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Marine (n-3) Fatty Acids, Fish Consumption, and the 10-Year Risk of Fatal and Nonfatal Coronary Heart Disease in a Large Population of Dutch Adults with Low Fish Intake[1,2]

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Abstract

We assessed the dose-response relations within a low range of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and fish intake on fatal coronary heart disease (CHD) and nonfatal myocardial infarction (MI). In a Dutch population-based cohort study, EPA+DHA and fish intake were assessed at baseline among 21,342 participants aged 20–65 y with no history of MI or stroke. Hazard ratios were calculated with Cox proportional-hazard models. During 9–14 y of follow-up (mean 11.3 y), 647 participants (3%) died, of which 82 of CHD. Fatal CHD mainly comprised MI (64 cases). In total, 252 participants survived an MI. Median intakes in quartiles of EPA+DHA were 40, 84, 151, and 234 mg/d. Medians of fish consumption in quartiles were 1.1, 4.2, 10.7, and 17.3 g/d. Compared with the lowest quartile of EPA+DHA, participants in the top quartile had a 49% lower risk of fatal CHD (95% CI: 6–73%) and a 62% lower risk of fatal MI (95% CI: 23–81%). We observed inverse dose-response relations for EPA+DHA intake and fatal CHD (P-trend = 0.05) and fatal MI (P-trend = 0.01). Results were similar for fish consumption. Nonfatal MI was not associated with EPA+DHA or fish intake. In conclusion, in populations with a low fish consumption, EPA+DHA and fish may lower fatal CHD and MI risk in a dose-responsive manner. Low intakes of EPA+DHA or fish do not seem to protect against nonfatal MI. J. Nutr. 140: 1023–1028, 2010.

Introduction

In 1985, Kromhout et al. (1) showed that a small amount of fish in the diet was associated with a lower risk of coronary heart disease (CHD)[6] mortality in the Zutphen Study of 852 elderly Dutch men. In a metaanalysis of prospective cohort studies, He et al. (2) estimated that eating fish once per week was associated with a 15% lower risk of coronary death compared with a fish intake of less than once per month. Each 20-g/d increase in fish consumption was related to a 7% lower risk of CHD mortality (P-trend = 0.03). The marine-derived, very-long chain (n-3) PUFA eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are assumed to be primarily responsible for these health effects of fish. The metaanalysis of He et al. (2) also showed that the evidence for an inverse association of fish intake and risk of nonfatal myocardial infarction (MI) was weak (P-trend = 0.40), even though there was a significant inverse association of eating fish ≥5 times/wk compared with less than once per month.

Several randomized controlled trials (RCT) on fish and fish oil in relation to coronary and all-cause mortality have been conducted in cardiac patients. In the context of this paper, the findings in patients with a low level of fish consumption are most relevant. The first RCT using low levels of fatty fish or fish oil capsules as interventions showed significant reductions in fatal CHD (3,4) and sudden death (4). Recent metaanalyses of RCT showed that fish oil supplementation significantly reduced fatal CHD (5) and fatal MI (6) in coronary patients.

Mozaffarian and Rimm (7) combined data from prospective cohort studies and RCT and estimated that a reduction of CHD mortality may be achieved with relatively low intakes of EPA and DHA. Modest consumption of fish (1–2 servings/wk, which is ~100–200 g fish/wk) was associated with a 36% lower risk of coronary death. They suggested that for the general population an intake of 250 mg/d of EPA+DHA (1 serving of fatty fish/wk) would be sufficient. Others have recommended target intakes of ~500 mg/d (8–11). Most studies have mainly focused on fish

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[6] Abbreviations used: CHD, coronary heart disease; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HDR, hospital discharge register; ICD, International Classification of Diseases; MI, myocardial infarction; MORGEN, Monitoring Project on Risk Factors for Chronic Diseases; RCT, randomized controlled trial.
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consumption (12) as the main source of EPA and DHA. However, other foods like meat and eggs also contribute to the intake of these fatty acids (13) and may be important to take into account.

