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Fish Consumption and Coronary Heart Disease Mortality in Finland, Italy, and the Netherlands

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Fish consumption seems to protect against death from coronary heart disease (CHD). If this association is due to n-3 polyunsaturated fatty acids, especially fatty fish may be responsible for this protective effect. The association between total, lean, and fatty fish consumption and the risk of CHD mortality was examined in 1,088 Finnish, 1,097 Italian, and 553 Dutch men participants in the Seven Countries Study who were aged 50–69 years and free of CHD around 1970. After 20 years of follow-up, 242 (22.2%) men in Finland, 116 (10.6%) men in Italy, and 105 (19.0%) men in the Netherlands had died of CHD. Cox proportional hazards analysis showed no association between total fish consumption and CHD mortality. After adjustments were made for age, body mass index, smoking, energy intake, and relevant dietary variables, the pooled relative risk for the highest quartile of total fish compared with no fish consumption in the three countries was 1.08 (95% confidence interval: 0.76, 1.53). Lean fish consumption also was not associated with CHD mortality in any country. Fatty fish compared with non-fatty-fish consumption was associated with lower CHD mortality; the adjusted, pooled relative risk for fatty fish consumers was 0.66 (95% confidence interval: 0.49, 0.90). These data suggest that especially fatty fish is protective against CHD mortality. *Am J Epidemiol* 2000;151:999–1006.

coronary disease; diet; fatty acids, unsaturated; fishes; mortality

Since Bang et al. suggested that the low mortality rate from coronary heart disease (CHD) among Eskimo compared with Danes may be due to their consumption of large quantities of seafood (1), the health effects of fish have attracted considerable scientific interest. Results from several cohort studies have suggested that consumption of a small amount of fish is inversely associated with CHD mortality (2–7). However, in some studies that examined the impact of fish consumption on nonfatal CHD, no association was observed (8, 9). In populations whose average fish intake was high, such as those in Finland, Norway, and Hawaii, also no inverse association between fish consumption and CHD risk was observed (10–13). Among the people in these studies, almost everyone eats fish regularly; therefore, these populations probably are not suited to studying the impact of the consumption of a small amount of fish on CHD mortality.

A difference in the type of fish consumed, for example, fatty fish or lean fish, might explain further inconsistency in the relation between fish intake and CHD mortality across populations. In the diet and reinfarction trial, carried out among cardiac patients, a modest intake of fatty fish was found to reduce all-cause mortality by about 29 percent, which was entirely attributable to a reduction in the number of deaths from coronary heart disease (14). Consumption of fatty fish may be protective because this type of fish contains high levels of the n-3 fatty acids eicosapentanoic acid and docosahexaenoic acid. N-3 fatty acids have important metabolic effects, such as inhibiting platelet aggregation and lowering serum triglyceride levels, which could play a role in the prevention of CHD (15). In addition, instead of the inconsistent results found in some prospective studies that examined the dose-response relation between fish consumption and CHD mortality, one study observed a dose-response relation between n-3 fatty acids, quantified in both the diet and red blood cell membranes, and the risk of primary cardiac arrest (16).

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Abbreviations: CHD, coronary heart disease; CI, confidence interval; SD, standard deviation.

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We hypothesized that because of its higher n-3 fatty acid content, especially fatty fish may be responsible for the protective effect of fish consumption. We analyzed the association between total, lean, and fatty fish consumption and 20-year CHD mortality in the Finnish, Italian, and Dutch cohorts of the Seven Countries Study.

MATERIALS AND METHODS

Study population

Between 1958 and 1964, 16 population samples of men aged 40–59 years from seven countries were enrolled in and were examined for the Seven Countries Study (17). In five population samples from Finland, Italy, and the Netherlands, individual dietary information was collected during follow-up. The two Finnish cohorts from two geographically defined areas, Ilomantsi in east Finland and Pöytyä and Mellilä in west Finland, were enrolled in 1959, and participation rates were high (99.3 and 97.0 percent, respectively). The cohorts from two small, rural villages in Italy, Crevalcore and Montegiorgio, and from a small town in the Netherlands, Zutphen, were enrolled in 1960 (participation rates: Italy, 98.5 and 99.0 percent; the Netherlands, 84.3 percent). Baseline dietary information used in this study was gathered in 1969 for participants in east Finland (n = 608) and west Finland (n = 694) and in 1970 for participants in the Netherlands (n = 615) and in Crevalcore (n = 592). For Montegiorgio, dietary information collected in 1965 was used for the men still alive in 1970 (n = 627), because the 1970 dietary data were collected for only a subset of men.

