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# Fish, ω-3 Polyunsaturated Fatty Acids, and Mortality From Cardiovascular Diseases in a Nationwide Community-Based Cohort of Japanese Men and Women

## The JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk) Study

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**Objectives** The objective of our study was to test the hypothesis that fish or ω-3 polyunsaturated fatty acids (PUFA) intakes would be inversely associated with risks of mortality from ischemic heart disease, cardiac arrest, heart failure, stroke, and total cardiovascular disease.

**Background** Data on associations of dietary intake of fish and of ω-3 PUFA with risk of cardiovascular disease among Asian societies have been limited.

**Methods** We conducted a prospective study consisting of 57,972 Japanese men and women. Dietary intakes of fish and ω-3 PUFA were determined by food frequency questionnaire, and participants were followed up for 12.7 years. Hazard ratios and 95% confidence intervals were calculated according to quintiles of fish or ω-3 PUFA intake.

**Results** We observed generally inverse associations of fish and ω-3 PUFA intakes with risks of mortality from heart failure (multivariable hazard ratio [95% confidence interval] for highest versus lowest quintiles = 0.76 [0.53 to 1.09] for fish and 0.58 [0.36 to 0.93] for ω-3 PUFA). Associations with ischemic heart disease or myocardial infarction were relatively weak and not statistically significant after adjustment for potential risk factors. Neither fish nor ω-3 PUFA dietary intake was associated with mortality from total stroke, its subtypes, or cardiac arrest. For mortality from total cardiovascular disease, intakes of fish and ω-3 PUFA were associated with 18% to 19% lower risk.

**Conclusions** We found an inverse association between fish and ω-3 PUFA dietary intakes and cardiovascular mortality, especially for heart failure, suggesting a protective effect of fish intake on cardiovascular diseases. (J Am Coll Cardiol 2008;52:988–96) © 2008 by the American College of Cardiology Foundation

Inverse associations of dietary intake of fish and ω-3 polyunsaturated fatty acids (PUFA) with the risk of ischemic heart disease (IHD) have been well described mainly in Western populations (1), but the data on Asian societies have been limited. There have been only 3 cohort studies in China (2) and Japan (3,4), and a recent randomized con-

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trolled trial among hypercholesterolemic patients in Japan (5). The evidence for an association between fish intake and the risk of stroke has also been limited, although a protective effect was suggested from a meta-analysis (6). Further, it is possible that dietary intakes of fish and ω-3 PUFA may reduce the risk of heart failure (7), but the data on this issue are quite limited (8,9).

Several mechanisms, including antiarrhythmic effects, modulation of autonomic function, decreased platelet aggregation, and vasodilation, have been suggested for the association between fish or ω-3 PUFA and risk of cardiovascular disease (10). From an epidemiological standpoint, it is important to replicate the results in different populations and confirm the associations with large representative data. The JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk) study is a nationwide, community-based follow-up study of cardiovascular disease with one of the largest number of subjects in Asia, including many cases of heart failure, which has not been examined in Asia. Thus, we used these data to examine the associations of dietary intakes of fish and ω-3 PUFA with the risk of mortality from cardiovascular disease in Japan, where average fish intake is high compared with that of Western countries—approximately 3 to 4 times more among Japanese than among white Americans (11). Our a priori hypothesis was that the dietary intakes of fish and ω-3 PUFA would be associated with reduced risk of mortality from IHD, cardiac arrest, heart failure, stroke, and total cardiovascular disease in this population with high fish intake.

## Methods

**Study cohort.** The JACC study comprised a nationwide community-based sample of 110,792 persons (46,465 men and 64,327 women) from 45 administrative districts of Japan. Participants were 40 to 79 years of age during the baseline period (1988 to 1990) and completed self-administered questionnaires concerning their life-styles and medical histories of previous cardiovascular disease or cancer (12). We excluded persons who reported a history of heart disease (IHD, arrhythmia, heart failure, or unspecified heart disease), stroke, or cancer at the baseline survey, or those missing the fresh fish item, with more than 1 item missing from the other 3 fish items, or with more than 4 missing items from the 33 items on the dietary questionnaire. As a result, we included 22,881 men and 35,091 women from 34 communities with complete information on their dietary information. Written or explicitly verbal informed consent was obtained before participants completed the questionnaire. In several communities, the informed consent was obtained from community leaders instead of individual participants, which had been in common practice for informed consent in Japan at that time. The JACC study protocol was approved by the Medical Ethical Committees of the Nagoya University School of Medicine.

**Abbreviations and Acronyms**

CI = confidence interval
HR = hazard ratio
IHD = ischemic heart disease
PUFA = polyunsaturated fatty acids

**Mortality surveillance.** In each community, investigators conducted a systematic review of death certificates. In Japan, registration of death is legally required and is believed to be followed across Japan. Thus, all deaths that occurred in the cohort were ascertained by death certificates from a public health center, except for subjects who died after they had moved from their original community, in which case the subject was censored. The date of moving from the community was verified by population-register sheets. In the present study, the follow-up was conducted through the end of 2003, except for 2 communities in which the follow-up had ended in 1999. The average follow-up period for the participants was 12.7 years. We used the underlying cause of death coded by the International Statistical Classification of Diseases and Related Health Problems-10th Revision (ICD-10) to identify mortality end points: I60 to I69 for stroke, I60 for subarachnoid hemorrhage, I61 for intraparenchymal hemorrhage, I63 for ischemic stroke, I20 to I25 for IHD, I21 for myocardial infarction, I46 for cardiac arrest, I47 to I49 for arrhythmic death, I50 for heart failure, and I00 to I99 for total cardiovascular disease. Because of the small number of cases, we pooled cardiac arrest and other arrhythmic death as "cardiac arrest."

