# Fish consumption and risk of major chronic disease in men[1–3]

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## ABSTRACT

**Background:** Although fish consumption may reduce specific disease endpoints, such as sudden cardiac death and prostate cancer, the effects of major chronic disease on total burden, reflecting sums of effects on a variety of endpoints and risk pathways, are not well established. Higher n−6 fatty acid consumption has also been hypothesized to reduce the health benefits of n−3 fatty acids in fish.

**Objective:** The aim was to study the associations of fish and n−3 fatty acid consumption with risk of total major chronic disease (cardiovascular disease, cancer, and death) and to determine whether a high n−6 intake modifies the associations.

**Design:** Lifestyle and other risk factors were assessed every 2 y and diet every 4 y in 40,230 US male health professionals aged 40–75 y and free of major chronic disease at baseline in 1986. During 18 y of follow-up, 9715 major chronic disease events occurred, including 3639 cardiovascular disease events, 4690 cancers, and 1386 deaths from other causes.

**Results:** After multivariable adjustment, neither fish nor dietary n−3 fatty acid consumption was significantly associated with risk of total major chronic disease. Compared with fish consumption of <1 serving/mo, consumption of 1 serving/wk and of 2–4 servings/wk was associated with a lower risk of total cardiovascular disease of ≈15%. No significant associations were seen with cancer risk. Higher or lower n−6 fatty acid intake did not significantly modify the results ($P$ for interaction > 0.10).

**Conclusions:** Modest fish consumption was associated with a lower risk of total cardiovascular disease, consistent with cardiac mortality benefits but not with total cancer or overall major chronic disease; n−6 fatty acid consumption did not influence these relations. *Am J Clin Nutr* 2008;88:1618–25.

## INTRODUCTION

Fish consumption has various effects on chronic diseases, particularly cardiovascular disease (CVD) and cancer. Evidence from prospective cohort studies in generally healthy populations and randomized controlled trials in patients with known coronary heart disease suggest that the n−3 polyunsaturated fatty acids in fish—eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)—are likely to prevent sudden cardiac death, manifested as fatal ischemic heart disease or arrhythmic death (1–4) and possibly as ischemic stroke (5). However, the effects of modest fish consumption (eg, 1–2 servings/wk) on other CVD events, such as nonfatal myocardial infarction or nonischemic strokes, have been less consistent (4, 6, 7). Fish consumption may also have various effects on cancer risk (8, 9). For example, in prospective cohort and case-control studies, men with higher EPA+DHA intakes had a lower incidence of prostate cancer and longer survival after prostate cancer diagnosis (10, 11), but neither fish nor EPA+DHA intake were associated with colon cancer or bladder cancer (12, 13). Additionally, concern has been raised that contaminants in some fish may lead to increases in total cancer risk because of organochlorine contaminants (14) and in CVD risk because of mercury (15, 16).

Although the effects on specific disease outcomes elucidate physiologic mechanisms and populations at particular risk, the overall effects of fish consumption on major chronic disease provide insight into total public health effects, including whether overall harm could occur because of potentially adverse effects of contaminants. However, the relations between fish or EPA+DHA consumption and overall major chronic disease are not well established. To elucidate the sum of effects on chronic disease endpoints, we investigated the relations of fish and dietary EPA+DHA consumption, assessed with serial food-frequency questionnaires (FFQs), with total major chronic disease, including total CVD, cancer, and death due to other diseases. Given the hypotheses that n−6 fatty acids compete with or counteract potential benefits of fish or n−3 fatty acid intake (17), we also investigated whether n−6 fatty acid intake modified associations between fish or EPA+DHA consumption and risk of major chronic disease.

## SUBJECTS AND METHODS

### Design and population

The Health Professionals Follow-Up Study (HPFS) is a prospective cohort study of 51,529 US male dentists, pharmacists, veterinarians, optometrists, osteopathic physicians, and podiatrists aged 40–75 y at baseline in 1986. Self-administered questionnaires were mailed to each participant at baseline and then

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biennially to ascertain lifestyle and medical conditions (18–20). Validated FFQs have been sent every 4 y to evaluate diet (21). After the exclusion of men with baseline prevalent myocardial infarction, angina, other heart disease (eg, aortic stenosis and heart rhythm disturbances), stroke, or cancer and of men with ≥70 items missing on the 131-item FFQ or with a reported energy intake <800 or >4200 kcal/d, 40,230 men were included in these analyses. Responses to the questionnaires constituted written informed consent, and the protocol was approved by the Institutional Review Board at the Harvard University School of Public Health.

