n−3 Fatty acid dietary recommendations and food sources to achieve essentiality and cardiovascular benefits[1–3]

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ABSTRACT

Dietary recommendations have been made for n−3 fatty acids, including α-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) to achieve nutrient adequacy and to prevent and treat cardiovascular disease. These recommendations are based on a large body of evidence from epidemiologic and controlled clinical studies. The n−3 fatty acid recommendation to achieve nutritional adequacy, defined as the amount necessary to prevent deficiency symptoms, is 0.6–1.2% of energy for ALA; up to 10% of this can be provided by EPA or DHA. To achieve recommended ALA intakes, food sources including flaxseed and flaxseed oil, walnuts and walnut oil, and canola oil are recommended. The evidence base supports a dietary recommendation of ≈500 mg/d of EPA and DHA for cardiovascular disease risk reduction. For treatment of existing cardiovascular disease, 1 g/d is recommended. These recommendations have been embraced by many health agencies worldwide. A dietary strategy for achieving the 500-mg/d recommendation is to consume 2 fish meals per week (preferably fatty fish). Foods enriched with EPA and DHA or fish oil supplements are a suitable alternate to achieve recommended intakes and may be necessary to achieve intakes of 1 g/d. *Am J Clin Nutr* 2006; 83(suppl):1526S–35S.

KEY WORDS Dietary recommendations, EPA, eicosapentaenoic acid, DHA, docosahexaenoic acid, cardiovascular disease, n−3 fatty acids, fish oil, fish intake

INTRODUCTION

Dietary guidance for n−3 fatty acids has progressed significantly in the past 5 y. Recommendations have been made both for α-linolenic acid (ALA) and eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). One focus has been on establishing the amount of the individual n−3 fatty acids needed to ensure nutrient adequacy and thereby prevent nutrient deficiency. An important principle in developing nutrient requirements is to define the clinical or disease benchmark to use. Frequently, this is defined as intake in the initial phases of the nutrient inadequacy. However, it is important to consider that nutrients must be viewed both in the context of preventing a nutrient inadequacy (as defined by the initial clinical lesion or symptom) and in the context of reducing the risk of chronic diseases. Therefore, nutrient requirements should be viewed from the perspective of the intake that is required to reduce disease risk rather than solely the amount that prevents nutrient inadequacy as defined historically by classic deficiency symptoms. In so doing, this different quantitative approach defines a requirement endpoint more broadly and includes chronic risk reduction. Implicit to this approach is that increasing the range to include the amount needed to reduce chronic disease risk will increase the recommended amount, with the associated benefit of reducing nutrient inadequacy.

The purpose of this article is to review current dietary recommendations for n−3 fatty acids that have been made in the United States and other countries. In addition, epidemiologic and controlled clinical trials or studies that have shown beneficial effects of n−3 fatty acids will be reviewed to summarize the intakes associated with cardiovascular disease (CVD) risk reduction. On this basis, in conjunction with existing recommendations for n−3 fatty acids, a new paradigm will be proposed for meeting these dietary recommendations through a food-based approach.

NUTRIENT REQUIREMENTS TO PREVENT DEFICIENCY

In humans, ALA is an essential fatty acid because it cannot be synthesized from saturated fatty acids, n−9 monounsaturated fatty acids, or n−6 polyunsaturated fatty acids (PUFAs). Humans lack the desaturase that inserts a double bond at the C-15 position of a fatty acid carbon chain. Evidence for the essentiality of n−3 fatty acids for humans was first observed in a 7-y-old girl maintained on a total parenteral nutrition formula that contained safflower oil (1). When the formula was changed by substituting soybean oil (a source of ALA) for safflower oil, the sensory neuropathy and visual problems that had been observed were reversed. Subsequent research established that resolution of the deficiency symptoms was due to ALA (2). In addition, further studies showed that dietary or intravenous ALA increases red blood cell and plasma phospholipid DHA in hospitalized patients who were previously fed a diet that was inadequate in n−3 fatty acids (1, 3, 4). Of note, an n−3 deficiency is not associated with skin lesions, which is a hallmark symptom of an n−6 deficiency (5). In addition to impaired visual acuity (6) and abnormal results

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on electroretinograms observed in animal studies (7, 8), n−3 deficiency is associated with learning deficiency (9, 10).

The discussion of the essentiality of ALA begs the question of whether it is ALA per se that is essential or the other fatty acids, EPA and DHA, which are derived from ALA. Interestingly, small amounts of EPA and DHA can reverse an n−3 fatty acid deficiency. As noted by Spector (11), EPA is a substrate for eicosanoid synthesis; however, no requirement has been shown for eicosanoids derived from EPA. DHA, however, is the most abundant n−3 fatty acid present in tissues, which has led to the conclusion that DHA is an essential n−3 fatty acid. Because of the multiple, unique metabolic functions of DHA, which are not replicated by other fatty acids, a prevailing view is that this is the essential n−3 fatty acid (11).

Recently, significant progress was made in terms of setting recommendations for n−3 fatty acids for the prevention and treatment of chronic disease, especially CVD. In 2002, the focus of the dietary recommendations for n−3 fatty acids was on establishing nutrient adequacy and preventing an essential fatty acid deficiency. Presently, the focus has shifted to a model for making dietary recommendations that feature the prevention and treatment of CVD. Impressive evidence from both epidemiologic and controlled clinical trials and studies forms the basis for these new recommendations. This evidence base is reviewed herein.

EVIDENCE OF CARDIOPROTECTIVE EFFECT OF n−3 FATTY ACIDS

Epidemiologic studies

Plant-derived n−3 fatty acids

Numerous epidemiologic studies have shown a beneficial association of ALA and CVD risk, including the National Heart, Lung, and Blood Institute Family Heart Study (12), the Nurses' Health Study (13), and the Health Professionals Follow-Up Study (14).