**Intakes of fish and ω-3 PUFA.** The food frequency questionnaire included 33 foods, including 4 fish items: fresh fish, *kamaboko* (steamed fish paste), dried or salted fish, and deep-fried foods or *tempura* (a common form of deep-fried fish or shellfish). Five choices were presented for each item: rarely, 1 to 2 days a month, 1 to 2 days a week, 3 to 4 days a week, and almost every day; these choices were converted to scores of 0, 0.05 (1.5 of 30), 0.214 (1.5 of 7), 0.5 (3.5 of 7), and 1, respectively. The portion size was estimated by a previous validation study (13) described in the following text, and assigned as 63 g for fresh fish, 20 g for steamed fish paste, 29 g for dried or salted fish, and 29 g for deep-fried fish, which was estimated as 26% of 113 g for deep-fried foods or *tempura* calculated by dietary records of the validation study. The consumption of fish (g/day) was calculated by multiplying the frequency scores and portion sizes, and summing across the 4 items. For missing data on either dried or salted fish, deep-fried fish, or steamed fish paste (n = 5,300), we assigned the median consumption values in the total sample.

The previous validation study also provided the values for nutrient and fatty acid intake, based on the Japan Food Table-4th Version. The values of ω-3 PUFA (including non–long-chain ω-3 PUFA) assigned for 1 portion were, for example, 1.009 g for fresh fish, 0.042 g for steamed fish

paste, 0.544 g for dried or salted fish, 0.929 g for deep-fried foods or *tempura*, 0.357 g for fried vegetables, 0.230 g for boiled beans, and 0.184 g for *miso* soup. The amounts of nutrients consumed were calculated by multiplying the frequency scores and estimated nutrients for each portion and summing across all 33 items. Data on fish oil supplementation were not available in the baseline survey, but supplement use was not common among Japanese adults. The details of the validation study and methods for the estimation of nutrient factors were reported previously (13).

Subjects missing the fresh fish intake item and subjects missing more than 1 of the other 3 fish items were excluded during fish or ω-3 PUFA estimation. Furthermore, subjects with a missing response to more than 4 of the 33 items on the food frequency questionnaire were also excluded, leaving 57,972 eligible for the analyses. Energy adjustments were done for dietary intakes of fish, vegetables, fruit, ω-3 and ω-6 PUFA, saturated fatty acids, and cholesterol, using the nutrient residual model (14).

We previously had performed another validation study of the frequency of fresh fish, steamed fish paste, and dried or salted fish captured by the JACC study questionnaires compared with serum ω-3 PUFA levels in a subsample (n = 1,319) (15). We also tested the validity of dietary intakes of fish and ω-3 PUFA: The age- and gender-adjusted mean plasma ω-3 PUFA levels (weight percent of total fatty acids) across quintiles of energy-adjusted fish intake were 9.5, 9.8, 10.4, 10.5, and 11.2 (p for trend $<0.001$), and respective values across quintiles of energy-adjusted ω-3 PUFA intake were 9.5, 10.0, 10.4, 10.3, and 11.2 (p for trend $<0.001$).

The quintiles of energy-adjusted fish intake were 0 to 27, 27 to 39, 39 to 53, 53 to 72, and 72 to 229 g/day, and those of ω-3 PUFA intake were 0.05 to 1.18, 1.18 to 1.47, 1.47 to 1.75, 1.75 to 2.11, and 2.11 to 5.06 g/day. The validation study showed that the estimated mean fish intake in this study compared with dietary records in a subsample (n = 88, mostly female) were one-half that in the dietary record (42.9 vs. 87.2 g/day).

