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Hiroyasu Iso, Minatsu Kobayashi, Junko Ishihara, Satoshi Sasaki, Katsutoshi Okada, Yoshikuni Kita, Yoshihiro Kokubo and Shoichiro Tsugane

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Intake of Fish and n3 Fatty Acids and Risk of Coronary Heart Disease Among Japanese

The Japan Public Health Center-Based (JPHC) Study Cohort I

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Background—Once- or twice-weekly consumption of fish (or a small amount of fish intake) reduces the risk of coronary heart disease and sudden cardiac death in Western countries. It is uncertain whether a high frequency or large amount of fish intake, as is the case in Japan, further reduces the risk.

Methods and Results—To examine an association between high intake of fish and n3 polyunsaturated fatty acids and the risk of coronary heart disease, a total of 41 578 Japanese men and women aged 40 to 59 years who were free of prior diagnosis of cardiovascular disease and cancer and who completed a food frequency questionnaire were followed up from 1990–1992 to 2001. After 477 325 person-years of follow-up, 258 incident cases of coronary heart disease (198 definite and 23 probable myocardial infarctions and 37 sudden cardiac deaths) were documented, comprising 196 nonfatal and 62 fatal coronary events. The multivariable hazard ratios (HRs) and 95% confidence intervals in the highest (8 times per week, or median intake=180 g/d) versus lowest (once a week, or median intake=23 g/d) quintiles of fish intake were 0.63 (0.38 to 1.04) for total coronary heart disease, 0.44 (0.24 to 0.81) for definite myocardial infarction, and 1.14 (0.36 to 3.63) for sudden cardiac death. The reduced risk was primarily observed for nonfatal coronary events (HR=0.43 [0.23 to 0.81]) but not for fatal coronary events (HR=1.08 [0.42 to 2.76]). Strong inverse associations existed between dietary intake of n3 fatty acids and risk of definite myocardial infarction (HR=0.35 [0.18 to 0.66]) and nonfatal coronary events (HR=0.33 [0.17 to 0.63]).

Conclusions—Compared with a modest fish intake of once a week or ≈20 g/d, a higher intake was associated with substantially reduced risk of coronary heart disease, primarily nonfatal cardiac events, among middle-aged persons. **(*Circulation*. 2006;113:195-202.)**

Key Words: fatty acids ■ diet ■ epidemiology ■ myocardial infarction ■ follow-up studies

Once- or twice-weekly consumption of fish (or a small amount of fish intake, ie, ≈30 to 60 g/d, of fish intake) is associated with reduced risk of coronary heart disease in Western countries[1–6] and in Shanghai, China.[7] A biomarker of fish intake, blood or tissue n3 polyunsaturated fatty acid levels, is also associated with reduced risk.[8–11] In the majority of previous studies,[1–4,6–8,10,11] this inverse association has been observed for fatal coronary heart disease or sudden cardiac death, which implicates an antiarrhythmic effect of n3 polyunsaturated fatty acids. Other studies,[5,6] however, have shown an inverse association with nonfatal coronary heart disease. Other than an antiarrhythmic effect, the beneficial effects of n3 polyunsaturated fatty acids include inhibition of platelet aggregation,[12,13] reduction of blood viscosity,[13] suppression of leukotriene (lipid mediators for neutrophil and macrophage aggregation) formation,[14] inhibition of endothe-

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lial cell proliferation,[15] and reduction of insulin resistance,[16] triglycerides,[17] fibrinogen,[18] and blood pressure levels.[19]

There is little evidence about whether a fish intake of several times or more per week or >60 g/d may further reduce the risk of initial coronary heart disease events compared with low or modest fish intake. A prospective study in Japan, where 95% of adults eat fish at least once a week and the average fish intake is ≈100 g/d,[20] should provide evidence. It is also of value to separately examine the association of fish consumption with fatal and nonfatal events in Japan, where case fatality of coronary heart disease was reported at ≈25%,[21] far lower than the 50% rate reported in Western countries.[22]

We investigated this relation prospectively in a large follow-up study of middle-aged Japanese men and women. Our a priori hypothesis was that the intake of fish and n3 polyunsaturated fat is associated with a reduced risk of coronary heart disease within a population with a high mean fish intake.

Methods

Study Cohort

The Japan Public Health Center-Based (JPHC) Study Cohort I was a population-based sample of 27 063 men and 27 435 women who were born between 1930 and 1949 (40 to 59 years of age) and who were registered in 14 administrative districts supervised by 4 public health center (PHC) areas on January 1, 1990. The male population included 6022 from Ninohe city and Karumai town in the Ninohe PHC area of Iwate prefecture, 7559 from Yokote city and Omonogawa town in the Yokote PHC area of Akita, 6173 from 8 districts of Minami-Saku county in the Saku PHC area of Nagano, and 7309 men from Gushikawa city and Onna village in the Ishikawa PHC area of Okinawa.[23] The respective female populations were 6269, 8223, 6046, and 6897. The present study was approved by the human ethics review committees of the National Cancer Center and the University of Tsukuba.

