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Fish Consumption, Omega-3 Fatty Acids, and Risk of Cardiovascular Disease

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Abstract

Introduction—Data on omega-3 polyunsaturated fatty acids in relation to cardiovascular disease are limited in women. The aim of this study was to examine longitudinal relations of tuna and dark fish, alpha-linolenic acid, and marine omega-3 fatty acid intake with incident major cardiovascular disease in women.

Methods—This was a prospective cohort study of U.S. women participating in the Women's Health Study from 1993 to 2014, during which the data were collected and analyzed. A total of 39,876 women who were aged ≥45 years and free of cardiovascular disease at baseline provided dietary data on food frequency questionnaires. Analyses used Cox proportional hazards models to evaluate the association between fish and energy-adjusted omega-3 polyunsaturated fatty acid intake and the risk of major cardiovascular disease, defined as a composite outcome of myocardial infarction, stroke, and cardiovascular death, in 38,392 women in the final analytic sample (96%).

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Results—During 713,559 person years of follow-up, 1,941 cases of incident major cardiovascular disease were confirmed. Tuna and dark fish intake was not associated with the risk of incident major cardiovascular disease (p-trend >0.05). Neither alpha-linolenic acid nor marine omega-3 fatty acid intake was associated with major cardiovascular disease or with individual cardiovascular outcomes (all p-trend >0.05). There was no effect modification by age, BMI, or baseline history of hypertension.

Conclusions—In this cohort of women without prior history of cardiovascular disease, intakes of tuna and dark fish, alpha-linolenic acid, and marine omega-3 fatty acids were not associated with risk of major cardiovascular disease.

Introduction

Cardiovascular disease (CVD) is one of the leading causes of death and premature disability in the U.S.[1] Over the last few decades, the nutritional benefits of fish and polyunsaturated fatty acids on cardiovascular health have garnered great public health attention. Long-chain omega-3 polyunsaturated fatty acids (PUFAs) may prevent CVD by rendering antiarrhythmic effects and reduced blood viscosity,[2,3] inhibiting platelet aggregation,[4] lowering blood viscosity,[3] suppressing inflammation,[4] improving blood vessel function,[5] and reducing plasma fibrinogen[6] and insulin resistance.[7] Previous studies have suggested that increased fish intake may lead to decreased risk of CVD in populations characterized by high levels of fish consumption such as those of Alaskan Natives, Greenland Eskimos, and the Japanese.[8–11] However, findings from more recent cohort studies have been largely inconsistent.[12–28] Many of these studies found no statistically significant inverse associations between fish intake and coronary heart disease (CHD) mortality,[12,13,15,17,18,20] and some but not all cohort studies reported an inverse association between fish consumption and stroke risk.[21–28] As most of the previous studies on fish and omega-3 PUFA intake and CVD have been conducted in non-U.S. populations or in populations that primarily consisted of men, data in U.S. women are limited. Therefore, this observational study prospectively examined the association between consumption of fish, specifically tuna and dark fish (mackerel, salmon, sardines, bluefish, and swordfish), long-chain omega-3 PUFA (alpha-linolenic acid [ALA] and marine omega-3 fatty acids) intake, and the incidence of major CVD among initially apparently healthy women enrolled in the Women's Health Study (WHS) during 22 years of follow-up.

Methods

Study Design and Population

The WHS was a randomized, placebo controlled trial of the effects of low-dose aspirin and vitamin E in the primary prevention of CVD and cancer. The design, methods, and main findings from the trial have been published previously.[29,30] Briefly, at baseline, the study randomized 39,876 U.S. female health professionals aged ≥45 years without a history of CVD, cancer, or other major illnesses to receive either active aspirin and placebo vitamin E, active vitamin E and placebo aspirin, both active agents, or both placebos in a 2 X 2 factorial design. After the end of the trial in March 2004, women continued to be followed on an observational basis. Twice during the first year and yearly thereafter, women were sent

questionnaires asking about demographic, lifestyle, and health information, including the occurrence of stroke events.

Study subjects included in this analysis were all participants in the WHS, and follow-up information from the time of randomization through December 31, 2014 was collected and analyzed. Of the 39,876 participating women, 15 participants with a history of CVD events (myocardial infarction [MI], stroke, coronary artery bypass grafting, and percutaneous transluminal coronary angioplasty) prior to randomization and 1,469 with missing data on dietary variables of interest were excluded, leaving 38,392 women (96%) available for the analytic sample (Appendix Figure 1). This study was approved by the IRB of Brigham and Women's Hospital.

