Intakes of Long-Chain Omega-3 Fatty Acid Associated with Reduced Risk for Death from Coronary Heart Disease in Healthy Adults

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Numerous organizations and national health agencies have begun to recommend consumption of the long-chain omega-3 fatty acids (FAs) eicosapentaenoic acid and docosahexaenoic acid (EPA and DHA), respectively, in pill or fish form for general cardiovascular health. The purpose of this article is to present a rationale for an official target intake of 400 to 500 mg/d of EPA + DHA in the United States. Six epidemiologic studies reporting EPA + DHA intake and risk of coronary heart disease (CHD) death have been conducted in the United States, and five studies reported statistically significant inverse trends. Meta-analysis of these data showed a significant dose-response relationship between risk for CHD death and intake ($P = 0.03$), with relative risk reductions of 37% at an average EPA + DHA intake of 566 mg/d. Coincidentally, two servings per week of oily fish (the current American Heart Association recommendation) would provide 400 to 500 mg/d. We conclude, therefore, that an intake of 400 to 500 mg/d of EPA + DHA is achievable by diet alone and would be expected to significantly reduce risk for death from CHD in healthy adults.

Introduction

The cardioprotective properties of the long-chain omega-3 fatty acids (FAs) eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) were summarized in a 2002 Science Advisory from the Nutrition Committee of the American Heart Association (AHA) [1] and by others in the intervening years [2–4]. The AHA made specific recommendations for the intake of EPA and DHA for those with existing coronary heart disease (CHD, about 1 g/d), those needing pharmacologic intervention for hypertriglyceridemia (2–4 g/d), and healthy adults. For the latter, the AHA recommended, both in the Advisory [1] and in its Dietary Guidelines for the general population [5], at least two servings per week of (preferably oily) fish. However, no specific amount of EPA and DHA was recommended, nor were "oily fish" specifically defined. The purpose of this article is to present a rationale for a target intake of EPA and DHA for healthy adults in the United States that would be achievable without supplementation to reduce risk of CHD mortality.

EPA + DHA Intakes in Epidemiologic Studies in the United States

Eight studies [6–13] have been reported with the following characteristics: 1) the population was from the United States and was free of known CHD at baseline, 2) risk for CHD death (including primary cardiac arrest and/or sudden cardiac death) was reported, 3) risk was assessed as a function of the estimated EPA + DHA intake by quintile, and 4) multivariate analysis was used to calculate relative risk or odds ratios. Two studies [6,7] fitting these criteria were not included because they reported results from either a shorter follow-up (4 years [6] vs 11 years in the Physicians' Health Study [9]) or a patient subset (only women with diabetes [7] from the Nurses' Health Study [8]) from other studies already included. Thus, six studies are available from which an estimate can be made of the EPA + DHA intake associated with the lowest risk for death from CHD in the United States (Table 1).

Nurses' Health Study

Beginning in 1976, the Nurses' Health Study enrolled 121,700 registered nurses who completed lifestyle and

Table 1. Risk for CHD death or SCD by quintile of estimated EPA + DHA intake in cohort and case-control studies in the United States

Study	Q1	Q2	Q3	Q4	Q5	*P* value
MRFIT [11]						
Person-years of follow-up*	13,724	12,569	13,136	13,146	13,136	
Fish servings	NR	NR	NR	NR	NR	
EPA + DHA, *mg/d*	0	9	46	153	664†	
RR of CHD death	1	1.08	0.92	0.89	0.61	< 0.05
Nurses' Health Study [8]						
Person-years of follow-up	255,434	270,898	263,131	259,454	258,583	
Fish servings	< 1/mo	1–3/mo	1/wk	2–4/wk	> 4/wk	
EPA + DHA, *mg/d*	67	100	178	311†	533	
RR of CHD death	1	0.93	0.69	0.54	0.62	< 0.001
Physicians' Health Study [9]						
Person-years of follow-up	7715	65,223	56,083	61,936	62,820	
Fish servings	< 1/mo	1–3/mo	1 to < 2/wk	2–4/wk	> 4/wk	
EPA + DHA, *mg/d*	10	10–90	90–163†	163–246	> 246	
RR of CHD death	1	0.58	0.34	0.6	0.43	0.21
Seattle Primary Cardiac Arrest Study [10]						
Person-years of follow-up	N/A	N/A	N/A	N/A	N/A	
Fish servings	NR	NR	NR	NR	NR	
EPA + DHA, *mg/d*	0	32	98	185	455†	
OR of primary cardiac arrest	1	0.9	0.7	0.5	0.4	< 0.05
Cardiovascular Health Study [12]						
Person-years of follow-up	3324	8156	7442	5683	11,593	
Fish servings	< 1/mo	1–3/mo	1/wk	2/wk	> 2/wk	
EPA + DHA, *mg/d*	0	128	267	547	919†	
RR of IHD death	1	0.78	0.77	0.53	0.47	0.002
Health Professionals Study [13]						
Person-years of follow-up	50,449	49,902	48,613	47,722	45,343	
Fish servings/wk	0.7	1.6	2.2	3.2	5.9	
Median EPA + DHA, *mg/d*	70	150	240	340	580	
RR of CHD death	1	1.14	0.95	1.03	1.03	NS