**Statistical analysis.** Age-adjusted means and proportions of selected cardiovascular risk factors and nutrients were calculated according to quintiles of energy-adjusted dietary intakes of fish and ω-3 PUFA, and the overall difference across the quintiles was tested by analysis of covariance. For each participant, we calculated the person-years of follow-up from baseline in 1988 to 1990 to the first end point: death, moving from the community, or the end of 2003. The mortality rates of each outcome were calculated according to quintiles of intakes of fish or ω-3 PUFA. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated after adjustment of age, gender, and other potential confounding factors with Cox proportional hazards survival models. The confounding factors included body mass index (quintiles), history of hypertension and diabetes mellitus (yes or no), smoking status (never, former smoker, and current smoker of 1 to 19 or ≥20 cigarettes/day), alcohol intake (never, former drinker, and current drinker of ethanol at 1 to 22, 23 to 45, 46 to 68, or ≥69 g/day; 23 g ethanol corresponds to 1 *go*, a Japanese traditional unit for volume), perceived mental stress (low, medium, or high), walking (rarely, 30, 30 to 60, or more than 60 min/day), sports (rarely, or more than 1 h/week), education levels (age of completed education of <13, 13 to 15, 16 to 18, or ≥19 years), and continuous values of total energy and energy-adjusted nutrient intakes (cholesterol, saturated fatty acids, and ω-6 PUFA), and quintiles of energy-adjusted vegetable and fruit intakes. Body mass index was calculated as body weight (kg) divided by the square of height ($m^2$), where weight and height were obtained from the baseline questionnaire. Histories of hypertension and diabetes were derived from the baseline questionnaire. The linear trend of HRs across the quintiles was tested by using variables with −2, −1, 0, 1, and 2 assigned to successive quintiles. Multiplicative interactions with gender were tested using a cross-product term (16). We excluded monounsaturated fatty acids from the models because of multicolinearity with dietary intakes of cholesterol and saturated fatty acids (Spearman correlation coefficient = 0.72 and 0.82, respectively).

We used SAS version 9.1.3 Service Pack 4 (SAS Institute, Cary, North Carolina) for the analyses. All probability values for statistical tests were two-tailed, and values of $p < 0.05$ were regarded as statistically significant.

## Results

During 735,905 person-years of follow-up for 57,972 persons, we documented 419 deaths due to IHD (including 329 myocardial infarctions), 107 due to cardiac arrest, 307 due to heart failure, and 972 due to stroke (including 223 intraparenchymal hemorrhages, 153 subarachnoid hemorrhages, and 319 ischemic strokes); there were 2,045 total cardiovascular deaths and 7,008 total deaths.

As shown in Table 1, several variables, such as age, mean body mass index, history of diabetes, current smoking, mean alcohol intake, high perceived mental stress, and all nutrient factors, were correlated with energy-adjusted fish intake. The Spearman correlation coefficient between energy-adjusted dietary intakes of fish and ω-3 PUFA was 0.84. As a result, we observed similar correlations between dietary intake of ω-3 PUFA and the preceding variables (not shown in the table).

Because no interactions with gender were observed for the association of fish or ω-3 PUFA intake with any end point, we combined men and women for further analyses. Table 2 shows the HRs of cardiovascular diseases according to dietary intake of fish. Fish intake tended to be inversely associated with age- and gender-adjusted risks of IHD, myocardial infarction, and heart failure. Risk of cardiac arrest tended to be higher in the second and third quintiles of fish intake but to be lower in the higher quintiles with no

**Table 1** Baseline Characteristics of Cardiovascular Risk Factors and Selected Dietary Variables in a Cohort of 22,881 Men and 35,091 Women to Quintile of Fish Intakes

| | Men | | | | | | Women | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Quintiles of Fish Intake* | | | | | | Quintiles of Fish Intake* | | | | | |
| | Q1 (Low) | Q2 | Q3 | Q4 | Q5 (High) | p Value† | Q1 (Low) | Q2 | Q3 | Q4 | Q5 (High) | p Value† |
| Median intake*, g/day | 20 | 33 | 45 | 62 | 86 | | 21 | 33 | 46 | 62 | 85 | |
| Number at risk | 4,845 | 4,608 | 4,345 | 4,446 | 4,637 | | 6,749 | 6,987 | 7,249 | 7,149 | 6,957 | |
| Age at baseline, yrs | 54.7 | 55.2 | 55.7 | 56.1 | 57.8 | <0.001 | 56.5 | 55.6 | 55.7 | 56.5 | 56.9 | <0.001 |
| Mean body mass index‡, kg/m$^2$ | 22.6 | 22.7 | 22.7 | 22.8 | 22.7 | 0.03 | 22.8 | 22.9 | 22.9 | 23.0 | 23.1 | <0.001 |
| History of hypertension‡, % | 18 | 17 | 18 | 18 | 18 | 0.39 | 19 | 20 | 19 | 19 | 20 | 0.61 |
| History of diabetes mellitus‡, % | 5 | 5 | 6 | 5 | 7 | 0.006 | 3 | 3 | 3 | 3 | 4 | 0.08 |
| Current smoker‡, % | 55 | 52 | 51 | 51 | 51 | <0.001 | 6 | 5 | 4 | 4 | 4 | <0.001 |
| Mean alcohol intake‡, g/day | 35.6 | 33.9 | 33.5 | 35.8 | 31.0 | <0.001 | 12.6 | 9.8 | 9.2 | 10.1 | 8.7 | <0.001 |
| Sports 5 h/week or more‡, % | 6 | 7 | 7 | 7 | 7 | 0.19 | 4 | 4 | 4 | 4 | 4 | 0.51 |
| Walking 1 h/day or more‡, % | 47 | 47 | 47 | 48 | 46 | 0.70 | 48 | 48 | 47 | 49 | 47 | 0.29 |
| College or higher education‡, % | 17 | 17 | 17 | 16 | 19 | 0.01 | 10 | 10 | 10 | 10 | 10 | 0.56 |
| High perceived mental stress‡, % | 23 | 25 | 24 | 24 | 26 | 0.01 | 22 | 21 | 20 | 21 | 20 | 0.12 |
| Mean energy intake‡, Kcal/day | 1,624 | 1,623 | 1,659 | 1,746 | 1,591 | <0.001 | 1,306 | 1,328 | 1,340 | 1,396 | 1,274 | <0.001 |
| Dietary cholesterol‡, mg/day | 186 | 219 | 242 | 272 | 291 | <0.001 | 192 | 220 | 243 | 270 | 276 | <0.001 |
| Saturated fatty acids‡, g/day | 7.9 | 8.7 | 9.3 | 9.9 | 10.0 | <0.001 | 8.2 | 9.0 | 9.4 | 10.0 | 9.4 | <0.001 |
| Monounsaturated fatty acids‡, g/day | 7.4 | 8.7 | 9.6 | 10.6 | 11.1 | <0.001 | 7.8 | 9.0 | 9.7 | 10.7 | 10.5 | <0.001 |
| Polyunsaturated fatty acids‡, g/day | 6.7 | 7.6 | 8.2 | 9.0 | 9.1 | <0.001 | 6.5 | 7.3 | 7.9 | 8.7 | 8.5 | <0.001 |
| ω-3 polyunsaturated fatty acids‡, g/day | 1.0 | 1.3 | 1.6 | 2.0 | 2.3 | <0.001 | 1.1 | 1.4 | 1.6 | 2.0 | 2.2 | <0.001 |
| ω-6 polyunsaturated fatty acids‡, g/day | 5.7 | 6.2 | 6.6 | 7.0 | 6.8 | <0.001 | 5.5 | 6.0 | 6.3 | 6.7 | 6.3 | <0.001 |
| Fish intake‡, g/day | 19 | 33 | 46 | 65 | 86 | <0.001 | 19 | 33 | 46 | 66 | 84 | <0.001 |
| Vegetable intake‡, g/day | 71 | 83 | 93 | 104 | 110 | <0.001 | 87 | 96 | 106 | 116 | 120 | <0.001 |
| Fruit intake‡, g/day | 101 | 110 | 117 | 126 | 132 | <0.001 | 131 | 139 | 145 | 153 | 148 | <0.001 |

