Fish and n−3 fatty acids for the prevention of fatal coronary heart disease and sudden cardiac death[1–4]

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ABSTRACT

Large observational studies, randomized clinical trials, and experimental studies have evaluated the effects of fish and n−3 fatty acid consumption on fatal coronary heart disease (CHD) and sudden cardiac death (SCD), clinically defined events that most often share the final common pathway of fatal ventricular arrhythmia. These different study designs, each having complementary strengths and limitations, provide strong concordant evidence that modest consumption of fish or fish oil (1–2 servings/wk of oily fish, or ~250 mg/d of EPA+DHA) substantially reduces the risk of CHD death and SCD. Pooled analysis of prospective cohort studies and randomized clinical trials demonstrates the magnitude and dose-response of this effect, with 36% lower risk of CHD death comparing 0 and 250 mg/d of EPA+DHA consumption ($P < 0.001$), but then little additional benefit with higher intakes. Reductions in risk are even larger in observational studies utilizing tissue biomarkers of n−3 fatty acids that more accurately measure dietary consumption. The concordance of findings from different studies also suggests that effects of fish or fish oil on CHD death and SCD do not vary depending on presence or absence of established CHD. The strength and consistency of the evidence, and the magnitude of this effect are each notable. Because more than one-half of all CHD deaths and two-thirds of SCD occur among individuals without recognized heart disease, modest consumption of fish or fish oil, together with smoking cessation and regular moderate physical activity, should be among the first-line treatments for prevention of CHD death and SCD. *Am J Clin Nutr* 2008;87(suppl):1991S–6S.

"Our food should be our medicine, and our medicine should be our food." - Hippocrates 431 BC

INTRODUCTION

In the traditional diet-heart paradigm, consumption of total fat, saturated fat, and dietary cholesterol raises blood total and LDL cholesterol levels, thereby causing coronary heart disease (CHD) (1). This paradigm, based largely on observations in ecologic (cross-population) studies and basic metabolic experiments, has proven to be grossly oversimplified. A wide range of dietary factors influence cardiovascular risk, including specific fatty acids (eg, n−3 fatty acids, *trans* fatty acids, and other specific saturated, polyunsaturated, and monounsaturated fatty acids); carbohydrate quantity, type, and quality; intakes of legumes, nuts, fruits, and vegetables; alcohol; micronutrients; food processing; and food preparation methods. Furthermore, the impact of diet on disease risk cannot be judged solely by effects on total and LDL cholesterol levels, as dietary habits also affect numerous other intermediary risk factors, including other circulating lipoproteins, vascular hemodynamics, inflammation, endothelial function, insulin sensitivity, satiety and weight gain, coagulation and thrombosis, and arrhythmic risk. Dietary habits and intermediary risk factors also do not cause CHD as one monolithic outcome, but differently impact a broad range of diverse cardiovascular phenotypes, including chronic progression of atherosclerosis, plaque instability and acute rupture, cardiac arrhythmias including ventricular fibrillation and sudden cardiac death, congestive heart failure, stroke and cognitive decline, and peripheral arterial disease. Finally, effects of dietary factors on intermediary risk factors and of intermediary risks on clinical outcomes may vary depending on underlying individual susceptibility because of potential modifying factors such as sex, physical activity, underlying insulin sensitivity, or genetic variation. Thus, understanding the effects of dietary habits on cardiovascular risk requires integration of these complex interrelationships (**Figure 1**). Whereas ecologic and basic metabolic studies are useful for hypothesis-generation, the impact of specific dietary factors on disease risk should be established from careful assessment of evidence from individual-level (cohort or case-control) observational studies, randomized clinical trials, and experimental studies, with causality and magnitudes of effect best established by concordance between these studies given the complementary strengths and limitations of each design. Utilization of these principles elucidates the role of fish and n−3 fatty acids for the prevention of CHD death and sudden cardiac death (SCD).