*This study included participants from Canada.
†Intake associated with lowest risk of CHD death.
CHD—coronary heart disease; DHA—docosahexaenoic acid; EPA—eicosapentaenoic acid; IHD—ischemic heart disease; MRFIT—Multiple Risk Factor Intervention Trial; N/A—not available; NR—not reported; NS—not significant; OR—odds ratio; Q—quintile; RR—relative risk; SCD—sudden cardiac death.

medical questionnaires [8]. A food frequency questionnaire (FFQ) was used to estimate omega-3 FA intake, from which the daily EPA + DHA intake was calculated and compared with the risk of CHD death over the ensuing 16 years.

United States Physicians' Health Study

This prospective cohort study initiated in 1982 was similar to the Nurses' Health Study and enrolled a total of 20,551 male physicians between the ages of 40 and 84 years who were free of major illness [9]. A FFQ was used to assess omega-3 FA intake. The association between the latter and the 11-year risk for sudden cardiac death (and total mortality) was ascertained.

Seattle Primary Cardiac Arrest Study

This was a population-based, case-control study conducted in King county (Seattle), Washington [10]. All cases of out-of-hospital primary cardiac arrest attended by paramedics in individuals between 25 and 74 years of age over a 6-year period were identified (n = 295). A

total of 398 age- and sex-matched controls were identified from the same population. Dietary intake of fish was ascertained using the Seafood Intake Scale, a quantitative FFQ developed for this study. Spouses of both cases and controls were interviewed regarding their partner's fish intake over the previous month. The odds ratio for being a case (vs a control) was calculated as a function of EPA + DHA intake.

Multiple Risk Factor Intervention Trial

This was a multicenter, open-label study in which 12,866 men at high risk for developing CHD (based on smoking status, serum cholesterol, and blood pressure) were randomized to either usual care or interventions addressing all three risk factors. Dietary data were collected at baseline by standardized 24-hour recall. The present analysis [11] included health outcomes over 10.5 years from those in the usual-care group.

Cardiovascular Health Study

This study focused on men and women over the age of 65 years at entry [12]. About 5200 individuals were recruited in four communities from Medicare rolls between 1989 and 1990. A picture version of the National Cancer Institute's FFQ was administered at baseline and specifically distinguished between tuna/non-fried fish and fried fish/fish sandwiches. Outcomes were collected for a mean of 9.3 years, and the risk for total ischemic heart disease death was determined in relation to the amount of EPA + DHA consumed.

Health Professionals' Follow-Up Study

This study, which was patterned after the Nurses' Health Study and the Physicians' Health Study, began in 1986 and enrolled 51,529 male health professionals (non-physicians such as dentists and pharmacists) between 40 and 75 years of age [13]. The same FFQ that was used in those studies was used here. A total of 44,895 men free of CHD who had satisfactorily completed the FFQ were followed for CHD events for 6 years.

Summarizing the Studies

Two statistical approaches were taken with these data. First, for each study, the reported omega-3 FA intakes associated with the quintile found to be at the lowest risk were simply averaged. Second, the risk ratios for each omega-3 FA intake were combined across studies using the odds ratio meta-analysis method of Haddock et al. [14]. Each risk ratio was converted into a log risk ratio and the corresponding variance was calculated using the number of CHD deaths and sample size in each quintile for each study. The 95% confidence intervals were calculated for each pooled relative risk using these variance estimates. Reported, pooled relative risks of the four highest omega-3 FA–intake groups were compared with that of the lowest, and regression analysis (mean FA intake vs relative risk) was utilized to determine if the trend was significant.

