

Dietary Intake and Cell Membrane Levels of Long-Chain n-3 Polyunsaturated Fatty Acids and the Risk of Primary Cardiac Arrest

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Objective.—To assess whether the dietary intake of long-chain n-3 polyunsaturated fatty acids from seafood, assessed both directly and indirectly through a biomarker, is associated with a reduced risk of primary cardiac arrest.

Design.—Population-based case-control study.

Setting.—Seattle and suburban King County, Washington.

Participants.—A total of 334 case patients with primary cardiac arrest, aged 25 to 74 years, attended by paramedics during 1988 to 1994 and 493 population-based control cases and controls, matched for age and sex, randomly identified from the community. All cases and controls were free of prior clinical heart disease, major comorbidity, and use of fish oil supplements.

Measures of Exposure.—Spouses of case patients and control subjects were interviewed to quantify dietary n-3 polyunsaturated fatty acid intake from seafood during the prior month and other clinical characteristics. Blood specimens from 82 cases (collected in the field) and 108 controls were analyzed to determine red blood cell membrane fatty acid composition, a biomarker of dietary n-3 polyunsaturated fatty acid intake.

Results.—Compared with no dietary intake of eicosapentaenoic acid ($C_{20:5n-3}$) and docosahexaenoic acid ($C_{22:6n-3}$), an intake of 5.5 g of n-3 fatty acids per month (the mean of the third quartile and the equivalent of one fatty fish meal per week) was associated with a 50% reduction in the risk of primary cardiac arrest (odds ratio [OR], 0.5; 95% confidence interval [CI], 0.4 to 0.8), after adjustment for potential confounding factors. Compared with a red blood cell membrane n-3 polyunsaturated fatty acid level of 3.3% of total fatty acids (the mean of the lowest quartile), a red blood cell n-3 polyunsaturated fatty acid level of 5.0% of total fatty acids (the mean of the third quartile) was associated with a 70% reduction in the risk of primary cardiac arrest (OR, 0.3; 95% CI, 0.2 to 0.6).

Conclusion.—Dietary intake of n-3 polyunsaturated fatty acids from seafood is associated with a reduced risk of primary cardiac arrest.

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increases the levels of these fatty acids in cell membranes and results in shifts in eicosanoid production that might reduce platelet aggregation and coronary spasm.⁶ Additionally, long-chain n-3 fatty acids may reduce the accumulation of myocardial cytosolic calcium during ischemia, a critical factor in the genesis of malignant arrhythmias.⁷⁻⁹

We conducted a population-based case-control study to determine whether the dietary intake of long-chain n-3 polyunsaturated fatty acids was associated with a reduced vulnerability to life-threatening arrhythmias. To address this question, we determined whether dietary intake and red blood cell membrane fatty acid levels, a biomarker of dietary intake of n-3 polyunsaturated fatty acids, were inversely related to the risk of primary cardiac arrest.

METHODS

Selection of Case Patients and Control Subjects

From reports filed out by paramedics, all cases of out-of-hospital primary cardiac arrest attended by paramedics were identified in Seattle and suburban King County, Washington, during the period October 1988 to July 1994. Cases were defined by the occurrence of a sudden pulseless condition and the absence of evidence of a noncardiac condition as the cause of cardiac arrest.¹⁰ In addition to emergency service incident reports, we reviewed death certificates, medical examiner reports, and autopsy reports, when available, to confirm the absence of evidence of a noncardiac condition as the cause of cardiac arrest.¹¹

We excluded case patients with a history of clinically recognized heart disease, such as angina pectoris, myocardial infarction, coronary bypass surgery and graft, angioplasty, congestive heart failure, arrhythmias, cardiomyopathy, or congenital or valvular disease, or life-threat-

DIETARY INTAKE of polyunsaturated fatty acids, particularly of the n-3 series, may reduce the vulnerability to ventricu-

lar fibrillation, a major cause of mortality from coronary heart disease.¹⁻⁴ Under conditions of pharmacological and ischemic stress—potential triggers of ventricular fibrillation—the occurrence of ventricular fibrillation has been reduced by 80% among small primates (marmoset monkeys) fed diets enriched in n-3 polyunsaturated fatty acids.⁵ Whether this protective effect of dietary intake of long-chain n-3 polyunsaturated fatty acids occurs among humans is unknown.