OBSERVATIONAL STUDIES

Landmark ecologic studies demonstrated low rates of CHD death among Greenland Eskimos, which appeared related to high consumption of marine n−3 fatty acids, eicosapentaenoic acid

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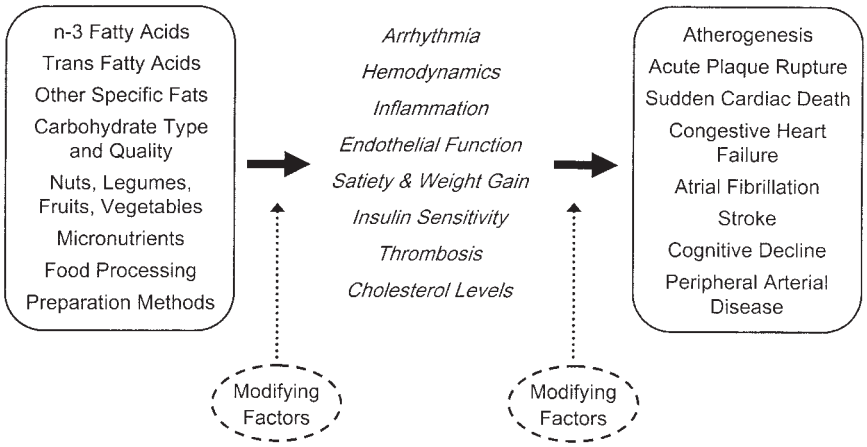

FIGURE 1. Effects of dietary habits on intermediary risk factors and cardiovascular outcomes.

(EPA), and docosahexaenoic acid (DHA) from whales and seals (2). These findings motivated numerous subsequent individual-level observational investigations of effects of seafood and n−3 fatty acids on cardiovascular risk. The relation of fish intake with SCD was first evaluated in a retrospective population-based case-control study among 334 cases of SCD and 551 controls, with seafood consumption assessed both by spousal dietary questionnaires and by direct measurement of erythrocyte n−3 fatty acid levels (3). After adjustment for other risk factors, individuals in the highest quartile of seafood intake had 60% lower risk of SCD [relative risk (RR) = 0.4; 95% CI = 0.2–0.7], compared with those with no seafood intake, whereas individuals in the highest quartile of n−3 fatty acid levels had 90% lower risk of SCD (RR = 0.1; 95% CI = 0.1–0.4) compared with the lowest quartile. These findings were confirmed in subsequent prospective studies of SCD (4) and CHD death (5). To date, at least 15 large prospective cohort studies have examined the relations of dietary fish or n−3 fatty acid consumption with CHD death (6). Although the underlying clinical risk, geographic location, and cultural background of these populations varied widely, the results of these diverse studies were remarkably consistent: compared with individuals with little or no seafood consumption, those with modest consumption (1–2 servings/wk of oily fish, or ~250–500 mg/d of EPA+DHA) experienced ~25–50% lower risk of CHD death, and much higher consumption did not substantially further lower this risk (6). A pooled analysis of these studies (also including randomized clinical trials, reviewed below) demonstrated the dose-response (**Figure 2**). Thirty-six percent lower risk of CHD death was evident between 0 and 250 mg/d of EPA+DHA consumption (RR = 0.64; 95% CI = 0.50–0.80; $P < 0.001$) and little further benefit was seen with higher intakes (0.0% change per each additional 100 mg/d; RR = 1.00; 95% CI = 0.99–1.01; $P = 0.94$).

Notably, at the modest levels of seafood consumption in most populations (eg, up to several servings per week), benefits for arrhythmic CHD death and SCD are distinctly seen, whereas benefits for other types of CHD events, such as nonfatal myocardial infarction (MI), are more equivocal (5–10). CHD death (defined as documented or suspected fatal MI) and SCD (defined as a sudden pulseless condition of presumed cardiac etiology) are clinically ascertained events that most often share the final physiologic pathway of fatal ventricular arrhythmia, often ischemia-induced ventricular fibrillation. The stronger effects of modest seafood consumption on risk of CHD death and SCD, compared with nonfatal CHD events, suggests that modest consumption of marine n−3 fatty acids more strongly impacts fatal cardiac arrhythmias (particularly those related to acute myocardial ischemia) than chronic progression of atherosclerosis or acute plaque rupture (1). Higher levels of marine n−3 fatty acid consumption (eg, as seen in Japan or with high-dose fish oil supplements) may also modestly reduce nonfatal events, perhaps because of pleotropic effects of n−3 fatty acids on other risk factors at these higher doses (6, 11, 12).