As noted previously, one of the six studies failed to detect an association between omega-3 FA intake and risk for CHD death [13]. It is possible that the small number of men in the referent group (4.5% reported less than 1 fish meal per month) or the relatively short follow-up time (6 years vs 9–16 years) may have contributed to this finding. In the five positive studies, the average intake of EPA + DHA associated with the lowest risk for death from CHD was 496 mg/d. When the two studies at the extremes [9,12] were eliminated, the average intake was 477 mg/d. The two studies that characterized fish (and omega-3 FA) intakes most carefully were the Seattle Primary Cardiac Arrest Study [10] and the Cardiovascular Health Study [12]. In these two studies, the intakes associated with the lowest risk for primary cardiac arrest or ischemic heart disease death were 457 mg/d and 919 mg/d, respectively.

Two meta-analyses were computed, one for the five positive studies and another for all six studies (Fig. 1). In both cases, there was a statistically significant relationship between omega-3 FA intake and relative risk for death from CHD. The overall risk reduction at the highest EPA + DHA intake was 37% (from all studies) or 47% [13]. The average EPA + DHA intake associated with the greatest overall reduction in risk for death from CHD was about 560 mg/d.

The results from these studies in healthy adults suggest that an intake of about 500 mg/d of EPA + DHA afforded significant protection against death from CHD. This finding is compelling for several reasons: 1) it was derived from over 1.6 million person-years of follow-up, 2) the studies used four different dietary assessment tools, 3) eliminating the two extreme studies did not change the results, 4) the effects were independent of other known risk factors, 5) the benefit was dose dependent, and 6) the decrease in risk for CHD death was substantial (about 40%).

Is It Fish or Omega-3 Fatty Acids?

Epidemiologic findings are notoriously subject to bias, and conclusions drawn from them can, when subjected to the intense scrutiny of randomized controlled trials, prove faulty. The recent experiences with vitamin E [15] and hormone replacement therapy [16] are cases in point. The case for omega-3 FAs is stronger than that for vitamin E or estrogen because these FAs have already been shown in randomized controlled trials to reduce risk not only for CHD events [17], but also for CHD mortality [18,19]. In addition, the epidemiologic studies summarized here all included adjustment for a multitude of other known risk factors, including saturated fat intake, history of hypercholesterolemia, hypertension, and/or existing blood cholesterol levels (Table 1). This has also been the case in other case-control or observational studies [13,20–24].