Consumption of seafood, the primary dietary source of the long-chain n-3 fatty acids eicosapentaenoic acid (EPA, $C_{20:5n-3}$) and docosahexaenoic acid (DHA, $C_{22:6n-3}$),

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ening comorbidities, such as cancer or end-stage lung, liver, or renal disease. We further restricted the case patients to married residents of King County, 25 to 74 years of age. Because the focus of the study was on dietary intake, we excluded case patients who might have been taking fish oil supplements. The spouses of 347 (83%) of the 418 eligible case patients agreed to participate in an in-person interview. The mean (SD) interval between the date of the cardiac arrest and the in-person interview was 4 months (2 months).

For each case, control subjects matched for age (within 7 years) and sex were selected from the community by the sampling technique of random-digit dialing.¹² Of the known households, 95% were successfully screened to determine if a person eligible for the study was a resident. Potential control subjects who had had prior clinically recognized heart disease or major comorbidity, were not married, or might have been taking fish oil supplements were excluded from the study. The spouses of 551 (68%) of the 816 eligible control subjects participated in the in-person interview, yielding an overall response rate of 64%.

Dietary n-3 Fatty Acid Assessment

We developed a quantitative food-frequency questionnaire, the Seafood Intake Scale, to estimate the dietary intake of n-3 fatty acids from seafood during the prior month. The dietary assessment focused on the prior month because platelet and red blood cell composition reflects dietary intake during a period of weeks.^{13,14} The instrument included a list of 35 types of seafood available in the Pacific Northwest, including 25 fish and 10 shellfish. For each type of seafood consumed, spouses as proxy respondents for cases and controls were asked to estimate both the quantity (usual serving size) and frequency (number of servings) of consumption during the prior month. We used food models to demonstrate an average serving size (84 g [3 oz]) of a seafood meal. Subjects were asked to estimate whether the typical serving size consumed was twice as much, about the same, or half as much as the model.

We estimated the dietary intake of EPA and DHA, the two long-chain n-3 polyunsaturated fatty acids found in seafood. For each type of seafood consumed during the prior month, we multiplied the number of servings consumed by the average EPA and DHA content of the reported serving size consumed.¹⁵ The EPA and DHA content varies by type of seafood; for example, an 84-g serving of cooked fresh salmon (a fatty fish) contains 1.49 g, albacore tuna contains 0.74 g, and cod contains 0.23 g of combined EPA and DHA. Overall intake for each subject

was estimated by summing across all types of seafood.

Validity and Reliability of Spousal Data

We validated the estimates of dietary intake derived from the Seafood Intake Scale. For both case patients and control subjects, spousal estimates of the dietary intake of combined EPA and DHA were related to the levels of red blood cell membrane fatty acids of the case patients or control subjects themselves ($r=0.5$; $P<.001$ for each group). Details of the red blood cell membrane measurements are described herein.

To identify the presence of systematic bias in spousal reports of n-3 fatty acid intake, we interviewed 54 survivors of primary cardiac arrest and their spouses and 528 control subjects and their spouses independently. The 54 members of our case group were successfully resuscitated in the community by paramedics, discharged from the hospital, and had no evidence of gross neurological impairment at the time of the study. Compared with subject reports, both the spouses of case patients and the spouses of control subjects tended to underestimate n-3 fatty acid intake slightly. For case patients, the mean (SD) difference between spousal and subject estimates was -0.7 g (3.9 g) per month, and for control subjects, the mean difference was -0.4 g (5.2 g) per month ($P=.54$, for a two-sample t test comparing the spousal-subject differences between the cases and controls).