Djousse et al (12) assessed the diets of 4584 participants from The National Heart, Lung, and Blood Institute Family Heart Study by use of semiquantitative food-frequency questionnaire (FFQ) in a cross-sectional design. The mean intakes (g/d) from the lowest to the highest quintile were 0.53, 0.67, 0.78, 0.90, and 1.14 for men and 0.46, 0.58, 0.65, 0.76, and 0.96 for women. From the lowest to the highest quintile of ALA, the odds ratios for prevalence of coronary artery disease after multivariate adjustment were 1.0, 0.77, 0.61, 0.58, and 0.60 for men (P for trend = 0.012), and 1.0, 0.57, 0.52, 0.30, and 0.42 for women (P for trend = 0.014).

In a study conducted by Hu et al (13), intakes of ALA were assessed by use of an FFQ in 76 283 women without previously diagnosed cancer or CVD from the Nurses' Health Study. After multivariate adjustment, a higher intake of ALA was associated with a lower relative risk of fatal ischemic heart disease (IHD). The mean intakes (g/d) from the lowest to the highest quintiles were 0.71, 0.86, 0.98, 1.12, and 1.36, with relative risks for fatal coronary heart disease (CHD) after multivariate adjustment of 1.0, 0.99, 0.90, 0.67, and 0.55, respectively (P for trend = 0.01). For nonfatal myocardial infarction (MI), there was a nonsignificant trend toward a reduced risk when extreme quintiles were compared (relative risk: 0.85; 95% CI: 0.61, 1.19; P for trend = 0.50). In addition, a higher intake of oil and vinegar salad dressing, a good source of ALA, was associated with a reduced risk of fatal IHD when comparing those with intakes ≥5–6 times/wk with those who rarely consumed this food (relative risk: 0.46; 95% CI: 0.27, 0.76; P for trend = 0.001).

The Health Professionals Follow-Up Study, a study in 43 757 health professionals aged 40–75 y and free of diagnosed CVD or diabetes, reported that a 1% increase in ALA intake was associated with a 39% lower risk of MI after adjustment for nondietary risk factors and total fat intake (95% CI: 0.21, 0.80; $P < 0.01$) (14).

The Multiple Risk Factor Intervention Trial (15), a primary prevention study in 12 866 men at high risk of CHD on the basis of smoking status, diastolic blood pressure, and cholesterol concentrations, also gathered data on ALA (although this was not part of the intervention) and mortality. Mean ALA intakes were calculated from dietary recall interviews at baseline and at years 1, 2, and 3 of follow-up. The mean intakes (g/d) from the lowest to the highest quintiles were 0.87, 1.27, 1.58, 1.93, and 2.81 with multivariate-adjusted relative risks for all-cause mortality of 1.0, 0.94, 0.68, 0.86, and 0.67, respectively ($P = 0.0059$). CVD mortality also was significantly reduced with increasing intakes of ALA ($P = 0.0329$) (16). In addition, there was a significant inverse relation between fish consumption and CHD mortality in high-risk men ($P < 0.02$). Overall, these studies show that intakes of ALA ranging from 0.58 to 2.81 g/d are associated with a reduced risk of CVD all-cause mortality.

Marine-derived n−3 fatty acids

Many epidemiologic studies have also assessed the relation between marine-derived n−3 fatty acids, namely EPA and DHA, and CVD. Major studies showing a cardioprotective effect of EPA and DHA and fish intake on CVD risk in healthy subjects include the Nurses' Health Study (17), the Physicians' Health Study (18), the Cardiovascular Health Study (19), the Chicago Western Electric Study (20, 21), an ecologic study by Zhang et al (22), and, most recently, the Japan Public Health Center-Based Study Cohort I (23).

The Nurses' Health Study, a longitudinal study in 84 688 healthy women aged 34–59 y, used FFQs to assess dietary intake of n−3 fatty acids and fish consumption. Fish consumption was classified as <1 time/mo, 1-3 times/mo, 1 time/wk, 2-4 times/wk, and ≥5 times/wk. Compared with women who rarely consumed fish (<1 time/mo), the multivariate-adjusted relative risks for all CHD across quintiles (from lowest to highest) were 0.79, 0.71, 0.69, and 0.66 (P for trend = 0.001). A reduction in CHD risk also was reported with increasing intake of n−3 fatty acids. Median intakes of n−3 fatty acids (g/d) of 0.03, 0.05, 0.08, 0.14, and 0.24 were associated with relative risks of 1.0, 0.93, 0.78, 0.68, and 0.67, respectively ($P < 0.001$ for trend) (17).

In the Physicians' Health Study (18), a prospective cohort study in 20 551 healthy US male physicians aged 40–84 y, fish consumption assessed by semiquantitative FFQ was associated with a reduced risk of sudden cardiac death. Compared with individuals who consumed less than one serving of fish per month, relative risk for sudden cardiac death was 0.64 for those consuming fish 1-3 times/mo and 0.48 for those consuming fish ≥1 time/wk (P for trend = 0.03). Dietary fish consumption was not associated with a reduction in risk of total MI, nonsudden cardiac death, or total CVD mortality. However, there was a significant reduction in risk of total mortality with increasing

intake (<1 time/mo, 1-3 times/mo, and ≥1 time/wk), with relative risks of 1.0, 0.79, and 0.70, respectively (P for trend = 0.003).

In a nested case-control study of the Cardiovascular Health Study (19), a prospective study in 4775 men and women aged ≥65 y and free of CVD, fish consumption was assessed by FFQ and the relation between CHD and PUFA concentration of plasma phospholipids among cases of fatal IHD (n = 54) and cases of nonfatal MI (n = 125) was determined. Subjects who subsequently experienced an incident fatal IHD event had significantly lower baseline plasma phospholipid concentrations of combined EPA and DHA (P = 0.02) and higher concentrations of linoleic acid (LA) (P = 0.03) than did controls. The odds ratio for IHD death corresponding to an increase of 1 SD in plasma phospholipid fatty acid concentration for EPA + DHA and ALA over 4 y was 0.30 (95% CI: 0.12, 0.76; P = 0.01) and 0.48 (95% CI: 0.24, 0.96; P = 0.04), respectively. In contrast, the odds ratio for LA was 2.42 (95% CI: 1.07, 5.43; P = 0.03) (19). The results for nonfatal MI cases were nonsignificant. A subsequent study by Mozaffarian et al (24) showed that stroke mortality was reduced in individuals in the Cardiovascular Health Study who consumed fish ≥1 time/mo (P for trend = 0.06). Classification of stroke as either ischemic or hemorrhagic revealed a significant decrease in ischemic stroke ranging from 11–28% with fish consumption ≥1 time/mo compared with <1 time/mo (P for trend = 0.03); whereas there was no protection against hemorrhagic stroke (P = 0.63).