### Dietary assessment

A semiquantitative FFQ was sent to participants in 1986, 1990, 1994, 1998, and 2002 (21, 22). On each questionnaire, participants were asked to indicate how often, on average, they had consumed given amounts of various specified foods during the past year. Nutrient intakes were calculated as the frequency of intake multiplied by the nutrient composition of the specified portion size, computed with and without vitamin and mineral supplements. In the FFQ, participants were asked about consumption of the following amounts of 4 different seafood items: canned tuna fish (3–4 oz, 84–112 g); dark-meat fish such as mackerel, salmon, sardines, bluefish, and swordfish (3–5 oz, 84–140 g); other (not specified) fish (3–5 oz, 84–140 g); and shrimp, lobster, or scallops as a main dish (3.5 oz, 98 g). Total fish intake was computed as the sum of frequencies of the canned tuna fish, dark-meat fish, and other fish. The inclusion or exclusion of shrimp, lobster, and scallops did not appreciably change the results (data not shown); for this report, shellfish were not included in the final analyses because the focus was on fish consumption. Intake of the marine fatty acids EPA (20:5) and DHA (22:6) was estimated from the consumption of all seafood. Use of fish-oil supplements was first assessed in 1988 and then every 2 y thereafter. Nutrient estimates were based on US Department of Agriculture (23) and Harvard University food-composition database sources; the latter is continually updated over time to reflect the composition of new foods in the marketplace. We adjusted all nutrient values for total energy intake by separate regression analyses (24, 25). The FFQ has been validated against multiple weighed 1-wk dietary records and adipose tissue stores (21, 22); the correlation between estimated fish intake on the FFQ and that on the diet records was 0.56 for canned tuna, 0.42 for dark-meat fish, and 0.39 for other fish. The correlation between estimated EPA+DHA intake and the proportion in adipose tissue was 0.47 (22).

### Events

Methods for ascertainment and classification of outcomes have been described (26). In brief, when an outcome of interest was reported, we sought permission from participants (or next of kin for fatal events) to review medical records, which were used to confirm and classify self-reported diagnoses against standardized criteria by physicians blinded to the information reported on the questionnaires. Deaths were ascertained from relatives, postal authorities, or the National Death Index, and cause of death was classified according to medical records, death certificates, and autopsy findings. Nonrespondents to biennial questionnaires were assumed to be alive if not listed in the National Death Index. The level of nonresponses was < 8% for each 2-y cycle.

The primary endpoint of this analysis was incident major chronic disease, defined as the sum of incident total CVD, total cancer, or other nontraumatic death (27). Total CVD included fatal or nonfatal myocardial infarction and fatal or nonfatal stroke. Myocardial infarction was confirmed on the basis of World Health Organization criteria (28), supplemented after 1998 by guidelines accounting for troponin measurements. Stroke was confirmed by diagnosis of a typical neurological defect of sudden or rapid onset lasting ≥24 h that was attributable to a cerebrovascular event (29). We included all cancers except nonmelanoma skin cancer and low-grade, organ-confined prostate cancer because of the relatively low mortality from these highly prevalent lesions and because diet may more strongly affect more aggressive forms of prostate cancer. CVD or cancers that were verified by letter or telephone interview but for which medical records or pathology reports were unavailable were defined as "probable" cases. The reported analyses used both confirmed (≈80% of total CVD events and 90% of cancer events) and probable cases; analyses were similar when restricted to confirmed cases (data not shown). Traumatic deaths (eg, those due to accidents and suicides) were excluded from the definition of major chronic disease because of the low likelihood of effects of diet on such endpoints.

### Statistical analysis

We used Cox proportional hazards models with time-varying covariates to evaluate risk. Each eligible participant contributed person-time until the first diagnosis of CVD, cancer, or death or until 31 January 2004. Each participant could contribute only one endpoint, and the cohort at risk at any time point included only that free of the primary outcome.

We assessed fish intake in categories of <1 serving/mo, 1–3 servings/mo, 1 serving/wk, 2–4 servings/wk, and ≥5 servings/wk and classified intake of EPA+DHA as <0.05 (similar to the reference category for fish consumption; 30), 0.05 to <0.2, 0.2 to <0.4, 0.4 to <0.6, and ≥0.6 g/d. The data from multiple FFQs over time were used to compute cumulative averages of dietary intake to reduce measurement error and provide more accurate estimates of average dietary intake (24). Because intermediate events may lead to systematic changes in dietary intake, we stopped updating dietary information after new diagnoses of CVD (myocardial infarction, stroke, angina, and coronary bypass surgery), hypercholesterolemia, hypertension, colon polyps, or diabetes.

To determine whether the effects of long-term compared with most recent fish consumption or EPA+DHA intake differed, we also compared results using only baseline reported diet and most recent reported diet in relation to incidence of major chronic disease. These different methods of dietary updating did not produce appreciable differences in the findings; therefore, only the results for cumulative updating diet are presented.

To assess potential confounding, multivariate models were evaluated adjusted for CVD risk factors, lifestyle habits, and other dietary habits, including age (1-y increments); BMI (quintiles); smoking (5 categories); physical activity (quintiles); diabetes, hypertension or hypercholesterolemia; first-degree family history of myocardial infarction before age 60 y; first-degree family history of colon cancer; aspirin use; alcohol intake (quintiles); multivitamin use and intakes of fiber, *trans* fatty acids, saturated fatty acids, α-linolenic acid, n−6 fatty acids (linoleic acid + arachidonic acid), glycemic load, red meat, and total

calories (each in quintiles). All covariates were updated over time, except for incident diabetes, hypertension, or hypercholesterolemia, because dietary intake was not updated after a new diagnosis of these conditions (avoiding potential confounding due to changes in diet after a new diagnosis) and because the incidence of these conditions may be in the causal pathway relating diet to CVD. Tests of linear trend in 5 categories were conducted by assigning the median values for each category of consumption and treating this as a continuous variable. Interactions between fish consumption or EPA+DHA intake and n−6 fatty acid intake were assessed by stratified analyses and by use of a cross-product (multiplicative) term, with each exposure in tertiles. Correlations were evaluated by using Pearson correlation. Use of fish-oil supplements was low (3.3% of participants), and inclusion of fish oil as a covariate in the models or exclusion of individuals using fish-oil supplements had no appreciable effect on the results (data not shown); the results are presented for dietary n−3 intakes (from seafood). All probability values were 2-tailed ($P \leq 0.05$). Analyses were performed with SAS 9.0 software (SAS Institute Inc, Cary, NC).