Exposure

Participants of the WHS completed a 131-item validated semiquantitative food frequency questionnaire (SFFQ) at baseline,[31] from which total intakes of tuna (canned 3–4 ounces), dark fish (mackerel, salmon, sardines, bluefish, swordfish), and energy-adjusted ALA and marine omega-3 (eicosapentaenoic acid + docosahexaenoic acid, no alpha 18:3) fatty acids were assessed. The SFFQ has been tested and validated as a measure of long-term average dietary intakes in similar populations, and details on reliability and validity of estimates of fish and omega-3 fatty acid intakes have been published previously.[32–35] This analytic approach of using self-reported SFFQ data follows recent recommendations for nutritional epidemiologic analyses.[36]

To show how frequently each food was consumed on average during the previous year, the SFFQ data were reported on a 9-point scale: 1, never or less than once per month; 2, one to three times per month; 3, one time per week; 4, two to four times per week; 5, five to six times per week; 6, once per day; 7, two to three times per day; 8, four to five times per day; and 9, six or more times per day. Given the small number of cases in the higher SFFQ frequency groups, the frequency groups were re-categorized to a 4-point scale. For tuna, Groups 4–9 were merged, and frequency values were added and redefined as more than one time per week. Likewise, Groups 3–7 were merged for dark fish, as there were no respondents in Groups 8–9, and then the frequency values were added and redefined as once or more per week. The frequency data for tuna and dark fish were added by taking the midpoint of each original frequency category value of the two variables separately, and converting it to a continuous measure of servings per day. The numbers obtained for tuna and dark fish were then added. The "never, or less than once per month" category was taken as the reference group. For ALA and marine omega-3 fatty acids, the frequency categories were divided into quintiles and the first quintile was taken as the reference category.

Nutrient values in foods were computed by multiplying the frequency of responses by the nutrient content of specified portion sizes based on the U.S. Department of Agriculture food composition data.[37]

Outcome Measures

The primary outcome of this analysis was a composite endpoint of nonfatal MI, nonfatal stroke, and cardiovascular death. During follow-up, participants provided self-reported data

on incident physician diagnoses of cardiovascular events. Medical records were obtained for all cardiovascular events and reviewed by an Endpoints Committee of Physicians. The occurrence of MI was confirmed if symptoms met the WHO criteria of symptoms plus either typical electrocardiographic changes or abnormal levels of cardiac enzymes.[38] Nonfatal stroke was confirmed if the participant had a new focal neurologic deficit of sudden or rapid onset that persisted for >24 hours, and then classified into major subtypes (ischemic, hemorrhagic, or unknown) based on available clinical and diagnostic information with good inter-rater agreement.[39] Cardiovascular deaths were confirmed by review of autopsy reports, death certificates, medical records, or information obtained from next of kin or family members. The composite endpoint of medical record–confirmed MI, stroke, and cardiovascular death was defined as a major CVD event.

Statistical Analysis

Beginning at baseline, each participant was followed until the day of diagnosis of a major CVD event or censoring due to death from causes other than CVD or end of study, whichever came first. Cox proportional hazards models were used to calculate age-adjusted and multivariable-adjusted hazard ratios (HRs) and their 95% CIs when analyzing the association between fish and energy-adjusted omega-3 PUFA intake and the risk of major CVD. The multivariable-adjusted model controlled for randomized treatment assignment, age, BMI, smoking, alcohol intake, physical activity, oral contraceptive use, hormone replacement therapy, multivitamin use, total energy intake, family history of MI, and baseline history of hypertension, high cholesterol, and diabetes. In a separate model, intakes of dietary fiber, fruits and vegetables, trans fat, sodium, and ratio of polyunsaturated to saturated fat were additionally adjusted for as covariates.

The proportionality assumptions of the Cox proportional hazards models were tested by including a logarithm of time–exposure interaction term and found no significant violation. To test for a linear trend, the median value of the energy-adjusted ALA and marine omega-3 PUFA intake was assigned to each quintile and modeled this variable as a continuous variable. To test for a linear trend for tuna and dark fish intake, a categorical variable was modeled as an ordinal variable.