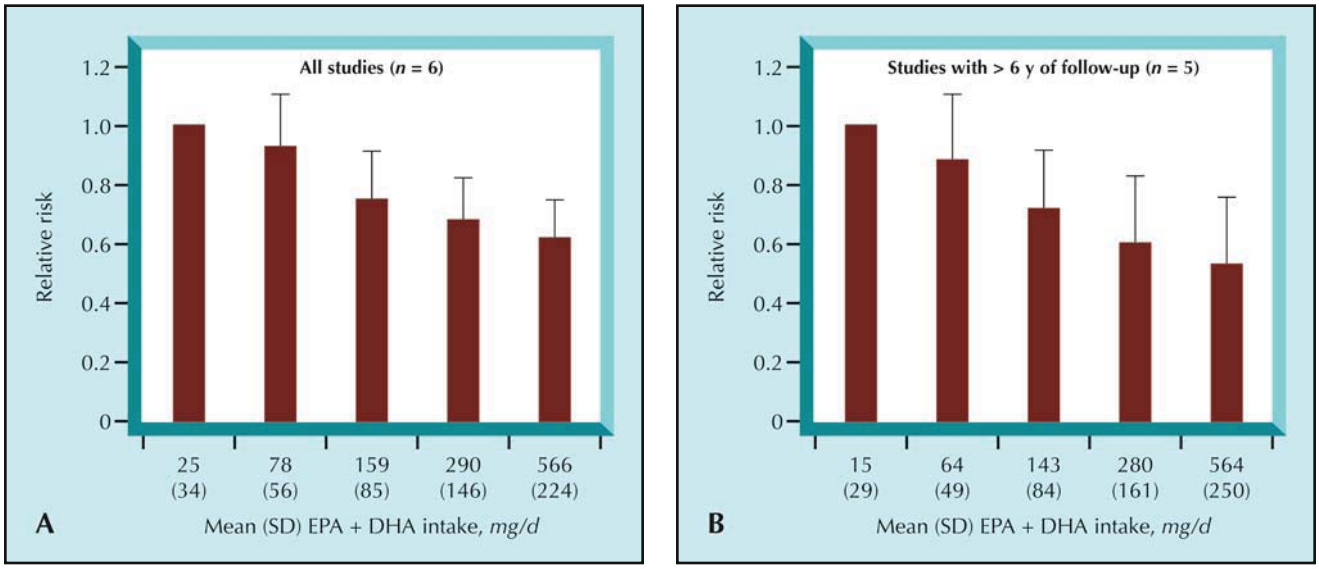

Figure 1. Meta-analysis comparing relative risks for death from coronary heart disease and eicosapentaenoic acid and docosahexaenoic acid (EPA + DHA) intakes from all studies in Table 1 (**A**), and for all studies but Ascherio et al. [38] (**B**). *Error bars* reflect the upper bound of the 95% confidence interval. *P* values for trends were 0.022 and 0.028, respectively.

A comparison of the two trials, one of which used fish [25] and the other purified EPA and DHA [26], both undertaken in post–myocardial infarction patients, is illuminating. Similar reductions in coronary mortality were observed in each, which strongly suggests that it is the omega-3 FAs present in oily fish that are the cardioprotective factors. Thus, although the analysis presented here is based on epidemiologic data, a solid scientific foundation including randomized controlled trials [1,2] undergirds the claim for a cardioprotective effect of omega-3 FAs.

"Two Servings of (Preferably Oily) Fish per Week"

This is the current AHA recommendation for primary prevention of CHD. How much EPA + DHA would be provided by this intake? Clearly, this depends on the definition of an "oily fish" and a "serving." With respect to the former, Table 2 includes a list of 37 fish commonly consumed in the United States ranked by their EPA + DHA content based on United States Department of Agriculture Nutrient Data Laboratory values [27]. There is an apparent break between those fish that provide less than and those that provide more than 500 mg EPA + DHA per 3-oz serving. If the 17 species in the latter category are averaged, the amount of EPA + DHA in a 3-oz serving is 1115 mg. Hence, it is not unreasonable to define an oily fish as one that provides about 1 g of EPA + DHA per 3-oz serving. Secondly, although a standard serving of fish is defined as 3 oz, the actual average serving sizes as determined by the Continuing Survey of Food Intakes by Individuals survey are 4 oz [27], similar to the 140 g reported in Great Britain [28] and the Dutch recommendations that consider a portion to be 100 to 150 g [29]. Therefore, in reality, a recommendation to consume two servings per week of oily fish would translate into 8 oz of fish, which would provide 2667 mg of EPA + DHA, or 381 mg/d of EPA + DHA. Perhaps not surprisingly, this value is close to the 400- to 500-mg/d range derived from the epidemiologic studies examined previously.

International Recommendations

A variety of expert panels and national committees have made recommendations for dietary intake of long-chain omega-3 FAs (Table 3). These range from 200 to 800 mg/d. Thus, an intake of about 400 to 500 mg/d as proposed here is not inconsistent with previous recommendations. Notably, Mozaffarian and Rimm [30••] estimated cardioprotective intakes by combining epidemiologic and interventional studies from around the world done with both healthy volunteers and CHD patients. Their analysis suggested an intake of about 250 mg/d.

Is an Intake of 500 mg/d of EPA + DHA Safe?

Several populations are known to consume at least 500 mg/d of EPA + DHA. In Japan, the average intake is nearly twice this value [31••,32], and average intakes in Norway are reported to be 504 mg/d in women and 940 mg/d in men [33]. The traditional Eskimo diet contained approximately 2.6 g/d and 4.5 g/d of EPA + DHA for women and men, respectively [34]. There is no evidence that any of these intake levels are associated with adverse health outcomes. In 1997, the US Food and Drug Administration (FDA) granted "generally recognized as safe" status to refined, unhydrogenated menhaden oil. (Menhaden is an abundant but bony,