## RESULTS

At baseline, mean (± SD) fish consumption was 0.3 ± 0.3 servings/d, and EPA+DHA consumption was 0.3 ± 0.2 g/d. Compared with men with lower fish consumption, men with higher fish consumption were more likely to be physically active, have hypercholesterolemia and hypertension, use aspirin and multivitamin supplements, drink more alcohol, and smoke (**Table 1**). Men with higher fish consumption also had higher intakes of energy, protein, EPA+DHA, polyunsaturated fatty acids, fiber, fruit, and vegetables and lower intakes of saturated fat, monounsaturated fat, and *trans* fat. Similar patterns in baseline characteristics were observed according to intake of EPA+DHA (data not shown).

During 18 y of follow-up, a total of 9715 subjects (24.1%) developed a major chronic disease event. These included 3639 total CVD events, 4690 cancer events, and 1386 deaths from other causes (eg, pneumonia, kidney, or liver disease). In age-adjusted analyses, fish consumption was inversely associated with risk of major chronic disease ($P$ for trend = 0.02; **Table 2**),

**TABLE 1**
Age-standardized mean values for baseline characteristics by levels of total fish consumption in 1986 in men in the Health Professionals Follow-Up Study[1]

| | Fish consumption (servings) | | | | | |
|---|---|---|---|---|---|---|
| | <1/mo | 1–3/mo | 1/wk | 2–4/wk | ≥5/wk | $P$ for trend[2] |
| No. of participants | 2483 | 4171 | 23148 | 7332 | 3099 | — |
| Age (y) | 53.3 ± 0.2 | 53.3 ± 0.2 | 53.4 ± 0.1 | 53.5 ± 0.1 | 53.6 ± 0.2 | 0.18 |
| BMI (kg/m$^2$) | 25.5 ± 0.07 | 25.6 ± 0.05 | 25.5 ± 0.02 | 25.4 ± 0.04 | 25.6 ± 0.07 | 0.30 |
| Physical activity (MET/wk) | 18.0 ± 0.7 | 17.3 ± 0.4 | 20.8 ± 0.2 | 24.5 ± 0.4 | 27.4 ± 0.6 | <0.001 |
| Aspirin use (%) | 24.0 | 24.7 | 26.3 | 26.6 | 28.0 | <0.001 |
| Diabetes (%) | 2.8 | 2.9 | 2.4 | 2.1 | 3.0 | 0.39 |
| Hypercholesterolemia (%) | 6.7 | 6.7 | 9.5 | 12.5 | 15.2 | <0.001 |
| Hypertension (%) | 17.9 | 17.9 | 19.2 | 20.7 | 20.4 | <0.001 |
| Alcohol (g/d) | 9.1 ± 0.3 | 10.5 ± 0.3 | 11.8 ± 0.1 | 11.4 ± 0.2 | 10.9 ± 0.3 | <0.001 |
| Multivitamin use (%) | 10.0 | 7.0 | 18.0 | 27.0 | 34.0 | <0.001 |
| Smoking (%) | | | | | | |
| Never | 51 | 46 | 46 | 46 | 47 | 0.02 |
| Past | 34 | 39 | 40 | 42 | 42 | <0.001 |
| Current, 1–14 cigarettes/d | 2 | 2 | 3 | 3 | 2 | 0.21 |
| Current, ≥15 cigarettes/d | 8 | 8 | 7 | 4 | 3 | <0.001 |
| Missing | 4 | 3 | 4 | 4 | 5 | 0.01 |
| Dietary daily intakes | | | | | | |
| Total energy intake (kcal) | 1857 ± 12 | 1868 ± 9 | 1981 ± 4 | 2069 ± 7 | 2185 ± 12 | <0.001 |
| Protein (g) | 81.0 ± 0.3 | 85.2 ± 0.2 | 89.9 ± 0.1 | 99.4 ± 0.2 | 110.6 ± 0.3 | <0.001 |
| Total carbohydrates (g) | 241.1 ± 1.0 | 231.1 ± 0.7 | 233.1 ± 0.3 | 235.7 ± 0.5 | 234.5 ± 0.8 | 0.29 |
| Total fat intake (g) | 75.3 ± 0.3 | 76.3 ± 0.2 | 72.7 ± 0.1 | 68.2 ± 0.2 | 64.6 ± 0.3 | <0.001 |
| n−6 Fatty acid intake (g) | 11.9 ± 0.08 | 11.9 ± 0.06 | 11.7 ± 0.02 | 11.4 ± 0.04 | 11.0 ± 0.07 | <0.001 |
| EPA+DHA (g) | 0.04 ± 0.001 | 0.09 ± 0.001 | 0.24 ± 0.001 | 0.45 ± 0.002 | 0.85 ± 0.01 | <0.001 |
| Saturated fat (g) | 26.9 ± 0.15 | 27.2 ± 0.10 | 25.2 ± 0.04 | 22.8 ± 0.07 | 20.5 ± 0.10 | <0.001 |
| Polyunsaturated fat (g) | 12.8 ± 0.08 | 12.9 ± 0.06 | 13.2 ± 0.02 | 13.4 ± 0.04 | 13.7 ± 0.07 | <0.001 |
| Monounsaturated fat (g) | 29.0 ± 0.14 | 29.4 ± 0.09 | 27.8 ± 0.04 | 25.7 ± 0.07 | 24.2 ± 0.11 | <0.001 |
| *trans* Fat (g) | 3.2 ± 0.03 | 3.3 ± 0.02 | 2.9 ± 0.01 | 2.5 ± 0.01 | 2.1 ± 0.02 | <0.001 |
| Fiber intake (g) | 19.8 ± 0.17 | 18.7 ± 0.10 | 20.4 ± 0.04 | 22.4 ± 0.09 | 24.0 ± 0.14 | <0.001 |
| Fish intake (servings) | 0.0 ± 0.000 | 0.1 ± 0.000 | 0.2 ± 0.001 | 0.6 ± 0.001 | 1.1 ± 0.007 | <0.001 |
| Meat intake (servings) | 1.5 ± 0.02 | 1.7 ± 0.01 | 1.6 ± 0.01 | 1.5 ± 0.01 | 1.4 ± 0.02 | <0.001 |
| Fruit intake (servings) | 2.0 ± 0.03 | 1.8 ± 0.02 | 2.3 ± 0.01 | 2.7 ± 0.02 | 3.2 ± 0.04 | <0.001 |
| Vegetable intake (servings) | 2.4 ± 0.03 | 2.4 ± 0.02 | 2.9 ± 0.01 | 3.6 ± 0.02 | 4.2 ± 0.04 | <0.001 |