Analyses were performed to test whether the association between energy-adjusted ALA and marine omega-3 PUFA intake and the risk of major CVD was modified by age (<55, 55–64, or ≥65 years), BMI (<25, 25–30, or ≥30), baseline history of hypertension (systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mm Hg, or self-reported physician-diagnosed hypertension), or randomized treatment assignments.

All *p*-values were two-sided and analyses were performed at an alpha level of 0.05 using SAS, version 9.2.

Results

During 713,559 person years of follow-up, 1,941 incident major CVD cases were documented. Table 1 describes the distribution of baseline characteristics according to frequency of tuna and dark fish intake. Compared with women who rarely consumed tuna

and dark fish, those who consumed more tuna and dark fish had higher BMI, higher levels of alcohol intake, were more physically active, and more likely to have baseline history of hypertension and high cholesterol. Women in the highest category of tuna and dark fish consumption were more likely to be current multivitamin users, and women who consumed more tuna and dark fish had higher intakes of dietary fiber, fruits and vegetables, sodium, and total calories but lower trans fat intake, compared with women who rarely consumed fish.

Table 2 shows the HRs of major CVD according to frequency of tuna and dark fish intake. Compared with women who consumed tuna and dark fish less than once per month, the multivariable-adjusted HRs for major CVD were 1.05 (95% CI=0.92, 1.19) for those who had it one to three times per month, 1.01 (95% CI=0.88, 1.16) for those who had it once per week, and 1.01 (95% CI=0.87, 1.17) for those who had it more than one time per week (p-trend=0.89). Adjusting for additional dietary variables such as intakes of dietary fiber, fruits and vegetables, trans fat, sodium, and ratio of polyunsaturated to saturated fat did not change the HRs.

No statistically significant associations between energy-adjusted ALA (p-trend=0.64) or marine omega-3 fatty acids (p-trend=0.87) and risk of major CVD were found across quintiles of intake in multivariable models (Table 3). Compared with women in the first quintile of ALA intake, those in the second, third, fourth, and fifth quintiles had multivariable-adjusted HRs of 0.92 (95% CI=0.80, 1.06), 0.88 (95% CI=0.76, 1.02), 0.95 (95% CI=0.82, 1.09), and 0.99 (95% CI=0.87, 1.14), respectively. With regard to marine omega-3 fatty acid intake, compared with women in the first quintile, those in the second, third, fourth, and fifth quintiles had multivariable-adjusted HRs of 0.94 (95% CI=0.82, 1.08), 0.95 (95% CI=0.82, 1.09), 0.96 (95% CI=0.84, 1.11), and 0.99 (95% CI=0.86, 1.13), respectively. Adjusting for intakes of dietary fiber, fruits and vegetables, trans fat, sodium, and ratio of polyunsaturated to saturated fat did not alter the results.

Upon examining the associations between intakes of ALA and marine omega-3 fatty acids and the risk of individual cardiovascular endpoints, including MI, ischemic stroke, total stroke, and cardiovascular death (Table 4), there were no significant associations between either ALA or marine omega-3 fatty acids and the risk of any of the four individual cardiovascular endpoints (all p-trend >0.05). Adjusting for intakes of dietary fiber, fruits and vegetables, trans fat, sodium, and ratio of polyunsaturated to saturated fat did not lead to any substantial changes in the main findings.

Age and history of hypertension did not significantly modify the relationship between any of the main exposures of interest and the risk of major CVD (all p-values for interaction >0.05). The interaction p-value for BMI and marine omega-3 fatty acid intake was only marginally significant (p=0.04), and the associations across different strata of BMI were not statistically significant. There was no effect modification by BMI on the association between intakes of tuna and dark fish and ALA, and major CVD (all p-values for interaction >0.05). There was no statistically significant interaction of the association of primary exposure of interest (tuna and dark fish intake) with outcomes by randomized treatment assignments (for interaction, p=0.65).

Discussion

In this large prospective cohort of initially apparently healthy women, intakes of tuna and dark fish, ALA, and marine omega-3 PUFAs were not associated with the risk of major CVD. Long-chain omega-3 PUFAs were also not associated with individual CVD events such as MI, ischemic and total stroke, and CVD death. In stratified analyses, there was no evidence of effect modification by age, BMI, baseline history of hypertension, or randomized treatment assignments for any of the exposures.

