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DIETARY INTAKE OF MARINE n−3 FATTY ACIDS, FISH INTAKE, AND THE RISK OF CORONARY DISEASE AMONG MEN

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Abstract *Background.* It has been hypothesized that a diet containing n−3 fatty acids from fish reduces the risk of coronary heart disease, but few large epidemiologic studies have examined this question.

Methods. In 1986, 44,895 male health professionals, 40 to 75 years of age, who were free of known cardiovascular disease completed detailed and validated dietary questionnaires as part of the Health Professionals Follow-up Study. During six years of follow-up, we documented 1543 coronary events in this group: 264 deaths from coronary disease, 547 nonfatal myocardial infarctions, and 732 coronary-artery bypass or angioplasty procedures.

Results. After controlling for age and several coronary risk factors, we observed no significant associations between dietary intake of n−3 fatty acids or fish intake and the risk of coronary disease. For men in the top fifth of the group in terms of intake of n−3 fatty acids (median, 0.58 g per day), the multivariate relative risk of coronary heart disease was 1.12 (95 percent confidence interval, 0.96 to 1.31), as compared with the men in the bottom fifth (median, 0.07 g per day). For men who consumed six or more servings of fish per week, as compared with those who consumed one serving per month or less, the multivariate relative risk of coronary disease was 1.14 (95 percent confidence interval, 0.86 to 1.51). The risk of death due to coronary disease among men who ate any amount of fish, as compared with those who ate no fish, was 0.74 (95 percent confidence interval, 0.44 to 1.23), but the risk did not decrease as fish consumption increased.

Conclusions. Although the possibility of residual confounding by unmeasured factors cannot be entirely excluded, these data suggest that increasing fish intake from one to two servings per week to five to six servings per week does not substantially reduce the risk of coronary heart disease among men who are initially free of cardiovascular disease. (N Engl J Med 1995;332:977-82.)

THE low rates of coronary heart disease in Japan and Greenland, where fish is an important component of the diet, suggest that the consumption of fish may be protective against such disease.[1-3] Possible mechanisms of this effect include the ability of long-chain n−3 polyunsaturated fatty acids, which are abundant in fish, to decrease plasma levels of very-low-density lipoprotein cholesterol, increase vasodilatation, and reduce platelet aggregation.[4,5] An inverse association between fish intake and the risk of death from coronary disease has also been found in prospective studies in the Netherlands,[6] Sweden,[7] and the United States,[8,9] but not in similar investigations in Norway,[10] among Japanese men in Hawaii,[11] or among U.S. physicians.[12] Evidence concerning the incidence of coronary heart disease is sparse because most studies have examined only deaths. The intake of n−3 fatty acids was assessed in only two studies,[9,12] and the validity of reported fish consumption or calculated n−3 fatty-acid intake was not evaluated in previous investigations.

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METHODS

The Health Professionals Follow-up Study

The Health Professionals Follow-up Study began in 1986, when 51,529 male health professionals 40 to 75 years of age completed a detailed food-frequency questionnaire and provided information about their medical history, risk factors for heart disease, and dietary changes during the past 10 years.[13] Follow-up questionnaires were sent in 1988, 1990, and 1992 in order to determine the incidence of coronary end points. We excluded from our analysis 1595 men who did not satisfy the a priori criteria for daily calorie intake (between 800 and 4200 kcal) and completeness of data on food consumption (fewer than 70 blanks out of 131 listed food items). In addition, we excluded 5039 men who reported on the 1986 questionnaire that they had previously been given a diagnosis of myocardial infarction, angina, stroke, transient ischemic attack, or peripheral arterial disease or had undergone coronary artery surgery. We followed the 44,895 remaining men who were eligible in 1986 for the occurrence of coronary heart disease during the subsequent six years. Follow-up was complete for more than 94 percent of the eligible subjects in each two-year follow-up cycle. Nonresponding participants were assumed to be alive if they were not listed in the National Death Index.