Baseline Survey

A self-administered questionnaire was distributed to all registered noninstitutional community residents in 1990, which asked them to report on their demographic characteristics, medical history, smoking and drinking habits, and diet. Of these, 20 665 men (76%) and 22 484 women (82%) returned their questionnaires between January 1990 and May 1992, primarily between February and October 1990. We excluded men who reported myocardial infarction, angina pectoris, stroke, or cancer at baseline, which left for analysis a total of 41 578 persons (19 985 men and 21 593 women) who had reported their habit of fish consumption.

The 1990 food frequency questionnaire (FFQ) included 44 foods with 4 questions that assessed fresh fish, dried fish, and fish products, whereas the 1995 follow-up questionnaire assessed 147 foods with 19 fish questions. Each participant was asked how often on average during the previous month in the 1990 questionnaire and the previous year in the 1995 questionnaire he or she had consumed fish. A common unit or portion size for each food was specified in the 1995 questionnaire but not in the 1990 questionnaire. Possible responses for each food item ranged from "rarely," "1–2 days/week," and "3–4 days/week" to "almost every day" in the 1990 questionnaire, and from "rarely," "1–3 days/mo," "1–2 days/week," "3–4 days/week," "5–6 days/week," "once/day," "2–3 times/d," and "4–6 times/d" to "7 or more times/d." We calculated the consumption of each food by multiplying the frequency score of consumption of each food (0, 1.5, 3.5, and 6.0, respectively, in the 1990 questionnaire and 0, 0.07, 0.2, 0.5, 0.8, 1.0, 2.5, 5.0, and 8.0, respectively, in the 1995 questionnaire) with each portion size (for seafood, 100 g for fresh fish, 20 g for dried or salted fish, 20 g for salted fish roe, and 20 g for salted fish preserves, estimated from a validation study conducted in a sample of 94 men selected from the cohorts in 1990[24] and by predetermined portion size in the 1995 questionnaire[25]). The average daily intake of nutrients was calculated by multiplying the frequency of consumption of each item by its nutrient content per serving and totaling the nutrient intake for all food items.

To calculate dietary intake of long-chain n3 polyunsaturated fatty acids (eicosapentaenoic and docosahexaenoic acids), we assigned grams per serving as 1.22 g for fresh fish and shellfish, 0.40 g for dried fish, 0.52 g for salted eggs, and 0.11 g for salted fish gut in the 1990 questionnaire[24] and specific values for each of 19 fish and fish products in the 1995 questionnaire.[25] For reproducibility, the sex-specific Spearman correlation coefficients between 2 administrations of the 1990 questionnaires administered 5 to 6 years apart among 94 men and 107 women were 0.50 and 0.67 (both $P<0.001$) for total fish intake and 0.45 and 0.71 (both $P<0.001$) for n3 fatty acid intake, respectively.[26] Two administrations of the 1995 questionnaire, 1 year apart, among 101 men and 108 women yielded Spearman correlations of 0.65 and 0.61 (both $P<0.001$) for total fish intake and 0.61 and 0.74 (both $P<0.001$) for n3 fatty acid intake, respectively.[27] Validity was assessed by comparing the data from the 1990 and 1995 questionnaires with four 1-week dietary records, collected approximately 3 to 4 months apart, and with plasma phospholipid fatty acid composition.[25] The mean intake of total fish was 48 g/d in men and 40 g/d in women according to the 1990 questionnaire and 137 g/d in men and 108 g/d in women according to four 1-week dietary records, with the respective Spearman correlation coefficients equal to 0.49 and 0.45 (both $P<0.001$; n=94 and 107, respectively).[26] Values were 114 g/d in men and 105 g/d in women for the 1995 questionnaire and 136 g/d in men and 106 g/d in women for the dietary records, with the respective Spearman correlation coefficients equal to 0.46 and 0.42 (both $P<0.001$; n=102 and 113, respectively).[28] Intake of n3 fatty acids was correlated with the percentage of corresponding n3 fatty acids in serum phospholipids among men (Spearman correlation coefficient 0.48, $P<0.001$ for the 1990 questionnaire[26] and 0.29, $P<0.01$ for the 1995 questionnaire[25]). Intake of n3 polyunsaturated fatty acids was not adjusted for total energy intake by the residual approach[29] for the primary analysis because the nonadjusted value had a better reproducibility and validity. Again, the Spearman correlation coefficients for reproducibility of non–energy-adjusted intake were 0.65 in men and 0.61 in women for fish intake and 0.61 in men and 0.74 in women for n3 polyunsaturated fatty acid intake, whereas those of energy-adjusted intake were 0.44 and 0.34, and 0.51 and 0.41, respectively.[27] The correlation coefficients for validity of non–energy-adjusted intake of n3 fatty acids in the 1990 questionnaire were 0.33 compared with dietary records and 0.48 compared with serum fatty acids, whereas those of energy-adjusted intake were 0.20 and 0.31, respectively.[25,26] The corresponding coefficients in the 1995 questionnaire were 0.27, 0.29, 0.21, and 0.21. For the secondary analysis, the model of energy-adjusted intake was examined by the residual approach.