Many, but not all, previous cohort studies and RCTs of diet and fish oil supplements have reported an inverse association between fish or omega-3 PUFAs and CVD.[40–42] In the midst of limited prospective data on fish and omega-3 PUFAs and risk of CHD in women, a study conducted among women in the Nurses' Health Study reported an inverse association between fish intake and CHD death.[43] In the EURAMIC (EURopean multicentre case-control study on Antioxidants, Myocardial Infarction and Cancer of the breast) Study, Guallar et al.[44] found that adipose tissue ALA was associated with a lower risk of MI, but this association became nonsignificant after adjusting for other risk factors. By contrast, Hu and colleagues[45] reported a dose–response relationship between dietary ALA intake and risk of fatal ischemic heart disease, with a 45% reduction in risk in the highest quintile of intake. The null findings of this study are in accordance with other previous prospective studies.[13,17,18,46,47] For example, in a sample of postmenopausal women in the Iowa Women's Health Study, there was no association between fish intake and CHD or stroke mortality.[13] Similarly, a study done in middle-aged men in the Zutphen Study did not find an association between fatty fish consumption or eicosapentaenoic acid + docosahexaenoic acid intake and CHD death,[17] and there was no evidence in support of the relation of fish consumption with cerebral hemorrhage death, cerebral infarction death, or CHD death in a population of Japanese men and women.[18]

Studies on omega-3 PUFAs and stroke have also yielded mixed results. In a recent meta-analysis of prospective studies of fish intake and stroke risk, Larsson et al.[48] reported a weak inverse association with a relative risk of 0.94 (95% CI=0.89, 0.99) for an increase in consumption of three servings per day. The null findings of this study are consistent with results of a meta-analysis of eight prospective studies on long-chain omega-3 PUFAs and stroke, which showed no evidence for the association between omega-3 PUFA intake and the risk of stroke.[49]

Taken together, the inconsistencies in the literature on fish and omega-3 PUFA intake and CVD suggest that there could be substantial heterogeneity in the way fish, omega-3 PUFAs, and fish oil can have an effect on CVD risk. The cardioprotective effects of fish and long-chain omega-3 PUFAs may be influenced by other clinical conditions and comorbidities, and depend on whether the study is done in a primary or secondary prevention setting. Possible mechanisms for the known protective effects of fish and long-chain omega-3 PUFA may be lowered blood viscosity,[3] inhibition of platelet aggregation and decreased platelet retention,[3] generation of anti-inflammatory effects through the inhibition of leukotriene-mediated functions of neutrophils,[50] and possible modulation of membrane ion channel functions due to a change in the fatty acid distribution in plasma membrane phospholipids.[51]

Improved endothelial function and increased arterial compliance can work as a secondary mechanism to generate a mild hypotensive effect.[41,52,53] Fatty acids can further play a role in reducing the risk of CVD by eliciting antithrombogenic and hypotriglyceridemic effects.[54] Though the protective effects of fish and long-chain omega-3 PUFAs on CVD risk may have plausible biological basis, inconsistent epidemiologic data suggest that further investigation of the potential beneficial effects of fish and fatty acids on cardiovascular health is warranted in different study populations, especially those consisting of healthy women. On the other hand, high omega-3 indices have been associated with increased risk of CHD, which may influence detection of a positive effect for lower indices.[55] Future studies should also examine how and to what extent these biological effects of omega-3 fatty acids are influenced by various clinical factors, and what impact this would have on implementation of therapeutic interventions.

Limitations

Several limitations should be considered when interpreting these findings. Random misclassification of exposure resulting from self-reported information on dietary intake is possible, as this study is observational. However, health professionals are known to report their health status more accurately than the general population and the dietary assessment used in this study is identical to that used in many previously published population-based studies, which have been validated in similar populations. It is possible that this study did not capture complete information regarding fish and omega-3 PUFA consumption over time. In this study, only a single assessment of dietary exposure at baseline was used. This could fail to capture cumulative intake or changes in intake during long-term follow-up, making it subject to random error of self-report and underestimation of true associations. The generalizability of study findings may be limited because this study only consisted of relatively healthy women who were mostly white health professionals. Nevertheless, it is not expected that mechanisms of these agents that would affect health professional differently than other cohorts of women. Lastly, because this study was observational, residual confounding may be present despite the adjustments made for potential confounding factors.