In this prospective cohort study, we investigated the dose-response relations of habitual intake of EPA+DHA and fish on fatal CHD and fatal and nonfatal MI within the low range of fish intake in The Netherlands.

Methods

Design and study population. The Monitoring Project on Risk Factors for Chronic Diseases (MORGEN) study is a Dutch population-based cohort of 22,654 men and women, aged 20–65 y. The MORGEN Study contributes to the Dutch part of the European Prospective Investigation into Cancer and Nutrition (14). In the MORGEN Study, information on diet, lifestyle, and cardiovascular risk factors was collected in 1993–1997. For the MORGEN Study, random samples (stratified by gender and 5-y age groups) from civil registries of Amsterdam, Doetinchem, and Maastricht were drawn, representing 3 geographical parts of The Netherlands. The mean response rate was 45%. The study complies with the Declaration of Helsinki and the protocol was approved by the Medical Ethics Committee of the TNO Prevention and Health (Leiden, The Netherlands).

For the current analyses, we excluded participants who did not provide informed consent for vital status follow-up (n = 701). We also excluded participants without dietary information (n = 72) and 97 participants with extreme intakes of energy (<2094 or >18,844 kJ for women and <3350 and >20,938 kJ for men). Furthermore, participants with a history of MI or stroke at baseline (n = 442) based on self-report or hospital admission data were excluded, resulting in 21,342 participants for the current analyses.

Dietary assessment. Dietary information was assessed at baseline with a self-administered 178-item FFQ (15). The questionnaire included foods that covered the daily intake of each nutrient or food of interest for at least 90% of the population mean intake, based on the Dutch National Food Consumption Survey of 1987–1988. Participants were asked to report the usual frequency of consumption of the food items during the past year and their mean portion sizes. Participants indicated their answers in times per day, per week, per month, per year, or as never. For 28 food items, color photographs were used to estimate portion sizes. Information on habitual fish intake was obtained by questions on the absolute frequency of fish consumption combined with questions on the following types of fish: *1*) lean and moderately fatty fish, including plaice, cod, fried fish, fish fingers; *2*) fatty fish, including eel, mackerel, herring; and *3*) shrimps and mussels. Trained research assistants obtained information on unclear or missing items. After checking for improbable and inconsistent answers, the dietary data were converted into daily food and nutrient intakes and frequencies of food items by using the digital update (of 1998) of the Dutch food composition database (NEVO) of 1996 (16). The daily intakes of fatty acids were calculated with additional NEVO information of the 2001 release (17).

The relative validity (intake assessed by the FFQ compared with intakes assessed by 12 monthly 24-h recalls) and reproducibility (measured by 2 repeated measurements) of the FFQ for food groups and some nutrients were assessed among 121 Dutch men and women (15,18). The Spearman rank correlations for the reproducibility of the FFQ after 6 mo for fish intake were 0.49 for men and 0.61 for women. The relative validity (Spearman rank correlation) of the FFQ for fish intake was 0.32 for men and 0.37 for women (all $P < 0.05$).

Mortality and morbidity data. After enrolment in the MORGEN project, the participants were followed for the occurrence of fatal CHD and fatal or nonfatal MI by linkage with several registries, including Statistics Netherlands for cause-specific mortality and the hospital discharge register (HDR; in Dutch: Landelijke Medische Registratie) for hospital admissions (19).

Information on mortality follow-up was available from baseline until January 2007. CHD mortality was defined as International Classification of Diseases (ICD) 10 (20) codes I20-I25 or ICD9 (21) codes 410–414 and MI as ICD-10 codes I21-I22 or ICD-9 code 410 based on primary or secondary causes of death. For the analyses on fatal CHD and fatal MI, participants were followed until death, emigration, or they were censored at January 1, 2007. Deceased participants who had not given permission to obtain data on cause-specific death (n = 43) were censored at date of death. Causes of death could not be obtained for participants who died outside The Netherlands.