[1] All values are mean ± SE (continuous variables) or frequencies (categorical variables), adjusted for age. MET, metabolic equivalent; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.
[2] Values obtained by using median fish consumption continuously.

**TABLE 2**
Relative risk (Cox regression) of major chronic disease, cardiovascular disease (CVD), or cancer on the basis of fish consumption in 40,230 men in the Health Professionals Follow-Up Study with no major chronic disease at baseline in 1986[1]

| | Fish consumption (servings) | | | | | | |
|---|---|---|---|---|---|---|---|
| | <1/mo | 1–3/mo | 1/wk | 2–4/wk | ≥5/wk | *P* for trend | RR in deciles[2] |
| All events ($n$ = 9715) | | | | | | | |
| No. of cases | 665 | 1079 | 5395 | 1840 | 736 | | |
| Person-years | 39,174 | 67,143 | 356,456 | 117,310 | 42,796 | | |
| Model 1 | 1 | 0.95 (0.86, 1.05) | 0.88 (0.81, 0.96) | 0.86 (0.79, 0.94) | 0.88 (0.79, 0.98) | 0.02 | 0.982 (0.975, 0.989) |
| Model 2 | 1 | 0.95 (0.86, 1.05) | 0.91 (0.84, 0.99) | 0.91 (0.83, 1.00) | 0.94 (0.84, 1.04) | 0.53 | 0.991 (0.984, 0.998) |
| Model 3 | 1 | 0.96 (0.87, 1.05) | 0.92 (0.85, 1.00) | 0.94 (0.85, 1.03) | 0.96 (0.86, 1.08) | 0.87 | 0.994 (0.986, 1.002) |
| Total CVD ($n$ = 3639) | | | | | | | |
| No. of cases | 264 | 403 | 2000 | 664 | 308 | | |
| Person-years | 40,466 | 69,447 | 368,805 | 121,790 | 44,488 | | |
| Model 1 | 1 | 0.89 (0.76, 1.04) | 0.81 (0.71, 0.93) | 0.77 (0.66, 0.89) | 0.92 (0.78, 1.09) | 0.52 | 0.979 (0.968, 0.991) |
| Model 2 | 1 | 0.89 (0.76, 1.04) | 0.82 (0.72, 0.94) | 0.79 (0.68, 0.91) | 0.93 (0.79, 1.10) | 0.71 | 0.985 (0.973, 0.996) |
| Model 3 | 1 | 0.90 (0.77, 1.05) | 0.86 (0.75, 0.98) | 0.85 (0.73, 0.99) | 1.04 (0.87, 1.25) | 0.24 | 0.994 (0.981, 1.007) |
| Total cancer ($n$ = 4690) | | | | | | | |
| No. of cases | 301 | 511 | 2610 | 924 | 344 | | |
| Person-years | 40,576 | 69,061 | 366,259 | 120,568 | 44,392 | | |
| Model 1 | 1 | 1.01 (0.87, 1.17) | 0.96 (0.85, 1.08) | 0.98 (0.86, 1.12) | 0.92 (0.79, 1.08) | 0.36 | 0.991 (0.981, 1.002) |
| Model 2 | 1 | 1.01 (0.87, 1.16) | 0.97 (0.86, 1.10) | 1.01 (0.88, 1.15) | 0.96 (0.82, 1.12) | 0.92 | 0.997 (0.986, 1.007) |
| Model 3 | 1 | 1.01 (0.87, 1.16) | 0.98 (0.86, 1.10) | 1.02 (0.88, 1.17) | 0.96 (0.82, 1.14) | 0.99 | 0.997 (0.985, 1.008) |

[1] Values in the models are relative risks (RRs) and 95% CIs (in parentheses). Model 1: adjusted for age (in 1-y increments). Model 2: adjusted for model 1 plus BMI (quintiles); smoking (5 categories); physical activity (quintiles); history of diabetes, hypertension, or hypercholesterolemia; first-degree family history of myocardial infarction before age 60 y; first-degree family history of colon cancer; and aspirin use (yes or no). Model 3: adjusted for model 2 plus multivitamin supplement use (yes or no), glycemic load, and intakes of protein, fiber, *trans* fat, saturated fat, n−6 fatty acids, α-linolenic acid, red meat, total calories, and alcohol (each in quintiles).

