Accumulated Evidence on Fish Consumption and Coronary Heart Disease Mortality
A Meta-Analysis of Cohort Studies

Ka He, MD, ScD; Yiqing Song, MD; Martha L. Davíglus, MD, PhD; Kiang Liu, PhD; Linda Van Horn, PhD; Alan R. Dyer, PhD; Philip Greenland, MD

Background—Results from observational studies on fish consumption and coronary heart disease (CHD) mortality are inconsistent.

Methods and Results—A meta-analysis of cohort studies was conducted to examine the association between fish intake and CHD mortality. Studies were included if they provided a relative risk (RR) and corresponding 95% CI for CHD mortality in relation to fish consumption and the frequency of fish intake. A database was developed on the basis of 11 eligible studies and 13 cohorts, including 222,364 individuals with an average 11.8 years of follow-up. Pooled RR and 95% CI for CHD mortality were calculated by using both fixed-effect and random-effect models. A linear regression analysis of the log RR weighted by the inverse of variance was performed to assess the possible dose-response relation. Compared with those who never consumed fish or ate fish less than once per month, individuals with a higher intake of fish had lower CHD mortality. The pooled multivariate RRs for CHD mortality were 0.89 (95% CI, 0.79 to 1.01) for fish intake 1 to 3 times per month, 0.85 (95% CI, 0.76 to 0.96) for once per week, 0.77 (95% CI, 0.66 to 0.89) for 2 to 4 times per week, and 0.62 (95% CI, 0.46 to 0.82) for 5 or more times per week. Each 20-g/d increase in fish intake was related to a 7% lower risk of CHD mortality (P for trend=0.03).

Conclusions—These results indicate that fish consumption is inversely associated with fatal CHD. Mortality from CHD may be reduced by eating fish once per week or more. (Circulation. 2004;109:2705-2711.)

Key Words: diet • coronary heart disease • mortality • meta-analysis

Two decades ago, epidemiologists observed a low coronary heart disease (CHD) mortality rate among native Alaskan and Greenland Eskimos who consumed a large amount of fish.1,2 The same phenomenon was also seen among Japanese in Japan.3 On the basis of these ecological data, it has been hypothesized that dietary fish intake may reduce CHD mortality rates. Although many epidemiological studies have examined this hypothesis, data from randomized trials are limited,4 and case-control studies on fish intake and fatal CHD are sparse.5–8 In addition, the results from prospective cohort studies have been inconsistent: Some studies showed an inverse association between fish intake and CHD mortality,9–17 whereas others did not.18–26 In a review published in 1999,27 the authors quantified the fish-CHD mortality relation, mainly on the basis of only 4 cohort studies, and concluded that the inverse association between fish consumption and CHD mortality was evident among “high-risk” populations but not “low-risk” populations. However, a thoroughly systematic and quantitative assessment of published findings is not available. Therefore, we performed a meta-analysis by using all relevant prospective cohort studies that have the data available. We aimed to assess the dose-response relation between fish consumption and CHD mortality and to explore major sources of heterogeneity among studies.

Methods

Data Sources and Study Selection
All relevant observational studies were identified by searching MEDLINE and EMBASE (1966 to September 2003). Search terms included “fish,” “seafood,” “omega-3 fatty acids,” “n-3 fatty acids,” “cardiovascular disease,” “fatal coronary heart disease,” and “fatal myocardial infarction” (MI). The search was restricted to studies using prospective cohort study design and published in English-language journals. We also used information of bibliographies from retrieved articles and recent reviews.

Two of our investigators independently reviewed each published paper and extracted relevant information. Discrepancies were resolved by group discussion. In general, papers were included if (1) relative risks (RRs) and their corresponding 95% CIs of CHD mortality relating to each category of fish consumption were reported; and (2) frequency of fish intake was provided, which permitted standardizing categorization of fish consumption. When multiple published reports from the same study cohort were avail-
able, we included only the one with the most detailed information for RR estimation.

Of 18 identified studies, 5 were excluded because they were published as short reports (eg, letters to the editors) that provided incomplete information on RR estimation or fish intake.10,11,18,19,22 Two other studies were excluded because they had only two levels of fish intake (yes versus no; or high versus low).12,23 Of the 11 eligible published studies, one study14 that included data from 3 geographically different populations was counted as 3 separate cohorts in the meta-analysis. The final data set for our meta-analyses included 13 cohorts from 11 independent studies comprising 222,364 participants (3032 CHD deaths), with an average 11.8 years of follow-up.