Total energy was adjusted as a covariate in the multivariable model. Information on fish oil supplements was not requested in 1990 or 1995 because the prevalence of this supplement was assumed to be low.

Confirmation of Coronary Heart Disease

We registered a total of 30 hospitals with a department of cardiology in the 4 PHC areas (number of hospitals=10 for the Ninohe PHC area, 4 for the Yokote PHC area, 3 for the Saku PHC area, and 13 for the Ishikawa PHC area). They were all major hospitals at which acute coronary heart disease patients could be admitted. In each hospital, medical records were reviewed by registered hospital physicians or PHC physicians who were blinded to the lifestyle data. Acute coronary events were registered if they occurred after the date of return of the baseline questionnaire and before January 1, 2002.

Myocardial infarction was confirmed in the medical records according to the criteria of the MONICA (Monitoring Trends and Determinants of Cardiovascular Disease) project,[30] which requires evidence from ECGs, cardiac enzymes, and/or autopsy. When such a workup was not performed and there was typical chest pain, a

probable diagnosis was made. In the absence of diagnosis of myocardial infarction, deaths that occurred within 1 hour from onset of event were regarded as sudden cardiac deaths. Deaths within 28 days of the onset of myocardial infarction and sudden cardiac deaths were regarded as fatal coronary events. The cases registered in this registration system included 216 coronary heart disease events, and among them, we confirmed 171 definite myocardial infarctions, 8 probable myocardial infarctions, and 7 sudden cardiac deaths for the present analysis.

To complete the surveillance for nonfatal myocardial infarction, we asked participants by letter or telephone about the onset of coronary events and for permission to review the medical records. This included 141 persons who reported a history of myocardial infarction on the 10-year follow-up questionnaire (88% followed up) who had not been registered as having had a coronary event. Of these 141 individuals, 122 (87%) were contacted and 74 provided information on suspected myocardial infarctions. Of these 74 individuals, 63 (85%) provided written informed consent to review their medical records, and the medical records were reviewed by hospital physicians, PHC physicians, or research physicians. Among these participants, we confirmed definite myocardial infarctions in 23 individuals, who were included as having had myocardial infarction for analysis.

For fatal myocardial infarctions and sudden cardiac deaths, we conducted a systematic search of death certificates. All death certificates were forwarded to the PHC in the area of residency, and mortality data were sent centrally to the Ministry of Health, Welfare and Labor and coded for the National Vital Statistics. Registration of death is required by the Family Registration Law and is believed to be complete in Japan.

For all coronary heart disease and acute heart failure deaths (International Classification of Diseases, 10th Revision [ICD-10] I21–I23, I46, and I50) listed on the death certificate but not registered in hospitals, medical records in registered hospitals were reviewed by hospital personnel, PHC physicians, or research physician-epidemiologists. From this systematic review of death certificates, we added 4 definite and 15 probable myocardial infarctions and 30 sudden cardiac deaths. In total, we confirmed for analysis 198 definite and 23 probable myocardial infarctions and 37 sudden cardiac deaths.

Statistical Analysis

Statistical analyses were based on incidence rates of coronary heart disease during 11-year follow-up from 1990 to the end of 2001. For each individual, person-months of follow-up were calculated from January 1, 1990, to the first end point: Death, emigration, or January 1, 2002, whichever came first. The incidence rates of coronary heart disease were calculated according to total fish consumption or quintiles of intake of n3 polyunsaturated fatty acids.

The hazard ratio (HR) with 95% confidence intervals (CIs) was calculated after adjustment for age, sex, and other potential confounding factors with time-dependent Cox proportional hazards models. We updated the quintiles of dietary intake and the confounding factors listed below, except for age, sex, education level, and public health center, using the 5-year follow-up questionnaire survey, to which 80% of the baseline participants responded. For example, dietary intakes from 1990 FFQ were related to the incidence of coronary heart disease from 1990 through 1995, and those from the 1995 FFQ were related to the incidence from 1995 through 2001. For those who had not responded to the 1995 FFQ and had the incidence from 1995 through 2001, intakes reported on the 1990 FFQ were used. Potential confounding factors for statistical adjustment were baseline values of age (5-year categories); sex; smoking status (never, ex-smoker, and current smoker of 1 to 19 or ≥20 cigarettes per day); alcohol intake (nondrinkers [<1 day per month], occasional drinkers [1 to 3 days per month], or weekly ethanol intake of 1 to 149 g/wk, 150 to 299 g/wk, 300 to 449 g/wk, or ≥450 g/wk); body mass index (quintiles); history of hypertension or diabetes (yes or no); medication use for hypercholesterolemia (yes or no); education level (junior high school, high school, and college or more); sports at leisure time (< 1 day/mo, 1 to 3 days/mo, and ≥1 day/wk); quintiles of dietary intake of fruits, vegetables, saturated fat, monounsaturated fat, n6 polyunsaturated fat, cholesterol, and total energy; and PHC.