When evaluating results of observational studies, residual confounding from unmeasured factors is a potential limitation, and thus concordance between studies in diverse populations, as seen here, and with results of randomized clinical trials and experimental studies (each reviewed below) is important to establish causality. Another important limitation of observational studies is error or misclassification in the estimation of dietary intake, which can significantly attenuate results toward the null (no association). Utilization of dietary biomarkers may reduce such error and provide more accurate estimates of the true effect. Notably, studies utilizing tissue biomarkers of n−3 fatty acid consumption have demonstrated the most robust associations with risk of CHD death or SCD, with up to 90% lower

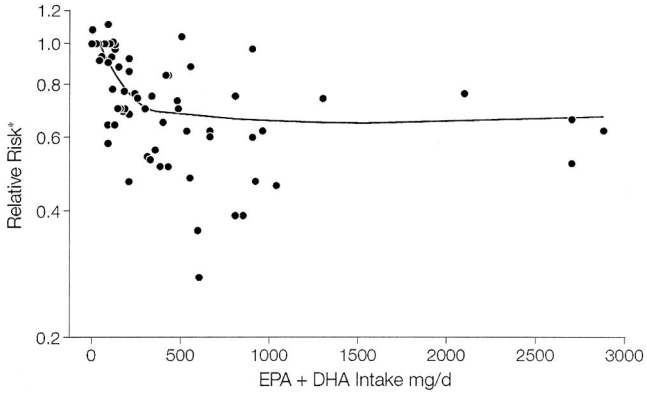

FIGURE 2. Pooled effects of fish or fish oil consumption on relative risk of CHD death in prospective cohort studies and randomized clinical trials. Reproduced with permission from reference 5. Journal of the American Medical Association, Oct 18 2006, 296:1885–99, *Copyright © 2006, American Medical Association*. All Rights reserved

multivariable-adjusted relative risk (RR = 10.0) comparing the highest to the lowest quartile of n−3 fatty acid levels (3–5).

RANDOMIZED CLINICAL TRIALS

The strength of randomized clinical trials is the ability of randomization to minimize residual confounding from other known or unknown risk factors. However, such studies may also be seriously limited by suboptimal duration, time period, or dose of treatment; unique populations enrolled; inadequate power; unblinding; noncompliance; and loss to follow-up; each of which can significantly bias results. Thus, as with observational and experimental studies, randomized clinical trials cannot be considered definitive but rather complementary to other research paradigms, and overall concordance with other evidence is most relevant.

Four large randomized clinical trials have evaluated effects of fish or fish oil consumption on risk of CHD death or SCD. Among 2033 English men with prior MI, advice to consume oily fish 2 servings/wk reduced total mortality by 29% (95% CI = 0.54–0.92) over 2 y, entirely resulting from 33% reduced risk of CHD death ($P < 0.01$) (8). Among 11 323 Italian patients with recent MI, fish oil supplementation (1 g/d) reduced total mortality by 14% (95% CI = 0.76–0.97) over 3.5 y, entirely resulting from 26% reduced risk of SCD (95% CI = 0.58–0.93) (9). Survival benefits were seen within 3 mo (13), indicating rapid effects of n−3 fatty acids on SCD risk, and effects were not significantly different whether patients were receiving antiplatelet medications, angiotensin-converting enzyme-inhibitors, β-blockers, or statins (14). The mortality benefits seen in these 2 large well-powered trials are remarkable; few medical interventions reduce total mortality to such an extent.

In contrast, among 3114 Welsh men with chronic stable angina, advice to consume oily fish 2 servings/wk or take fish oil 3 g/d had no significant effect on total mortality during the 9-y follow-up. In those assigned fish or fish oil advice, 54% higher risk of SCD was seen (95% CI = 1.06–2.23), with somewhat higher risk in those assigned fish oil compared with dietary fish advice (15). These findings must be interpreted cautiously given several major methodologic limitations in this trial, including interruption of recruitment because of inadequate funding, lack of blinding, and a lengthy follow-up period with little reinforcement of dietary advice or data on compliance (15). Also, mortality tended to be higher in both the group assigned fish or fish oil advice ($P = 0.08$) and a group assigned fruit, vegetable, and oats advice ($P = 0.07$) compared with the controls given sensible-eating advice, suggesting a possible unintentional beneficial effect (or simply chance lower risk) in the control group. In a fourth randomized trial among 18 645 Japanese men and women with hypercholesterolemia (3664 with established CHD) treated with statins, EPA supplementation (1.8 g/d) reduced major coronary events by 19% ($P = 0.01$) over 4.6 y (11). Benefits were largely attributable to reduced nonfatal coronary events rather than reduced CHD death, consistent with the very low rates of CHD death in Japan resulting from very high background seafood consumption (12).