[2] Deciles were used as a continuous variable in the models.

but this association was attenuated and no longer significant after adjustment for other risk factors and dietary habits (models 2 and 3). In fully adjusted multivariable models, compared with fish consumption of <1 serving/mo, fish consumption of 1 serving/wk (RR: 0.86; 95% CI: 0.75, 0.98), and 2–4 servings/wk (RR: 0.85; 95% CI: 0.73, 0.99) was associated with a lower risk of CVD (Table 2); fish consumption ≥5 servings/wk was not associated with lower risk. No significant associations were seen between fish consumption and incidence of total cancer (Table 2). When quintiles were used instead of predetermined categories for fish consumption, the RR in the highest quintile, compared with the lowest quintile, was 0.96 (95% CI: 0.89, 1.03; *P* for trend = 0.52) for major chronic disease, 0.99 (95% CI: 0.89, 1.11; *P* for trend = 0.96) for CVD, and 0.95 (95% CI: 0.86, 1.05; *P* for trend = 0.67) for cancer after multivariate adjustments (model 3). To compare extremes of fish consumption, we also evaluated deciles of fish consumption entered as a continuous variable in the models (Table 2). A modest decrease in risk of overall major chronic disease and CVD was found after adjustment for age and CVD risk factors (models 1 and 2), but this was attenuated and no longer statistically significant after adjustments for other dietary habits (model 3). No significant associations were found with cancer risk, even across extremes of fish intake (deciles).

For estimated dietary consumption of EPA+DHA from fish, no significant associations were seen with risk of major chronic disease, total CVD, or cancer after full multivariable adjustment (**Table 3**). When evaluated in quintiles, the RR in the highest quintile was 0.97 (95% CI: 0.90, 1.04; *P* for trend = 0.37) for major chronic disease, 0.97 (95% CI: 0.87, 1.09; *P* for trend = 0.93) for CVD, and 1.00 (95% CI: 0.90, 1.11; *P* for trend = 0.60) for cancer after multivariate adjustments. Decile analyses were also not significant (Table 3).

We also separately evaluated different types of fish consumed, including tuna fish, dark-meat fish, and other fish (**Table 4**). After adjustment for age, risk factors, and other nutrients, significant associations with major chronic disease were generally not seen, except for a modest inverse association between "other fish" consumption of 1 serving/wk, compared with <1 serving/mo, and total major chronic disease and total CVD (Table 4).

Fish or EPA+DHA consumption and n−6 fatty acid intake were not strongly correlated ($r$ = −0.09 and −0.11, respectively). The multivariate-adjusted RRs for major chronic disease, total CVD, and total cancer according to both fish and n−6 fatty acid intakes are shown in **Figure 1**. No significant effect modification by n−6 fatty acid intake was seen (*P* for interactions > 0.10). Results were similar for estimated dietary consumption of EPA+DHA (data not shown). Adjustment for total fat intake did not change the results (data not shown).

## DISCUSSION

In this large, prospective cohort study of US men, neither fish nor estimated dietary EPA+DHA consumption was significantly associated with the incidence of total major chronic disease, representing the sum of fatal + nonfatal CVD, fatal + nonfatal cancer and other deaths. Previous analyses from this and other cohorts found significant inverse associations between modest fish or EPA+DHA consumption and specific disease endpoints, including sudden cardiac death (31) and prostate cancer (10, 11). Such specific effects are relevant for highlighting potential pathways of effects and higher-risk populations that

**TABLE 3**
Relative risk (Cox regression) of major chronic disease, cardiovascular disease (CVD), or cancer on the basis of eicosapentaenoic acid + docosahexaenoic acid (EPA+DHA) intake in 40,230 men in the Health Professionals Follow-Up Study with no major chronic disease at baseline in 1986[1]