*Energy-adjusted values by nutrient residual model; †p values for overall difference among quintiles based on analysis of covariance; ‡age-adjusted.

significant trend. No associations were observed for total stroke or its subtypes. Inverse associations were observed for total cardiovascular disease, and less prominently, for total death. After further adjustment for cardiovascular risk factors and dietary variables, these inverse associations were generally weakened but were not altered substantially.

Similarly, Table 3 shows the HRs of cardiovascular diseases according to dietary intake of ω-3 PUFA. The results were essentially the same as those for fish intake. However, the associations of ω-3 PUFA with heart failure were more prominent than with fish intake. An inverse trend was also observed for intraparenchymal hemorrhage but was no longer significant after adjustment for cardiovascular risk factors. Our results were essentially the same when analyzed for long-chain ω-3 PUFA (a sum of eicosapentaenoic, docosapentaenoic, and docosahexaenoic acids), although the association for heart failure became weaker: the multivariable HR (95% CI) for the highest versus lowest quintiles was 0.80 (0.55 to 1.17), p for trend was 0.13.

There were no differences between genders in any associations shown in Tables 2 and 3. For example, the gender-specific multivariable HRs (95% CIs) for the highest versus lowest quintiles of fish intake for total cardiovascular disease were 0.84 (0.69 to 1.04) for men and 0.83 (0.68 to 1.02) for women, and respective HRs for ω-3 PUFA were 0.83 (0.63 to 1.08) for men and 0.84 (0.64 to 1.10) for women.

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**Table 2** Multivariate HRs and 95% CIs of Mortality From Ischemic Heart Disease, Cardiac Arrest, Heart Failure, Stroke, Total Cardiovascular Disease, and Total Death According to Quintiles of Fish Intake, 22,881 Men and 35,091 Women