Dietary Assessment

The 1986 questionnaire included items regarding the subject's average frequency of consumption during the previous year of specified portions of 131 foods. Four fish items were included: dark-meat fish

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such as bluefish (1.37 g of n−3 fatty acids per portion); canned tuna (0.69 g); other fish (0.17 g); and shrimp, lobster, or scallops (0.46 g). We calculated the average daily intake during that year of marine n−3 fatty acids as the sum of the daily consumption of each type of fish multiplied by the n−3 content of the specified portion,[14] and we adjusted this and other nutrient values for total energy intake by means of regression analysis.[15]

A question about the use of fish-oil supplements was included in the 1988 follow-up questionnaire; only 4 percent of the men reported using such supplements. The validity of the food-frequency questionnaire was assessed in a random sample of 127 men living in the Boston area, by comparing their calculated intake of n−3 fatty acids from fish with the concentrations of the fats in their adipose tissue.[16-18] The Spearman correlation coefficient for the correlation of the intake of eicosapentaenoic acid, adjusted for energy intake, and the percentage of eicosapentaenoic acid in adipose tissue was 0.49 ($P<0.001$); the mean percentage of eicosapentaenoic acid in adipose tissue was 0.04 percent for men in the bottom fifth of the sample in terms of their calculated, energy-adjusted intake of eicosapentaenoic acid, and it was 0.11 for men in the top fifth. In addition, we compared fish intake as reported in the questionnaire with two one-week dietary records obtained approximately six months apart.[18] The mean fish intake (calculated as the sum of the four fish items) was 3.7 servings per week according to the questionnaire and 3.6 servings per week according to the dietary records (Spearman correlation coefficient, 0.61; $P<0.001$). Mean fish consumption in the dietary records was 1.2 servings per week for the men in the lowest intake category, according to their responses to the questionnaire, and 5.8 servings per week in the highest intake category.

Ascertainment of End Points

The ascertainment of end points has been described in detail previously.[19] Briefly, fatal coronary disease (including sudden death), nonfatal myocardial infarction, coronary-artery bypass grafting, or angioplasty occurring between the return of the base-line questionnaire and January 31, 1992, were considered as end points. Participants who reported a myocardial infarction on a follow-up questionnaire were asked for permission to review their medical records. Nonfatal myocardial infarction was considered confirmed if the World Health Organization criteria were met[20]; specifically, this diagnosis required symptoms plus either typical electrocardiographic changes or elevated cardiac-enzyme levels.

To validate the report of coronary-artery bypass grafting or angioplasty, we obtained medical records for a sample of 102 participants who reported undergoing those procedures. Reports were confirmed for 98 men (96 percent), and we therefore considered the subjects' reports to be sufficiently accurate.

Deaths were reported by family members, coworkers, or postal authorities or were identified through the National Death Index. Fatal coronary disease was confirmed by reviews of medical records or autopsy reports. Fatal coronary disease was also considered confirmed if it was listed as the underlying cause of death on the death certificate and if a diagnosis of coronary disease was confirmed by other sources. Sudden death, defined as death within one hour of the onset of symptoms in men with no previous serious illness or plausible cause of death other than coronary heart disease, was included in our analysis as fatal coronary disease. Ten men with nonfatal end points (three with coronary-artery bypass procedures and seven with myocardial infarctions) died during the follow-up period; they were included in the analyses of the specific nonfatal end points but were counted only once in analyses of the total numbers with myocardial infarction or the total with coronary disease. The physicians who reviewed the subjects' medical records were blinded to the dietary-intake data.

Statistical Analysis

Participants contributed follow-up time from the date of return of the 1986 questionnaire up to the date of occurrence of an end point, the date of death, or January 31, 1992. Relative risks were calculated by dividing the incidence of coronary heart disease among men in each of five roughly equal quintile groups (defined by n−3 fatty-acid intake) by the incidence among men in the lowest fifth of the sample in terms of intake. The men were classified in six groups in terms of fish intake, ranging from those who never ate fish or consumed it less than once per month to those who consumed six or more servings per week. We adjusted the relative risks for age (in five-year age groups) using the Mantel–Haenszel method.[21] The Mantel extension test[22] was used to test for linear trend. To adjust for other risk factors, we used proportional-hazards models.[23] In multivariate models, we tested for significant trends by assigning each participant the median value of his category and modeling this as a continuous variable. All the reported P values are two-sided.

Results

During 242,029 person-years of follow-up, we documented 1543 coronary events (264 deaths due to coronary disease, 547 nonfatal myocardial infarctions, and 732 coronary-artery bypass or angioplasty procedures).