Data Extraction
The data that we collected included the first author’s name, year of publication, country of origin, duration of follow-up, range or mean of participants’ age, sample size, proportion of men, number of events, category amount of fish intake, methods for measurement of fish intake, adjusted covariates, as well as RR.s and 95% CIs of CHD mortality for each category of fish intake. RR.s transformed to their natural logarithms (ln) and the 95% CIs were used to calculate the corresponding standard errors (SE.s).

The amount of fish consumption (g/d) was estimated by multiplying the frequency of consumption (serving/d) by the corresponding portion size (g/serving). For example, the derived average portion size in the Health Professional Follow-up Study was 105 g/serving. The range of fish intake for 1 to 3 times per month was 3.5 g/d (105/30) to 10.5 g/d. When the range of fish intake in a particular category was not available from the paper, the corresponding values were determined on the basis of data from the two largest cohort studies (the Nurses’ Health Study and the Health Professional Follow-up Study), considering that the food frequency questionnaire (FFQ) used in these two studies has been validated.28 If the highest fish intake category had an open upper bound, for example, fish intake /H11021 5/week, we assigned 1 serving/d fish intake as the upper limit.

Data Synthesis
We standardized and categorized fish consumption into 5 intervals: “never or <1/month,” “1 to 3/month,” “1/week,” “2 to 4/week,” and

| TABLE 1. Characteristics of 13 Included Cohorts (From 11 Studies) of Fish Consumption and CHD Mortality |
|--------------------------------------------------|-----------------------------------------------|
| Source                                           | Participants (Events) | Age  | Men (%) | Duration of Follow-Up, y | Exposure Assessment                           |
| Kromhout et al.19 1985, the Netherlands          | 852 (78)             | 40–59| 100     | 20                         | Interview based on Burke’s diet history method |
| Fraser et al.20 1992, USA                        | 26 473 (260)         | 52 (mean) | 38   | 6                          | Self-administered questionnaire               |
| Ascherio et al.21 1995, USA                      | 44 895 (264)         | 40–75| 100     | 6                          | Self-administered questionnaire               |
| Daviglus et al.13 1997, USA                      | 18 22 (430)          | 40–55| 100     | 30                         | Interview based on Burke’s diet history method |
| Mann et al.24 1997, UK                           | 10 802 (64)          | 16–79| 38      | 13.3                       | Self-administered questionnaire               |
| Albert et al.25 1998, USA                        | 20 551 (308)         | 40–84| 100     | 11                         | Self-administered questionnaire               |
| Oomen et al.14 2000, Finland                     | 1088 (242)           | 50–69| 100     | 20                         | Interview based on Burke’s diet history method |
| Oomen et al.,14 2000, Italy                      | 1097 (116)           | 50–69| 100     | 20                         | Interview based on Burke’s diet history method |
| Oomen et al.14 2000, the Netherlands             | 553 (105)            | 50–69| 100     | 20                         | Interview based on Burke’s diet history method |
| Yuan et al.15 2001, China                        | 18 244 (187)         | 45–64| 100     | 12                         | Interview based on questionnaire               |
| Hu et al.16 2002, USA                            | 84 688 (484)         | 34–59| 0       | 16                         | Self-administered questionnaire               |
| Osler et al.26 2003, Denmark                     | 7389 (247)           | 30–70| 53      | 11                         | Self-administered questionnaire               |
| Mozaffarian et al.17 2003, USA                   | 3910 (247)           | ≥66  | 39      | 9.3                        | Self-administered picture-sort version of questionnaire |