| | Quintiles of Fish Intake* | | | | | |
|---|---|---|---|---|---|---|
| | Q1 (Low) | Q2 | Q3 | Q4 | Q5 (High) | p Value for Trend |
| Person-years | 144,903 | 146,244 | 147,322 | 148,797 | 148,639 | |
| Ischemic heart disease, n | 89 | 79 | 88 | 79 | 84 | |
| Age- and gender-adjusted | 1.0 | 0.93 (0.69–1.26) | 1.00 (0.75–1.35) | 0.85 (0.63–1.15) | 0.78 (0.58–1.06) | 0.09 |
| Multivariable† | 1.0 | 0.99 (0.73–1.34) | 1.11 (0.82–1.51) | 0.98 (0.71–1.34) | 0.86 (0.62–1.19) | 0.41 |
| Myocardial infarction, n | 74 | 59 | 73 | 59 | 64 | |
| Age- and gender-adjusted | 1.0 | 0.83 (0.59–1.17) | 1.00 (0.72–1.38) | 0.76 (0.54–1.07) | 0.72 (0.52–1.01) | 0.05 |
| Multivariable† | 1.0 | 0.87 (0.62–1.23) | 1.10 (0.79–1.54) | 0.87 (0.61–1.24) | 0.77 (0.53–1.10) | 0.22 |
| Cardiac arrest, n | 19 | 25 | 27 | 18 | 18 | |
| Age- and gender-adjusted | 1.0 | 1.39 (0.77–2.53) | 1.44 (0.80–2.59) | 0.89 (0.47–1.70) | 0.74 (0.39–1.42) | 0.15 |
| Multivariable† | 1.0 | 1.44 (0.79–2.62) | 1.49 (0.81–2.72) | 0.90 (0.46–1.76) | 0.73 (0.36–1.46) | 0.16 |
| Heart failure, n | 77 | 59 | 46 | 56 | 69 | |
| Age- and gender-adjusted | 1.0 | 0.82 (0.59–1.16) | 0.62 (0.43–0.89) | 0.71 (0.50–1.00) | 0.77 (0.55–1.06) | 0.07 |
| Multivariable† | 1.0 | 0.83 (0.59–1.17) | 0.63 (0.43–0.91) | 0.72 (0.50–1.03) | 0.76 (0.53–1.09) | 0.10 |
| Total stroke, n | 208 | 179 | 178 | 191 | 216 | |
| Age- and gender-adjusted | 1.0 | 0.91 (0.75–1.11) | 0.87 (0.71–1.07) | 0.88 (0.72–1.07) | 0.87 (0.72–1.06) | 0.17 |
| Multivariable† | 1.0 | 0.95 (0.78–1.16) | 0.93 (0.76–1.14) | 0.92 (0.75–1.14) | 0.91 (0.74–1.13) | 0.40 |
| Intraparenchymal hemorrhage, n | 53 | 43 | 41 | 37 | 49 | |
| Age- and gender-adjusted | 1.0 | 0.84 (0.56–1.26) | 0.78 (0.52–1.17) | 0.67 (0.44–1.01) | 0.80 (0.54–1.18) | 0.13 |
| Multivariable† | 1.0 | 0.93 (0.62–1.40) | 0.91 (0.60–1.39) | 0.78 (0.50–1.21) | 0.95 (0.62–1.47) | 0.58 |
| Subarachnoid hemorrhage, n | 30 | 33 | 27 | 33 | 30 | |
| Age- and gender-adjusted | 1.0 | 1.12 (0.68–1.83) | 0.89 (0.53–1.49) | 1.04 (0.63–1.70) | 0.91 (0.55–1.51) | 0.64 |
| Multivariable† | 1.0 | 1.18 (0.71–1.94) | 0.96 (0.57–1.65) | 1.12 (0.67–1.89) | 0.96 (0.55–1.68) | 0.84 |
| Ischemic stroke, n | 67 | 57 | 58 | 64 | 73 | |
| Age- and gender-adjusted | 1.0 | 0.92 (0.64–1.30) | 0.89 (0.63–1.26) | 0.93 (0.66–1.30) | 0.89 (0.64–1.24) | 0.56 |
| Multivariable† | 1.0 | 0.96 (0.67–1.37) | 0.97 (0.68–1.40) | 0.98 (0.68–1.40) | 0.93 (0.65–1.34) | 0.78 |
| Total cardiovascular disease, n | 453 | 384 | 383 | 389 | 436 | |
| Age- and gender-adjusted | 1.0 | 0.90 (0.78–1.03) | 0.86 (0.75–0.99) | 0.82 (0.72–0.94) | 0.81 (0.71–0.92) | <0.001 |
| Multivariable† | 1.0 | 0.93 (0.81–1.06) | 0.91 (0.79–1.05) | 0.86 (0.75–1.00) | 0.82 (0.71–0.95) | 0.007 |
| Total death, n | 1,429 | 1,288 | 1,328 | 1,397 | 1,566 | |
| Age- and gender-adjusted | 1.0 | 0.94 (0.87–1.01) | 0.94 (0.87–1.01) | 0.93 (0.87–1.00) | 0.93 (0.86–1.00) | 0.06 |
| Multivariable† | 1.0 | 0.96 (0.89–1.04) | 0.98 (0.90–1.05) | 0.96 (0.89–1.04) | 0.92 (0.85–1.00) | 0.08 |

*Energy-adjusted quintiles by nutrient residual model. †Further adjusted for history of hypertension and diabetes mellitus, smoking status, alcohol consumption, body mass index, mental stress, walking, sports, education levels, total energy, and dietary intakes of cholesterol, saturated and $\omega$-6 polyunsaturated fatty acids, vegetables, and fruit.

CI = confidence interval; HR = hazard ratio.

## Discussion

In this large, community-based, prospective cohort study, we observed generally inverse associations of fish and dietary $\omega$-3 PUFA intakes with risks of mortality from IHD, myocardial infarction, heart failure, and total cardiovascular disease. These inverse associations were more evident between dietary $\omega$-3 PUFA intake and heart failure. However, inverse associations with IHD or myocardial infarction were attenuated after adjustment for potential risk factors. As for stroke, neither fish nor $\omega$-3 PUFA dietary intakes were associated with mortality risk. Compared with the lowest quintile, dietary intakes of fish and $\omega$-3 PUFA in the highest quintile were associated with 18% to 19% lower mortality rates of total cardiovascular disease.