The strengths of this study include a large overall sample size, prospective study design, long follow-up period, high participation rate, detailed and standardized diet assessment, confirmation of cases of cardiovascular events after a thorough medical record review, and consideration of a wide range of potential confounders.

Conclusions

In this large prospective cohort study of women, tuna and dark fish intake and long-chain omega-3 PUFAs were not associated with risk of major CVD or individual CVD events, such as MI, ischemic and total stroke, and CVD death. As this study population was limited to those without prior CVD events, these data may suggest that low-risk groups may not necessarily benefit from fish and omega-3 fatty acid supplementation or intervention. Although some previous studies have suggested benefit of adding fish and omega-3 PUFAs as part of a healthy diet, the independent health benefits of fish consumption and intakes of ALA and marine omega-3 fatty acids could not be verified in this cohort of women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline Characteristics of 38,392 Women in the WHS According to Frequency of Tuna and Dark Fish Intake[a]

	Average frequency of tuna and dark fish intake				
Characteristics	**<1 per month (n=6,939)**	**1–3 times per month (n=12,332)**	**1 per week (n=10,368)**	**>1 per week (n=8,753)**	***p*-value**
Age, years, mean (SD)	54.8 (7.3)	54.5 (7.1)	54.5 (7.0)	54.8 (6.9)	**0.003**
BMI, kg/m^2, mean (SD)	25.7 (5.0)	26.0 (5.0)	26.0 (5.0)	26.3 (5.1)	**<0.001**
Alcohol intake, %					**<0.001**
Never	52.3	46.8	41.8	39.4	
1–3 drinks/month	12.2	13.0	13.5	13.9	
1–6 drinks/week	27.0	30.7	33.4	35.1	
≥1 drink/day	8.6	9.6	11.3	11.6	
Smoking, %					**<0.001**
Never	52.8	50.7	50.5	50.8	
Past	33.3	35.7	36.7	37.9	
Current <15 cigarettes/day	4.7	4.8	4.8	4.7	
Current ≥15 cigarettes/day	9.2	8.8	8.0	6.7	
Physical activity, %					**<0.001**
Never	43.3	41.6	36.5	31.5	
<1 time/week	18.5	20.6	19.6	20.2	
1–3 times/week	27.5	28.3	33.4	35.8	
≥4 times/week	10.7	9.5	10.5	12.5	
Family history of myocardial infarction, %	14.3	14.1	14.6	14.7	
Baseline history of hypertension, %	25.3	24.9	25.4	27.9	**<0.001**
Baseline history of high cholesterol, %	28.1	29.0	29.3	31.5	**<0.001**
Baseline history of diabetes, %	2.4	2.3	2.6	2.9	0.07
Oral contraceptive use, %	69.3	69.1	70.0	69.1	0.50
Use of HRT hormones, %					0.28
Never	49.1	50.7	49.8	49.6	
Past	9.3	9.1	8.9	8.9	
Current	41.7	40.1	41.3	41.5	
Multivitamin use, %					**<0.001**

	Average frequency of tuna and dark fish intake				
Characteristics	**<1 per month (n=6,939)**	**1–3 times per month (n=12,332)**	**1 per week (n=10,368)**	**>1 per week (n=8,753)**	***p*-value**
Never	14.9	12.8	12.8	13.3	
Past	56.0	58.9	58.3	55.7	
Current	29.0	28.4	28.9	31.1	
Dietary fiber intake, g/day, mean (SD)	18.8 (6.8)	18.4 (5.8)	19.0 (5.7)	20.0 (5.6)	**<0.001**
Fruits and vegetables intake, servings/day, mean (SD)	5.2 (3.1)	5.4 (2.9)	6.2 (3.0)	7.5 (3.6)	**<0.001**
trans fat intake, % energy, mean (SD)	2.5 (1.2)	2.4 (1.1)	2.2 (1.0)	2.0 (0.9)	**<0.001**
Ratio of polyunsaturated to saturated fats, mean (SD)	0.6 (0.2)	0.6 (0.2)	0.6 (0.2)	0.6 (0.2)	**<0.001**
Sodium, mg, mean (SD)	1,823 (384)	1,866 (348)	1,865 (325)	1,898 (314)	**<0.001**
Total energy intake, kJ/day[b], mean (SD)	6,435 (2,113)	6,874 (2,105)	7,389 (3,092)	8,150 (3,410)	**<0.001**

Note: Boldface indicates statistical significance ($p<0.05$)

[a]Percentages may not add up to 100 due to rounding; data were analyzed using ANOVA and chi-square tests for continuous variables and categorical variables respectively.