Intake of n−3 fatty acids from fish was associated, either inversely or directly, with a variety of dietary and nondietary risk factors (Table 1). We therefore analyzed the relation between n−3 fatty acids and the risk of coronary heart disease with and without adjustment for these variables.

In age-adjusted analyses, the intake of n−3 fatty acids from fish was directly associated with the overall risk of coronary events; the relative risk for the men with the highest intake, as compared with those with the lowest, was 1.19 (95 percent confidence interval, 1.02 to 1.39; P for trend, 0.03) (Table 2). This positive association was mostly due to an increased frequency of bypass grafting among men with a higher intake of n−3 fatty acids from fish. The risk of sudden death (89 cases, data not shown) was also found not to be inversely associated with the intake of n−3 fatty acids; the relative risk for the men with the highest intake, as compared with those with the lowest intake, was 1.10 (95 percent confidence interval, 0.56 to 2.13). After adjustment for coronary risk factors, the association between n−3 fatty-acid intake and the risk of coronary disease was attenuated (Table 2). However, further adjustment for physical-activity level and intake of vitamin E and carotene strengthened the association; the relative risk for the men with the highest intake of n−3 fatty acids, as compared with those with the lowest intake, was 1.22 (95 percent confidence interval, 1.03 to 1.44).

To reduce the possibility of residual confounding by the men's perceptions of their high risk of coronary events, we conducted two separate analyses, one after excluding the 12,614 men with diabetes, hypertension, or hyperlipidemia, and the other after excluding the 17,339 men who knew their serum cholesterol levels at base line. The results of the two analyses were similar: the multivariate relative risks of coronary heart disease for the men with the highest intake of n−3 fatty acids as compared with those with the lowest intake were 1.12 (95 percent confidence interval, 0.90 to 1.40) and 1.20 (95 percent confidence interval, 0.95 to 1.52), respectively. Also, we reduced the possibility of confounding by unreported coronary disease at base line by excluding events that occurred during the first four years of follow-up. We still found no inverse association between n−3 fatty-acid intake and the risk of coronary

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Table 1. Relation of the Intake of n−3 Fatty Acids from Fish to Selected Risk Factors for Coronary Heart Disease (CHD) at Base Line.*

VARIABLE	QUINTILE OF n−3 FATTY-ACID INTAKE				
	1	2	3	4	5
Median n−3 intake (g/day)	0.07	0.15	0.24	0.34	0.58
Total fish intake (servings/wk)	0.7	1.6	2.2	3.2	5.9
Cigarette smoking (% of group)	11.4	10.9	10.1	8.5	7.8
Alcohol intake (g/day)	11.4	12.1	13.1	11.6	10.8
Body-mass index†	24.9	24.9	24.9	24.8	24.8
Family history of CHD (%)	10.0	11.5	11.0	11.6	13.8
History at base line (%)					
Hypertension	18.1	19.5	20.6	20.7	21.8
High cholesterol	7.5	8.9	9.9	11.9	14.4
Diabetes	2.5	2.3	2.6	2.5	3.0
Serum cholesterol (mg/dl)‡	203	203	203	203	203
Physical activity (MET/wk)§	16.8	17.6	19.8	22.4	23.5
Use of vitamin supplements (%)					
Vitamin E	14	16	18	20	24
Vitamin C	19	21	23	25	30
Multivitamin	38	40	40	43	46
Intake of dietary fiber (g/day)	20.4	21.2	22.5	22.6	23.8
Intake of carotene (IU/day)	8305	9032	10,018	10,752	12,183
Intake of cholesterol (mg/day)	318	329	343	327	328
Intake of saturated fat (g/day)	27.3	26.4	26.5	24.0	22.2
Percentage of calories from fat	33.9	33.2	32.8	31.9	30.8
Intake of trans fatty acids (g/day)	3.98	3.76	3.70	3.25	2.90
Intake of polyunsaturated fat (g/day)	13.4	13.5	14.2	13.5	13.7
Food intake (servings/day)					
Red meat	1.2	1.1	1.1	0.9	0.7
Chicken	0.2	0.3	0.3	0.4	0.5
Cereals	3.5	3.4	3.4	3.2	3.1
Vegetables	2.9	3.2	3.6	3.8	4.4
Fruit	2.0	2.2	2.4	2.5	2.8
Sweets	1.7	1.5	1.5	1.3	1.1
Low-fat dairy products	1.0	1.0	1.0	0.9	0.9
High-fat dairy products	1.5	1.4	1.4	1.2	1.0

*Standardized for age to the total cohort; values are means, unless otherwise specified. Intake of n−3 fatty acids has been adjusted for total energy intake.