| | EPA+DHA (g/d) | | | | | | |
|---|---|---|---|---|---|---|---|
| | <0.05 | 0.05 to <0.2 | 0.2 to <0.4 | 0.4 to <0.6 | ≥0.6 | *P* for trend | RR in deciles[2] |
| All events ($n$ = 9715) | | | | | | | |
| No. of cases | 426 | 3295 | 3646 | 1404 | 944 | | |
| Person-years | 26,477 | 212,711 | 239,896 | 91,604 | 52,191 | | |
| Model 1 | 1 | 0.98 (0.88, 1.08) | 0.90 (0.81, 1.00) | 0.86 (0.77, 0.96) | 0.95 (0.84, 1.06) | 0.03 | 0.986 (0.979, 0.993) |
| Model 2 | 1 | 0.98 (0.89, 1.09) | 0.93 (0.84, 1.03) | 0.90 (0.81, 1.00) | 1.00 (0.89, 1.12) | 0.52 | 0.993 (0.986, 1.000) |
| Model 3 | 1 | 1.00 (0.90, 1.11) | 0.96 (0.86, 1.06) | 0.94 (0.84, 1.05) | 1.04 (0.92, 1.18) | 0.67 | 0.997 (0.989, 1.005) |
| Total CVD ($n$ = 3639 | | | | | | | |
| No. of cases | 163 | 1245 | 1340 | 514 | 377 | | |
| Person-years | 27,310 | 220,099 | 248,273 | 94,878 | 54,437 | | |
| Model 1 | 1 | 0.95 (0.80, 1.12) | 0.85 (0.72, 1.00) | 0.81 (0.68, 0.97) | 0.97 (0.80, 1.17) | 0.46 | 0.985 (0.974, 0.996) |
| Model 2 | 1 | 0.95 (0.80, 1.12) | 0.87 (0.74, 1.03) | 0.82 (0.69, 0.98) | 0.99 (0.82, 1.19) | 0.63 | 0.987 (0.976, 0.999) |
| Model 3 | 1 | 0.98 (0.83, 1.15) | 0.93 (0.78, 1.10) | 0.91 (0.76, 1.10) | 1.12 (0.92, 1.36) | 0.16 | 0.998 (0.985, 1.012) |
| Total cancer ($n$ = 4690) | | | | | | | |
| No. of cases | 197 | 1575 | 1783 | 682 | 453 | | |
| Person-years | 27,399 | 218,852 | 246,389 | 94,137 | 54,080 | | |
| Model 1 | 1 | 1.03 (0.88, 1.19) | 0.98 (0.84, 1.13) | 0.93 (0.79, 1.09) | 1.00 (0.84, 1.19) | 0.32 | 0.994 (0.984, 1.004) |
| Model 2 | 1 | 1.02 (0.88, 1.19) | 0.99 (0.85, 1.15) | 0.95 (0.81, 1.12) | 1.03 (0.87, 1.23) | 0.81 | 0.998 (0.988, 1.008) |
| Model 3 | 1 | 1.03 (0.88, 1.19) | 0.99 (0.85, 1.15) | 0.96 (0.81, 1.13) | 1.03 (0.86, 1.23) | 0.83 | 0.998 (0.987, 1.010) |

[1] Values in the models are relative risks (RRs) and 95% CIs (in parentheses). Model 1: adjusted for age (in 1-y increments). Model 2: adjusted for model 1 plus BMI (quintiles); smoking (5 categories); physical activity (quintiles); history of diabetes, hypertension, or hypercholesterolemia; first-degree family history of myocardial infarction before age 60 y; first-degree family history of colon cancer; and aspirin use (yes or no). Model 3: adjusted for model 2 plus multivitamin supplement use (yes or no), glycemic load, and intakes of protein, fiber, *trans* fat, saturated fat, n−6 fatty acids, α-linolenic acid, red meat, total calories, and alcohol (each in quintiles).

[2] Deciles were used as a continuous variable in the models.

might derive the greatest benefits. In contrast, the present analysis evaluated whether fish intake influences the total burden of major chronic disease, reflecting the sum of effects on a wide variety of endpoints with various underlying pathways of risk. Although less relevant to understanding the effects on specific disease outcomes or pathways of risk, these findings are relevant

**TABLE 4**
Consumption of different types of fish and risk of major chronic disease in 40,230 men in the Health Professionals Follow-Up Study with no major chronic disease at baseline in 1986[1]

| | Fish consumption (servings)[2] | | | | |
|---|---|---|---|---|---|
| | <1/mo | 1–3/mo | 1/wk | ≥2/wk[3] | *P* for trend |
| Tuna | | | | | |
| No. of cases[4] | 2601 | 3422 | 2493 | 1113 | |
| All | 1 | 0.96 (0.91, 1.01) | 0.97 (0.92, 1.03) | 0.97 (0.89, 1.04) | 0.48 |
| CVD | 1 | 0.96 (0.87, 1.04) | 0.94 (0.86, 1.04) | 0.98 (0.87, 1.10) | 0.84 |
| Cancer | 1 | 0.96 (0.89, 1.04) | 1.00 (0.92, 1.08) | 0.96 (0.86, 1.07) | 0.59 |
| Dark-meat fish | | | | | |
| No. of cases[4] | 4873 | 2767 | 1423 | 493 | |
| All | 1 | 0.97 (0.92, 1.01) | 0.98 (0.92, 1.04) | 1.04 (0.94, 1.15) | 0.75 |
| CVD | 1 | 0.96 (0.89, 1.04) | 1.00 (0.91, 1.11) | 1.10 (0.93, 1.29) | 0.35 |
| Cancer | 1 | 0.96 (0.90, 1.03) | 0.98 (0.90, 1.07) | 1.02 (0.88, 1.18) | 0.96 |
| Other fish | | | | | |
| No. of cases[4] | 2370 | 3160 | 2773 | 1130 | |
| All | 1 | 0.94 (0.89, 0.99) | 0.93 (0.88, 0.99) | 0.97 (0.89, 1.04) | 0.70 |
| CVD | 1 | 0.91 (0.83, 1.00) | 0.90 (0.82, 0.99) | 1.00 (0.88, 1.13) | 0.58 |
| Cancer | 1 | 0.95 (0.88, 1.03) | 0.95 (0.88, 1.04) | 0.97 (0.86, 1.08) | 0.75 |

[1] Cox regression was used. Values in the models are relative risks and 95% CIs (in parentheses). CVD, cardiovascular disease.