The Chicago Western Electric Study, a prospective study in 1847 healthy men aged 40–55 y, assessed the relation of fish consumption determined by diet history questionnaires on CVD endpoints at 30 y of follow-up. Across tertiles of mean fish consumption (g/d) of 1–17, 18–34, and ≥35, comparison of the highest versus lowest intake resulted in relative risks for fatal CVD, MI, all CHD, and all-cause mortality of 0.74 (P for trend = 0.01), 0.56 (P for trend = 0.02), 0.62 (P for trend = 0.04), and 0.85 (nonsignificant), respectively (20).

In addition to studies conducted in healthy subjects, the Honolulu Heart Program, a large prospective study among 8006 Japanese American male smokers aged 45–65 y, evaluated the relation of intake of fish assessed by FFQ on CVD in high-risk individuals. The relative risk for CHD mortality among heavy smokers (>30 cigarettes/d) with high fish intake (≥2 times/wk) was one-half that of those with low fish consumption (<2 times/wk) (relative risk = 0.5; 95% CI: 0.28, 0.91) (25).

In an ecologic study in individuals of varying health status aged 45–74 y, fish consumption was estimated on the basis of food balance sheets. Data were collected in 36 countries during periods from 1961 to 1991 by using Food and Agriculture Organization and World Health Organization data. Fish consumption (% of total energy) ranged from 0.23% to 10.43%, with a mean (±SD) of 1.53 ± 1.93%. After multivariate adjustment, there was a significant inverse correlation between fish intake and IHD in men during the periods of 1961–1963 (r = −0.4, P < 0.05), 1979–1981 (r = −0.39, P < 0.05), and 1989–1991 (r = −0.48, P < 0.01). A similar trend was observed among women with the relation being significant for 1961–1963 (r = −0.42, P < 0.01), 1979–1981 (r = −0.38, P < 0.05), and 1989–1991(r = −0.51, P < 0.01) (22). In addition, there was a significant inverse correlation between fish intake and stroke mortality in men and women during the period 1961–1963 (r = −0.34, P < 0.05, and r = −0.35, P < 0.05, respectively), and a significant inverse correlation between fish intake and all-cause mortality in men and women during 1961–1963 (r = −0.62, P < 0.001, and r = −0.6, P < 0.001, respectively), 1979–1981 (r = −0.54, P < 0.001, and r = −0.47, P < 0.01, respectively), and 1989–1991 (r = −0.54, P < 0.001, and r = −0.56, P < 0.001, respectively) (22).

Most recently, Iso et al (23) reported results from the Japan Public Health Center-Based Study Cohort I, in which >41 000 middle-aged Japanese subjects were followed for CHD outcomes over 10 y. In this population, the median intake of EPA+DHA was 900 mg/d, about 7 times that in the United States, and the highest quintile of intake was >2 g/d from 180 g fish. Even in this population, higher intakes of n−3 fatty acids were associated with reduced risk of MI (P for trend = 0.02). Compared with the lowest quintile of intake (300 mg EPA+DHA/d), the multivariable-adjusted hazard ratio for MI in the highest quintile was 0.43 (95% CI: 0.24, 0.78). These data suggest that higher intakes of n−3 fatty acids elicit even greater reductions in CHD risk.

Overall, epidemiologic evidence shows that consumption of as little as one serving of fish per month is associated with a reduced risk of CVD. The greatest reduction in risk found in these studies was associated with fish consumption ranging from 1 serving/wk up to ≥5 servings/wk.

Intervention studies

Plant-derived n−3 fatty acids

In the Lyon Diet Heart Study (26), a randomized controlled single-blinded secondary prevention study, a Mediterranean diet was compared with a National Cholesterol Education Program Step I diet in post-MI patients <70 y old. The study was designed to compare the effects of a Mediterranean-style diet, enriched with ALA (emphasizing more bread, root vegetables, green vegetables, and fish, less beef, lamb and pork replaced with poultry, daily fruit, and butter and cream replaced with margarine fortified with ALA) with those of a Step I diet on CVD endpoints. Patients who received the supplemented margarine, supplying 1.8 g ALA/d as part of a diet rich in fish, had significantly greater plasma concentrations of ALA than did control patients who received the placebo margarine, which supplied 0.67 g ALA/d (P < 0.001). After 46 mo, the relative risk for cardiac death and all-cause mortality in the experimental group versus the control group was 0.35 (95% CI: 0.15, 0.83; P = 0.01) and 0.44 (95% CI: 0.21–0.94; P = 0.03), respectively. In addition, the rate of nonfatal MI for the experimental and control groups was 0.83 and 2.7, respectively.

With regard to ALA, whereas the cardiovascular epidemiologic studies have been strongly supportive of benefit, there are disturbing findings from similar population studies in which higher intakes of ALA were linked to an increased risk of prostate cancer (27). Although no randomized controlled trials have examined the issue, and no mechanisms of action have been proposed, further research is warranted before firm recommendations can be made to increase ALA intakes beyond current levels.

Marine-derived n−3 fatty acids

Two major secondary prevention intervention studies found a cardioprotective effect of EPA and DHA and fish consumption—the Diet and Reinfarction Trial (28) and the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico

(GISSI) Prevention Study (29). In addition to the Diet and Reinfarction Trial and GISSI studies, the Japan EPA Lipid Intervention Study (30) analyzed the effects of highly purified EPA on cardiovascular endpoints in a population of varying health status.