We conducted tests for trend across the categories of fish or n3 polyunsaturated fatty acid intake by assigning median values for each category and testing the significance of this variable. Test for effect modification by sex was conducted with an interaction term generated by multiplying the median of each quintile of fish and n3 fatty acid intake by sex.

Results

During 477 325 person-years of follow-up of 41 578 middle-aged persons (19 985 men and 21 593 women), we documented 258 incident cases of coronary heart disease (207 men and 51 women), including 198 definite and 23 probable myocardial infarctions and 37 sudden cardiac deaths. These cases comprised 196 nonfatal and 62 fatal coronary events.

Table 1 shows cardiovascular risk factors and intake of selected nutrients and foods, according to dietary intake of fish. These variables, except for age, were updated by the 5-year follow-up survey. Compared with persons who ate less fish, those who ate more fish were slightly older, had a lower education level, and were less likely to be overweight but were more likely to be hypertensive and to have a higher alcohol intake. Fish intake was positively associated with total energy intake and intake of each fatty acid and cholesterol; beef, pork, or lamb; chicken; eggs; fruits; vegetables; and dairy foods. Very similar associations were observed between n3 polyunsaturated fatty acids and potential confounding variables (not shown in the Table). The mean frequency of fish intake was once per week in the lowest quintile of fish and n3 polyunsaturated fatty acid intake, whereas fish intake frequency was 8 times per week in the highest quintile.

Tables 2 and 3 present HRs of coronary heart disease according to dietary intake of fish and n3 polyunsaturated fatty acids. The age- and sex-adjusted incidence rates per 1000 person-years (95% CI) of coronary heart disease were 0.5 (0.4 to 0.5) for all subjects, 0.7 (0.5 to 0.9) for the lowest quintile of fish intake, 0.4 (0.3 to 0.6) for the second, 0.5 (0.4 to 0.7) for the third, 0.4 (0.3 to 0.6) for the fourth, and 0.3 (0.2 to 0.4) for the highest quintile. The associations of fish and n3 fatty acid intake with risk of coronary heart disease did not vary by sex (P for interaction >0.05).

There were significant inverse associations between fish intake and age- and sex-adjusted risk of total coronary heart disease, total and definite myocardial infarctions, and nonfatal coronary events but not of sudden cardiac death or fatal coronary events. After further adjustment for other cardiovascular and selected dietary variables, the inverse associations were weaker but remained significant for total coronary heart disease, total myocardial infarction, definite myocardial infarction, and nonfatal coronary events (Figure). The respective multivariable HRs (95% CIs) in the highest versus lowest quintiles of fish intake were 0.63 (0.38 to 1.04), 0.47 (0.26 to 0.85), 0.44 (0.24 to 0.81), and 0.43 (0.23 to 0.81). The multivariable HRs were 1.14 (0.36 to 3.63) for sudden cardiac death and 1.08 (0.42 to 2.76) for fatal coronary events, neither of which reached statistical significance. The results among men were similar and were somewhat, but not significantly,

TABLE 1. Distributions of Updated Cardiovascular Risk Factors and Selected Dietary Variables in a Cohort of 41 578 Men and Women According to Quintiles of Fish and n3 Polyunsaturated Fatty Acid Intake

	Quintiles of Fish Intake, g/d				
	1 (Low)	2	3	4	5 (High)
Median intake, g/d	23	51	78	114	180
No. at risk	8914	8527	8171	7946	8020
Men, %	48	49	46	49	48
Age at baseline, y	49.5	48.9	49.3	49.6	50.2
Current smoker, %	28	29	28	29	29
Mean alcohol intake, g/wk	246	250	250	265	299
Mean body mass index, kg/m^2	23.8	23.7	23.6	23.5	23.5
History of hypertension, %	14	15	17	16	17
History of diabetes, %	4	4	4	4	4
Treatment for hyperlipidemia, %	3	4	5	5	4
College or higher education, %	14	14	13	13	11
Sport at leisure time ≥1 day/wk, %	17	17	17	17	18
Vitamin supplement ≥1 time/wk, %	23	22	22	22	22
Dietary variables					
Mean daily total energy, kcal	1537	1806	1980	2235	2747
Mean daily intake, g					
Saturated fats	13.7	15.5	17.4	19.6	26.4
Monounsaturated fats	14.6	17.3	20.2	23.9	33.1
n3 Polyunsaturated fatty acids	0.3	0.6	0.9	1.3	2.4
n6 Polyunsaturated fatty acids	6.6	7.9	9.0	10.5	13.7
Cholesterol	197	253	303	361	517
Frequency, times/wk					
Fish	1.3	2.7	3.6	5.0	8.4
Beef, pork, or lamb	2.3	2.1	2.2	2.4	3.1
Chicken	1.1	1.3	1.5	1.8	2.6
Eggs	3.4	3.9	4.3	4.7	5.5
Fruits	3.1	4.7	5.8	6.9	8.4
Vegetables	13.0	16.9	20.0	23.5	28.9
Dairy foods	5.3	6.2	6.5	7.0	7.8