†The weight in kilograms divided by the square of the height in meters.

‡Based on the 17,339 men who reported their serum cholesterol levels at base line. To convert values for serum cholesterol to millimoles per liter, multiply by 0.02586.

§MET denotes metabolic equivalent, defined as the energy consumed per minute of sitting at rest.

disease; the relative risk for the highest intake group as compared with the lowest was 1.29 (95 percent confidence interval, 0.99 to 1.68).

The relation of coronary risk to fish intake was similar to that for intake of n−3 fatty acids. The relative risk of any coronary event for the men who consumed the most fish, as compared with those who consumed the least, was 1.16 (95 percent confidence interval, 0.89 to 1.53) in the age-adjusted analyses (Table 3) and 1.14 (95 percent confidence interval, 0.86 to 1.51) after adjustment for coronary risk factors (Table 3). The slightly higher risk of coronary disease among the men with the highest fish intake was once again due to an excess of coronary bypass grafting and angioplasty procedures. As was the case with n−3 fatty acids, only slight differences in these estimates were caused by further adjustment for the level of physical activity and intake of vitamin E or carotene; by the exclusion of men with a history of diabetes, hypertension, or high cholesterol levels or those who knew their base-line serum cholesterol levels; or by the exclusion of coronary events that occurred during the first four years of follow-up. In none of these analyses was there a significant inverse relation between fish intake and the risk of coronary heart disease. In analyses according to type of fish, the relative risk for the men in the highest intake group (three or more servings per week) as compared with those in the lowest intake group (less than one serving per month) was 1.18 (95 percent confidence interval, 0.95 to 1.48) for dark-meat fish and 0.92 (95 percent confidence interval, 0.76 to 1.10) for other fish.

The results of a secondary-prevention trial suggested that fish intake may reduce mortality due to coronary disease, but not the incidence of myocardial infarction.[24] We found the highest risk of fatal coronary disease among men who reported no fish consumption, but the risk did not decrease with increasing fish intake. The relative risk for men who ate any amount of fish, as compared with men who ate no fish, was 0.74 (95 percent confidence interval, 0.44 to 1.23) after adjustment for established risk factors (as in the multivariate model in Table 3) and 0.77 (95 percent confidence interval, 0.46 to 1.28) after further adjustment for physical-activity level and the intake of vitamin E and beta carotene.

To increase the probability of detecting an effect of fish intake that may occur only after several years of high levels of consumption, we repeated the analyses, including only the 14,230 men who reported at base line that there had been no change in their fish intake during the previous 10 years. There were 506 coronary events in this group. In these analyses the relative risk for the men with the highest intake of n−3 fatty acids from fish, as compared with those with the lowest intake, after adjustment for coronary risk factors (as in the multivariate model in Table 2), was 1.04 (95 percent confidence interval, 0.75 to 1.44). The comparable figure for fish intake was 1.25 (95 percent confidence interval, 0.71 to 2.19).

The use of fish-oil supplements (reported by 4 percent of the cohort in 1988) was not significantly associated with risk. The multivariate relative risk for users as compared with nonusers of such supplements was 0.96 (95 percent confidence interval, 0.68 to 1.35). There was also no significant inverse association between the intake of fish or n−3 fatty acids from fish and the risk of myocardial infarction in any of the subgroups defined according to risk factors for coronary disease.

DISCUSSION

In this large prospective cohort study, we found no evidence of an association between the intake of either marine n−3 fatty acids or fish and the risk of coronary heart disease. Potential bias due to incomplete follow-up was minimized by the high rate of follow-up. We also excluded from the analyses men with previous evidence of cardiovascular disease, who might have changed their diets as a consequence of the disease. A previous diagnosis of hypercholesterolemia, diabetes, or hypertension might also have caused an increase in

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Table 2. Relative Risk of Coronary Heart Disease (CHD) According to Dietary Intake of n–3 Fatty Acids.*