In the Diet and Reinfarction Trial (28), male MI survivors who received fish oil capsules containing 900 mg/d of EPA and DHA or 200–400 g fatty fish/wk, providing an additional 500–800 mg/d of n−3 fatty acids, had a 29% reduction in all-cause mortality over a 2-y period.

In the GISSI Prevention Study (29), subjects with preexisting CHD randomly assigned to the EPA + DHA supplement group (850–882 mg EPA + DHA as ethyl esters) with and without 300 mg vitamin E per day, experienced a 15% reduction in the primary endpoint of death, nonfatal MI, and nonfatal stroke after 42 mo ($P < 0.05$). In addition, all-cause mortality and sudden death were reduced by 21% ($P < 0.01$) and 45% ($P < 0.001$), respectively, compared with the control group (vitamin E provided no benefit).

The Japan EPA Lipid Intervention Study, a prospective, randomized, controlled study of 18 645 Japanese of varying health status, examined whether the long-term use of highly purified EPA in addition to a statin is effective in preventing cardiovascular events (30). Subjects were randomly assigned to 10 mg pravastatin/d or 5 mg simvastatin/d or the same statin doses plus 1800 mg highly purified EPA/d. After >4.5 y of follow-up, the risk of major coronary events, including sudden cardiac death, heart attack, unstable angina, angioplasty or stenting, or coronary artery bypass surgery, was lower by 19% in the EPA group than in the statin-only group (31). There was a similar trend in individuals with no history of coronary artery disease ($n = 14\,981$; 18% reduction in risk), although this trend was not significant. As with the epidemiologic study by Iso et al (23), the Japan EPA Lipid Intervention Study suggests that increasing n−3 fatty acid intakes are even more beneficial.

A recent meta-analysis of randomized controlled trials in patients with CHD showed a cardioprotective effect of n−3 fatty acids in studies of both dietary intake and supplements (0.3–0.6 g EPA/d, 0.6–3.7 g DHA/d). The relative risks of fatal MI, sudden cardiac death, and all-cause mortality were 0.7 (95% CI: 0.6, 0.8; $P < 0.001$), 0.7 (95% CI: 0.6, 0.9; $P < 0.01$), and 0.8 (95% CI: 0.7, 0.9; $P < 0.001$), respectively (32). There was no significant difference between the effects of dietary and nondietary interventions of n−3 fatty acids for all endpoints.

Although some studies have not shown a beneficial association of n−3 fatty acids and CVD risk for reasons that are not clear (33–39), most epidemiologic studies and randomized controlled trials have provided strong evidence of a cardioprotective effect of n−3 fatty acids, as reviewed in this section. On the basis of these findings, dietary recommendations have been made for the prevention of CVD.

SPECIAL POPULATIONS

Two studies have examined the effects of EPA and DHA in patients with implantable cardioverter defibrillators (40, 41). Both tested the hypothesis that n−3 fatty acids would protect against ventricular arrhythmias. Raitt et al (40) found no overall benefit of n−3 fatty acids on time to the first implantable cardioverter defibrillator therapeutic discharge, and in a subset of patients who had a history of ventricular tachycardia or fibrillation, the time to first discharge was actually shortened by n−3 supplementation. Total deaths, however, tended to be fewer in the n−3 group (4 versus 10; $P = 0.16$). On the other hand, Leaf et al (41) found a beneficial effect of n−3 fatty acids on a combined endpoint of time to discharge or death. The latter study provided twice as much n−3 fatty acids (2.6 g of EPA and DHA compared with 1.3 g) and included twice as many patients (402 compared with 200), and the patients were much less likely to have significant heart failure. These factors (and probably others) may explain the divergent results of these 2 studies. Raitt et al suggested that patients at risk of arrhythmic events because of myocardial scar-based re-entry may not benefit from n−3 fatty acids, whereas those at risk because of myocardial ischemia may benefit. At present, firm dietary recommendations for patients with implantable cardioverter defibrillators must await the results of other ongoing studies.

DIETARY RECOMMENDATIONS FOR n−3 FATTY ACIDS AND FOOD SOURCES

Dietary recommendations for n−3 fatty acids (including ALA, EPA, and DHA) have been set to achieve a nutrient adequacy that results in the prevention of an n−3 fatty acid deficiency. In addition, the more recent recommendations have been made to prevent and treat CVD. During the evolution of recommendations for n−3 fatty acids, guidelines for EPA and DHA have been at the forefront.

DIETARY REFERENCE INTAKES FOR MACRONUTRIENTS, 2002

Dietary Reference Intakes (DRIs) for macronutrients were set by the Institute of Medicine of the National Academies in 2002. An Adequate Intake (AI, an intake associated with a low prevalence of inadequacy) and an Acceptable Macronutrient Distribution Range (AMDR) were set for n−3 fatty acids. An AI was set for ALA as 1.6 g/d for men and 1.1 g/d for women aged 19–50 y (42). In addition, up to 10% of the AI for ALA can be provided by EPA or DHA. A dietary requirement could not be set for n−3 fatty acids because of insufficient information for healthy individuals to establish an estimated average requirement (EAR, the intake below which 50% of normal individuals show signs of deficiency), which is the basis for a recommended dietary allowance (RDA). Thus, an AI for n−3 fatty acids was set and was based on the observed median intake in the United States at which no nutrient deficiency is present. The DRI report also established an AMDR for n−3 fatty acids of 0.6–1.2% of energy (42). The AMDR is defined as a range of intake for a particular energy source that is associated with reduced risk of chronic disease while providing adequate intakes of essential nutrients. The lower range of the AMDR for ALA represents the AI. The upper boundary of the AMDR range corresponds to the highest ALA intake from foods consumed by individuals in the United States and Canada. The DRI report also noted that intakes of n−3 fatty acids above the AI confer health benefits, especially with respect to CVD. However, recommendations were not made for a greater intake for the prevention of CVD because of the lack of a robust database at the time of the report.