stronger than the results for women. The evaluation of results among women was limited by fewer numbers of coronary heart disease cases. For men, the multivariable HRs (95% CIs) in the highest versus lowest quintiles of fish intake were 0.53 (0.30 to 0.94) for total coronary heart disease, 0.41 (0.21 to 0.79) for total myocardial infarction, 0.38 (0.19 to 0.78) for definite myocardial infarction, 0.37 (0.18 to 0.77) for nonfatal coronary events, 0.91 (0.25 to 3.27) for sudden cardiac death, and 0.77 (0.28 to 2.13) for fatal coronary events.

Strong inverse associations were found between dietary intake of n3 polyunsaturated fatty acids and risk of coronary heart disease, more specifically, nonfatal coronary heart disease, for men and women (Figure). The multivariable HRs (95% CIs) in the highest versus lowest quintiles of n3 polyunsaturated fatty acids were 0.58 (0.35 to 0.97) for total coronary heart disease, 0.43 (0.24 to 0.78) for total myocardial infarction, 0.35 (0.18 to 0.66) for definite myocardial infarction, and 0.33 (0.17 to 0.63) for nonfatal coronary events; however, the multivariable HRs were 1.24 (0.39 to 3.98) for sudden cardiac death and 1.54 (0.60 to 3.99) for fatal coronary events. For men, the multivariable HRs (95% CIs) in the highest versus lowest quintiles of n3 polyunsaturated fatty acids were 0.54 (0.30 to 0.96) for total coronary heart disease, 0.41 (0.21 to 0.80) for total myocardial infarction, 0.35 (0.17 to 0.73) for definite myocardial infarction, 0.33 (0.16 to 0.69) for nonfatal coronary events, 0.99 (0.27 to 3.62) for sudden cardiac death, and 1.06 (0.37 to 2.99) for fatal coronary events.

When the energy-adjusted intake of n3 polyunsaturated fatty acids was entered into the model, the multivariable HRs (95% CIs) in the highest versus lowest quintiles of the intake among men and women were 0.61 (0.38 to 0.97) for total coronary heart disease, 0.44 (0.26 to 0.75) for total myocardial infarction, 0.33 (0.18 to 0.61) for definite myocardial infarction, 0.32 (0.17 to 0.61) for nonfatal coronary events, 2.52 (0.75 to 8.48) for sudden cardiac death, and 1.92 (0.79 to 4.66) for fatal coronary events. The respective HRs among men were 0.59 (0.36 to 0.99), 0.45 (0.25 to 0.80), 0.36 (0.18 to 0.69), 0.35 (0.17 to 0.69), 2.64 (0.65 to 10.8), and 1.62 (0.62 to 4.22).

TABLE 2. Age and Sex-Adjusted and Multivariable HRs and 95% CIs of Coronary Heart Disease According to Quintiles of Fish Intake

	Quintiles of Fish Intake, g/d					
	1 (Low)	2	3	4	5 (High)	*P* for Trend
Median intake, g/d	23	51	78	114	180	
Person-years	102 044	97 984	93 879	91 229	92 189	
Coronary heart disease						
No. of cases	78	46	52	45	37	
HR (95% CI)	1	0.57 (0.40–0.83)	0.74 (0.52–1.05)	0.60 (0.42–0.87)	0.47 (0.32–0.69)	0.001
Multivariable HR (95% CI)	1	0.71 (0.48–1.05)	0.93 (0.63–1.38)	0.83 (0.53–1.30)	0.63 (0.38–1.04)	0.25
Total MI						
No. of cases	71	46	42	37	25	
HR (95% CI)	1	0.63 (0.44–0.92)	0.65 (0.45–0.96)	0.55 (0.37–0.81)	0.35 (0.22–0.56)	<0.001
Multivariable HR (95% CI)	1	0.81 (0.54–1.20)	0.85 (0.55–1.31)	0.78 (0.48–1.27)	0.47 (0.26–0.85)	0.03
Definite MI						
No. of cases	69	39	35	33	22	
HR (95% CI)	1	0.55 (0.37–0.82)	0.56 (0.37–0.84)	0.50 (0.33–0.76)	0.32 (0.20–0.51)	<0.001
Multivariable HR (95% CI)	1	0.70 (0.46–1.07)	0.74 (0.47–1.16)	0.72 (0.44–1.21)	0.44 (0.24–0.81)	0.03
Sudden cardiac death						
No. of cases	7	0	10	8	12	
HR (95% CI)	1	...	1.60 (0.61–4.21)	1.15 (0.42–3.17)	1.60 (0.63–4.06)	0.04
Multivariable HR (95% CI)	1	...	1.25 (0.42–3.70)	0.88 (0.27–2.89)	1.14 (0.36–3.63)	0.15
Nonfatal coronary events						
No. of cases	67	41	36	31	21	
HR (95% CI)	1	0.60 (0.41–0.89)	0.60 (0.40–0.89)	0.49 (0.32–0.74)	0.31 (0.19–0.51)	<0.001
Multivariable HR (95% CI)	1	0.77 (0.51–1.16)	0.79 (0.50–1.24)	0.70 (0.42–1.18)	0.43 (0.23–0.81)	0.02
Fatal coronary events						
No. of cases	11	5	16	14	16	
HR (95% CI)	1	0.43 (0.15–1.24)	1.62 (0.75–3.48)	1.30 (0.59–2.85)	1.40 (0.65–3.01)	0.09
Multivariable HR (95% CI)	1	0.40 (0.13–1.19)	1.38 (0.59–3.22)	1.05 (0.42–2.64)	1.08 (0.42–2.76)	0.31