Data collection

Experienced dietitians and nutritionists conducted dietary interviews with all cohorts in Finland from September to November and in the Netherlands and Italy from March to June. Food consumption data were collected by using the cross-check dietary history method (18), which was adapted to each specific country; the methodology used was comparable across cohorts. This method provides information about habitual food consumption during the 6–12 months preceding the interview. First, the habitual food consumption pattern of a person was assessed during the week and weekends. This part of the interview contained questions about the foods consumed at breakfast, lunch, and dinner and between meals. Second, a checklist with an extensive number of foods was used, and the frequencies and quantities of the different foods consumed were recorded. The information about the food consumption pattern was then compared with the information from the checklist. Total fish consumption was computed by adding the number of grams of all fish consumed per day per subject. The following subgroups of types of fish were discerned: 1) lean (unprepared, ≤10 percent fat; prepared, ≤12 percent fat; e.g., plaice, codfish, bream, perch, pike); 2) fatty (e.g., mackerel, (salted) herring, eel); and 3) canned (e.g., sardines, salmon). Local food tables were used to convert food intake data into intake of energy and nutrients, including alcohol, for participants in the three different countries (19–21).

Information about the number of cigarettes smoked was collected by using a standardized questionnaire; participants were categorized as men who had never smoked, had stopped smoking, or currently smoked fewer or more than 20 cigarettes a day. Other risk factors such as serum total cholesterol, blood pressure, and anthropometric measures were determined according to a standardized protocol (18). Body mass index (kg/m^2) was calculated from weight and height measurements.

Ascertainment of mortality and causes of death was complete for all men in the subsequent 20 years. None of the men was lost to follow-up. All mortality data collected from death certificates, hospital records, or information from the general practitioner, family members, and other witnesses to the death were coded by one reviewer according to the World Health Organization's *International Classification of Diseases*, Eighth Revision by using standard criteria for interpretation and coding. In case of multiple causes of death, priority was given to accidents, followed by advanced-stage cancer, CHD, and stroke. For the present analyses, CHD referred to the primary or secondary cause of death based on *International Classification of Diseases* codes 410–414 (Finland, 223; Italy, 81; the Netherlands, 88) and, when a cardiac origin was mentioned, to the primary cause of sudden cardiac death based on code 795 (Finland, 19; Italy, 35; the Netherlands, 17).

Statistical methods

All statistical analyses were conducted by using the SAS statistical analysis computer package (version 6.11; SAS Institute, Inc., Cary, North Carolina). Men with a field diagnosis of CHD based on the standardized criteria were excluded from analysis (Finland, n = 214; Italy, n = 122; the Netherlands, n = 62), leaving a total of 2,738 men. For each country, the men were divided into categories based on the number of grams of fish they consumed per day (g/day). Categories of 0, 1–19, 20–39, and ≥40 g/day were used for total and lean fish consumption and 0, >0 g/day for fatty fish consumption, since only a small proportion of the men

consumed fatty fish. Canned fish was assigned to neither the lean nor the fatty fish category and, because of a low level of consumption, was not found to be related to CHD mortality. Because of small numbers, Finnish men who consumed 0 g/day of total or lean fish (no fish, $n = 33$; no lean fish, $n = 48$) were grouped with men who consumed 1–19 g/day. For the Netherlands, the total and lean fish consumption category of 20–39 g/day was merged with the category of ≥40g/day of total fish ($n = 63$) or lean fish ($n = 41$). However, excluding these men from the analyses did not change our results.

To compare the baseline risk factors and dietary variables across categories of fish consumption, we used analysis of variance for normally distributed variables, the Kruskal-Wallis test for skewed variables, and the chi-square test for categorical variables. Cox proportional hazards analyses were performed by using the SAS procedure PHREG, and the analyses were stratified by cohort using the STRATA statement (22). Relative risks, 95 percent confidence intervals, and p values for linear trend were calculated to investigate the association between fish consumption categories and CHD mortality for each country. Fish consumption was not used as a continuous variable, since none of the tests for linear trend supported a linear relation.