[2] Adjusted for age (in 1-y increments); BMI (quintiles); smoking (5 categories); physical activity (quintiles); history of diabetes, hypertension, or hypercholesterolemia; first-degree family history of myocardial infarction before age 60 y; first-degree family history of colon cancer; aspirin use (yes or no); multivitamin supplement use (yes or no); glycemic load; and intakes of protein, fiber, *trans* fat, saturated fat, n−6 fatty acids, α-linolenic acid, red meat, total calories, and alcohol (each in quintiles).

[3] Few subjects consumed these individual fish types ≥5 times/wk and were combined with those consuming them 2–4 times/wk.

[4] Numbers represent major chronic disease cases ("all" category).

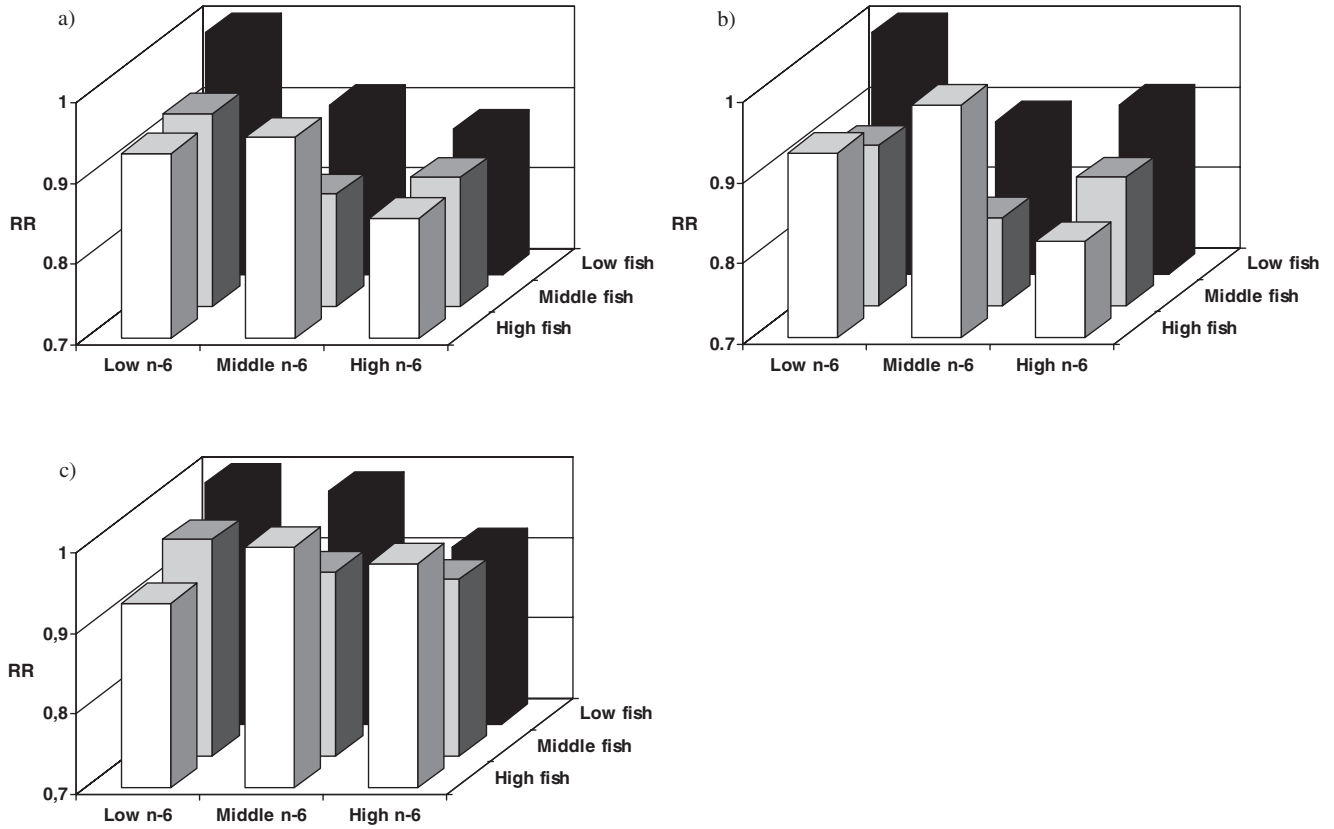


**FIGURE 1.** Relative risk (RR) of major chronic disease (A), total cardiovascular disease (B), and total cancer (C) according to both fish and n−6 fatty acid intake in 40,230 men in the Health Professionals Follow-Up Study. Adjusted for age (1-y increments); BMI (quintiles); smoking (5 categories); physical activity (quintiles); presence of diabetes, hypertension, or hypercholesterolemia; family history of myocardial infarction; family history of colon cancer; aspirin use; multivitamin supplement use; glycemic load; and intakes of protein, fiber, *trans* fat, saturated fat, α-linolenic acid, red meat, total calories, and alcohol (each in quintiles). There was no statistical evidence that n−6 consumption modified any of the relations between fish consumption and the disease outcomes (*P* for interactions > 0.10).

to the overall public health effects of fish consumption, including whether overall harm could occur because of potentially adverse effects of mercury or other contaminants in fish on a broad range of potential outcomes.