[b]To convert total energy intake to kcal/day, divide values by 4.1868.

HRT, hormone replacement therapy; WHS, Women's Health Study.

Table 2

HRs (95% CI) of Major CVD According to Frequency of Tuna and Dark Fish Intake

	Average frequency of tuna and dark fish intake				
	<1 per month	**1–3 times per month**	**1 per week**	**>1 per week**	***p* for trend**
No. of cases	358	641	507	435	
No. of participants	6,939	12,332	10,368	8,753	
Events per participants	0.052	0.052	0.049	0.050	
Person-years	128,043	230,096	192,886	162,534	
Age-adjusted	1.00	1.03 (0.91–1.17)	0.97 (0.85–1.12)	0.98 (0.85–1.12)	0.48
Multivariate 1[a]	1.00	1.05 (0.92–1.19)	1.01 (0.88–1.16)	1.01 (0.87–1.17)	0.89
Multivariate 2[b]	1.00	1.04 (0.91–1.19)	1.00 (0.87–1.15)	1.00 (0.86–1.16)	0.78

[a]Hazard ratio was adjusted for randomized treatment, age, BMI, smoking, alcohol intake, physical activity, oral contraceptive use, use of hormones as defined under hormone replacement therapy, multivitamin use, total energy intake, family history of myocardial infarction, and baseline history of hypertension, high cholesterol, and diabetes.

[b]Also adjusted for intakes of dietary fiber, fruits and vegetables, trans fat, ratio of polyunsaturated to saturated fat, and sodium.

CVD, cardiovascular disease; HR, hazard ratio.

Table 3

HRs (95% CI) of Major CVD According to Quintiles of Energy-Adjusted PUFA Intake

	Quintiles of polyunsaturated fatty acids					
	1	**2**	**3**	**4**	**5**	***p* for trend**
Alpha-linolenic acid						
Median intake, % energy	0.74	0.88	0.99	1.12	1.36	
No. of cases	364	361	363	394	459	
No. of participants	7,426	7,836	7,856	7,470	7,804	
Events per participants	0.049	0.046	0.046	0.053	0.059	
Person-years	137,869	146,522	146,457	138,918	143,794	
Age-adjusted	1.00	0.93 (0.81–1.08)	0.91 (0.79–1.06)	1.00 (0.87–1.16)	1.09 0.95–1.25)	0.06
Multivariate 1[a]	1.00	0.92 (0.80–1.06)	0.88 (0.76–1.02)	0.95 (0.82–1.09)	0.99 (0.87–1.14)	0.64
Multivariate 2[b]	1.00	0.91 (0.79–1.06)	0.87 (0.75–1.01)	0.92 (0.80–1.07)	0.95 (0.82–1.11)	0.83
Marine omega-3 fatty acids[c]						
Median intake, % energy	0.06	0.11	0.16	0.25	0.40	
No. of cases	409	387	344	404	397	
No. of participants	7,876	7,886	6,916	8,120	7,594	
Events per participants	0.052	0.049	0.050	0.050	0.052	
Person-years	145,655	147,766	129,032	150,921	140,184	
Age-adjusted	1.00	0.94 (0.82–1.08)	0.96 (0.83–1.11)	0.93 (0.81–1.07)	0.96 (0.84–1.10)	0.93
Multivariate 1[a]	1.00	0.94 (0.82–1.08)	0.95 (0.82–1.09)	0.96 (0.84–1.11)	0.99 (0.86–1.13)	0.87
Multivariate 2[b]	1.00	0.94 (0.82–1.08)	0.94 (0.82–1.09)	0.96 (0.84–1.11)	0.98 (0.85–1.13)	0.93

[a]Hazard ratio was adjusted for randomized treatment, age, BMI, smoking, alcohol intake, physical activity, oral contraceptive use, use of hormones as defined under hormone replacement therapy, multivitamin use, family history of myocardial infarction, and baseline history of hypertension, high cholesterol, and diabetes.