For total fish consumption, men who consumed no fish (Italy, the Netherlands) or the lowest amount of fish (Finland) were considered the reference group. For lean fish consumption, participants who consumed the lowest amount of lean fish (irrespective of their fatty fish intake) were taken as the reference group, and intake of fatty fish was included in the model as a confounder. For fatty fish consumption, the reference group consumed no fatty fish. Additional adjustments were made for age, cigarette smoking, body mass index, intake of energy and alcohol, and consumption of vegetables, fruit, meat, margarine, and butter—the food products associated with fish consumption in our data and potentially associated with CHD mortality. Alcohol intake (0, 1–39, 40–59, ≥60 g/day) was used as a categorical variable. If the association of fish consumption with CHD mortality was similar between the countries, data from the three countries were pooled and analyses were stratified by cohort. Two-tailed significance levels of 0.05 were used.

RESULTS

The average age of the men in this study was 58.0 years at baseline. The mean daily fish intake was 39 g (standard deviation (SD), 47) in Finland, 20 g (SD, 21) in Italy, and 18 g (SD, 20) in the Netherlands. In Finland, 77 percent of the fish consumed was lean and 23 percent was fatty. In Italy, 86 percent was lean and 14 percent was fatty; in the Netherlands, 80 percent was lean and 11 percent was fatty. Less than 1 percent of the fish consumed in Finland and Italy was canned compared with 9 percent in the Netherlands. We found that total fish consumption was positively associated with cigarette smoking and with serum cholesterol levels in Finland and inversely associated with age in Italy (table 1). No significant association between total

TABLE 1. Baseline level of major risk factors for coronary heart disease, according to categories of fish consumption, for men aged 50–69 years in Finland, Italy, and the Netherlands, 1970–1990

Country and fish consumption (g/day)	No. of men	Risk factor*				
		Age (years)	Body mass index (kg/m²)	Systolic blood pressure (mmHg)	Serum total cholesterol (mmol/liter)	Cigarette smoking (%)
Finland						
0–19	476	58.2 (5.7)	24.5 (3.6)	145 (23)	6.77 (1.20)	43.9
20–39	263	57.4 (5.4)	24.6 (3.5)	146 (21)	6.96 (1.33)	51.7
≥40	349	57.7 (5.4)	24.9 (4.1)	148 (23)	7.18 (1.40)†	56.2†
Italy						
0	264	59.1 (5.1)	25.9 (3.7)	153 (21)	5.64 (1.22)	51.5
1–19	347	58.5 (4.7)	25.4 (3.9)	154 (22)	5.67 (1.24)	53.6
20–39	323	57.6 (4.8)	26.0 (4.0)	153 (23)	5.75 (1.13)	48.0
≥40	163	57.7 (5.2)†	26.1 (4.3)	151 (22)	5.66 (1.13)	50.9
The Netherlands						
0	157	58.3 (5.4)	25.4 (2.9)	145 (21)	6.23 (1.15)	55.8
1–19	169	58.6 (5.3)	24.9 (2.3)	145 (19)	6.06 (1.02)	54.4
≥20	227	58.2 (5.3)	25.1 (2.8)	149 (22)	6.18 (1.08)	50.2

* Values in the first four columns are expressed as mean (standard deviation).

† Statistically significantly different ($p < 0.05$) between fish consumption categories (analysis of variance for normally distributed variables, chi-square test for dichotomous variables).

fish consumption and major risk factors was observed for the Netherlands.

Total fish consumption was positively associated with vegetable and fruit consumption in Finland and the Netherlands (table 2). In contrast, fish consumption was inversely associated with fruit consumption in Italy. Alcohol intake was positively associated with fish consumption, especially in Italy. Meat intake and butter intake were positively associated with fish consumption in Finland, whereas these associations were inverse in Italy. Total fish consumption was positively associated with energy intake in all three countries, with monounsaturated fatty acid intake in Italy, and with polyunsaturated fatty acid intake in the Netherlands. An inverse association was observed for saturated fatty acid intake in Italy and the Netherlands. For lean and fatty fish consumption, similar associations for dietary variables were observed (data not shown).