TABLE 1
International recommendations for long-chain n−3 fatty acids[1]

Source and reference	Date	Recommendation			n−6:n−3
		Total n−3	ALA	EPA + DHA	
		% of energy	*g*	*mg*	
NATO workshop (44, 45)	1989	—	3	800	4:1
UK Committee on Medical Aspects of Food Policy (46)	1994	0.2	—	100–200	—
ISSFAL workshop (47)	1999	1	2.2	650	—
ANC (France) (48)	2001	0.8–1	1.8	450 (DHA, 110–120)	5:1
Eurodiet (49)	2000	—	2	200	—
Health Council of the Netherlands (50)	2001	1	—	200	7.5:1
American Heart Association (51)	2002	—	—	≈1 g/d (2° prev CHD)	—
US National Academics of Science, Institute of Medicine (42)	2002	—	1.4	≈140	—
European Society of Cardiology (52)	2003	—	—	≈1 g/d (2° prev CHD)	—
WHO FAO (53)	2003	1–2	—	400–1000 (1–2 fish meals/wk)	—
ISSFAL (54)	2004	—	1.6	≥500	
UK Scientific Advisory Committee on Nutrition (55)	2004	—	—	Minimum 2 portions fish/wk (1 oily); assumes 450 mg	

[1] ALA, α-linolenic acid; ANC, Apports Nutritionnels Conseilles; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FAO, Food and Agriculture Organization; ISSFAL, International Society for the Study of Fatty Acids and Lipids; NATO, North Atlantic Treaty Organization; WHO, World Health Organization.

DIETARY RECOMMENDATIONS FOR FISH AND EPA AND DHA

The *Dietary Guidelines for Americans 2005* report states, "Evidence suggests consuming approximately two servings of fish per week (approximately 227 g; 8 ounces total) may reduce the risk of mortality from CHD and that consuming EPA and DHA may reduce the risk of mortality from CVD in people who have already experienced a cardiac event" (43). Other national, international, and professional organizations have made recommendations for fish or EPA and DHA consumption (**Table 1**). It is evident that several health agencies worldwide recognize the importance of increasing EPA and DHA intake from fish to decrease the risk of CVD. Because n−3 fatty acid intake in the United States is appreciably lower than recommended, it is important that strategies be implemented to increase consumption.

CURRENT INTAKE OF n−3 FATTY ACIDS

Based on dietary estimates for fats and fatty acids from the National Health and Nutrition Examination Survey (NHANES), 1999–2000, for the US population (**Table 2**), the mean PUFA intake for men is 20.0 g/d and that for women is 16 g/d (ages 20–59 y) (56), primarily from LA. For LA, the mean intake for men is 17.9 g/d and that for women is 13.5 g/d (ages 20–59 y) (56). In contrast, the mean intake of ALA is 1.7 g/d for men and 1.3 g/d for women (ages 20–59 y) (56). For EPA + DPA + DHA, the mean intake for men is 0.17 g/d and that for women is 0.11 g/d (ages 20 to 59 y) (56). According to data from the 1994–1996 Continuing Survey of Food Intakes by Individuals (CSFII; **Table 3**), grain products, meat, poultry, and fish account for most ALA intake in men and women over the age of 20 y (57). Meat, poultry, and fish contribute all of the EPA and DHA in women's diets and account for most of the intake in men. Eggs also contribute to DHA intake in men (57). CSFII data from 1994–1996 and 1998 indicate that the mean intake of finfish, the primary source of EPA and DHA in the diet, for all individuals in the United States is 9.1 g/d (2.2 oz/wk; <1 serving), with the 50th percentile at 0 g/d and the 90th percentile at 34.83 g/d (8.6 oz/wk; 2.9 servings) (58). Mean shellfish intake for all individuals in the United States, as indicated by CSFII data from 1994–1996 and 1998, is

TABLE 2
Dietary intake of polyunsaturated fatty acids (PUFAs) by sex and age: United States, 1999–2000[1]

Sex and age	Total PUFAs	18:2 (linoleic)	18:3 (linolenic)	18:4 (octadecatetraenoic)	20:4 (arachidonic)	20:5 (EPA)	22:5 (DPA)	22:6 (DHA)
				g				
Men								
20–39 y (n = 635)	20 ± 0.6	18.0 ± 0.57	1.7 ± 0.06	0.005 ± 0.0013[2]	0.18 ± 0.006	0.04 ± 0.005	0.02 ± 0.002	0.07 ± 0.006
40–59 y (n = 577)	20 ± 0.7	17.8 ± 0.66	1.7 ± 0.07	0.007 ± 0.0016[2]	0.18 ± 0.009	0.06 ± 0.009	0.02 ± 0.003	0.09 ± 0.009
≥60 y (n = 767)	16 ± 0.6	14.3 ± 0.58	1.4 ± 0.06	0.004 ± 0.0007[2]	0.13 ± 0.007	0.04 ± 0.005	0.02 ± 0.002	0.07 ± 0.004
Women								
20–39 y (n = 849)	16 ± 0.5	13.9 ± 0.46	1.3 ± 0.05	0.003 ± 0.0006[2]	0.12 ± 0.004	0.03 ± 0.004	0.01 ± 0.001	0.06 ± 0.006
40–59 y (n = 641)	15 ± 0.5	13.2 ± 0.47	1.3 ± 0.05	—[3]	0.11 ± 0.005	0.04 ± 0.008[2]	0.01 ± 0.002	0.07 ± 0.012
≥60 y (n = 770)	13 ± 0.4	11.3 ± 0.36	1.2 ± 0.04	0.005 ± 0.0010[2]	0.10 ± 0.004	0.03 ± 0.004	0.01 ± 0.001	0.06 ± 0.005

[1] All values are $\bar{x}$ ± SE. Adapted from reference 56. EPA, eicosapentaenoic acid; DPA, docosapentaenoic acid; DHA, docosahexaenoic acid.
[2] Means and SEs have a relative standard error >20% but <30%. These estimates may be unreliable and should be interpreted with caution.
[3] Means and SEs have a relative standard error ≥30%. These estimates are considered to be highly unreliable and are not shown.