MI indicates myocardial infarction.

HRs were adjusted for age and sex. Multivariable models were adjusted for age; sex; cigarette smoking; alcohol intake; body mass index; histories of hypertension and diabetes; medication use for hypercholesterolemia; education level; sports at leisure time; quintiles of dietary intake of fruits, vegetables, saturated fat, monounsaturated fat, n6 polyunsaturated fat, cholesterol, and total energy; and PHC.

Discussion

In the present large prospective study of middle-aged Japanese, we found a significant inverse association between fish intake and risk of coronary heart disease, primarily myocardial infarction or nonfatal coronary events, after adjustment for cardiovascular risk factors and selected dietary variables. Our finding is unique because the risk of coronary heart disease was ≈40% lower among persons at the highest quintile of fish intake (8 times per week, or median intake=180 g/d) than among those at the lowest quintile (once per week, or median intake=23 g/d). This implies that a high intake of fish can further reduce the risk of initial coronary heart disease events compared with a moderate fish intake, which has never been tested by previous observational studies in Western countries.[1–6,8–11] In secondary prevention trials for coronary heart disease, a modest intake of fatty fish (200 to 400 g/wk) or supplemental intake of n3 polyunsaturated fatty acids (1 g/d) was demonstrated to reduce mortality by approximately 20% to 30% among patients with myocardial infarction.[31,32]

Some previous observational studies, although not all, showed that fish intake once or twice per week[5,6] or a small intake of fish (approximately 30 to 60 g/d)[1,3,4,7] was associated with a 30% to 60% lower risk of fatal coronary heart disease or sudden cardiac death. These studies also found a 40% to 80% reduction in the risk of fatal coronary heart disease or sudden cardiac death for the highest compared with the lowest quintiles or quartiles of dietary, blood, or tissue n3 polyunsaturated fatty acids.[2,8–11] In some studies, however, the risk reduction was observed for nonfatal coronary heart disease[5] or nonsudden fatal coronary heart disease.[3] It is noteworthy that the first quintile of fish intake in the present study corresponded to the third quintile of fish intake in Western populations, in which a reduction of risk of coronary heart disease was found in the highest quintile of fish intake. To assess the association between fish intake and risk of coronary heart disease systematically, a large variability of exposure would be needed.

In the present study, the reduced risk associated with dietary intake of fish and n3 polyunsaturated fatty acids was confined to nonfatal coronary heart disease, not fatal coronary

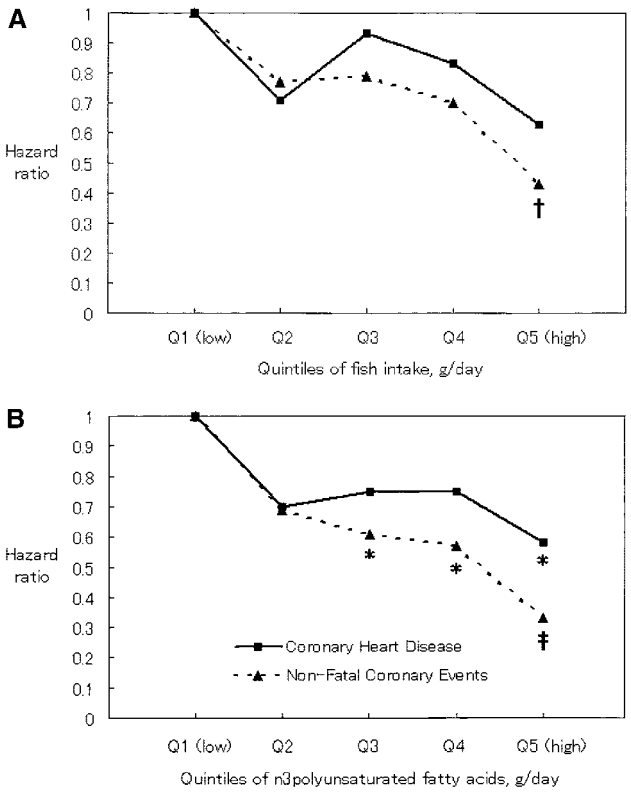
TABLE 3. Age and Sex-Adjusted and Multivariable HRs and 95% CIs of Coronary Heart Disease According to Quintiles of n3 Polyunsaturated Fatty Acid Intake