Detailed Nutrient Assessment

To determine whether the dietary intake of long-chain n-3 polyunsaturated fatty acids was related to total caloric intake and the intake of other nutrients, we also obtained a detailed assessment of nutrient intake among a subset of control subjects ($n=73$). Control subjects were asked to complete two 4-day food records during the 3-week period after the in-person interview. Among the subset of control subjects, both spousal and subject reports of n-3 fatty acid intake from the Seafood Intake Scale were only weakly related to total caloric intake, the percentage of energy from total and saturated fat, or the intake of protein, carbohydrates, fiber, vitamins, and minerals, based on the average of 8 days of food records completed by the control subjects themselves ($r=0.004$ to 0.155). A weak correlation also was noted between dietary intake of n-3 fatty acids and dietary intake of selenium ($r=0.17$; $P=.14$), based on the food records.

Dietary Fat Assessment

We also assessed the dietary intake of fat with a qualitative measure, the North-

west Lipid Research Clinic Fat Intake Scale, derived from spousal responses to nine questions that reflect usual consumption of foods high in fat and saturated fat.¹⁶ Among the subset of control subjects who completed the detailed nutrient assessment, the Fat Intake Scale scores derived from spousal reports were directly related to the percentage of energy from saturated fat ($r=0.6$; $P<.001$), based on the average of 8 days of food records completed by the control subjects themselves.

Other Risk Factor Assessment

The interview also covered other risk factors for primary cardiac arrest. Other factors assessed included age, sex, race, weight, and height; physician-diagnosed diabetes mellitus, hypertension, and hypercholesterolemia; cigarette smoking; physical activity; alcohol and caffeine consumption; family history of myocardial infarction or sudden death in a first-degree relative; and education.

Red Blood Cell Membrane Fatty Acid Measurements

Paramedics obtained blood specimens in the field from a subset of case patients ($n=95$) after essential emergency medical care had been provided and either the patient was clinically stable or resuscitation had proven ineffective, usually within 30 to 45 minutes of the cardiac arrest. Data from a preliminary study of 18 primates suggested that cardiac arrest itself altered red blood cell membrane n-3 polyunsaturated fatty acid levels only slightly: the mean (SD) difference of the postmortem values minus the premortem values of combined EPA and DHA was 0.33% (0.77%) of total fatty acids (for paired t test, $P=.09$). Blood specimens were only obtained from case patients for whom an intravenous line was placed as part of emergency medical care. In some cases, the circumstances of cardiac arrest or the provision of emergency care precluded the blood draw. Blood specimens were obtained at the time of the in-person spousal interview from the control subjects ($n=133$) matched to the case patients who had had a blood specimen drawn. The protocol was approved by the University of Washington Human Subjects Review Committee.

For both the cases and controls, the subjects with and without blood specimens available for the red blood cell membrane analyses had had similar dietary intake of n-3 fatty acids and levels of other risk factors, including age, sex, race, education, smoking, history of hypertension and diabetes, family history, weight, physical activity, alcohol and caffeine consumption, and Fat Intake Scale scores (data not shown).

Table 1.—Risk Factors for Primary Cardiac Arrest Among the Case Patients and Control Subjects

Risk Factor	Case Patients (n=334)*	Control Subjects (n=493)†	P‡
Age, y§	59 (10)	58 (10)	.08
Men, %	80	79	.74
White, %	94	94	.85
Education, high school graduate, %	61	77	<.001
Current smoker, %	35	11	<.001
Former smoker, %	38	43	.18
Hypertension, %	28	15	<.001
Diabetes mellitus, %	13	4	<.001
Hypercholesterolemia, %	24	22	.52
Family history of myocardial infarction or sudden death, %	54	41	<.001
Weight, kg§	82.4 (16.9)	80.5 (15.9)	.12
Physical activity, kJ/wk [kcal/wk]§	4301 (6552) [1024 (1560)]	5502 (6875) [1310 (1637)]	.01
Alcohol intake, drinks/d§	1.1 (2.3)	0.9 (1.4)	.18
Caffeine intake, mg/d§	467 (519)	335 (413)	<.001
Fat Intake Scale score§	22 (4)	21 (4)	.003
Dietary EPA and DHA intake, g/mo§	4.3 (6.0)	5.3 (5.6)	.02
Red blood cell membrane EPA and DHA, % of total fatty acids§	4.3 (1.1)	4.9 (1.4)	.002

*Missing values for hypertension (n=1), diabetes (n=2), hypercholesterolemia (n=8), family history of myocardial infarction or sudden death (n=4), weight (n=8), and Fat Intake Scale (n=9).