ICD indicates International Classification of Diseases.
TABLE 1. Continued

<table>
<thead>
<tr>
<th>Fish Intake Categories</th>
<th>Outcome Assessment</th>
<th>Adjusted Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 g/d; 1–14 g/d; 15–29 g/d; 30–44 g/d; ≥45 g/d</td>
<td>ICD-8 (codes 410–413)</td>
<td>Age, systolic blood pressure, serum total cholesterol, cigarette smoking, subscapular skinfold thickness, physical activity, energy intake, dietary cholesterol, prescribed diet and occupation</td>
</tr>
<tr>
<td>None; &lt;1/ wk; ≥1/ wk</td>
<td>ICD-8 (codes 410–414)</td>
<td>Age, sex, smoking, exercise, relative weight, high blood pressure</td>
</tr>
<tr>
<td>&lt;1/mo; 1–3/mo; 1/ wk; 2–3/wk; 4–5/wk; ≥6/wk</td>
<td>Based on medical records and autopsy report</td>
<td>Age, body mass index, smoking habits, alcohol consumption, history of hypertension, history of diabetes, history of hypercholesterolemia, family history of myocardial infarction before 60 y of age and profession</td>
</tr>
<tr>
<td>0 g/d; 1–17 g/d; 18–34 g/d; ≥35 g/d</td>
<td>ICD-8 (codes 410–414)</td>
<td>Age, education, religion, systolic pressure, serum cholesterol, No. of cigarettes smoked per day, body mass index, diabetes, ECG abnormalities, daily intake of energy, cholesterol, saturated, monounsaturated, and polyunsaturated fatty acids, total protein, carbohydrate, alcohol, iron, thiamine, riboflavin, niacin, vitamin C, beta carotene, and vitamin E, vitamin C, and multivitamin use</td>
</tr>
<tr>
<td>Never; &lt;1/ wk; ≥1/ wk</td>
<td>ICD-9 (codes 410–414)</td>
<td>Age, sex, smoking and social class</td>
</tr>
<tr>
<td>&lt;1/mo; 1–3/mo; 1–2/wk; 2–5/wk; ≥5/wk</td>
<td>ICD-9 (codes 410–414)</td>
<td>Age, aspirin, β-carotene treatment assignment, evidence of cardiovascular disease before 12-mo questionnaire, body mass index, smoking status, history of diabetes, history of hypertension, history of hypercholesterolemia, alcohol consumption, vigorous exercise, and vitamin E, vitamin C, and multivitamin use</td>
</tr>
<tr>
<td>0–19 g/d; 20–39 g/d; ≥40 g/d</td>
<td>ICD-8 (codes 410–414, 795)</td>
<td>Age, body mass index, cigarette smoking, intake of energy, vegetables, fruits, alcohol, meat, butter, and margarine</td>
</tr>
<tr>
<td>0 g/d; 1–19 g/d; 20–39 g/d; ≥40 g/d</td>
<td>ICD-8 (codes 410–414, 795)</td>
<td>Age, body mass index, cigarette smoking, intake of energy, vegetables, fruits, alcohol, meat, butter, and margarine</td>
</tr>
<tr>
<td>0 g/d; 1–19 g/d; ≥20 g/d</td>
<td>ICD-8 (codes 410–414, 795)</td>
<td>Age, body mass index, cigarette smoking, intake of energy, vegetables, fruits, alcohol, meat, butter, and margarine</td>
</tr>
<tr>
<td>&lt;50 g/wk; 50–&lt;100 g/wk; 100–&lt;150 g/wk; 150–200 g/wk; ≥200 g/wk</td>
<td>ICD-9 (codes 410–414)</td>
<td>Age, total energy intake, level of education, body mass index, current smoker, average no. of cigarettes smoked per day, no. of alcoholic drinks consumed per week, history of diabetes, and history of hypertension</td>
</tr>
<tr>
<td>&lt;1/mo; 1–3/mo; 1/wk; 2–4/wk; ≥5/wk</td>
<td>Based on medical records, death certificate and autopsy report; ICD codes are not available</td>
<td>Age, time periods, smoking status, body mass index, alcohol intake, menopausal status and postmenopausal hormone use, vigorous to moderate activity, No. of times aspirin was used per week, multivitamin use, vitamin E supplement use, and history of hypertension, hypercholesterolemia, diabetes, intake of trans-fat, the ratio of polyunsaturated fat to saturated fat, and dietary fiber</td>
</tr>
<tr>
<td>&lt;1/mo; 2/mo; 1/wk; ≥2/wk</td>
<td>ICD-8 (codes 410–414)</td>
<td>Familial predisposition, smoking status, physical activity, alcohol, educational status, healthy diet score, total cholesterol, and body mass index</td>
</tr>
<tr>
<td>&lt;1/mo; 1–3/mo; 1/wk; 2/wk; ≥3/wk</td>
<td>Based on medical records and death certificate. ICD codes are not available</td>
<td>Age, gender, education, diabetes, smoking, body mass index, systolic blood pressure, LDL cholesterol, HDL cholesterol, triglycerides, C-reactive protein, saturate fat, alcohol, beef/pork, fruit and vegetables</td>
</tr>
</tbody>
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“≥5/week.” According to the range or average amount of fish intake in each category, we then assigned each RR reported from each individual study into its corresponding intervals. If the average fish consumption from more than one category in a single study fell into the same category of fish intake in our meta-analysis, we then pooled these RRs with inverse variance weight and used the combined estimate for that group. We also combined RRs if the individual study reported RRs based on multiple outcomes (ie, death from acute MI or other ischemic heart disease) or multiple exposures (types of fish intake). As compared with the lowest category, the pooled RRs and 95% CIs of CHD mortality for all other categories of fish consumption were estimated by using both fixed-effects and random-effects models. The pooled RR was obtained by averaging the ln RRs and their respective SEs as weights. In the absence of publication bias, one would expect studies of all sizes to be scattered equally above and below the line showing the pooled estimate of ln RR. Publication bias was also assessed by two formal tests: the Begg-adjusted rank correlation test and the Egger’s regression asymmetry test. All analyses were performed with the use of the STATA statistical software (Version 7.0, STATA Corp).
Results