Thus, results of 3 of these 4 randomized clinical trials are highly concordant with findings in observational studies. Compared with little or no intake, modest n−3 fatty acid consumption greatly reduces risk of fatal cardiac arrhythmias (ie, CHD death or SCD), whereas, at higher doses and with longer durations of intake, some benefits may also occur for nonfatal CHD events. This strong concordance, seen with both dietary fish intake and fish oil consumption in diverse populations, provides robust evidence for the effects of marine n−3 fatty acids on CHD risk. The pooling of these results with those of prospective cohort studies indicates the likely dose-response for CHD death (Figure 2).

Several smaller randomized trials have evaluated effects of fish oil supplementation on other clinical phenotypes, including progression of carotid and coronary atherosclerosis (16–18), coronary restenosis following angioplasty (19), recurrent tachyarrhythmias in patients with implantable cardiodefibrillators (20–22), and atrial fibrillation following coronary surgery (23). Many of these trials were underpowered, and larger trials or meta-analyses will be needed to establish these effects more conclusively. Additionally, given the differing pathoetiologies of each outcome, conclusions regarding effects of fish or fish oil consumption on one endpoint should not be drawn from studies of a different endpoint. Thus, findings from these smaller trials of specific endpoints neither support nor refute conclusions about effects of fish or fish oil supplementation on CHD death and SCD that have been established in much larger and more numerous randomized trials and observational studies that have directly evaluated these outcomes.

EXPERIMENTAL STUDIES

Experimental studies in both animals and humans demonstrate that marine n−3 fatty acids improve a broad range of overlapping cardiovascular risk factors, including resting heart rate (24), systolic and diastolic blood pressure (25), systemic arteriolar resistance and left ventricular diastolic filling (26), vascular endothelial function (27), circulating triacylglycerol levels (28), inflammatory pathways (29), and autonomic activity (30). Numerous in vitro studies indicate that n−3 fatty acids are strongly antiarrhythmic, (31–33), and multiple in vivo animal experiments have demonstrated clear effects of fish oil on risk of fatal cardiac arrhythmias, including studies in rats, dogs, and nonhuman primates (31–33). For example, among marmoset monkeys fed diets containing 3.8% energy from fish oil compared with sunflower oil for 16 wk, the propensity for ventricular fibrillation was significantly reduced in the fish oil group, whether tested via programmed electrical stimulation at rest, during ischemia, or during isoproterenol infusion ($P < 0.05$ for each) (34). Notably, this modest fish oil consumption increased myocardial membrane n−3 fatty acid levels from 12.6% to 31.3% ($P < 0.0001$) (34), indicating strong preferential incorporation of dietary n−3 fatty acids into heart tissue.

The precise molecular mechanisms for the anti-arrhythmic effects of fish oil are not yet well established. Reduction of arrhythmias may be due to indirect effects (eg, related to changes in arrhythmia-related risk factors, such as left ventricular work and afterload, autonomic function, or inflammation), due to direct effects on myocyte membrane ion channels, (31–33), or due to a combination of such effects. For most of these risk factors affected by fish oil, effects are seen within weeks of changes in dietary consumption and may result from incorporation of n−3 fatty acids into cell membrane lipid rafts (35, 36), which alters local membrane fluidity and function of transmembrane protein receptors, or direct binding of n−3 fatty acids to cytosolic nuclear receptors that regulate gene transcription, such as the peroxisome proliferator-activated receptors (37).

The different effects of fish or fish oil consumption on different cardiovascular outcomes is likely related to varying dose-responses and time-responses of the effects of n−3 fatty acids on different cardiovascular risk factors (**Figure 3**). At typical dietary intakes in most populations (eg, <750 mg/d of EPA+DHA), antiarrhythmic effects predominate, reducing the risk of sudden death and CHD death within weeks to months. At higher doses, maximum antiarrhythmic effects have been achieved, but other physiologic effects may modestly reduce the risk of other clinical outcomes that for some effects may also require longer durations of intake. For instance, nonfatal MI may not be significantly affected by lower doses or shorter durations of fish or fish oil intake but may be modestly reduced by higher doses or more prolonged intake [eg, as seen in the Japan EPA Lipid Intervention Study (JELIS) trial] (38).