VARIABLE†	QUINTILE GROUP					χ FOR TREND	P FOR TREND
	1	2	3	4	5		
Age-adjusted analysis							
Range of intake of n−3 fatty acids (g/day)	0.01–0.11	0.12–0.19	0.20–0.28	0.29–0.41	0.42–6.52		
No. of men	9,329	9,220	9,005	8,860	8,481		
No. of person-years of follow-up	50,449	49,902	48,613	47,722	45,343		
Coronary-artery bypass grafting							
No. of cases	131	132	142	161	169		
RR	1.0	0.99	1.07	1.20	1.27	2.63	0.01
95% CI	—	0.78–1.26	0.85–1.36	0.95–1.51	1.01–1.60		
Nonfatal myocardial infarction							
No. of cases	116	110	104	92	132		
RR	1.0	0.93	0.89	0.78	1.13	0.40	0.69
95% CI	—	0.72–1.21	0.68–1.15	0.52–1.02	0.89–1.45		
Fatal CHD							
No. of cases	50	58	49	53	54		
RR	1.0	1.14	0.96	1.04	1.06	0.00	1.0
95% CI	—	0.78–1.66	0.65–1.42	0.71–1.53	0.72–1.55		
Any myocardial infarction‡							
No. of cases	163	166	153	144	185		
RR	1.0	1.00	0.92	0.87	1.13	0.46	0.65
95% CI	—	0.81–1.24	0.74–1.15	0.69–1.08	0.91–1.39		
Any CHD							
No. of cases	294	296	295	305	353		
RR	1.0	0.99	0.99	1.02	1.19	2.15	0.03
95% CI	—	0.84–1.16	0.84–1.16	0.87–1.19	1.02–1.39		
Multivariate analysis§							
Coronary-artery bypass grafting	1.0	0.97	1.05	1.15	1.16	1.71	0.09
RR	—	0.76–1.24	0.82–1.33	0.91–1.45	0.92–1.47		
95% CI							
Nonfatal myocardial infarction							
RR	1.0	0.93	0.89	0.78	1.09	0.77	0.44
95% CI	—	0.72–1.21	0.68–1.16	0.59–1.03	0.85–1.41		
Fatal CHD							
RR	1.0	1.14	0.95	1.03	1.03	0.08	0.94
95% CI	—	0.78–1.66	0.64–1.41	0.70–1.52	0.70–1.52		
Any myocardial infarction‡							
RR	1.0	1.00	0.92	0.86	1.09	0.71	0.48
95% CI	—	0.81–1.25	0.74–1.15	0.69–1.08	0.88–1.35		
Any CHD							
RR	1.0	0.98	0.97	0.99	1.12	1.71	0.09
95% CI	—	0.83–1.15	0.83–1.15	0.84–1.17	0.96–1.31		

*Intake of n−3 fatty acids has been adjusted for total energy intake. Relative risks are for the comparison with the men with the lowest intake (group 1).

†CI denotes confidence interval, and RR relative risk.

‡Includes nonfatal myocardial infarction and fatal CHD.

§The multivariate model includes age (seven categories); body-mass index (five categories); smoking habits (current smoker [number of cigarettes smoked], former smoker, or person who never smoked); alcohol consumption (four categories); history of hypertension; history of diabetes; history of hypercholesterolemia; family history of myocardial infarction before 60 years of age; profession; and quintile group for intake of n−3 fatty acids.

fish intake among some participants in the study, but the exclusion of men with these disorders did not appreciably change the results.

Errors in assessing fish intake may have weakened the evidence of a protective effect of marine n−3 fatty acids or fish intake against coronary disease. However, our validation study indicated that there was a genuine fourfold difference in fish consumption between men in the lowest and highest intake categories based on the questionnaire. A related source of potential error is a change in fish intake in the years before the beginning of the study. In 1986, two thirds of the men reported having greatly increased their intake of fish during the past 10 years. However, the lack of association between fish intake and the risk of coronary disease among men who did not change their fish intake argues against this possibility. Although we cannot exclude the possibility of residual confounding — as might occur if men at higher risk because of unmeasured or imperfectly measured covariates ate more fish in an attempt to lower their risk — the small change in the relative-risk estimates caused by adjustment for the known risk factors makes such confounding unlikely.