Table 1 lists the 13 eligible cohorts (from 11 studies) and selected characteristics. Six cohorts were from the United States, 6 from Europe, and 1 from China. The number of participants ranged from 852 in the study by Kromhout et al\(^9\) to 84,688 in the study by Hu et al.\(^{16}\) Of the 13 cohorts, 8 included only male participants. The range of follow-up period was from 6 to 30 years. Data on fish consumption were collected by using self-administered FFQ (7 cohorts) or in-person interview (6 cohorts). Fish intake was classified into 3 to 6 categories. All studies reported multivariate adjusted RRs and 95% CIs.

Table 2 presents pooled RRs and 95% CIs of CHD mortality according to fish consumption. Compared with those who never consumed fish or ate fish less than once per month, individuals who ate fish once per week had significantly lower CHD mortality rates (pooled multivariate RR, 0.85; 95% CI, 0.76 to 0.96). Beneficial effects on CHD mortality gradually increased as a function of fish consumption. For individuals who ate fish 5 or more times per week, CHD mortality was lower by 38% (RR, 0.62; 95% CI, 0.46 to 0.82).

In stratified analyses, gender did not appear to materially modify the inverse association between fish intake and CHD mortality. Of the 13 cohorts, the average duration of follow-up was 11.8 years. We found that the inverse associations were more evident among those studies with a follow-up of 12 years or longer. In addition, when we examined studies using self-administered FFQ dietary assessment or using in-person interview separately, the results did not materially alter. All above sources of heterogeneity were further confirmed with meta-regression analysis. The pooled RR did not substantially differ between studies (data not shown).

Five included studies also presented data on nonfatal MI.\(^{16,17,20,21,33}\) The pooled RRs across 5 categories of fish intake were 1.0; 0.88 (95% CI, 0.70 to 1.10), 0.95 (95% CI, 0.75 to 1.22), 0.86 (95% CI, 0.67 to 1.09), and 0.79 (95% CI, 0.64 to 0.99; \(P\) for trend=0.40) for nonfatal MI.

Figure 1 shows the estimated RR and 95% CI for each individual study comparing fish consumption once per week with never or less than once per month, through the use of a fixed-effects model. There was no evidence for the presence
of significant heterogeneity among 13 cohorts ($\chi^2_{12}=10.6; P=0.57$). The estimated overall dose-response relation is shown in Figure 2. For each 20-g/d increase in fish intake, the pooled RR was estimated to be 0.93 (95% CI, 0.87 to 0.99; $P$ for trend=0.03). Figure 3 shows a Begg’s funnel plot for the visual assessment of publication bias. The plot showed slightly more data points above the horizontal line (representing the pooled estimate of ln RR), indicating a possible minor publication bias in favor of the null association. In addition, both Begg’s adjusted rank correlation test and Egger’s regression asymmetry test indicated no evidence of substantial publication bias ($P=0.99$ for Begg’s test; $P=0.68$ for Egger’s test).

### Comments

In this meta-analysis of prospective cohort studies, we found a consistently inverse association between fish consumption and CHD mortality rates. Our results suggested that eating fish once per week might significantly reduce death from CHD by 15%. A dose-response relation was evident between fish consumption and risk of CHD mortality. An increment of 20 g/d of fish intake could possibly lower CHD mortality rates by 7%. The inverse association was more apparent among studies with a follow-up period of 12 years or longer. On the basis of the available data, the beneficial effects of fish intake on CHD mortality rates were not materially modified by gender or methods of dietary assessment.

Our meta-analysis has several strengths. First, our quantitative assessment was based on published cohort studies; the prospective study design minimizes selection bias and recall bias compared with retrospective case-control studies. Also, most of the included studies had a large sample size and long-term follow-up periods. Thus, meta-analysis of these studies provides relatively high statistical power for estimating a true beneficial effect of habitual fish intake on CHD mortality. In addition, this meta-analysis allowed us to explore some possible major sources of heterogeneity across cohort studies. However, the best approach to examine a cause-effect relation is to perform a double-blinded and placebo-controlled randomized trial. Although desirable, it is practically unfeasible to conduct such a trial for primary prevention of CHD mortality. Therefore, a meta-analysis of prospective cohort studies is a potentially powerful approach to reliably quantify the optimal amount and long-term benefits of fish intake in reducing CHD death.