During 20 years of follow-up, 242 (22.2 percent) men died of CHD in Finland, 116 (10.6 percent) in Italy, and 105 (19.0 percent) in the Netherlands. In Finland, for men with the highest compared with the lowest levels of fish consumption, the crude relative risk for CHD mortality was 1.39 (95 percent confidence interval (CI): 1.00, 1.92) (table 3). Adjustment for age, energy intake, body mass index, and cigarette smoking, and further adjustment for dietary variables, attenuated this relative risk to 1.25 (95 percent CI: 0.89, 1.76). In Italy, men who consumed ≥40 g/day of fish had a relative risk for CHD mortality of 0.67 (95 percent CI: 0.33, 1.39) compared with men who consumed no fish, after adjustment for potential confounders. In the Netherlands, no association—neither crude nor after adjustment for potential confounders—between total fish consumption and CHD mortality was observed. The overall estimated relative risks for total fish consumption compared with no fish consumption in the three countries, pooled after stratification by cohort, were 0.93 (95 percent CI: 0.68, 1.27) for 1–19 g/day, 0.95 (95 percent CI: 0.69, 1.31) for 20–39 g/day, and 1.08 (95 percent CI: 0.76, 1.53) for ≥40 g/day.

Lean fish was consumed by 96 percent of the men in Finland, 71 percent in Italy, and 61 percent in the Netherlands; the proportions of fatty fish consumers were 36, 16, and 18 percent, respectively. The average fatty fish consumption for those who consumed fatty fish was 25 (SD, 28) g/day in Finland, 17 (SD, 16) g/day in Italy, and 11 (SD, 9) g/day in the Netherlands. Crude inverse associations were observed between fatty fish consumption and CHD mortality for all three countries; adjustment for potential confounders, including age, body mass index, cigarette smoking, energy intake, and relevant dietary variables, did not substantially change the relative risks. In Italy, fatty fish consumption was most strongly associated with a reduced risk for CHD (adjusted relative risk = 0.40, 95 percent CI: 0.19, 0.84) (table 4). For fatty fish consumers in Finland and the Netherlands, the adjusted relative risks were 0.80 (95 percent CI: 0.51, 1.26) and 0.70 (95 percent CI: 0.38, 1.27), respectively, compared with non-fatty-fish consumers. For the three

TABLE 2. Baseline daily intake of various foods and other nutrients, according to categories of fish consumption,* in men aged 50–69 years in Finland, Italy, and the Netherlands, 1970–1990

Item (unit of intake)	Fish consumption (g/day)									
	Finland			Italy				The Netherlands		
	0–19	20–39	≥40	0	1–19	20–39	≥40	0	1–19	≥20
Lean fish (g)	8 (6)	24 (8)	61 (47)†	0	10 (5)	23 (9)	50 (25)†	0	9 (6)	29 (19)†
Fatty fish (g)	1 (2)	5 (8)	23 (29)†	0	2 (4)	4 (8)	7 (18)†	0	2 (4)	3 (8)†
Meat (g)	136 (77)	150 (76)	161 (89)†	151 (72)	108 (77)	119 (74)	118 (81)†	138 (44)	139 (44)	143 (41)
Vegetables (g)	66 (48)	84 (66)	94 (68)†	60 (54)	63 (51)	72 (50)	80 (60)†	180 (61)	178 (59)	184 (57)
Fruit (g)	158 (164)	191 (233)	184 (173)†	190 (204)	138 (143)	134 (152)	144 (171)†	153 (116)	156 (104)	191 (153)
Alcohol (g)	6 (11)	8 (18)	7 (11)†	77 (53)	81 (60)	87 (57)	91 (66)†	9 (17)	8 (10)	11 (13)
Margarine (g)	3 (8)	3 (7)	4 (10)	8 (13)	16 (16)	16 (16)	16 (15)†	48 (21)	53 (22)	56 (25)†
Butter (g)	67 (39)	75 (43)	85 (54)†	15 (14)	8 (14)	7 (12)	6 (12)†	8 (16)	8 (15)	6 (14)
Energy (MJ)	14.9 (4.1)	16.1 (4.8)	16.6 (5.0)†	12.3 (3.3)	11.9 (3.2)	12.6 (3.1)	12.9 (3.3)†	10.6 (2.3)	11.0 (2.1)	11.2 (2.2)†
Total protein (en%‡)	12.9 (1.7)	13.0 (1 8)	13.7 (2.0)†	12.0 (2.7)	10.3 (2.8)	10.7 (2.5)	11.1 (2.5)†	12.4 (2.0)	12.4 (1.7)	12.9 (2.0)†
Total fat (en%)	37.4 (6.7)	36.6 (6.4)	37.9 (7.2)	28.6 (7.6)	27.9 (7.8)	27.4 (7.6)	27.2 (6.8)	40.5 (5.6)	41.7 (4.8)	40.7 (5.3)
Saturated fatty acids (en%)	21.8 (4.5)	21.4 (4.4)	22.1 (5.0)	11.0 (3.6)	9.2 (3.5)	8.8 (3.4)	8.4 (3.4)†	16.9 (3.1)	17.2 (2.8)	16.2 (2.6)†
Monounsaturated fatty acids (en%)	11.5 (2.2)	11.3 (2.1)	11.8 (2.3)†	13.8 (4.3)	15.1 (4.7)	15.3 (4.8)	15.3 (4.2)†	17.1 (3.0)	17.6 (2.6)	17.2 (2.8)
Polyunsaturated fatty acids (en%)	2.9 (0.4)	2.8 (0.4)	2.9 (0.5)	3.9 (1.9)	3.6 (2.0)	3.3 (1.4)	3.5 (1.6)†	6.2 (2.0)	6.7 (2.0)	7.1 (2.3)†
Dietary cholesterol (mg/day)	641 (248)	685 (256)	762 (285)†	348 (159)	261 (158)	294 (153)	303 (144)†	392 (178)	413 (150)	438 (176)†