	Quintiles of n3 Polyunsaturated Fatty Acid Intake					
	1 (Low)	2	3	4	5 (High)	*P* for Trend
Median intake, g/d	0.3	0.6	0.9	1.3	2.1	
Person-years	102 711	95 861	95 258	91 435	92 062	
Coronary heart disease						
No. of cases	83	44	48	45	38	
HR (95% CI)	1	0.57 (0.39–0.82)	0.60 (0.42–0.86)	0.58 (0.40–0.83)	0.46 (0.32–0.68)	0.001
Multivariable HR (95% CI)	1	0.70 (0.47–1.03)	0.75 (0.50–1.12)	0.75 (0.48–1.18)	0.58 (0.35–0.97)	0.18
Total MI						
No. of cases	76	44	39	36	26	
HR (95% CI)	1	0.62 (0.43–0.89)	0.53 (0.36–0.79)	0.51 (0.34–0.75)	0.35 (0.22–0.55)	<0.001
Multivariable HR (95% CI)	1	0.77 (0.52–1.15)	0.68 (0.43–1.05)	0.66 (0.40–1.09)	0.43 (0.24–0.78)	0.02
Definite MI						
No. of cases	73	39	33	32	21	
HR (95% CI)	1	0.57 (0.39–0.84)	0.47 (0.31–0.71)	0.47 (0.31–0.71)	0.29 (0.18–0.48)	<0.001
Multivariable HR (95% CI)	1	0.70 (0.46–1.07)	0.59 (0.37–0.94)	0.59 (0.35–1.01)	0.35 (0.18–0.66)	0.005
Sudden cardiac death						
No. of cases	7	0	9	9	12	
HR (95% CI)	1	...	1.32 (0.49–3.55)	1.33 (0.49–3.57)	1.65 (0.65–4.19)	0.03
Multivariable HR (95% CI)	1	...	1.04 (0.34–3.16)	1.03 (0.32–3.37)	1.24 (0.39–3.98)	0.12
Nonfatal coronary events						
No. of cases	73	38	34	31	20	
HR (95% CI)	1	0.56 (0.38–0.82)	0.49 (0.32–0.73)	0.45 (0.30–0.69)	0.28 (0.17–0.46)	<0.001
Multivariable HR (95% CI)	1	0.69 (0.45–1.05)	0.61 (0.38–0.97)	0.57 (0.34–0.98)	0.33 (0.17–0.63)	0.003
Fatal coronary events						
No. of cases	10	6	14	14	18	
HR (95% CI)	1	0.64 (0.23–1.76)	1.44 (0.64–3.24)	1.46 (0.65–3.29)	1.79 (0.82–3.87)	0.03
Multivariable HR (95% CI)	1	0.62 (0.21–1.79)	1.27 (0.52–3.11)	1.29 (0.50–3.33)	1.54 (0.60–3.99)	0.10

MI indicates myocardial infarction.
HRs were adjusted for age and sex. Multivariable models were adjusted for the same variables noted in Table 2.

heart disease or sudden cardiac deaths. This finding was in contrast to the results reported by other investigators[1–4,6–8,10,11] but in agreement with others.[5] One of the reasons for the lack of a significant association with fatal coronary heart disease or sudden cardiac death may be the low statistical power (40% and 49%, respectively) to detect an association, because the respective numbers of cases were 62 and 37. The trend tests for these end points were not reliable because of the limited number of cases. The low proportions of fatal coronary events among total coronary heart disease (25%) and myocardial infarction (20%) cases were reported previously in a population-based study in Japan.[21] The 95% CIs, however, included the possibility of up to a 58% reduction in fatal coronary events and a 64% reduction in sudden cardiac death. Another reason is the potential misdiagnosis of fatal coronary events. In the present study, only 27% of fatal coronary events were confirmed by laboratory findings or autopsy, whereas 98% of nonfatal coronary events were confirmed clinically and by investigative tests. It is possible that almost every subject in the present study population was above a threshold of fish intake for prevention of fatal coronary events or sudden cardiac deaths. One potential reason why a strong inverse association with nonfatal coronary heart disease was seen in this cohort, but not generally in Western populations, is that fish or n3 fatty acid intake may affect its risk only at very high levels of intake.