Information on nonfatal MI (defined as ICD-9 code 410) was based on hospital admission data. These data were available from baseline until January 2006. Hospital admissions followed by death at the same date were regarded as fatal events. Participants with both information on vital status and hospital admissions (n = 20,880) were followed until the first nonfatal MI event or they were censored at death, emigration, or January 1, 2006, whichever occurred first. In The Netherlands, hospital admissions are coded by gender, date of birth, and the numeric part of the postal code. At least 88% of the hospital admissions of our cohort could be uniquely linked to a participant in our cohort (19).

Assessment of covariates. Body weight, height, and blood pressure were measured by trained research nurses at a municipal health service site (22). A self-administered questionnaire was used to assess the presence of known diabetes, history of MI and stroke, medication use, vitamin or mineral supplement use (yes/no), family history of MI, educational level, alcohol consumption, and cigarette smoking. Physical activity was assessed only during baseline measurements in 1994–1997, which comprised 77% of our cohort (23). For this subset, we calculated whether participants complied with being physically active during 30 min with a moderate intensity on 5 d/wk.

Participants donated blood (nonfasting) in which the levels of total serum cholesterol and serum HDL cholesterol were assessed at the Lipid Reference Laboratory of the Erasmus Medical Center in Rotterdam, using enzymatic methods (24). Blood pressure was measured, with the participant in a sitting position. Systolic pressure was recorded at the appearance of sounds (first-phase Korotkoff) and diastolic blood pressure was recorded at the disappearance of sounds (5th-phase Korotkoff). Blood pressure was measured twice, after the first measurement heart rate was counted for 30 s, followed by the second measurement (25). The mean of the 2 measurements was used in the analyses.

Statistical analysis. We used Cox proportional-hazard models with follow-up time as time metric to estimate relative risks of fatal CHD, fatal MI, and nonfatal MI in quartiles of habitual intake of EPA+DHA and total fish. We calculated hazard ratios with 95% CI with the lowest quartiles of EPA+DHA and fish intake as the reference category. Our models fulfilled the proportional-hazards assumption. Participants' characteristics in quartiles of EPA+DHA intake are presented as mean ± SD, median [interquartile range (Q1–Q3)], or percentages, unless otherwise noted. The correlation between the intake of EPA+DHA and total fish was assessed with the Spearman rank correlation test.

In addition to an age- and gender-adjusted model (model 1), we used multivariable-adjusted models (model 2) that included total energy intake (kJ/d), BMI (kg/m^2), alcohol intake (based on the calculation of total ethanol intake in g/d by FFQ), cigarette smoking (never, former, current), socioeconomic status (primary school, secondary school, up to higher vocational training, completed higher vocational training or university), vitamin or mineral supplement use (yes/no), use of drugs for hypertension or hypercholesterolemia (yes/no), family history (yes/no) of CHD (MI of father before age of 55 y or MI of mother before age of 65 y), fruit consumption (g/d), vegetable consumption (g/d), and saturated fat intake (g/d). Covariates were selected based on what we know from the literature to be important confounders of the relation between (n-3) PUFA and CHD. Stratified analyses did not provide evidence for interaction by gender or age of the association of EPA+DHA or fish intake with different outcomes. Therefore, we combined men and women and different age groups. Possible confounding by physical activity was checked in the subgroup of participants with information on physical activity (n = 16,421). Analyses were repeated for quartiles of EPA+DHA from marine sources only. All probability values are 2-tailed with α = 0.05 (SAS/STAT software, version 9.1; SAS Institute).

Results

Population characteristics. Participants were 42.1 ± 11.2 y old at baseline and 45% were male. Median intakes of EPA+DHA and fish were 114 (62–195) mg/d and 7.4 (3.3–14.0) g/d, respectively. About 40% of the participants consumed fish less than once per month and 8.5% reported eating no fish at all. The median frequency of fish consumption was 2 (1–4) times/mo. The consumption of lean fish + moderately fatty fish, which were combined in our questionnaire, was 3–4 times as high as the consumption of fatty fish. This resulted in a higher absolute intake of EPA+DHA from lean + moderately fatty fish than from fatty fish (data not shown).