* Expressed as mean (standard deviation).

† Statistically significantly different ($p < 0.05$) between fish consumption categories (analysis of variance for normally distributed variables, Kruskal-Wallis test for skewed variables).

‡ en%, percentage of energy intake.

TABLE 3. Relative risks (95% confidence intervals) for 20-year CHD* mortality, according to categories of fish consumption, for men aged 50–69 years in Finland, Italy, and the Netherlands, 1970–1990

Country and fish consumption (g/day)	No. of men	No. of CHD deaths (%)	Mortality rate†	Relative risk (95% confidence interval)		
				Crude	Adjusted‡	Adjusted§
Finland						
0–19	476	100 (21.0)	13.9	1.00	1.00	1.00
20–39	263	52 (19.8)	13.1	0.95 (0.67, 1.34)	0.98 (0.69, 1.40)	0.97 (0.68, 1.38)
≥40	349	90 (25.8)	18.5	1.39 (1.00, 1.92)	1.31 (0.94, 1.84)	1.25 (0.89, 1.76)
p for trend¶				0.05	0.12	0.20
Italy						
0	264	32 (12.1)	8.2	1.00	1.00	1.00
1–19	347	37 (10.7)	7.1	0.87 (0.52, 1.46)	0.93 (0.55, 1.57)	0.94 (0.55, 1.59)
20–39	323	34 (10.5)	6.7	0.81 (0.47, 1.38)	0.99 (0.57, 1.72)	0.93 (0.53, 1.63)
≥40	163	13 (8.0)	5.0	0.56 (0.27, 1.13)	0.69 (0.34, 1.42)	0.67 (0.33, 1.39)
p for trend¶				0.11	0.38	0.33
The Netherlands						
0	157	29 (18.5)	11.7	1.00	1.00	1.00
1–19	169	30 (17.8)	11.6	1.00 (0.60, 1.66)	1.01 (0.60, 1.69)	1.00 (0.59, 1.68)
≥20	227	46 (20.3)	13.1	1.13 (0.71, 1.80)	1.16 (0.72, 1.86)	1.10 (0.68, 1.79)
p for trend¶				0.60	0.55	0.69

* CHD, coronary heart disease.
† Per 1,000 person-years.
‡ Adjusted for age, body mass index (kg/m^2), cigarette smoking, and energy intake.
§ Adjusted for age, body mass index (kg/m^2), cigarette smoking, and intake of energy, vegetables, fruit, alcohol, meat, butter, and margarine.
¶ Values for linear trend across categories of total fish consumption.

countries, the overall estimated relative risks for fatty fish consumption, pooled after stratification by cohort, were 0.57 (95 percent CI: 0.40, 0.80) for 1–19 g/day and 0.87 (95 percent CI: 0.59, 1.27) for ≥20 g/day compared with no fatty fish consumption. The pooled estimated relative risk for fatty fish consumers in the three countries was 0.66 (95 percent CI: 0.49, 0.90). Lean fish intake was not associated with CHD risk in any of the three countries; neither the relative risks nor the tests for linear trend were statistically significant (table 4).