†Missing values for education (n=1), smoking (n=2), hypertension (n=6), diabetes (n=2), hypercholesterolemia (n=4), family history of myocardial infarction or sudden death (n=3), weight (n=42), alcohol (n=21), caffeine (n=1), and Fat Intake Scale (n=23).

‡Based on the two-sample *t* test or the χ^2 test.

§Values are shown as mean (SD).

||EPA indicates eicosapentaenoic acid; and DHA, docosahexaenoic acid.

¶Case patients (n=82) and control subjects (n=108) with red blood cell membrane measurements.

ratio test. We excluded 13 case patients and 58 control subjects with a completed spousal interview but without an age- and sex-matched control subject or case patient from the analyses. Since in both the diet and the red blood cell membrane EPA and DHA were highly correlated ($r=0.9$, $P<.001$; and $r=0.7$, $P<.001$, respectively), we combined levels of EPA and DHA in the analysis of both dietary intake and red blood cell membrane fatty acids.

For both dietary intake and red blood cell membrane n-3 fatty acid levels, conditional logistic regression models that compared each of the three upper quartiles with the lowest quartile suggested dose-response relations. We then examined both dietary intake of n-3 fatty acids and red blood cell membrane fatty acid levels as continuous variables. After adjustment for potential confounding factors, the addition of a quadratic term to the linear term for dietary long-chain n-3 fatty acid intake improved the fit of the logistic regression model ($P=.002$). The addition of the quadratic term to the linear term for red blood cell membrane-combined EPA and DHA did not improve the fit of the logistic model ($P=.80$).

RESULTS

Compared with control subjects, case patients were slightly older, less educated, weighed more, expended less energy in leisure-time physical activity, and had higher mean caffeine intake and Fat Intake Scale scores (Table 1). Case patients were also more likely to be current smokers and have hypertension, diabetes, and a family history of myocardial infarction or sudden death. The dietary intake and red blood cell membrane levels of n-3 fatty acids were lower among case patients compared with control subjects.

An inverse relation was noted between the dietary intake of long-chain n-3 polyunsaturated fatty acids and the risk of primary cardiac arrest, based on the conditional logistic regression model with both the linear and quadratic term for dietary n-3 fatty acid intake (Table 2). Compared with no seafood intake, an intake of 2.9 g of n-3 polyunsaturated fatty acids per month (the mean of the second quartile of dietary intake among seafood eaters and the equivalent of two fatty fish meals per month) was associated with a 30% reduction in the risk of primary cardiac arrest (odds ratio [OR], 0.7; 95% confidence interval [CI], 0.6 to 0.9), and an intake of 5.5 g of n-3 polyunsaturated fatty acids per month (the mean of the third quartile of intake and the equivalent of one fatty fish meal per week) was associated with a 50% reduction (OR, 0.5; 95% CI, 0.4 to 0.8), after adjustment for age, current smoking, former smoking, family history of myocardial infarction or

Blood specimens were obtained in the nonfasting state and mixed with ethylenediaminetetraacetic acid. Within 48 hours of collection, the blood was centrifuged and the red blood cells were separated from the plasma. Red blood cells were washed three times with an equal volume of isotonic saline, followed each time by centrifugation for 10 minutes at 800g. Washed red blood cells were stored until extraction at -70°C in 1.2-mL cryovials with excluded head space. An equivalent volume of distilled water was mixed with 1 mL of red blood cells, and lipids were extracted with 2-propyl alcohol and chloroform according to Rose and Oklander.¹⁷ A total of 5 mg of butylated hydroxytoluene per 100 mL of 2-propyl alcohol was added as an antioxidant. The lipid extract was dissolved in 5 mL of acetyl chloride reagent and processed according to Lepage and Roy.¹⁸ After transesterification, fatty acid methyl esters (FAME) were recovered in hexane, dried under nitrogen (30°C to 50°C), and redissolved in 80 μL of hexane for gas chromatography analysis.