The limitations of the present study warrant discussion. First, it is possible that participants who had a high intake of fish and n3 polyunsaturated fatty acids were at lower risk of coronary heart disease because of other health habits and behaviors. This likelihood was reduced by the multivariable adjustment for a variety of potential confounding variables, including traditional cardiovascular risk factors, education level, physical activity, vitamin use, selected dietary variables, and total energy intake, which only had a small effect on the associations observed. Confounding of fish intake by higher education, as observed in Western populations,[3] did not appear to be a concern in Japanese populations. Second, measurement errors in assessing nutrient intake are inevitable. The reproducibility for fish intake in the baseline and 5-year follow-up questionnaires was fairly good and was compatible with that reported in the Nurses Health Study.[6] In



Multivariable HRs of total coronary heart disease and nonfatal coronary events according to dietary intake of fish (A) and n3 polyunsaturated fatty acids (B) for men and women. Difference from lowest quintile: *$P<0.05$; †$P<0.01$; ‡$P<0.001$.

the present study, any errors are likely nondifferential and would have tended to attenuate associations with fish and n3 polyunsaturated fatty acid intakes toward the null. As for validity, the baseline FFQ underestimated fish intake by one third, whereas the 5-year follow-up questionnaire did so only by 16% in men and 1% in women. Because fish intake was updated among 80% of the participants by the 5-year follow-up questionnaire, the underestimation of fish intake was not as large.

We found a strong association between n3 polyunsaturated fatty acids and reduced risk of coronary heart disease. This result suggests that n3 polyunsaturated fatty acids per se may provide protection against the occurrence of coronary heart disease. However, we can exclude neither the possible contribution of some other nutrients in the fish to the reduction in risk nor residual confounding effects of other risk factors.

Several mechanisms may be involved in the lower risk of nonfatal coronary heart disease associated with n3 polyunsaturated fatty acids. These fatty acids reduce the formation of thromboxane A_2 in platelets, thus leading to reduced platelet aggregation, and enhance its transformation into a nonaggregatory agent, thromboxane A_3, which increases the synthesis of the vasodilator prostaglandin I_3.[12,13] N3 polyunsaturated fatty acids decrease the production of leukotrienes by neutrophils and monocytes, thus attenuating the leukotriene-mediated chemotaxis and endothelial cell adherence of neutrophils[14] and the reduced production of platelet-derived growth factor,[15] which may attenuate the proliferation of endothelial cells in the process of atherosclerosis. These fatty acids also reduce insulin resistance in rats,[16] serum triglyceride levels in hyperlipidemic patients,[17] and plasma fibrinogen concentrations in healthy volunteers,[18] and they lower blood pressure levels in hypertensive individuals.[19]

In conclusion, our large prospective study indicated that a high consumption of fish (8 times per week, or 180 g/d) was associated with reduced risk of coronary heart disease, more specifically, myocardial infarction and nonfatal coronary heart disease, compared with a modest fish consumption (once a week, or 23 g/d). Our results suggest that a high fish intake may add a further beneficial effect for the prevention of coronary heart disease among middle-aged persons.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Once- or twice-weekly consumption of fish (or a small amount of fish intake) reduces the risk of coronary heart disease and sudden cardiac death; however, it is uncertain whether a high frequency or large amount of fish intake further reduces the risk. To examine an association between high intake of fish and n3 polyunsaturated fatty acids and the risk of coronary heart disease, a total of 41 578 Japanese men and women aged 40 to 59 years who were free of prior diagnosis of cardiovascular disease and cancer and who completed a food frequency questionnaire were followed up from 1990–1992 to 2001. After 477 325 person-years of follow-up, 258 incident coronary heart diseases (198 definite and 23 probable myocardial infarctions and 37 sudden cardiac deaths) were documented, comprising 196 nonfatal and 62 fatal coronary events. The multivariable hazard ratios (HRs) and their 95% confidence intervals in the highest (8 times per week, or median intake=180 g/d) versus lowest (once a week, or median intake=23 g/d) quintiles of fish intake were 0.63 (0.38 to 1.04) for total coronary heart disease, 0.44 (0.24 to 0.81) for definite myocardial infarction, and 1.14 (0.36 to 3.63) for sudden cardiac death. The reduced risk was observed primarily for nonfatal coronary events (HR=0.43 [0.23 to 0.81]) but not for fatal coronary events (HR=1.08 [0.42 to 2.76]). Strong inverse associations existed between dietary intake of n3 fatty acids and risk of definite myocardial infarction (HR=0.35 [0.18 to 0.66]) and nonfatal coronary events (HR=0.33 [0.17 to 0.63]). Compared with a modest fish intake of once per week or ≈20 g/d, a higher intake was associated with a substantially reduced risk of coronary heart disease, primarily nonfatal cardiac events, among middle-aged persons.