DISCUSSION

This prospective study of men in three European countries showed an inverse association of fatty fish consumption, but not of lean or total fish consumption, with 20-year CHD mortality. The pooled results for fatty fish were consistent with a 34 percent (95 percent CI: 10–51 percent) reduction in CHD mortality.

Our results suggest that n-3 fatty acids are responsible for the protective effect of fish. Consumption of 15 g/day of lean fish (e.g., plaice or codfish), as consumed by our populations, results in a daily intake of about 50 mg of n-3 fatty acids; in contrast, 15 g/day of fatty fish (e.g., mackerel or herring) provides about 400 mg of n-3 fatty acids a day (23). In this study, the direct relation between n-3 fatty acids and CHD mortality was not analyzed because of rather limited information about the type of fish consumed by our cohorts, which could have introduced misclassification regarding intake of this nutrient.

Several earlier studies showed an inverse relation between n-3 fatty acids from seafood and (sudden) cardiac mortality (5, 16, 24). However, some prospective studies observed a stronger beneficial effect of fish consumption than of intake of n-3 fatty acids (8, 24). This observation may be partly explained by a random misclassification of dietary exposure due to error in the quantification of n-3 fatty acids in food tables, which tends to attenuate existing associations. Another inconsistency in previous results concerned the dose-response relation between fish consumption and CHD mortality. Our results suggest that differences in lean and fatty fish consumption could also explain this inconsistency, since the n-3 fatty acid content of lean and fatty fish is dissimilar.

A variety of actions could explain the beneficial effects of n-3 fatty acids on CHD mortality. Experimentally, n-3 fatty acids in the form of fish oil supplements lower triglyceride and very low density lipoprotein cholesterol levels in animals and humans

TABLE 4. Adjusted* relative risks (95% confidence intervals) for 20-year CHD† mortality, according to categories of fatty and lean fish consumption, for men aged 50–69 years in Finland, Italy, and the Netherlands, 1970–1990

Country and fish consumption (g/day)	No. of men	No. of CHD deaths	Adjusted relative risk
Finland			
Fatty fish			
0	697	155	1.00
>0	391	87	0.80 (0.51, 1.26)
Lean fish			
0			
<20	568	124	1.00
≥20	253	51	0.95 (0.68, 1.33)
≥40	267	67	1.08 (0.78, 1.50)
p for trend‡			0.63
Italy			
Fatty fish			
0	923	106	1.00
>0	174	10	0.40 (0.19, 0.84)
Lean fish			
0	318	34	1.00
<20	365	41	1.09 (0.66, 1.81)
≥20	281	30	0.97 (0.55, 1.69)
≥40	133	11	0.80 (0.38, 1.66)
p for trend‡			0.57
The Netherlands			
Fatty fish			
0	451	92	1.00
>0	102	13	0.70 (0.38, 1.27)
Lean fish			
0	216	38	1.00
<20	146	24	0.93 (0.55, 1.55)
≥20	191	43	1.29 (0.82, 2.03)
≥40			
p for trend‡			0.27

* Adjusted for age, body mass index (kg/m²), cigarette smoking, and intake of energy, vegetables, fruit, alcohol, meat, butter, and margarine, with fatty and lean fish consumption as dummy variables in one model.

† CHD, coronary heart disease.

‡ Values for linear trend across categories of lean fish consumption.

(25) and inhibit platelet aggregation as a result of reduced synthesis of thromboxane A_2 (26). N-3 fatty acids also influence antiarrhythmic pathways because they have been shown in in vitro studies to synchronize the beating rate of the heart (27), and they have been shown to reduce the incidence of ventricular fibrillation in rats (28) as well as in patients with frequent ventricular arrhythmias (29).

The physiologic effects of consuming small amounts of fish have been investigated in observational studies. Men from Zutphen who habitually consumed about 30 g/day of fish for 26 years had lower serum triglyceride levels and lower triglyceride concentrations in the intermediate density lipoprotein fraction than the control group (30). In this study, however, small amounts of fish were not associated with platelet function (31). On the other hand, in the ARIC Study, one serving of fish per day was inversely associated with hemostatic factors such as fibrinogen and factor VII (32). Furthermore, consumption of one fish meal per week versus no fish was associated with an increase in heart rate variability as large as that observed for fish oil supplementation (33, 34). Arterial compliance was better in healthy subjects and diabetic patients who consumed one serving of fish per week than in those who consumed no fish (35). Finally, fish consumption at least two times per week was inversely associated with small myocardial lesions (36). Thus, our results are consistent with experimental and observational evidence on the beneficial physiologic effects of a small quantity of n-3 fatty acids.