Our study also bears several limitations. First, analyses are based on observational studies, and the inherent limitations of such studies may affect our findings. The possibility of residual confounding or bias including measurement errors cannot be excluded. Second, dietary assessment, the number of exposure categories, and the reference group varied across individual studies. These differences might lead to difficulties in estimating the true effect. However, our subgroup analyses did not support the presence of potential effect modification by these factors. Third, our results were likely to be affected by misclassification of fish intake. Nevertheless, the likelihood of this bias should be small because most of the studies provided data on portion size or range of fish consumption in each exposure category. Finally, 7 of 18 relevant published studies were excluded because the presentation of results was too uninformative to allow extraction of a credible effect estimate or weight. The possibility that our findings were affected by the exclusion cannot be completely ruled out. We also considered publication bias because our analyses were based on published studies. However, we found little evidence of publication bias involved in our results by visual examination and statistical tests.

It has been established that the onset of CHD in women compared with men is generally delayed by 10 to 15 years. Estrogen level was thought to be associated with the thrombogenesis and inflammation that are related to CHD events. Although we did not find a significant gender difference, our capacity to determine a gender-specific effect might be reduced by the fact that 12% of the participants in the women subgroup analysis were men because most of the eligible studies did not report RRs for women separately.
Further studies of fish intake and CHD mortality in women are warranted. In addition, we found that the inverse association appeared to be more evident in studies with 12 or more years of follow-up. This may indicate a long-term benefit of fish intake in the primary prevention of CHD death.

Fish intake may reflect other factors related to healthy lifestyle. For example, individuals with higher fish consumption generally exercise more, smoke less, and are less likely to be overweight. Such healthier lifestyles have been shown to reduce risk of CHD. Even though most of the studies included were well designed and adjusted for major lifestyle variables in the analyses, we could not exclude the possibility that the inverse association between fish intake and CHD mortality is in part explained by other underlying healthy-lifestyle factors not measured in the studies.

Beneficial effects of fish intake on CHD mortality are biologically plausible. Marine-derived long-chain omega-3 polyunsaturated fatty acids (PUFA), including eicosapentaenoic acid and docosahexaenoic acid, have been shown to have antiarrhythmic properties that could be protective against death from CHD. Other favorable effects of long-chain omega-3 PUFA on lipid profile and platelet aggregation can also be related to a decreased risk of CHD events. However, how much intake of long-chain omega-3 PUFA may be enough to significantly lower CHD mortality is still unclear. Numerous experimental studies have indicated benefit from the use of fish oil supplements on cardiovascular disease risk. However, the dose of long-chain omega-3 PUFA used in these experimental studies exceeded that typically found in the diet. In addition, whether pure fish oil supplement use has the same effect on CHD mortality as does whole fish intake remains questionable. Because the long-term benefits or safety of high-dose fish oil supplements for the general population or for persons with CHD remain uncertain, one should be cautious when recommending people use fish oil supplements instead of eating whole fish. Moreover, data on the effect of intake of different types of fish on CHD mortality rates are limited. Considering the different amounts of long-chain omega-3 PUFA in different types of fish, we would expect to have more benefit by eating fatty fish rich in long-chain omega-3 PUFA if it is true that long-chain omega-3 PUFA is solely responsible for any beneficial effect in reducing death from CHD. Nevertheless, one study indicated that lean fish, which contains relatively low levels of long-chain omega-3 PUFA, was also inversely associated with CHD mortality. The possibility of interactions between long-chain omega-3 PUFA and some unknown constituents in fish providing synergistic benefits cannot be ruled out. Furthermore, the questions of how cooking affects the benefit from fish consumption and how to optimally cook fish remain unanswered and call for future research. Finally, there is a concern about mercury contamination in fish. People are at risk of consuming fish that have absorbed mercury from contaminated bay water. Whether intake of mercury-contaminated fish increases the risk of cardiovascular diseases is still controversial. In 2001, the Food and Drug Administration issued a recommendation for pregnant women to avoid certain types of fish that may have relatively high mercury content. The balance between mercury toxicity and beneficial effects of fish consumption merits future investigation.

On the basis of the available data for nonfatal MI, the evidence for an inverse association of fish intake and risk of nonfatal MI appeared to be weak, even though there was significant risk reduction by eating fish 5 times per week or more. Further studies are warranted.

In conclusion, our meta-analysis of prospective cohort studies indicated an inverse association between fish consumption and CHD mortality rates. Eating fish once per week may significantly reduce CHD mortality rates. Further reduction in CHD mortality rates may be attained by additional fish intake. Our results support the dietary guidelines to eat fish twice per week to reduce CHD risk.

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