A true protective effect of n−3 fatty acids from fish could also have been missed if the fish consumed by the men in our cohort was mainly fried commercially in cholesterol-raising fat. However, the consumption of fried food away from home at least once per week was reported more frequently by men with the lowest intake of fish (31 percent) than by those with the highest intake (25 percent); a difference in the same direction was reported for food fried at home (35 percent vs. 20 percent). These results, which are consistent with the overall healthier lifestyle of the men with higher fish intake, make increased consumption of fried food an unlikely explanation of our findings. In addition, no inverse relation was observed between the risk of coronary disease and the intake of dark-meat fish, which is usually not fried.

In a prospective investigation of the risk of coronary disease among 852 middle-aged Dutch men who were followed for 20 years, men who consumed more than 30 g of fish per day at base line had only about half the risk of fatal coronary disease of men who consumed none.[6] Similar findings were reported among 1931 men in the Western Electric Study who were followed for 25 years.[8] Inverse relations between fish intake and mortality from coronary disease among men and women were also observed in two prospective studies[7,9] and a case–control study.[25] However, no association between fish intake and deaths due to coronary disease was observed in a large study of Norwegian men[10] or in a study of Japa-

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Table 3. Relative Risk of Coronary Heart Disease (CHD) According to Dietary Fish Intake.*

VARIABLE†	FISH INTAKE CATEGORY						P FOR TREND
	1	2	3	4	5	6	
Servings of fish consumed	<1/mo	1–3/mo	1/wk	2–3/wk	4–5/wk	≥6/wk	
Mean fish intake (g/day)	0	7	18	37	69	119	
Age-adjusted analysis							
No. of men	2,042	3,314	12,296	16,920	6,271	4,052	
Person-years of follow-up	10,975	17,886	66,367	91,370	33,779	21,652	
Coronary-artery bypass grafting							
No. of cases	23	48	192	261	127	84	
RR	1.0	1.31	1.42	1.38	1.71	1.73	0.01
95% CI	—	0.80–2.14	0.93–2.19	0.90–2.10	1.11–2.65	1.10–2.72	
Nonfatal myocardial infarction							
No. of cases	34	34	159	184	74	69	
RR	1.0	0.63	0.79	0.65	0.67	0.95	0.97
95% CI	—	0.39–1.01	0.55–1.14	0.45–0.94	0.45–1.01	0.63–1.42	
Fatal CHD							
No. of cases	16	19	80	93	28	28	
RR	1.0	0.76	0.86	0.73	0.57	0.82	0.19
95% CI	—	0.39–1.48	0.50–1.47	0.43–1.24	0.31–1.03	0.45–1.52	
Any myocardial infarction‡							
No. of cases	49	52	236	277	102	95	
RR	1.0	0.67	0.82	0.69	0.65	0.91	0.47
95% CI	—	0.46–0.99	0.60–1.11	0.51–0.94	0.47–0.92	0.64–1.28	
Any CHD							
No. of cases	72	100	427	537	229	178	
RR	1.0	0.88	1.01	0.91	0.99	1.16	0.17
95% CI	—	0.65–1.19	0.79–1.30	0.71–1.16	0.76–1.29	0.89–1.53	
Multivariate analysis§							
Coronary-artery bypass grafting	1.0	1.31	1.43	1.40	1.71	1.65	0.02
RR	—	0.80–2.16	0.93–2.21	0.91–2.15	1.09–2.68	1.03–2.64	
95% CI							
Nonfatal myocardial infarction							
RR	1.0	0.62	0.80	0.67	0.69	0.96	0.62
95% CI	—	0.39–1.00	0.55–1.17	0.46–0.97	0.46–1.04	0.63–1.47	
Fatal CHD							
RR	1.0	0.74	0.86	0.71	0.54	0.77	0.14
95% CI	—	0.38–1.45	0.50–1.47	0.41–1.21	0.29–1.00	0.41–1.44	
Any myocardial infarction‡							
RR	1.0	0.66	0.82	0.69	0.65	0.90	0.70
95% CI	—	0.44–0.97	0.60–1.12	0.51–0.94	0.46–0.92	0.63–1.28	
Any CHD							
RR	1.0	0.87	1.02	0.92	0.99	1.14	0.19
95% CI	—	0.64–1.18	0.79–1.31	0.71–1.18	0.76–1.30	0.86–1.51	

*All relative risks are for the comparison of the men in the intake category in question with those who ate no fish (group 1).