A recent epidemiologic study suggests that fish consumption may have an especially beneficial effect on sudden cardiac death (24). In the present study, sudden cardiac death was included in the outcome variable coronary heart disease mortality; however, because the number of sudden cardiac deaths was small, it was not possible to separate them from nonsudden cardiac deaths.

In our analyses of the Zutphen cohort from the Netherlands, a small decrease in CHD mortality was observed for fatty fish but not for lean or total fish consumers. Previous results from this cohort showed that consumption of (total) fish once or twice a week in 1960 was associated with a 50 percent reduction in CHD mortality during 20 years of follow-up (2). One explanation could be that the coronary events that occurred during the first years of follow-up, when men were younger, were more severe and were strongly associated with fish consumption (24).

For Finnish men, we observed a small increase in CHD mortality for those who consumed ≥40 g/day of fish (mostly lean fish) and a small decrease for those who consumed fatty fish. A possible harmful effect of fish consumption was observed in two other studies from Finland (10, 11). Several methodological issues may account for the difference in the effect of (type of) fish consumption observed in Finland compared with Italy and the Netherlands. First, the mercury content of fish may explain the more harmful effect of fish in Finland. In the eastern Finnish study, lean fish but not fatty fish was associated with mercury intake and with an excess CHD risk (10). In general, the mercury content of fish depends on its size, its age, and the concentration of mercury in the area (37, 38). Thus, besides the difference in the n-3 fatty acid content of

lean fish and fatty fish, in Finland the mercury content of the type of fish consumed may also differ. Second, the high level of fish consumption observed in all Finnish studies, including our cohorts, may limit the possibility of studying the effect of consuming small amounts of fish (especially of total and lean fish). This issue does not apply to the strength of this association between fatty fish intake and CHD risk, since the majority of the Finnish men in our study consumed no fatty fish. Third, we cannot exclude the possibility that the associations between consumption of lean and fatty fish and CHD risk observed in the Finnish cohorts were partly affected by random misclassification due to rather limited information about the type of fish consumed by each man in our Finnish population.

Although an inverse association was observed between fatty fish consumption and CHD mortality in the three countries, no linear trend was found in the pooled analyses of fatty fish consumption. However, the quantity of fatty fish consumption in the three countries overlapped only to a small extent, and the highest consumption was in Finland. Therefore, by categorizing fatty fish consumption in the pooled analysis, the difference in the effect of fatty fish consumption between the countries was examined rather than a dose-response relation of fatty fish consumption. In addition, the effects of total and lean fish consumption in Finland, Italy, and the Netherlands were rather heterogeneous. In general, this finding might partly be explained by cultural influences, since fish consumption itself, as well as its association with dietary and lifestyle factors, varied among the three countries.

Our results could have been influenced by residual confounding. Inadequate measurement of habitual dietary intake seems unlikely, since the cross-check dietary history method used in all three countries is acknowledged to be valid in an epidemiologic setting (39, 40). Additionally, the results could have been biased because of a healthier lifestyle practiced by (fatty) fish consumers. In our data, consumption of fish was associated with a lower intake of saturated fatty acids in the Netherlands and Italy, probably because fish-substitute foods, for example, meat, contain a relatively high level of saturated fatty acids. Furthermore, in all three countries, consumption of vegetables and fruit was positively associated with the amount of fish consumed. In the present study, no reliable measure for physical activity was available. Alternatively, an approximation of physical activity was calculated (energy intake per kilogram of body weight); in all three countries, this variable was positively associated with fish consumption (data not shown). Because these associations were observed for fatty fish as well as for lean fish consumers, and no protective effect of lean fish consumption was observed, the more healthy lifestyle of fish consumers may not have biased the specific effect of fatty fish consumption. Also, when we adjusted our analysis for dietary variables such as intake of vegetables, fruit, and saturated fatty acids or included the proxy of physical activity instead of energy intake, the estimated relative risks did not change appreciably.

In conclusion, our data suggest that especially fatty fish is protective against CHD mortality. Independent of lean fish consumption and potential confounders, we found that consumption of fatty fish was associated with a reduction of 34 percent (95 percent CI: 10–51 percent) in CHD mortality in three different European countries.

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