TABLE 3
Polyunsaturated fatty acids from selected food groups: mean intakes for adults aged ≥20 y, Continuing Survey of Food Intakes by Individuals, 1994–1996[1]

Subjects and food groups	18:3 (ALA)	20:5 (EPA)	22:6 (DHA)
		g	
Men (n = 5056)			
Grain products	0.41	—[2]	—[2]
Vegetables	0.23	—[2]	—[2]
Fruit	0.03	0[3]	0[3]
Milk and milk products	0.14	0[3]	—[2]
Meat, poultry, fish	0.38	0.04	0.07
Eggs	0.03	—[2]	0.01
Legumes	0.04	0	0[3]
Fats and oil	0.34	0	0
Nuts and seeds	0.01	0	0
Women (n = 4816)			
Grain products	0.29	—[2]	—[2]
Vegetables	0.17	—[2]	—[2]
Fruit	0.03	0	0
Milk and milk products	0.10	0[3]	—[2]
Meat, poultry, fish	0.23	0.03	0.05
Eggs	0.02	—[2]	—[2]
Legumes	0.03	0	0[3]
Fats and oil	0.28	0	0[3]
Nuts and seeds	0.01	0	0

[1] Adapted from reference 57. ALA, α-linolenic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid.
[2] Value <0.005 and >0.
[3] Statistic is potentially unreliable because of small sample size or large CV.

3.7 g/d (0.9 oz/wk; 1/3 serving), with the 50th and 90th percentiles at 0 g/d (58). More recent data from NHANES 1999–2000 show that the mean intake of fish is 83 g/d (2.9 oz/wk) (43). Most fish consumed (63%) is finfish and shellfish that contain <500 mg of n−3 fatty acids per 85 g (3 oz) serving. The most commonly consumed fish is tuna (representing 22% of total fish consumption), with shrimp (16%), salmon (9%), mixed fish (8%), and crab (7%) also regularly reported (43).

On the basis of the data for mean finfish intake (≈2.2 oz/wk, or ≈1 serving; 58) and the most commonly consumed finfish (tuna; 43), persons who are consuming only finfish would have EPA and DHA intakes of 77 mg/d. Persons consuming only shellfish would have EPA and DHA intakes of 11 mg/d on the basis of data for mean shellfish intake (≈0.9 oz/wk, or 1/3 serving; 58) and the most commonly consumed shellfish (shrimp; 43). However, most persons consume a combination of finfish and shellfish. For example, persons consuming the mean weekly intakes for both finfish and shellfish would have daily EPA and DHA intakes of 88 mg/d (on the basis of the EPA and DHA content of tuna and shrimp).

To put these data in context, dietary information was collected by 24-h recalls on 2 d for CSFII and 1 d for NHANES 1999–2000, which subsequently captures a mean daily intake of fish. These data may underestimate the actual consumption of fish in the United States, however, because fish is not commonly consumed on a daily basis. Therefore, more persons (>50%) may consume fish than represented by these data. Furthermore, persons may meet the recommendation for 2 servings of fish per week from one meal, because portions are often larger than 1 serving (3 oz). However, if they are meeting the recommendation for 2 servings/wk by consuming the most common finfish and shellfish, they are not meeting the most recent recommendations, which range from 400 to 1000 mg of EPA and DHA/d (53–55, 59).

TABLE 4
α-Linolenic acid (ALA) content of selected oils, seeds, and nuts and amounts needed to meet adequate intakes[1]

Source of ALA	ALA	Amount needed by men to meet recommendation (1.6 g ALA/d)	Amount needed by women to meet recommendation (1.1 g ALA/d)
	g/tbsp	*tbsp*	*tbsp*
Pumpkin seeds	0.051	31.4	21.6
Olive oil	0.103	15.5	10.7
Walnuts, black	0.156	10.3	7.05
Soybean oil	1.231	1.3	0.89
Rapeseed oil	1.302	1.2	0.84
Walnut oil	1.414	1.1	0.78
Flaxseeds	2.350	0.68	0.47
Walnuts, English	2.574	0.62	0.43
Flaxseed oil	7.249	0.22	0.15

[1] From reference 60. 1 tbsp oil = 13.6 g; 1 tbsp seeds or nuts = 28.35 g.

n−3 FATTY ACID–RICH FOODS

Plant-based foods, such as oils, nuts, and seeds, are rich sources of ALA; whereas fish is the primary food source of EPA and DHA. Dietary sources of ALA include flaxseeds and flaxseed oil, walnuts and walnut oil, soybeans and soybean oil, pumpkin seeds, rapeseed (canola) oil, and olive oil. In addition to providing ALA, these foods are good sources of a variety of nutrients, such as fiber, monounsaturated fatty acids, vitamins, and minerals. The intake of various oils needed to meet current recommendations of ALA for women and men varies from 2.2–3.2 mL/d (0.15–0.22 tablespoons/d) of flaxseed oil to 158–229 mL/d (10.7–15.5 tablespoons/d) of olive oil (60). The intake of various nuts and seeds needed to meet current recommendations of ALA for women and men varies from 12.2–17.6 g/d (0.43–0.62 oz/d) of English walnuts to 4.8–7.0 g/d (0.17–0.25 oz/d) of flaxseeds to 612–890 g/d (21.6–31.4 oz/d) of pumpkin seeds (60). The intake of food sources lower in ALA, such as olive oil or pumpkin seeds, alone to meet current recommendations is impractical because of the calories associated with the amounts needed to meet current recommendations. Therefore, a combination of oils, nuts, seeds, and other foods rich in ALA, such as leafy greens (ie, 1 cup of kale contains 0.121 g ALA, ≈25% of total fat from ALA), is optimal. ALA content of selected oils, seeds, and nuts and the amount of each needed to reach the AI levels for men and women are shown in **Table 4**.