During 9–14 y of follow-up (mean 11.3 y), 647 (3%) participants died, of which 82 died of CHD. Fatal CHD mainly comprised MI (64 cases). In total, 252 participants survived an MI.

Median EPA+DHA intakes in quartiles were 40, 84, 151, and 234 mg/d. The ratio of EPA:DHA was ~1:2. The main source of EPA+DHA was fish (63%). In all quartiles, the amount of EPA +DHA from other sources than fish was ~30 mg/d. In the higher quartiles, participants were slightly older, more likely to be male, and higher educated. In the lowest quartile, 63% of the participants complied with the Dutch guideline for physical activity. In the other 3 quartiles 67% complied. Higher intakes of EPA+DHA were associated with a higher intake of energy and alcohol (**Table 1**). The Spearman rank correlation between total EPA+DHA intake and fish consumption was 0.95.

EPA+DHA intake, fish consumption, and CHD. After adjustment for potential confounders, the risk of fatal CHD was inversely associated with EPA+DHA intake, with a 49% lower risk (95% CI 6–73%) in the top quartile of EPA+DHA compared with the reference group. We found a stronger association between fatal MI and EPA+DHA intake, with a 62% lower risk in the top quartile. A dose-response relation was

TABLE 1 Baseline characteristics of 21,342 Dutch adults, aged 20–65 y, by quartiles of EPA+DHA intake[1]

	Quartiles of EPA+DHA intake, *mg/d (range)*			
	1 (<62)	2 (62–113)	3 (114–194)	4 (>194)
n	5336	5335	5335	5336
Median EPA+DHA intake, *mg/d*	40	84	151	234
Male gender, *%*	39	45	45	51
Age, *y*	41.1 ± 11.8	41.8 ± 11.2	42.4 ± 10.8	43.3 ± 10.8
BMI, *kg/m²*	24.8 ± 4.0	25.0 ± 3.9	25.0 ± 3.9	25.2 ± 4.0
Fish consumers (≥1 servings/mo),[2] *%*	<1	40	98	100
Fish intake, *g/d*	1.4 ± 1.4	4.9 ± 2.2	10.9 ± 3.7	22.0 ± 14.3
EPA, *mg/d*	10 ± 6	25 ± 7	48 ± 11	98 ± 60
DHA, *mg/d*	28 ± 11	61 ± 11	105 ± 18	197 ± 106
EPA+DHA, *mg/d*	39 ± 15	86 ± 16	152 ± 25	295 ± 163
EPA+DHA from fish, *mg/d*	13 ± 13	53 ± 21	117 ± 33	255 ± 164
PUFA, *% of energy intake*	6.6 ± 1.7	6.8 ± 1.6	6.8 ± 1.7	7.0 ± 1.7
SFA, *% of energy intake*	14.6 ± 2.7	14.6 ± 2.4	14.3 ± 2.5	14.1 ± 2.6
Total fat, *% of energy intake*	34.7 ± 5.1	35.3 ± 4.8	34.9 ± 5.0	34.9 ± 5.1
Energy intake, *MJ/d*	8.9 ± 2.7	9.5 ± 2.7	9.6 ± 2.7	9.8 ± 2.9
Smoking, *%*				
Never	37	34	34	33
Former	28	30	31	29
Current	35	35	36	38
Alcohol consumption,[3] *g/d*	3.1 (0.3–11.8)	5.8 (1.1–16.1)	7.5 (1.5–19.5)	8.7 (1.5–22.5)
Highly educated,[4] *%*	19	22	28	27
Dutch ethnicity, *%*	98	97	97	94
Physically active,[5] *%*	63	67	67	67
Family history of CHD, *%*	10	9	9	10
Self-reported diabetes mellitus, *%*	1.0	0.8	1.0	1.7
Serum total cholesterol,[6] *mmol/L*	5.3 ± 1.0	5.2 ± 1.0	5.3 ± 1.1	5.3 ± 1.1
Serum HDL-cholesterol,[6] *mmol/L*	1.4 ± 0.4	1.4 ± 0.4	1.4 ± 0.4	1.4 ± 0.4
Systolic blood pressure, *mm Hg*	120.4 ± 15.9	120.4 ± 15.9	120.8 ± 16.1	121.7 ± 16.6
Diastolic blood pressure, *mm Hg*	76.5 ± 10.4	76.6 ± 10.5	76.6 ± 10.7	76.9 ± 10.9
Use of cholesterol-lowering drugs, *%*	1.0	0.7	0.9	1.3
Use of antihypertensive drugs, *%*	4.5	4.0	4.7	4.8
Supplement use,[7] *%*	28	29	33	34