†CI denotes confidence interval, and RR relative risk.

‡Includes nonfatal myocardial infarction and fatal CHD.

§The multivariate model includes age (seven categories); body-mass index (five categories); smoking habits (current smoker [number of cigarettes smoked], former smoker, or person who never smoked); alcohol consumption (four categories); history of hypertension; history of diabetes; history of hypercholesterolemia; family history of myocardial infarction before 60 years of age; and profession.

nese men living in Hawaii[11]; both cohorts — like that in our study — were characterized by high fish intake. In a preliminary report from the Physicians' Health Study, no association between intake of either fish or n−3 fatty acids and the incidence of coronary disease was observed.[12]

Levels of long-chain n−3 fatty acids in adipose tissue or blood have been found to be inversely associated with the risk or severity of coronary disease in some investigations,[27-29] but not all.[26,30,31] An important limitation of those studies, however, is the lack of control for other dietary risk factors for coronary disease.

A wide variety of presumably favorable physiologic effects are associated with n−3 fatty acids: a reduction in very-low-density lipoprotein cholesterol levels; inhibition of thromboxane production and an increase in prostacyclin synthesis, with a resulting reduction in the likelihood of thrombosis; a reduction in blood viscosity; and a reduced risk of cardiac arrhythmias.[4,5] However, these cardiovascular effects occur at doses of 3 g or more of n−3 fatty acids per day, amounts several times higher than those consumed by men in the highest intake categories in epidemiologic studies. Thus, it seems unlikely that the reduction in mortality due to coronary disease in some of these studies is caused by the known cardiovascular effects of n−3 fatty acids.

Several factors may contribute to the apparently discordant results of studies of fish consumption and coronary heart disease. A possible explanation is that fish intake is protective in very small amounts (one to two servings per week), perhaps providing an essential minimal amount of long-chain n−3 polyunsaturated fatty acids or of some still unidentified nutrient. If so, the lack of association in our study could be explained by the small proportion of men who consumed less than one serving of fish per week. Moreover, dietary fish intake could be unrelated to the incidence of myocardial infarction but might reduce mortality due to coronary disease, perhaps by reducing the risk of fatal arrhythmias. Consistent with this interpretation are the results of previous prospective studies, which reported inverse associations between fish intake and mortality due to coronary events,[5-9] the reduction in mortality but not in the incidence of reinfarction in the Diet and Reinfarction Trial,[24] and the lower (albeit not significantly lower) risk of death due to coronary disease among men who consumed any amount of fish, as compared with those who consumed none, in this study.

Finally, other factors may modify the effect of the intake of fish or of n−3 fatty acids from fish on the risk of coronary disease. Linolenic acid can be elongated after ingestion to eicosapentaenoic acid,[4] and high intake

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of this n−3 fatty acid from nonmarine sources may compensate for low intake of the long-chain n−3 fatty acids provided by fish. However, we did not find an association between fish intake or the intake of n−3 fatty acids from fish and the incidence of coronary disease among men with low linolenic acid intake. Because n−3 fatty acids may compete with n−6 polyunsaturated fatty acids for conversion to eicosanoids,[4] high intake of linoleic acid may dampen the cardiovascular effects of small changes in intake of n−3 fatty acids from fish. In view of changes over time in diet,[32] linoleic acid intake is likely to have been higher in our cohort than among participants in the studies that support an inverse association between fish intake and mortality due to coronary disease. We found no association, however, between the ratio of n−3 to n−6 fatty acids and the risk of coronary disease.

We have no convincing explanation for the suggestion of an increased frequency of coronary-artery bypass surgery among men with higher fish intake in this study. Perhaps men with higher fish intake are more health-conscious and more willing to undergo angiography and elective coronary surgery. We also cannot exclude the possibility that coronary surgery is less likely to be performed in geographic areas where fish may be less available. However, relative-risk estimates for coronary-artery bypass grafting or myocardial infarction did not change materially after adjustment for the region of residence (data not shown).

Our results suggest that increasing fish intake from one to two servings per week to five to six servings per week is unlikely to reduce the risk of coronary disease substantially among men without preexisting cardiovascular disease. However, an effect of fish or fish oil at lower or higher levels of intake, or among persons with dietary habits or other risk factors that are markedly different from those of the men in our cohort, cannot be excluded by these data.

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