The FAME were injected in a split mode (1:50) and were separated on a gas chromatograph (model 5890B, Hewlett-Packard Co, Avondale, Pa). The gas chromatograph system was equipped with a flame ionization detector, Chemstation software (Hewlett-Packard Co), and automatic sampler (model HP7673). The FAME were separated on a 30-m by 0.25-mm internal diameter capillary column

(DB23 specification) with 0.25- μm coating (J & W Scientific, Folsom, Calif). The carrier gas was helium at 60 psi, and make-up gas was nitrogen at 60 psi at the tank. Column linear velocity was set at 33 cm per second at an oven temperature of 200°C . The injector and the detector port temperatures were both at 250°C . The initial oven temperature was 165°C , and initial hold was 10 minutes; then the oven temperature was increased to 188°C at 10° per minute and held for 8 minutes. Next, the oven temperature was increased to 198°C at 4° per minute and held for 16 minutes. Finally, the oven temperature was raised at 15° per minute to 248°C and held for 30 minutes.

Laboratory analyses were conducted by technicians blinded to case and control status. Blood specimen analyses were conducted only after informed consent had been obtained from either the subject or (for fatal cases) the spouse. Quality control included repeated measurements and the use of pooled red blood cells and internal standards. The interassay coefficient of variation for combined EPA and DHA was 4%. One specimen with evidence of oxidation, based on an arachidonic acid ($\text{C}_{20:4n-6}$) level less than 10% of total fatty acids, was excluded from the analyses.

Statistical Analysis

We used conditional logistic regression analysis. The statistical significance associated with the addition of a variable to the model was based on the likelihood

Table 2.—Risk of Primary Cardiac Arrest Associated With Dietary Intake of Long-Chain n-3 Polyunsaturated Fatty Acids

Variable	No Seafood Intake	Quartile of Dietary Intake of n-3 Fatty Acids			
		1	2	3	4
Mean dietary intake of n-3 fatty acids, g/mo (range)*	0	0.96 (0.12-1.95)	2.94 (1.96-4.05)	5.54 (4.06-7.40)	13.65 (7.41-42.72)
No. of case patients (n=295)†	34	92	77	45	47
No. of control subjects (n=398)†	19	91	101	94	95
Unadjusted OR (95% CI)‡	1.0	0.9 (0.8-0.9)	0.7 (0.6-0.8)	0.5 (0.4-0.7)	0.3 (0.2-0.5)
Adjusted OR (95% CI)§	1.0	0.9 (0.8-1.0)	0.7 (0.6-0.9)	0.5 (0.4-0.8)	0.4 (0.2-0.7)

*Quartile means and ranges of control subjects; for comparison, mean of the third quartile is equivalent to 3.7 servings (84 g) of fresh salmon per month.

†Matched case patients and control subjects with complete data on dietary intake and covariates.

‡From a conditional logistic model that included both the linear and quadratic terms for dietary n-3 fatty acids; odds ratio (OR) (95% confidence interval [CI]) was calculated using the mean value for each category.

§Adjusted for age, current smoking, former smoking, family history of myocardial infarction or sudden death, Fat Intake Scale, hypertension, diabetes mellitus, physical activity, weight, height, and education. OR (95% CI) was calculated using the mean value for each category.

Table 3.—Risk of Primary Cardiac Arrest Associated With Red Blood Cell Membrane Levels of Long-Chain n-3 Polyunsaturated Fatty Acids

Variable	Quartile of Red Blood Cell n-3 Fatty Acids			
	1	2	3	4
Mean red blood cell membrane n-3 fatty acid level, % of total fatty acids (range)*	3.3 (2.0-4.0)	4.3 (4.1-4.6)	5.0 (4.7-5.4)	6.5 (5.5-10.9)
No. of case patients (n=82)†	36	21	15	10
No. of control subjects (n=108)†	25	24	26	33
Unadjusted OR (95% CI)‡	1.0	0.6 (0.5-0.9)	0.5 (0.3-0.8)	0.2 (0.1-0.6)
Adjusted OR (95% CI)§	1.0	0.5 (0.4-0.8)	0.3 (0.2-0.6)	0.1 (0.1-0.4)

*Quartile means and ranges of control subjects.