[1] Values are means ± SD, unless indicated otherwise.
[2] 1 serving =~100 g.
[3] Median with interquartile range.
[4] University or higher vocation training.
[5] Compliant to being physically active during 30 min with a moderate intensity on 5 d/wk. Available in subsample of participants enrolled between 1994 and 1997 (*n* = 16,421).
[6] Nonfasting.
[7] Vitamin or mineral supplement.

found for both fatal CHD (P-trend = 0.05) and fatal MI (P-trend = 0.01). EPA+DHA intake was not associated with nonfatal MI (**Table 2**). We repeated our analyses for quartiles of EPA+DHA from marine sources only. These results did not differ from the results on total EPA+DHA (data not shown).

Median intakes in quartiles of fish consumption were 1.1, 4.2, 10.7, and 17.3 g/d. Like for EPA+DHA, consuming more fish was associated with a lower risk of fatal CHD and fatal MI. Similar to our results on EPA+DHA intake, the associations were dose dependent. Fish consumption was not associated with nonfatal MI (**Table 3**). We have additionally included monounsaturated fatty acids, linoleic acid, and α-linolenic acid in our multivariable models. However, this yielded similar results for both our analyses on total EPA+DHA and fish consumption. Our population consisted of only 1% of diabetic patients and our results did not change when we excluded diabetic patients (data not shown).

Discussion

In our healthy Dutch population with a low habitual fish intake, EPA+DHA and fish consumption were inversely associated with fatal CHD and fatal MI, but not with nonfatal MI. The risk of fatal CHD in the highest quartile of EPA+DHA intake (~250 mg/d) was ~50% lower compared with the lower quartile (~40 mg/d). Within this low range of intake, the inverse associations with fatal CHD and fatal MI risk were graded. Similar results were found for fish, i.e. participants who consumed only 17g/d (~1 portion of fish/wk) had an ~50% lower risk of fatal CHD.

This study has several strengths, including complete information on vital status with little loss to follow-up of a large population-based cohort and detailed information on potential confounders. Both fatal and nonfatal CHD could be studied in relation to fish and EPA+DHA. An extensive FFQ was used that allowed calculation of EPA+DHA from the whole diet. However, there were also limitations. First, data on physical activity, which could be an important confounder, was available for only 77% of the participants. We performed multivariable analyses with and without adjustment for physical activity in this subgroup, which yielded similar risk estimates for EPA+DHA and fish intake in relation to CHD. We therefore think that residual confounding by physical activity is not a major issue in the present study. Second, misclassification of participants for EPA+DHA and fish intake may have occurred. The relative validity of our FFQ for fish intake was only 0.32 for men and 0.37 for women (15). Because we excluded participants with a history of MI or stroke, we expect misclassification at baseline to be random rather than dependent on disease outcome. Random misclassification could have attenuated the risk estimates in the present study. Third, we obtained data on nonfatal MI via linkage with the national HDR. Eighty-eight percent of the hospital admissions can be uniquely linked to an individual on the basis of gender, date of birth, and postal code (19). In a validation study, the HDR was compared with the detailed clinical registry of cardiovascular patients of the Cardiology Department of the Maastricht University Hospital, showing a relatively high sensitivity (84%) and positive predictive value (97%) for MI (26). The region of Maastricht is 1 of the 3 regions of the MORGEN study. Should nonfatal MI cases in our study be missed by this procedure, this is unlikely to be related to the fish intake and will therefore not have biased our results.