Table 2. Content of EPA and DHA in 37 commonly consumed types of fish*†

Fish	EPA, *mg*	DHA, *mg*	EPA + DHA, *mg*
Orange roughy	5	21	26
Tilapia	4	111	115
Mahi-mahi (dolphin fish)	22	96	118
Cod	3	131	134
Catfish (farmed)	42	109	151
Catfish (wild)	85	116	201
Light chunk tuna (canned)	40	190	230
Yellowfin Tuna	40	197	237
Clams	117	124	241
Mixed shrimp	145	122	267
Skipjack tuna	77	201	278
Scallops	141	169	310
Dungeness crab	239	96	335
Walleye	93	245	338
King crab	251	100	351
Oysters (farmed)	195	179	374
Halibut	77	318	395
Blue crab	207	196	403
Flat fish (flounder/sole)	207	219	426
Pollock	77	383	460
Sea bass	175	473	648
Swordfish	117	579	696
Shark (raw)	267	444	711
White tuna (canned)	198	535	733
Sardines (canned)	402	433	835
Coho salmon (wild)	341	559	900
Rainbow trout (farmed)	284	697	981
Chum salmon (canned)	402	597	999
Mackerel (canned)	369	677	1046
Sockeye salmon (wild)	451	595	1046
Coho salmon (farmed)	347	740	1087
Pink salmon (wild)	456	638	1094
Bluefin tuna	309	970	1279
Atlantic salmon (wild)	349	1215	1564
Atlantic herring	773	939	1712
Pacific herring	1056	751	1807
Atlantic salmon (farmed)	587	1238	1825

*Per 3-oz (85 g) serving.
†Cooked with dry heat unless otherwise noted.
DHA—docosahexaenoic acid; EPA—eicosapentaenoic acid.

oily, and inedible relative of herring that has been used for many years as a fertilizer). The FDA set an upper (safety) limit for EPA + DHA intake at 3 g/d [35]. The 500 mg/d proposed here is only 17% of that limit.

Although omega-3 FAs themselves appear to be safe, certain fish are known to contain elevated levels of methylmercury, which may pose a health risk, especially to babies in utero, infants, and children during early development [36]. The FDA currently recommends that pregnant and lactating women and women likely to become pregnant avoid consumption of four species of fish that can be especially contaminated (tile fish, king mackerel, shark, and swordfish), and to limit consumption of albacore (white) tuna to one 6-oz serving per week. At the same time, the agency notes that these women may consume up to 12 oz per week of other fish [37]. Based on the preceding discussion, 8 oz per week of low-mercury, oily fish would provide the proposed amount of EPA + DHA without exceeding the FDA limits on mercury.

Conclusions

Currently, there is a dearth of guidance from leading health organizations in the United States regarding a specific amount of long-chain omega-3 FAs that would be cardioprotective in apparently healthy adults. A critical examination of epidemiologic studies suggests that 400 to 500 mg/d is reasonable intake target. Individuals following the AHA recommendations to consume at least two servings of (preferably oily) fish a week would be consuming approximately this amount, but if fish with less than 1 g of EPA + DHA per 3-oz serving are consumed, then foods fortified with omega-3 FAs or fish oil supplements may be needed to provide a consistent target intake. For pregnant and lactating women, 400 to 500 mg/d can be obtained from fish while keeping within current FDA guidelines for mercury intake. Establishing a recommended intake range of 400 to 500 mg/d of EPA + DHA for healthy Americans could encourage increased omega-3 FA consumption and thus be expected to reduce the burden of CHD in the United States. Based on a robust database, such a recommendation is timely and should be considered in future nutrition policy reviews.

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Disclosures

No potential conflicts of interest relevant to this article were reported.

Table 3. International recommendations for EPA + DHA for primary prevention of CHD

Agency or country	Year	Recommendation
Eurodiet Conference, University of Crete [39]	2000	200 mg/d EPA + DHA
France [40]	2001	500 mg/d EPA + DHA; minimum 120 mg/d DHA
American Heart Association [1]	2002	Two servings per week of (preferably oily) fish
UK Scientific Advisory Committee on Nutrition [28]	2004	Fish twice per week, one of which should be oily; minimum intake of 450 mg/d EPA + DHA
ISSFAL [41]	2004	500 mg/d EPA + DHA
Australia and New Zealand [42]	2005	442 mg/d* EPA + DHA for men, 318 mg/d* for women
Dutch Health Council [29]	2006	Fish twice per week, one of which should be oily, to achieve the dietary reference intake of 450 mg/d of omega-3 fatty acids from fish
Superior Health Council of Belgium [43]	2006	Minimum of 0.3% of energy from EPA + DHA for adults (667 mg/d)†
American Dietetic Association / Dietitians of Canada [44••]	2007	500 mg/d EPA + DHA; minimum 120 mg/d DHA

*The published guidelines include DPA with EPA and DHA; the values here exclude the contribution of DPA [45].
†Assuming a diet of 2000 kcal/d.
CHD—coronary heart disease; DHA—docosahexaenoic acid; DPA—docosapentaenoic acid; EPA—eicosapentaenoic acid; ISSFAL—International Society for the Study of Fatty Acids and Lipids.

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