[b]Also adjusted for intakes of dietary fiber, fruits and vegetables, trans fat, ratio of polyunsaturated to saturated fat, and sodium.

[c]Includes EPA + DHA fatty acids, but not α-linolenic acid.

CVD, cardiovascular disease; HR, hazard ratio; PUFA, polyunsaturated fatty acid.

Table 4

HRs (95% CI) of Individual Cardiovascular Events According to Quintiles of Energy-Adjusted PUFA Intake

	Quintiles of polyunsaturated fatty acids					
	1	**2**	**3**	**4**	**5**	***p* for trend**
Alpha-linolenic acid						
Median intake, % energy	0.74	0.88	0.99	1.12	1.36	
Myocardial infarction						
No. of cases	129	145	152	150	169	
No. of participants	7,426	7,836	7,856	7,470	7,804	
Events per participants	0.017	0.019	0.019	0.020	0.022	
Person-years	134,955	143,408	143,324	136,226	140,960	
Age-adjusted	1.00	1.06 (0.83–1.34)	1.09 (0.86–1.37)	1.09 (0.86–1.38)	1.16 (0.92–1.45)	0.22
Multivariate 1[a]	1.00	1.05 (0.83–1.33)	1.04 (0.82–1.31)	1.01 (0.79–1.27)	1.03 (0.82–1.29)	0.97
Multivariate 2[b]	1.00	1.04 (0.82–1.32)	1.02 (0.80–1.30)	0.98 (0.77–1.26)	0.98 (0.76–1.27)	0.74
Ischemic stroke						
No. of cases	148	143	149	176	191	
No. of participants	7,426	7,836	7,856	7,470	7,804	
Events per participants	0.020	0.018	0.019	0.024	0.024	
Person-years	134,840	143,442	145,425	136,042	140,829	
Age-adjusted	1.00	0.90 (0.72–1.13)	0.91 (0.73–1.15)	1.09 (0.87–1.35)	1.09 (0.88–1.35)	0.13
Multivariate 1[a]	1.00	0.89 (0.71–1.13)	0.89 (0.71–1.12)	1.05 (0.84–1.30)	1.02 (0.82–1.27)	0.38
Multivariate 2[b]	1.00	0.88 (0.70–1.11)	0.86 (0.68–1.09)	1.00 (0.80–1.26)	0.95 (0.75–1.21)	0.85
Total stroke						
No. of cases	185	175	179	210	238	
No. of participants	7,426	7,836	7,856	7,470	7,804	
Events per participants	0.025	0.022	0.023	0.028	0.030	
Person-years	134,840	143,442	143,425	136,042	140,829	
Age-adjusted	1.00	0.88 (0.72–1.09)	0.88 (0.72–1.08)	1.04 (0.85–1.27)	1.09 (0.90–1.33)	0.08
Multivariate 1[a]	1.00	0.88 (0.72–1.08)	0.86 (0.70–1.06)	1.02 (0.83–1.24)	1.03 (0.85–1.25)	0.26
Multivariate 2[b]	1.00	0.88 (0.71–1.08)	0.86 (0.69–1.06)	1.00 (0.81–1.23)	1.00 (0.80–1.24)	0.54