With respect to fatal CHD, our results are comparable to the Zutphen Study, in which the consumption of 1–2 fish meals/wk was associated with half the risk of CHD mortality compared with lower intakes (1). In a pooled analysis of prospective cohort studies and clinical trials, Mozaffarian and Rimm (7) estimated that a daily intake of 250 mg of EPA+DHA (1–2 servings fish/wk) was associated with a 36% lower risk of fatal CHD with little additional benefit above 250 mg/d. The range of EPA

TABLE 2 Associations of fatal CHD and (non)fatal MI by quartiles of EPA+DHA intake in 21,342 Dutch men and women[1]

	Quartiles of EPA+DHA intake, *mg/d (range)*				
	1 (<62)	2 (62–113)	3 (114–194)	4 (>194)	*P*- trend
n	5336	5335	5335	5336	
Median EPA+DHA, *mg/d*	40	84	151	234	
Fatal CHD					
Events, *n*	24	18	20	20	
Model 1[2,3]	1.0 (ref)	0.74 (0.40–1.36)	0.76 (0.42–1.37)	0.68 (0.38–1.23)	0.27
Model 2[4,5]	1.0 (ref)	0.68 (0.36–1.25)	0.65 (0.36–1.19)	0.51 (0.27–0.94)	0.05
Fatal MI					
Events, *n*	21	13	16	14	
Model 1[2,3]	1.0 (ref)	0.60 (0.30–1.20)	0.69 (0.36–1.31)	0.54 (0.27–1.06)	0.13
Model 2[4,5]	1.0 (ref)	0.57 (0.28–1.14)	0.56 (0.29–1.09)	0.38 (0.19–0.77)	0.01
Nonfatal MI					
Events, *n*	57	61	61	73	
Model 1[2,6]	1.0 (ref)	1.06 (0.74–1.52)	0.99 (0.69–1.42)	1.10 (0.78–1.56)	0.10
Model 2[4,7]	1.0 (ref)	1.07 (0.74–1.55)	1.04 (0.72–1.50)	1.07 (0.74–1.54)	0.18

[1] Values are hazard ratios (95% CI), with the first quartile as the reference category.
[2] Model 1: adjusted for age and gender.
[3] n = 21,342.
[4] Model 2: model 1 with additional adjustments for BMI, total energy intake, ethanol intake, cigarette smoking, social economic status, vitamin or mineral supplement use, use of drugs for hypertension or hypercholesterolemia, family history of cardiovascular disease, SFA, fruit, and vegetables.
[5] n = 21,055.
[6] n = 20,880.
[7] n = 20,605.

TABLE 3 Associations of fatal CHD and (non)fatal MI by quartiles of fish intake in 21,342 Dutch men and women[1]

	Quartiles of fish intake, *g/d (range)*				
	1 (<3.3)	2 (3.3–7.3)	3 (7.4–14.0)	4 (>14)	*P*-trend
n	5284	5401	5258	5399	
Median fish intake, *g/d*	1.1	4.2	10.7	17.3	
Median EPA:DHA, *mg/d*	39	82	148	228	
Median EPA:DHA from fish, *mg/d*	11	46	119	191	
Fatal CHD					
Events, *n*	25	24	14	19	
Model 1[2,3]	1.0 (ref)	0.95 (0.54–1.66)	0.52 (0.27–0.99)	0.63 (0.35–1.15)	0.06
Model 2[4,5]	1.0 (ref)	0.92 (0.52–1.61)	0.50 (0.26–0.97)	0.52 (0.28–0.95)	0.02
Fatal MI					
Events, *n*	19	22	11	12	
Model 1[2,3]	1.0 (ref)	1.13 (0.61–2.10)	0.53 (0.25–1.11)	0.53 (0.25–1.09)	0.02
Model 2[4,5]	1.0 (ref)	1.12 (0.60–2.08)	0.50 (0.24–1.06)	0.40 (0.19–0.86)	<0.01
Nonfatal MI					
Events, *n*	61	57	66	68	
Model 1[2,6]	1.0 (ref)	0.92 (0.64–1.32)	1.02 (0.72–1.44)	0.96 (0.68–1.36)	0.15
Model 2[4,7]	1.0 (ref)	0.96 (0.67–1.39)	1.07 (0.75–1.54)	1.01 (0.71–1.45)	0.14