†Matched case patients and control subjects with complete data on red blood cell membrane n-3 fatty acid levels and covariates.

‡From a conditional logistic model that included the linear term for red blood cell membrane n-3 fatty acids; odds ratio (OR) (95% confidence interval [CI]) was calculated using the mean value for each category.

§Adjusted for age, current smoking, former smoker, family history of myocardial infarction or sudden death, Fat Intake Scale, hypertension, diabetes mellitus, physical activity, weight, height, and education. OR (95% CI) was calculated using the mean value for each category.

sudden death, Fat Intake Scale score, hypertension, diabetes, weight, height, physical activity, and education. Further adjustment for hypercholesterolemia and alcohol and caffeine consumption altered the findings only slightly (data not shown).

Among the case patients and control subjects with blood specimens, there also was an inverse relation between red blood cell membrane—combined EPA and DHA levels and the risk of primary cardiac arrest, based on the conditional logistic regression model with the linear term for red blood cell membrane n-3 fatty acid level (Table 3). Compared with a red blood cell n-3 polyunsaturated fatty acid level of 3.3% of total fatty acids (the mean of the lowest quartile), a red blood cell membrane n-3 polyunsaturated fatty acid level of 4.3% of total fatty acids (the mean value of the second quartile) was associated with a 50% reduction in the risk of primary cardiac arrest (OR, 0.5; 95% CI, 0.4 to 0.8), and a level of 5.0% of total fatty acids (the mean of the third quartile) was associated with a 70% reduction (OR, 0.3; 95% CI, 0.2 to 0.6), after adjustment for age, current smoking, former smoking, family history, Fat Intake Scale score, hypertension, diabetes, weight, height, physical activity, and education. Further adjustment for hypercholesterolemia, alcohol and caffeine consumption, and the levels of other red blood cell membrane fatty acids altered the results only slightly (data not shown).

We also examined the effect of dietary

intake after adjusting for red blood cell membrane levels of long-chain n-3 fatty acids and other clinical characteristics in a logistic regression model (Table 4). Among the subset of cases and controls with blood specimens, dietary intake of n-3 fatty acids was inversely related to the risk of primary cardiac arrest. However, after taking into account the effect of red blood cell membrane levels, dietary intake of n-3 fatty acids was not related to the risk of primary cardiac arrest ($P[2df]=.80$, for the addition of the linear and quadratic terms for dietary intake); the ORs associated with each quartile of dietary intake of n-3 fatty acids were close to 1.0. In contrast, the risk reduction associated with increasing red blood cell membrane n-3 fatty acid levels was altered only slightly after taking into account dietary intake of n-3 fatty acids ($P[1df]=.006$, for the addition of the linear term for red blood cell membrane n-3 fatty acid level).

COMMENT

Our findings suggest an inverse relation of both dietary intake and red blood cell membrane levels of n-3 polyunsaturated fatty acids with the risk of primary cardiac arrest. Consumption of modest amounts of long-chain n-3 polyunsaturated fatty acids, the equivalent of one fatty fish meal per week, was associated with a reduction in the risk of primary cardiac arrest. Similarly, small absolute increases in the levels of red blood cell membrane

n-3 polyunsaturated fatty acids (one to two percentage points of total fatty acids) were associated with a reduction in the risk of primary cardiac arrest. The consistency of the findings using the two different approaches to the measurement of n-3 polyunsaturated fatty acid intake from seafood—a food-frequency questionnaire and a biomarker—enhances considerably the validity of our findings.

While we cannot exclude the possibility of uncontrolled confounding in this observational study, we sought to minimize potential bias in both the design and analysis of our study. In general, adjustment for other risk factors had only a slight effect on the strength of the association between dietary intake and the risk of primary cardiac arrest. Additionally, we demonstrated in a substudy conducted among control subjects that dietary long-chain n-3 fatty acid intake was only weakly related to the dietary intake of other nutrients.