PRIMARY COMPARED WITH SECONDARY PREVENTION

Most large observational case-control and cohort studies have evaluated populations free of known cardiovascular disease (which minimizes bias from changes in dietary habits resulting from known disease), whereas randomized controlled trials have generally evaluated populations with established CHD (which minimizes costs and maximizes power by enrolling subjects at higher risk). The concordance of findings from these different studies suggests that effects of fish or fish oil on CHD death and SCD do not vary depending on presence or absence of recognized coronary disease. Although generally higher doses of EPA+DHA consumption (1 g/d) are recommended for prevention of CHD death in patients with established CHD (39, 40), the current evidence does not strongly support a need for different doses in secondary compared with primary prevention populations. For example, reductions in CHD death with modest fish intake (2 servings/wk) in one secondary prevention trial (8) were similar to effects seen with fish oil supplementation (1 g/d) in another secondary prevention trial (9), and both results were similar to findings seen with modest fish intake (1–2 servings/wk) in numerous observational studies of primary prevention (6). Thus, modest consumption (1–2 servings/wk of oily fish, or ~250 mg/d EPA+DHA) may be sufficient for individuals with and without established coronary disease to prevent CHD death and SCD. On the other hand, given the much higher absolute mortality risk of patients with established disease, compared with the general population, current recommendations for somewhat higher consumption of EPA+DHA (1 g/d) are not unreasonable to ensure maximal benefits. Of note, although not as well established, effects of n−3 fatty acids on nonfatal events may also be similar for primary compared with secondary prevention. In the JELIS trial, the magnitude of risk reduction for major coronary events was very similar among those with (n = 14 981) in comparison to without (n = 3664) established CHD (11). Ongoing trials in other specific patient subgroups, specifically congestive heart failure (41) and diabetes (42), will further elucidate the extent of generalizability of effects of n−3 fatty acids.

DIET COMPARED WITH SUPPLEMENTS

Depending on the source and concentration, a 1-g fish oil capsule may contain between 200 to 800 mg of EPA+DHA (43, 44). Thus, intake of one capsule daily is sufficient in most cases to achieve the target intake for primary prevention. Because marine n−3 fatty acids persist for weeks to months in tissues and membranes (45, 46), a target intake of ~250 mg/d EPA+DHA can be converted to average dietary consumption of ~1500–2000 mg/wk, achievable with 1 serving/wk of oily fish or more frequent intake of less n−3 fatty acid-rich species (6). Higher intakes (eg, 1 g/d) can be achieved by 2–3 servings/wk of fish richest in n−3 fatty acids (eg, farmed salmon, anchovies, herring), more frequent consumption of other types of fish, or supplements. EPA+DHA-supplemented functional foods (eg, in dairy products, salad dressings, cereals) can also provide a reasonable intake of n−3 fatty acids (47), although consumers should check that the food contains marine (EPA+DHA), rather than only plant (see below), n−3 fatty acids to ensure an adequate intake. Compared with supplements or functional foods, consumption of fish also provides potentially beneficial protein, vitamin D, and selenium (48), which each may provide additional health benefits. Nevertheless, the concordance of results of observational studies, randomized clinical trials, and experimental studies using either fish or fish oil indicates that effects on CHD death and SCD are largely related to the marine n−3 fatty acid

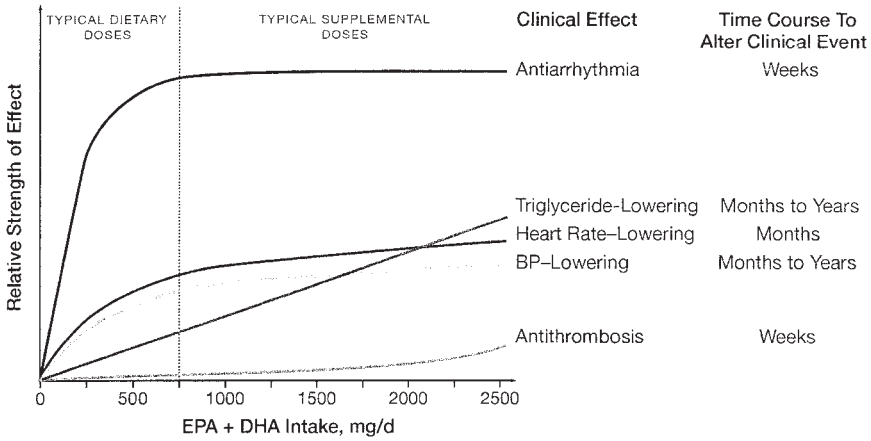

FIGURE 3. Potential dose-response and time course for altering clinical events of physiologic effects of fish or fish oil consumption. Reproduced with permission from reference 6. Journal of the American Medical Association, Oct 18 2006, 296:1885–99, *Copyright © 2006, American Medical Association*. All Rights reserved

content. Thus, any source of EPA+DHA will likely provide similar clinical benefits for these outcomes, and the choice of fish compared with fish oil can be based on personal preference. Among different species of fish and shellfish, those that contain higher levels of n−3 fatty acids, identified as oily or dark-meat species, are preferable to maximize benefits.