No overall effect on combined major chronic disease was evident. Compared with little or no fish consumption (<1 serving/mo), consumption of 1 serving/wk and of 2–4 servings/wk was associated with a lower risk of total CVD of ≈15%. This is consistent with a relatively strong benefit of modest fish consumption in reducing sudden cardiac death and relatively small effects on other CVD outcomes (31). Observational, clinical trial, and experimental evidence indicates that the major CVD effects of modest fish consumption (eg, 1–2 servings/wk) protect against CHD mortality (particularly sudden cardiac death), with possible additional benefits for ischemic stroke (4). Of the 3639 total CVD events in this analysis, only 262 (7%) were sudden cardiac deaths. Because moderate fish consumption may not have strong effects on other CVD events (eg, nonfatal myocardial infarction and nonischemic stroke), only a modest lowering of total CVD risk would be expected, as seen in this study. Interestingly, fish consumption of ≥5 servings/wk was not associated with total CVD. In post hoc analyses, we found a significant U-shaped association for total CVD; reasons for the lack of a linear component to this association are unclear, and confirmation of this dose-response in other studies is warranted.

No significant associations were seen between fish or EPA+DHA consumption and cancer incidence, even when extremes of consumption across deciles were compared. Although animal studies found that long-chain n−3 fatty acids can modulate tumor formation and proliferation (32) and some epidemiologic studies showed protective effects of EPA+DHA intake on some cancer types (9), little evidence of protection against total cancer risk has been found in prospective studies (9). The lack of association with total cancer events observed in this study suggests that either fish and n−3 fatty acid consumption has no effect on cancer risk or that, similar to CVD, the protective effect may be specific to only certain types of cancer, which makes it difficult to detect reductions in overall cancer risk.

Fish contain organochlorine contaminants, such as dioxins and polychlorinated biphenyls, which—even at the low concentrations present (4)—are associated with cancer risk. With the inclusion of nearly 5000 cancer cases, our study had considerable power to detect a higher cancer risk with fish intake (eg, 80% power to detect a 15.5% higher risk and 90% power to detect an 18.0% higher risk). The absence of such an effect is reassuring that habitual fish intake over ≥18 y is not associated with a higher overall risk of cancer. It is also possible that small cancer benefits of n−3 fatty acids in fish are counterbalanced by small cancer risks of contaminants, so that consumption of fish very high in n−3 fatty acids and very low in contaminants might modestly

reduce cancer risk, but this hypothesis requires confirmation in future studies.

We found no evidence that a high n−6 fatty acid intake modifies the effects of fish or EPA+DHA intake on incidence of major chronic diseases. Compared with very traditional diets, industrialized diets have seen an increase in n−6 fatty acid intake and a decrease in n−3 fatty acid intake over the past 150 y, which raises concerns about the impact of this change on the risk of chronic diseases (33, 34). n−6 fatty acids have beneficial effects on cholesterol concentrations and are associated with a lower CVD risk (35). Conversely, n−6 fatty acids can also act as precursors to proinflammatory eicosanoids and can compete with n−3 fatty acids for common metabolic enzymes or during incorporation into plasma lipid fractions (17, 36), which could diminish the protective effects of n−3 fatty acids. Although these limited ecologic and animal studies suggest that high n−6 consumption can reduce the possible beneficial effects of n−3 fatty acids (33, 34), our findings and other studies in humans do not support this hypothesis (31, 37, 38).

Our study has several strengths, including its evaluation of a well-described cohort including large numbers of events and participants with standardized examinations of other risk factors. Relatively little loss to follow-up occurred, minimizing selection bias or missed cases. Detailed and serially updated dietary data allowed evaluation of usual dietary habits over time. The prospective design and discontinuation of dietary updating after intermediate events reduced bias from changes in diet due to known disease (confounding by indication).

The study had potential limitations. The study population consisted of generally healthy men; therefore, the results may not be generalizable to women or to other populations. Dietary questionnaires can be limited by errors in reporting and recall. Because diet was assessed prospectively, these errors would likely be random with respect to outcomes and would bias results toward the null. This could explain in part the absence of modest associations with major chronic disease in this cohort or the lack of interaction with n−6 fatty acids. Conversely, nearly 10,000 events were included in the analysis, and the accuracy of self-reported fish intake in this cohort, using validated and cumulatively updated dietary intake data to reduce within-individual variation and better represent long-term intake, was previously shown (21, 22). Although we are constantly updating our nutrient composition databases, we cannot exclude the possibility that the databases do not reflect the rapid changes in the use of different types of vegetable oils in the food supply, which could explain the lack of interaction with n−6 fatty acids. Our focus was on the effects of seafood consumption, and plant-based n−3 fatty acids might have different relations with major chronic disease or n−6 fatty acids (although a prior paper found that n−6 consumption did not modify CHD effects of plant-derived n − 3 fatty acids; 31). We did not evaluate the potential effects of fish or EPA+DHA intake on other specific disease outcomes, such as heart failure, atrial fibrillation, cognitive decline, or dementia, that may be improved by fish consumption.

In conclusion, consumption of fish and EPA+DHA was not associated with the overall incidence of major chronic disease in generally healthy men. Modest fish intakes (between 1 and 4 servings/wk) were associated with a lower risk of total CVD. A high n−6 fatty acid intake did not modify these results.

The authors' responsibilities were as follows—JKV: design of the study, analysis of data, and writing of the manuscript; DM and SEC: critical review of the manuscript; and EBR: design of the study and critical review of the manuscript. None of the authors had a conflict of interest.

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