Previous Asian reports (2,4,5) have shown that fish or $\omega$-3 PUFA was associated inversely with the risk of IHD. The relatively weak association in the present study may be partly due to the use of mortality, rather than incidence, data. A previous prospective study of a national representative sample of 8,879 Japanese men and women (NIPPON DATA 80) did not show a significant association between fish intake and coronary mortality (3). The Japan Public Health Center-based prospective study (4), a cohort study of 41,578 men and women, showed a strong inverse association primarily for nonfatal coronary events but not for fatal events. Furthermore, the JELIS (Japan EPA Lipid Intervention Study), a recent Japanese intervention trial of 18,645 hypercholesterolemic patients (5), demonstrated a protective effect of eicosapentaenoic acid supplementation on nonfatal coronary events, but an effect on fatal coronary

**Table 3** Multivariate HRs and 95% CIs of Mortality From Ischemic Heart Disease, Cardiac Arrest, Heart Failure, Stroke, Total Cardiovascular Disease, and Total Death According to Quintiles of ω-3 PUFA Intake, 22,881 Men and 35,091 Women

| | Quintiles of ω-3 PUFA Intake* | | | | | |
|---|---|---|---|---|---|---|
| | Q1 (Low) | Q2 | Q3 | Q4 | Q5 (High) | p Value for Trend |
| Person-years | 143,208 | 145,552 | 148,548 | 149,359 | 149,237 | |
| Ischemic heart disease, n | 75 | 86 | 78 | 81 | 99 | |
| Age- and gender-adjusted | 1.0 | 1.06 (0.78–1.45) | 0.86 (0.62–1.18) | 0.84 (0.61–1.15) | 0.82 (0.61–1.11) | 0.07 |
| Multivariable† | 1.0 | 1.17 (0.84–1.62) | 0.98 (0.69–1.40) | 1.00 (0.68–1.45) | 0.95 (0.62–1.43) | 0.58 |
| Myocardial infarction, n | 65 | 65 | 60 | 60 | 79 | |
| Age- and gender-adjusted | 1.0 | 0.93 (0.66–1.31) | 0.77 (0.54–1.09) | 0.73 (0.51–1.03) | 0.78 (0.56–1.08) | 0.05 |
| Multivariable† | 1.0 | 0.97 (0.67–1.40) | 0.81 (0.54–1.20) | 0.77 (0.51–1.18) | 0.75 (0.47–1.19) | 0.14 |
| Cardiac arrest, n | 14 | 18 | 38 | 17 | 20 | |
| Age- and gender-adjusted | 1.0 | 1.14 (0.57–2.29) | 2.05 (1.11–3.79) | 0.87 (0.43–1.77) | 0.78 (0.40–1.56) | 0.33 |
| Multivariable† | 1.0 | 1.07 (0.51–2.22) | 1.86 (0.92–3.74) | 0.76 (0.33–1.73) | 0.64 (0.26–1.59) | 0.24 |
| Heart failure, n | 68 | 53 | 50 | 58 | 78 | |
| Age- and gender-adjusted | 1.0 | 0.73 (0.51–1.04) | 0.61 (0.42–0.88) | 0.68 (0.48–0.96) | 0.73 (0.53–1.01) | 0.07 |
| Multivariable† | 1.0 | 0.69 (0.47–1.01) | 0.56 (0.37–0.85) | 0.60 (0.39–0.92) | 0.58 (0.36–0.93) | 0.03 |
| Total stroke, n | 159 | 166 | 201 | 186 | 260 | |
| Age- and gender-adjusted | 1.0 | 0.97 (0.78–1.20) | 1.04 (0.85–1.28) | 0.92 (0.74–1.14) | 1.04 (0.85–1.26) | 0.93 |
| Multivariable† | 1.0 | 0.95 (0.75–1.19) | 1.00 (0.79–1.26) | 0.87 (0.67–1.12) | 0.93 (0.70–1.22) | 0.46 |
| Intraparenchymal hemorrhage, n | 49 | 44 | 42 | 39 | 49 | |
| Age- and gender-adjusted | 1.0 | 0.85 (0.56–1.27) | 0.74 (0.49–1.12) | 0.65 (0.43–0.99) | 0.69 (0.47–1.03) | 0.03 |
| Multivariable† | 1.0 | 0.87 (0.56–1.35) | 0.77 (0.48–1.24) | 0.68 (0.41–1.14) | 0.70 (0.40–1.24) | 0.16 |
| Subarachnoid hemorrhage, n | 28 | 28 | 33 | 32 | 32 | |
| Age- and gender-adjusted | 1.0 | 0.94 (0.56–1.59) | 1.04 (0.63–1.72) | 0.98 (0.59–1.63) | 0.91 (0.55–1.52) | 0.80 |
| Multivariable† | 1.0 | 0.98 (0.56–1.70) | 1.08 (0.61–1.93) | 1.02 (0.55–1.89) | 0.90 (0.44–1.81) | 0.83 |
| Ischemic stroke, n | 43 | 50 | 71 | 62 | 93 | |
| Age- and gender-adjusted | 1.0 | 1.07 (0.71–1.61) | 1.32 (0.91–1.93) | 1.10 (0.75–1.63) | 1.27 (0.88–1.83) | 0.22 |
| Multivariable† | 1.0 | 1.06 (0.69–1.63) | 1.31 (0.85–2.01) | 1.07 (0.68–1.69) | 1.17 (0.71–1.92) | 0.58 |
| Total cardiovascular disease, n | 360 | 367 | 412 | 388 | 518 | |
| Age- and gender-adjusted | 1.0 | 0.94 (0.81–1.09) | 0.94 (0.82–1.08) | 0.84 (0.73–0.97) | 0.90 (0.79–1.04) | 0.04 |
| Multivariable† | 1.0 | 0.93 (0.80–1.09) | 0.91 (0.78–1.07) | 0.81 (0.68–0.96) | 0.81 (0.67–0.98) | 0.01 |
| Total death, n | 1,252 | 1,262 | 1,328 | 1,415 | 1,751 | |
| Age- and gender-adjusted | 1.0 | 0.95 (0.88–1.02) | 0.90 (0.84–0.98) | 0.91 (0.84–0.98) | 0.93 (0.87–1.00) | 0.03 |
| Multivariable† | 1.0 | 0.97 (0.90–1.06) | 0.94 (0.86–1.02) | 0.94 (0.85–1.03) | 0.92 (0.84–1.02) | 0.10 |