In addition to being an excellent source of the marine-derived n−3 fatty acids, fish is a good source of protein, B vitamins, and minerals, such as potassium, phosphorous, and selenium. The n−3 fatty acid content of fish, specifically EPA and DHA, varies by species and by how the fish are raised (ie, wild or farm-raised). EPA and DHA ranges from as low as 0.134 g/85 g for cod (3-oz serving) to as much as 1.825 g/85 g for salmon (3-oz serving) (60). Furthermore, Pacific cod is lower in saturated fatty acids (SFAs) than is Atlantic cod (0.88 g/85 g compared with 0.143 g/85 g, respectively), but higher in EPA and DHA (0.235 g/85 g compared with 0.134 g/85 g, respectively) (60). In contrast,

TABLE 5
Top finfish and shellfish consumed in the United States and eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) content[1]

Fish	EPA + DHA	Amount needed to get 500 mg EPA + DHA/d[2]	Amount needed to get 500 mg EPA + DHA/d[2]	Mean mercury concentration
	mg/serving	*serving*	*servings/wk*	*ppm*
Cod	134	3.7	25.9	0.11
Catfish	151	3.3	23.1	0.05
Haddock	203	2.5	17.5	0.03
Clams	241	2.1	14.7	ND
Shrimp	267	1.9	13.3	ND
Flounder	426	1.2	8.4	0.05
Pollock	460	1.1	7.7	0.06
Flatfish	498	1	7	0.05
Tuna, canned	733	0.68	4.8	0.12 (light); 0.35 (Albacore)
Salmon	1825	0.27	1.9	0.01

[1] From references 58 and 60. ND, mercury concentration below the level of detection (0.01 ppm).
[2] 1 serving = 85 g (3 oz) cooked portions.

Greenland halibut is higher in SFAs (2.637 g/85 g compared with 0.354 g/85 g, respectively) and EPA and DHA (1.001 g/85 g compared with 0.395 g/85 g) than are Atlantic or Pacific halibut (60). The total EPA and DHA content of the most commonly eaten fish and shellfish in the United States is shown in **Table 5**.

Farm-raised and wild fish of the same species are comparable in total amounts of EPA and DHA. The total amount of PUFAs in farm-raised fish is higher than in wild fish of the same species; this difference is attributed to higher n−6 fatty acid concentrations. In addition, farm-raised fish is higher in SFAs. The SFA content of farm-raised and wild catfish is 1.521 g SFA/85 g and 0.632 g SFA/85 g, respectively (60). The total amount of PUFAs is 1.183 g/85 g and 0.541 g/85 g for farm-raised and wild catfish, respectively, with EPA and DHA amounts of 0.151 g/85 g and 0.201 g/85 g, respectively (60). Furthermore, farm-raised Atlantic salmon has 2.128 g SFA/85 g and 1.825 g EPA+DHA/85 g; whereas wild Atlantic salmon has 1.068 g SFA/85 g and 1.564 g EPA+DHA/85 g, respectively (60). The SFA, EPA, and DHA contents of common wild and farm-raised fish are shown in **Table 6**.

CHALLENGES IN MEETING THE RECOMMENDATIONS

One of the main considerations when trying to meet current recommendations for n−3 fatty acids is that current intake of PUFAs consists primarily of n−6 fatty acids. The competition for desaturases and elongases in n−3 and n−6 PUFA metabolism results in inverse affects on tissue concentrations of these fatty acids (reviewed in reference 62). Therefore, this would be a concern for those consuming a typical Western diet, which is characterized by foods high in refined carbohydrates, saturated and *trans* fatty acids, and vegetable oils high in n−6 fatty acids that contain little n−3 fatty acids (63). This is of even greater concern in vegetarians and vegans, who have relatively high intakes of LA combined with low intakes of EPA and DHA (64). Cross-sectional data collected in this population indicate that plasma DHA concentrations are lower but stable compared with those in nonvegetarians and are inversely correlated with plasma LA. This illustrates the inverse relation between n−3 and n−6

TABLE 6
Saturated fatty acid (SFA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) contents of 85 g (3 oz) cooked wild and farm-raised fish of various species[1]

Fish species and raising method	Energy	SFA	Total PUFAs	18:2n−6 (linoleic)	18:3n−3 (ALA)	20:5n−3 (EPA)	22:6n−3 (DHA)	EPA + DHA
	kcal	*g/85 g*	*g/85 g*	*g/85 g*	*g/85 g*	*g/85 g*	*g/85 g*	*g/85 g*
Catfish, channel								
Wild	89	0.632	0.541	0.121	*0.082*	*0.085*	*0.116*	*0.201*
Farm	*129*	*1.521*	*1.183*	*0.875*	0.07	0.042	0.109	0.151
Trout, rainbow								
Wild	128	1.376	1.556	0.245	*0.159*	*0.398*	0.442	0.84
Farm	*144*	*1.789*	*1.981*	*0.807*	0.07	0.284	*0.697*	*0.981*
Salmon, coho								
Wild	118	0.896	1.082	0.048	0.047	0.341	0.559	0.9
Farm	*151*	*1.652*	*1.669*	*0.317*	*0.065*	*0.347*	*0.740*	*1.087*
Salmon, Atlantic								
Wild	155	1.068	2.768	0.187	*0.321*	0.349	1.215	1.564
Farm	*175*	*2.128*	*3.762*	*0.566*	0.096	*0.587*	*1.238*	*1.825*

[1] From references 60 and 61. Higher amounts for each species are italicized.

fatty acids and the particular concern for vegetarians and vegans in attaining n−3 fatty acid recommendations (65).

Another consideration for meeting recommendations for marine-derived n−3 fatty acids is that some populations do not consume fish because of concerns about environmental toxins, taste preferences, or ethical reasons. Studies have shown that certain fish contain high levels of environmental toxins, such as mercury and polychlorinated biphenyls (PCBs) (66, 67). Therefore, one challenge faced when increasing dietary fish intake is methylmercury, a heavy metal toxin found in varying amounts in different types of fish. Of particular importance is the neurologic damage to developing fetuses and young children caused by toxic levels of methylmercury. In response to these concerns, the Food and Drug Administration and the Environmental Protection Agency issued a joint advisory in March 2004 for women who are pregnant or might become pregnant, nursing mothers, and young children (68). Three recommendations made in the advisory, such that these women and young children can benefit from n−3 fatty acid intake while minimizing their exposure to mercury are

1) Do not eat shark, swordfish, king mackerel, or tilefish because they contain high levels of mercury.