CONTAMINANTS

For both the general population and individuals with established CHD, any potential health risks of contaminants (eg, mercury or polychlorinated biphenyls/dioxins) in fish are substantially outweighed by cardiovascular benefits of fish consumption, and modest consumption (eg, 1–3 servings/wk) of a variety of different seafood species will ensure sufficient cardiovascular benefit with negligible health risks (6). The same is generally true for women of childbearing age (6), although, to maximize infant neurodevelopment, the US Environmental Protection Agency/Food and Drug Administration recommends consumption of up to 2 servings/wk of fish and other seafood lower in mercury (including up to 1 serving/wk of albacore tuna) and avoidance of 4 fish species (49).

GAPS THAT REQUIRE FURTHER RESEARCH

Molecular mechanisms

As described above, observational studies, randomized clinical trials, and in vivo experimental studies have established the likely magnitude and dose-response of benefits of fish or fish oil consumption for prevention of CHD death and SCD as well as the effects of n−3 fatty acids on a wide range of cardiovascular risk factors. The molecular mechanisms underlying these benefits are not as well established, and continued experimental investigation is needed to clarify the effects of n−3 fatty acids in different tissues on ion channels, other transmembrane protein receptor and lipid rafts, endoplasmic reticulum and mitochondrial function, and cytosolic nuclear receptors.

EPA compared with DHA

Because EPA and DHA are both concentrated in seafood (48), dietary consumption of these marine n−3 fatty acids is highly correlated. Similarly, most fish oil capsules contain both EPA and DHA. Thus, potentially distinct effects of EPA compared with DHA cannot be evaluated in most observational studies or randomized clinical trials. Many, although not all, experimentally characterized effects of EPA and DHA are similar (27, 32, 33), but some experiments suggest that DHA may be more preferentially antiarrhythmic (31), and DHA tissue levels may more strongly predict lower CHD risk (50). Conversely, the largest published randomized trial of fish oil ($n = 18\,645$) used only concentrated EPA, which reduced major coronary events by 19% ($P = 0.01$) (11). Thus, current evidence does not allow strong conclusions about relative cardiovascular benefits of EPA compared with DHA, and preferential consumption of one or the other is not currently indicated. Practically, this is of little consequence because both are present in all seafood species and most fish oil capsules.

Plant sources

α-Linolenic acid (ALA, 18:3n−3) is the plant n−3 fatty acid present in flaxseed, canola, soybeans, and walnuts (48). In humans, only very small quantities of ALA are converted to EPA (slightly more so in women compared with men), and further conversion to DHA is very limited (51). On the other hand, ALA may have health benefits unrelated to subsequent conversion to longer-chain marine n−3 fatty acids. Some evidence suggests that ALA consumption may reduce cardiovascular risk (52) and that benefits in women may be relatively specific for SCD (53) but more similar for fatal compared with nonfatal events in men, particularly men with low seafood consumption (7). However, compared with EPA+DHA, higher doses are required (eg, 2–3 g/d) and benefits are not as well established (52). Thus, while ALA consumption may itself be beneficial, the current evidence is insufficient to recommend ALA consumption as a replacement for seafood to prevent CHD death or SCD.

CONCLUSIONS

Observational studies, randomized clinical trials, and experimental studies provide concordant evidence that modest consumption of fish or fish oil (~250 mg of EPA+DHA, or 2.25 calories/d) reduces the risk of CHD death and SCD. The strength and consistency of the evidence and the dose-response are each notable. The magnitude of the effect is also substantial, with pooled analysis indicating 36% lower risk of CHD death with modest consumption compared with no consumption (and even larger risk reductions in observational studies utilizing objective biomarkers of consumption). Although targeted interventions such as implantable cardiodefibrillators can reduce risk of fatal cardiac arrhythmias in specific high-risk subgroups, only a small minority of the population is eligible for such invasive and costly treatments. Furthermore, more than one-half of all CHD deaths and two-thirds of SCD occur among individuals without recognized heart disease (54). Thus, together with smoking cessation and regular moderate physical activity, modest consumption of fish or fish oil should be among the first-line treatments for the prevention of CHD death and SCD.

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