The red blood cell membrane level of n-3 fatty acids also is a biomarker of the composition of other cell membranes; cell membrane composition of the platelet, leukocyte, endothelial cell, myocardial cell, and other tissues also is altered in response to changes in dietary intake.¹⁹ Feeding studies suggest that an increase in cell membrane long-chain n-3 polyunsaturated fatty acid levels leads to shifts in the production of eicosanoids that may reduce platelet aggregation and coronary spasm.^{20,21} Alternatively, n-3 polyunsatu-

Table 4.—Risk of Primary Cardiac Arrest Associated With Dietary Intake of Long-Chain n-3 Polyunsaturated Fatty Acids With and Without Adjustment for Red Blood Cell Membrane n-3 Fatty Acid Levels*

Dietary Intake of n-3 Fatty Acids	OR (95% CI)†	
	Adjusted for Other Risk Factors‡	Adjusted for Other Risk Factors and Red Blood Cell Membrane n-3 Fatty Acid Levels§
No seafood intake	1.0	1.0
Seafood intake, quartile		
1	0.8 (0.7-1.0)	1.0 (0.8-1.2)
2	0.6 (0.4-0.9)	0.9 (0.5-1.5)
3	0.4 (0.2-0.8)	0.8 (0.3-2.1)
4	0.2 (0.1-0.7)	0.8 (0.2-4.4)

*Among cases (n=82) and controls (n=108) with both red blood cell membrane and dietary fatty acid levels.

†OR indicates odds ratio; and CI, confidence interval.

‡Quartile means and ranges as noted in Table 3; adjustment for other risk factors as noted in Table 3.

§From conditional logistic models that included the linear and quadratic terms for dietary n-3 fatty acids with and without the linear term for red blood cell n-3 fatty acids; OR (95% CI) calculated as noted in Table 3.

rated fatty acids may suppress the automaticity of cardiac contraction and thereby alter vulnerability to life-threatening arrhythmias.⁷⁻⁹ While the specific mechanism remains unknown, the finding that dietary intake was not associated with the risk of primary cardiac arrest after taking into account differences in red blood cell membrane fatty acid composition is consistent with the hypothesis that the effect of dietary fatty acids on the risk of primary cardiac arrest is mediated through changes in cell membrane fatty acid composition.

Our findings are consistent with experimental evidence in animals that n-3 polyunsaturated fatty acids have a profound effect on the vulnerability to ventricular fibrillation in the setting of myocardial ischemia.^{15,22} In the experimental animal studies, there was little evidence that the effect of n-3 fatty acids on life-threatening arrhythmias was the result of an effect of the fatty acids on atherosclerosis.

Low mortality rates of coronary heart disease in populations with high dietary intake of marine oils led to the hypothesis that consumption of these fatty acids reduces coronary heart disease.²³ Results of several cohort studies^{24,25} suggest that consumption of one to two servings of fish per week is associated with a marked reduction in coronary heart disease mortality when compared with no fish intake. However, other studies conducted among populations with high levels of fish consumption have not demonstrated an association between the amount of fish (or n-3 fatty acid) intake and the risk of coronary heart disease.²⁶⁻²⁸

The results of secondary prevention trials of dietary interventions among patients

with prior myocardial infarction also suggest that n-3 fatty acid intake may influence the risk of life-threatening arrhythmias.^{29,30} Among patients randomized to dietary advice to increase the intake of fish (or n-3 fatty acids from fish oil), there was a 27% reduction in the incidence of fatal coronary heart disease; the incidence of nonfatal coronary heart disease was not reduced by the dietary intervention.²⁹ Similarly, post-myocardial infarction patients randomized to a diet that included a high intake of linolenic acid (C_{18:3n-3}), the precursor of the long-chain n-3 polyunsaturated fatty acids, experienced a significant reduction in total mortality, primarily as a result of a profound effect on the incidence of sudden cardiac death (eight events in the control group and no events in the intervention group).³⁰

Taken together, the data suggest that when compared with no seafood intake, dietary intake of modest amounts of n-3 fatty acids from seafood may reduce vulnerability to ventricular fibrillation and, thereby, reduce the risk of coronary heart disease mortality. Additional clinical trials to assess the effectiveness of efforts to enhance dietary intake of n-3 polyunsaturated fatty acids for the prevention of primary cardiac arrest should be considered.

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