2) Eat up to 340 g (12 oz)/wk (2 average meals) of a variety of fish and shellfish that are lower in mercury, such as shrimp, canned light tuna, salmon, pollock, and catfish. Furthermore, albacore (white) tuna has more mercury than canned light tuna. So, when choosing your 2 meals of fish and shellfish, you may eat up to 170 g (6oz)/wk (1 average meal) of albacore tuna.

3) Check local advisories about the safety of fish caught by family and friends in your local lakes, rivers, and coastal areas. If no advice is available, eat up to 170 g (6 oz)/wk (one average meal) of fish you catch from local waters, but do not consume any other fish during that week (68).

In addition to mercury, PCBs, which were reported to be higher in farm-raised than in wild salmon (69, 70), are another concern for persons who consume fish. Hites et al (69, 71) found median PCB concentrations of 42 ppb in farmed and 3 ppb in wild salmon (including the skin in the analysis). To put these amounts in context, the FDA limit for PCBs in foods is 2000 ppb (72); thus, neither presents a significant risk. Preparation methods, such as cooking the fish and removing its skin, reduces the amount of environmental toxins in the fish (73). New research is focusing on assessing amounts of PCBs in other species of fish besides salmon, determining ways to minimize contaminants in farm-raised fish, and establishing consistent methods for consumption advice. Because of the varying amounts of mercury and PCBs in fish, consumption of a variety of fish species, both wild and farmed, is recommended to minimize exposure to environmental toxins while maximizing health benefits.

Another challenge in meeting n−3 fatty acid recommendations is that some persons do not enjoy the taste of fish; whereas some vegetarians, such as vegans, do not consume any animal products, including fish. Because only a small amount of ALA can be converted to DHA and a minimal amount is converted to EPA, other options need to be utilized by vegetarians and persons who do not eat fish. One dietary option for increasing dietary intake of EPA is seaweed, which is incorporated into dishes growing in popularity, such as sushi. Kelp, laver, and wakame are types of seaweed that range in EPA content from 0.004 to 0.186 g per 100-g portion (60).

Another option for increasing the intake of EPA and DHA for persons who do not consume fish is DHA-rich microalgae supplementation or fish oil supplementation. DHA-rich microalgae, which is available in supplement form, provides 10–40% DHA by dry weight (64). When supplementing with DHA-rich microalgae capsules, a direct DHA source, 100–300 mg/d is suggested. Fish oil capsules vary widely in amounts of EPA and DHA, with the most common fish oil capsules currently in the US providing 180 mg EPA and 120 mg DHA per capsule (51). A recent review suggests that an EPA-to-DHA ratio in fish oil capsules between 2:1 and 1:2 appears optimal. The reasons for this recommendation are the apparent synergistic relation of EPA and DHA and that substantial evidence to suggest that either one is the principal bioactive fatty acid is currently lacking (74). Studies have also shown that several over-the-counter brands of fish oil supplements contain negligible amounts of mercury (75); whereas PCBs are below the limit of detection (76). Thus, persons concerned with environmental toxins from fish may also opt for fish oil supplementation. The American Heart Association recommends ≈1 g EPA+DHA/d for patients with known CHD (51). For persons without CHD, the American Heart Association recommends the consumption of 2, preferably oily, fish meals per week (51), which would provide 400–500 mg EPA+DHA/d. For persons who do not consume fish, this intake could be relatively easily achieved with capsules.

In addition to supplements of marine-derived fatty acids and seaweed, other important dietary options for persons who do not consume fish are continually being developed. These dietary options include a variety of n−3-enriched food products.

n−3 FATTY ACID–RICH FOODS OF THE FUTURE

The extensive evidence of the health benefits of n−3 fatty acids (74, 77–79) has prompted the development of food products enriched in these fatty acids. Genetic modification has been used to develop a new generation of plants (eg, corn and soybeans) that produce seeds that have a modified fatty acid profile. Strategies are available to increase (80) or decrease (81, 82) specific fatty acids in the target plant. Research is ongoing to increase the n−3 fatty acid content of animal products, such as eggs (83, 84), milk (85), and cuts of meat (84, 86, 87) by altering the composition of animal feed (88). The n−3 fatty acid content of animal feed is increased with the addition of fishmeal, flax, and n−3 fatty acids (88). New n−3 fatty acid–enriched products include oils, bakery products, eggs, mayonnaise, margarines, salad dressings, pasta, milk, meat, and poultry (88). Consequently, the evolving marketplace will help individuals meet fatty acid recommendations in a way that could not be envisioned 25 y ago. Thus, it will be far easier for individuals to meet the contemporary recommendations for n−3 fatty acids than in the past.

SUMMARY

Epidemiologic and controlled clinical trial studies have shown beneficial effects of n−3 fatty acid consumption, both marine- and plant-derived, on CVD. Cardioprotective benefits have been associated with intakes of ALA as low as 0.58 g/d, and potentially greater benefits are achievable with intakes up to 2.81 g ALA/d. On the other hand, protection from cardiovascular events from

marine-derived n−3 fatty acids has been reported with consumption of as little as one serving of fish per month, with even greater benefits achievable with intakes up to ≥5 servings/wk. Because of these cardiovascular health benefits, recent dietary recommendations have been made for ALA, EPA, and DHA, and for fish, to decrease the risk of CVD. The challenge looming ahead is to devise strategies that are effective on a population-wide basis that increase consumption of these important bioactive fatty acids. These strategies will span the spectrum from increasing fish consumption to using other means such as n−3 fatty acid–fortified foods and fish oil supplements. It is clear that a modest increase in intake can have important and beneficial public health outcomes.

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