancy. The ratio of omega-3 to omega-6 fatty acids in the total diet is also important, and many scientists believe current diets in the United States are too low in omega-3 fatty acids, compared to the relatively high intakes of omega-6 fatty acids. (Hornstra, 2000)

Long-chain omega-3 fatty acids are present in breast milk and have been related to improved visual acuity and cognitive function in infants. (Birch, Garfield, et al., 2000) In many countries, including the United States, omega-3 fatty acids are added to infant formula.

In older adults, low blood levels of omega-3 fatty acids have been linked to cognitive impairment and dementia. (Conquer, Tierney, et al., 2000)

COST OF 500 to 600 mg OMEGA-3 EPA AND DHA

Long-chain omega-3 fatty acids are naturally found in fish, especially in fatty fish such as salmon, but also occur in smaller amounts in other types of fish

and seafood. These nutrients (EPA and DHA) are also available in dietary supplements. The following table shows relative costs, based on the amount of fish or supplements needed to provide roughly 500 or 600 mg of long-chain omega-3 fatty acids. The amount of omega-3 in fresh salmon is based on data provided on the website of the National Fisheries Institute, while the amounts in other products are based on information provided in nutrition labeling. Costs are based on prices in supermarkets or drug stores in the upper Midwest early in 2012.

COST OF 500 TO 600 mg EPA AND DHA

PRODUCT	COST
Brand A fish oil capsules, two capsules providing 600 mg EPA and DHA	$ 0.26
Brand B fish oil capsules, two capsules providing 600 mg EPA and DHA	$ 0.40
Canned red salmon, one ounce providing about 500 mg EPA and DHA	$ 0.53
Fresh salmon, one ounce providing about 600 mg EPA and DHA	$ 0.56
Canned tuna, eight ounces providing about 500 mg EPA and DHA	$ 3.27

Bottom Line

An abundance of scientific evidence suggests that most American diets are very low in long-chain omega-3 fatty acids EPA and DHA and that increasing intakes could potentially reduce the risk of cardiovascular disease. Eating more fish is an excellent way to increase the consumption of omega-3 fatty acids, but only a few varieties of fish are rich in these compounds. Another way to increase consumption is to use a dietary supplement providing these critical nutrients.

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