	Quintiles of polyunsaturated fatty acids					
	1	**2**	**3**	**4**	**5**	***p* for trend**
CVD death						
No. of cases	100	89	96	99	117	
No of participants	7,426	7,836	7,856	7,470	7,804	
Events per participants	0.013	0.011	0.012	0.013	0.015	
Person-years	139,958	148,661	148,532	141,266	146,561	
Age-adjusted	1.00	0.85 (0.64–1.13)	0.88 (0.66–1.16)	0.89 (0.67–1.17)	0.95 (0.73–1.24)	0.97
Multivariate 1[a]	1.00	0.85 (0.64–1.13)	0.85 (0.64–1.12)	0.81 (0.61–1.07)	0.86 (0.66–1.13)	0.38
Multivariate 2[b]	1.00	0.86 (0.65–1.15)	0.86 (0.65–1.15)	0.83 (0.62–1.11)	0.88 (0.65–1.18)	0.47
Marine omega-3 fatty acids[c]						
Median intake, % energy	0.06	0.11	0.16	0.25	0.40	
Myocardial infarction						
No. of cases	152	148	144	160	141	
No. of participants	7,876	7,886	6,916	8,120	7,594	
Events per participants	0.019	0.019	0.021	0.020	0.019	
Person-years	142,673	145,039	126,246	148,008	136,908	
Age-adjusted	1.00	0.97 (0.77–1.21)	1.08 (0.86–1.35)	0.99 (0.79–1.24)	0.93 (0.74–1.17)	0.51
Multivariate 1[a]	1.00	0.98 (0.78–1.23)	1.08 (0.86–1.36)	1.06 (0.85–1.33)	0.98 (0.78–1.24)	0.93
Multivariate 2[b]	1.00	0.98 (0.78–1.23)	1.09 (0.86–1.37)	1.07 (0.85–1.34)	0.99 (0.78–1.25)	0.98
Ischemic stroke						
No. of cases	167	168	135	161	176	
No. of participants	7,876	7,886	6,916	8,120	7,594	
Events per participants	0.021	0.021	0.020	0.020	0.023	
Person-years	142,447	145,056	126,440	147,980	136,655	
Age-adjusted	1.00	1.00 (0.81–1.24)	0.92 (0.73–1.15)	0.90 (0.73–1.12)	1.04 (0.84–1.29)	0.80
Multivariate 1[a]	1.00	0.99 (0.80–1.23)	0.90 (0.72–1.14)	0.92 (0.74–1.14)	1.04 (0.84–1.29)	0.71
Multivariate 2[b]	1.00	1.00 (0.80–1.24)	0.91 (0.72–1.14)	0.92 (0.74–1.15)	1.04 (0.83–1.30)	0.72
Total stroke						
No. of cases	205	201	165	199	217	
No. of participants	7,876	7,886	6,916	8,120	7,594	

	Quintiles of polyunsaturated fatty acids					
	1	**2**	**3**	**4**	**5**	***p* for trend**
Events per participants	0.026	0.025	0.024	0.025	0.029	
Person-years	142,447	145,056	126,440	147,980	136,655	
Age-adjusted	1.00	0.97 (0.80–1.18)	0.91 (0.75–1.12)	0.91 (0.75–1.10)	1.05 (0.87–1.27)	0.60
Multivariate 1[a]	1.00	0.97 (0.80–1.18)	0.89 (0.73–1.10)	0.92 (0.76–1.13)	1.05 (0.87–1.28)	0.51
Multivariate 2[b]	1.00	0.97 (0.80–1.18)	0.89 (0.73–1.10)	0.92 (0.75–1.12)	1.04 (0.85–1.27)	0.59
CVD death						
No. of cases	102	90	87	105	117	
No. of participants	7,876	7,886	6,916	8,120	7,594	
Events per participants	0.013	0.011	0.013	0.013	0.015	
Person-years	148,134	150,079	130,980	153,375	142,412	
Age-adjusted	1.00	0.90 (0.68–1.19)	1.00 (0.75–1.33)	0.97 (0.74–1.28)	1.13 (0.87–1.48)	0.19
Multivariate 1[a]	1.00	0.90 (0.69–1.20)	1.01 (0.75–1.35)	1.04 (0.78–1.36)	1.17 (0.89–1.54)	0.10
Multivariate 2[b]	1.00	0.89 (0.67–1.18)	0.99 (0.74–1.33)	1.02 (0.77–1.34)	1.15 (0.87–1.51)	0.15

[a]Hazard ratio was adjusted for randomized treatment, age, BMI, smoking, alcohol intake, physical activity, oral contraceptive use, use of hormones as defined under hormone replacement therapy, multivitamin use, family history of myocardial infarction, and baseline history of hypertension, high cholesterol, and diabetes.

[b]Also adjusted for intakes of dietary fiber, fruits and vegetables, trans fat, ratio of polyunsaturated to saturated fat, and sodium.

[c]Includes EPA + DHA fatty acids, but not α-linolenic acid.

CVD, cardiovascular disease; HR, hazard ratio; PUFA, polyunsaturated fatty acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.