*Energy-adjusted quintiles by nutrient residual model. †Further adjusted for history of hypertension and diabetes mellitus, smoking status, alcohol consumption, body mass index, mental stress, walking, sports, education levels, total energy, and dietary intakes of cholesterol, saturated and ω-6 PUFA, vegetables, and fruit.

PUFA = polyunsaturated fatty acids; other abbreviations as in Table 2.

events was not confirmed because of the small numbers (n = 60).

As for stroke, 3 previous observational studies have examined the associations between fish and stroke mortality among Asian populations (2,3,17). A study of 18,244 men in Shanghai, China (2), showed no association; the multivariable-adjusted HR (95% CI) for fish/shellfish intake of ≥200 g/week compared with <50 g/week was 1.11 (0.83 to 1.47). The NIPPON DATA 80 (3) reported a HR (95% CI) for fish intake of twice a day or more of 1.26 (0.70 to 2.29) and for intake of once a day of 1.20 (0.82 to 1.75) compared with once or twice a week. That study also showed no association with cerebral hemorrhage or infarction, separately. Another study of 40,349 men and women in Hiroshima and Nagasaki, Japan (17), showed 15% lower mortality from total stroke among persons with intake of fish products of ≥46 g/day compared with persons consuming ≤18 g/day. In that study, the risk reduction was primarily observed for intraparenchymal hemorrhage (HR: 0.70 [95% CI: 0.54 to 0.92]) but not for ischemic stroke (HR: 0.94 [95% CI: 0.77 to 1.14]). We observed a similar and nonsignificant inverse association with intraparenchymal hemorrhage. Taken together, dietary intakes of fish and ω-3 PUFA seem unlikely to have a protective effect on mortality from ischemic stroke and a harmful effect on mortality from intraparenchymal hemorrhage among Asian populations. As for incident stroke, a nested case-control study in a Japanese community cohort of approximately 10,000 subjects (18) showed no association between serum ω-3 PUFA (eicosapentaenoic, docosapentaenoic, or docosahexaenoic acid) concentrations and risk of stroke and its subtypes (HR for 1 SD changes ranged 1.01 to 1.17 for total stroke, 0.99 to 1.21 for ischemic stroke, and 0.87 to 1.09 for intraparenchymal hemorrhage; none of these reached sta-

tistical significance). The JELIS trial (5) showed no protective effect of eicosapentaenoic acid supplementation on risk of incident total stroke (HR: 1.02 [95% CI: 0.91 to 1.13]), ischemic stroke (HR: 0.97 [95% CI: 0.85 to 1.10]), or hemorrhagic stroke (HR: 1.12 [95% CI: 0.91 to 1.39]) among Japanese hypercholesterolemic patients. Yet, to date, there are no reports on inverse associations between fish or ω-3 PUFA and the incidence of stroke among general populations of Asia. By contrast, inverse associations between fish or ω-3 PUFA and the incidence of total or ischemic stroke have been reported for Western populations, for example, Dutch (19) or Americans (20–23). However, consistent with the present study, such an association was not observed with stroke mortality in the Chicago Western Electric Study (24) or the Iowa Women's Health Study (25).

We did not observe clear inverse associations between dietary intake of fish or ω-3 PUFA with the risk of mortality from cardiac arrest, although a tendency of lower risk was observed in the top 2 quintiles of fish intake. Despite growing evidence of an antiarrhythmic effect of fish oil (26), a number of trials have shown that ω-3 PUFA supplements have little effect on the rate of defibrillator firings in patients with implantable cardioverter-defibrillators (27). The JELIS trial (5) did not find that eicosapentaenoic acid supplementation reduced sudden death (HR: 1.06 [95% CI: 0.55 to 2.07]), probably because of a small number of cases (n = 35) and the high background fish consumption among Japanese. It has been suggested that the slope of the dose-response curve for the antiarrhythmic effect of ω-3 PUFA is steep at modest levels (<750 mg eicosapentaenoic plus docosahexaenoic acid) but plateaus thereafter (28).