[1] Values are hazard ratios (95% CI), with the first quartile as the reference category.
[2] Model 1: adjusted for age and gender.
[3] *n* = 21,342.
[4] Model 2: model 1 with additional adjustments for BMI, total energy intake, ethanol intake, cigarette smoking, social economic status, vitamin or mineral supplement use, use of drugs for hypertension or hypercholesterolemia, family history of cardiovascular disease, SFA, fruit, and vegetables.
[5] *n* = 21,055.
[6] *n* = 20,880.
[7] *n* = 20,605.

+DHA intake in our study was mostly below 250 mg/d and we found risk reductions up to 49% for fatal CHD. This is also larger than observed in the metaanalysis by He et al. (2), who found a 15% lower risk of fatal CHD for weekly fish consumption. The dose-response relation of He et al. (2) might be attenuated by studies with much higher intakes of fish with little extra benefit. Another reason for our stronger associations could be that our relatively young cohort had a lower baseline risk to develop fatal CHD compared with the cohorts in the above-mentioned metaanalysis, which may have inflated our risk estimates to some extent. In a recent metaanalysis of fish oil supplementation trials, a 20% reduced risk of cardiac death was found compared with placebo (5). Fish oil doses in these trials amounted to several grams per day, which cannot be achieved through diet alone. Furthermore, the Japanese JELIS trial (27) in 18,645 hypercholesterolemic patients largely influenced the overall risk estimates of this metaanalysis. In this trial, on top of a high habitual fish intake, no effect of 5-y supplementation with 1.8 g/d EPA on fatal CHD was found.

We found no associations between nonfatal MI and low levels of EPA+DHA or fish intake. These findings are concordant with the metaanalysis of prospective cohort studies of He et al. (2) in which a significant inverse association for fish intake and nonfatal CHD was found only for eating fish ≥5 times/wk compared with less than once per month, which is much higher than the intake in our cohort (2). In addition, Japanese studies showed that at high levels of intake, fish and EPA+DHA may be protective against nonfatal CHD. In the Japan Public Health Center-Based Study, the relative risk for nonfatal MI was 0.43 (95% CI: 0.23–0.81) in participants with a median fish intake of 180 g/d compared with participants with a daily intake of 23 g/d (28). In the above-mentioned JELIS trial, the risk of nonfatal CHD was reduced by 19% (27). However, the Japanese habitual intake of fish (mean of 85 g/d) is much higher than the Dutch diet. Currently, no data are available for RCT with low levels of EPA and DHA intake in relation to CHD incidence and mortality.

In the present cohort with a low range of fish consumption, EPA+DHA intake was inversely related to CHD mortality and even stronger to fatal MI. In various studies, low doses of EPA and DHA are associated with a lower risk of fatal CHD but not nonfatal CHD (2). A hypothesis for this differential effect is that EPA and DHA could prevent fatal cardiac arrhythmia (9,29–31). Life-threatening cardiac arrhythmias are major contributors to fatal CHD. These arrhythmias are less likely to occur in the case of a less-severe MI with less cardiac tissue damage. Although in recent RCT, marine (n-3) PUFA did not protect against arrhythmia in ICD patients (32), the arrhythmia hypothesis is still the major hypothesis in CHD primary prevention studies (33). Regrettably, we were not able to examine sudden cardiac death as a separate outcome in the present study because of the limited number of cases.

We conclude that in a population with low levels of fish consumption, higher intakes of EPA+DHA and fish may protect against fatal CHD in a dose-responsive manner. Intake of only a small amount of fish may be beneficial to cardiac health, although no protection against nonfatal MI may be expected.

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