Few studies have examined the association of fish and ω-3 PUFA intakes with the incidence of congestive heart failure. The Cardiovascular Health Study, involving 4,738 men and women ages ≥65 years (8), found an inverse association of baked/broiled fish intake with congestive heart failure; the HR (95% CI) for baked/broiled fish intake of ≥5 times a week versus <1 time a month was 0.68 (0.45 to 1.03), and the trend across the frequency categories was statistically significant (p = 0.009). A similar inverse association was observed for quintiles of long-chain ω-3 PUFA (eicosapentaenoic and docosahexaenoic acids). This result was supported by a recent report from the ARIC (Atherosclerosis Risk in Communities) study, showing an inverse association between plasma long-chain ω-3 PUFA and incident heart failure among women (29). Our findings are in line with these studies. On the other hand, another ARIC study (9) found no association between dietary fish intake ascertained by food frequency questionnaire and incident heart failure, probably because fried fish could not be differentiated from other fish. The Cardiovascular Health Study (8) reported that fried fish, unlike baked/broiled fish, increased the risk of incident heart failure. Our questionnaire did not directly ask about fried fish intake, but when we excluded the estimated amount of deep-fried fish from the present analysis for fish intake, the inverse association with heart failure did not change materially: the multivariate HR (95% CI) for the highest versus lowest quintiles of fish intake was 0.78 (0.55 to 1.10), p for trend was 0.14. This finding may reflect a cultural difference in fried fish intake between Western and far-Eastern countries, namely, that fried fish in Japan is usually rich in ω-3 PUFA, unlike the white fish used in the United States. Japanese also use less cooking oil containing trans fats.

For heart failure, however, the accuracy of death certificate diagnosis in Japan is a concern. It is generally believed that death certificate diagnosis for heart failure before 1994 was not necessarily accurate, because Japanese physicians were inclined to diagnose deaths of unknown origin or deaths occurring during the end stages of chronic diseases as "unspecified heart failure" (I50.9 for ICD-10) (30). Sudden death of unknown origin, such as cardiac arrest or arrhythmic death, was especially likely to be classified as heart failure, whereas these deaths have been mainly diagnosed as IHD in the U.S. (31). Sudden death was reported to account for 27% to 50% of diagnosed heart failure as the underlying cause of death in Japan (30). Therefore, we speculate that one-fourth to one-half of the heart failure in this study was contaminated with cardiac arrest, and that may have affected the association of fish or ω-3 PUFA intake with heart failure.

It has been speculated that docosahexaenoic acid is most important for cardioprotection (10), because sudden cardiac deaths were not reduced by eicosapentaenoic acid supplementation in the JELIS trial (5). The aforementioned ARIC study reported that higher plasma docosahexaenic, but not eicosapentaenoic, acid was inversely associated with incident heart failure among white women (29). In the present study, however, eitacopentaenoic and docosahexaenoic acids were highly correlated with each other (r = 0.99), and therefore dietary intakes of these were similarly associated with cardiovascular outcomes (not shown).

The JACC study is a large, nationwide, community-based Japanese cohort, which allowed us to examine the associations of fish and ω-3 PUFA intakes with heart failure for the first time in Asian populations. Another advantage of the present study was the wider distribution of fish intake than that in Western studies. Therefore, we could test the potential effect of very high intake of fish or ω-3 PUFA, which cannot be studied in Western populations.

**Study limitations.** Dietary intakes in this study were based on a food frequency questionnaire. Although this questionnaire has been previously validated (13,15), there are several limitations. First, for people who picked the highest categories of frequency, namely, almost every day, we could not estimate how many times they ate fish in a day. A previous

study (3) showed approximately 6% of Japanese men and women eat fish twice or more in a day. In the present study, 73% of people who responded "almost every day" for fish frequency fell into the highest quintile of nonenergy-adjusted fish intake, and 27% of them were in the second highest quintile of fish intake. Thus, the impact of misclassification may weaken the association to some extent but not substantially. Yet, it should be noted that the absolute amount of fish or ω-3 PUFA intake in the present study is probably underestimated; the estimated mean fish intake in the present study (49.5 g/day) was much lower than in a National Nutrition Survey in 1990 (95.3 g/day). Indeed, the estimated fish intake in this study was one-half that using dietary records in a subsample. Second, we excluded 23,339 subjects because of incomplete dietary information. Excluded subjects were older (60.8 vs. 56.1 years) and more likely to be men than women (45% vs. 39%) compared with included subjects, but there were only slight differences between them in other baseline characteristics, thus suggesting bias is unlikely. Lastly, we cannot negate the possibility of residual confounding by other factors, healthy life-styles, or socioeconomic status.

## Conclusions

We found an inverse association between fish and ω-3 PUFA dietary intakes and cardiovascular mortality, especially for heart failure in a large, nationwide, community-based Japanese cohort. This finding, taken together with those from prior studies, suggests a protective effect of fish intake on cardiovascular diseases.

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