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Intake of polyunsaturated fat in relation to mortality among statin users and non-users in the Southern Community Cohort Study

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Abstract

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Yu and Munro had full access to the data and take full responsibility for the integrity and accuracy of the analyses. Study concept and design: Kabagambe, Sampson, Lipworth and Blot. Acquisition of data: All authors. Statistical analysis: Yu, Munro and Kabagambe. Interpretation of data: All authors. Drafting the manuscript: Kiage and Kabagambe. Critical revision of manuscript for important intellectual content: All authors. Final manuscript approval: All authors.

Supplementary data

Supplementary tables are available at the Nutrition Metabolism and Cardiovascular Disease Journal website.

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Background and aims—Consumption of polyunsaturated fatty acids (PUFA), especially the n3-series, may protect against cardiovascular disease (CVD), but recent randomized studies have failed to demonstrate these benefits. One of the prevailing hypotheses is that PUFA intake may not confer benefits beyond those provided by statins, but studies comparing statin users to non-users with regard to effects of PUFA are lacking.

Methods and results—Black and white men and women (n=69,559) in the Southern Community Cohort Study were studied. Cox regression models adjusting for age, sex, race, BMI, recruitment site, education, income, smoking, diabetes, and dietary variables were used.

Results—At baseline the mean±SD age was 52±9 years, 60% of participants were women, 54% had hypertension and 16% used statins. We observed modest inverse associations between n3-PUFA and n6-PUFA intake with mortality among non-statin users but not among statin users. In adjusted analyses, the HRs (95% CIs) for all-cause mortality (6,396 deaths over a median of 6.4 years) comparing the highest to the lowest quintile were 0.90 (0.82-1.00) for n3-PUFA and 0.80 (0.70-0.92) for n6-PUFA among non-statin users, whereas they were 1.06 (0.87-1.28) and 0.96 (0.78-1.19) for n3-PUFA and n6-PUFA, respectively, among statin users.

Conclusions—Our results suggest potential benefits of PUFA consumption on mortality which are only apparent in the absence of statin therapy. It seems prudent to consider the potential benefit of PUFA consumption in the primary prevention of CVD among patients who are not candidates for statin therapy but are at increased risk for CVD and mortality.

Keywords

PUFA; fish; hypertension; mortality; cardiovascular disease; prospective

Introduction

Numerous observational studies and clinical trials have shown an inverse association between the intake of polyunsaturated fatty acids (PUFA), especially long-chain n3-fatty acids from fish, and blood pressure, myocardial infarction, and cardiovascular and total mortality [1-4]. However, recent findings from large randomized controlled trials have failed to demonstrate cardiovascular benefits of PUFA [5-7]. It is conceivable that the substantial increase in use of statins, which in most studies lower CVD- and all-cause mortality [8,9] and may reduce the efficacy of n3-fatty acids [10], could in part explain these different results. In this regard, Bjorck *et al* [11] showed a huge increase in the use of lipid-lowering medications (mainly statins) among patients with first acute myocardial infarction in Sweden (10% in 1994 to 90% in 2002). Similarly, using data from the National Health and Nutrition Examination Survey, Mann *et al* [12] showed that the use of statins among adults with high LDL-C concentration in the United States (US) has nearly doubled (19.6% in 1999 to 35.6% in 2004). It is noteworthy that 86% of participants in the Alpha Omega trial that was initiated in 2002 [5] were on lipid-lowering medications, mainly statins, at baseline compared to only 5% in the GISSI-Prevenzione trial that was initiated a decade earlier [2,13].

Apart from their potent effects on lipids [14], statins have pleotropic effects that contribute to their cardiovascular benefits, among them blood pressure reduction [15,16]. A meta-

analysis by Strazzullo *et al* [17] combining results from 20 clinical trials shows that use of statins is associated with reduced diastolic and systolic blood pressure [17]. More recently, Golomb *et al* [18] showed a modest but significant reduction in both diastolic and systolic blood pressure among non-hypertensive participants after 9 months of follow-up. Concordant with a view held by the investigators of the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) study [6], we hypothesized that in the context of widespread use of statins, which substantially lower background cardiovascular risk, increased intake of PUFA does not confer additional cardiovascular benefit, or that any benefits would be small and difficult to detect using typical sample sizes in randomized studies. To test this hypothesis, we used data from the Southern Community Cohort Study (SCCS), a large cohort of black and white participants living in the southeastern USA.

Methods

The design and methods of the SCCS have been described in detail [19]. Briefly, between 2002 and 2009, more than 85,000 adults aged 40-79 years were recruited from Alabama, Arkansas, Florida, Georgia, Kentucky, Louisiana, Mississippi, North Carolina, South Carolina, Tennessee, Virginia and West Virginia. Most participants (86%) were recruited at community health centers (CHC) where they completed computer-assisted personal interviews, including an 89-item food frequency questionnaire (FFQ) (www.southerncommunitystudy.org), with the assistance of trained staff; the remaining 14% were recruited via mail-based sampling of the general population and they completed mailed questionnaires. The questionnaire ascertained information on demographic and anthropometric characteristics, diet, lifestyle, medical history and use of selected medications, including statins [9,20]. Estimates for PUFA (and other nutrient) intakes were calculated by utilizing sex- and race-specific nutrient databases derived from government food consumption surveys in the southern USA [21]. Except for the overall fish intake, methods of preparation and specific questions on how tuna fish was consumed (e.g., as salad or casserole), specific information on other types of fish was not collected. Data on mortality was ascertained through linkage with the Social Security Administration and the National Death Index. The questionnaire adopted for the study has been widely validated within the SCCS and other populations in the USA [19,21,22]. The length of follow-up was computed as the difference between date of enrollment and the time a participant died, was lost to follow-up or until December 31, 2011, whichever came first. The study was approved by the institutional review boards of Vanderbilt University and Meharry Medical College, and all participants gave written informed consent.

Definitions and covariates

The dependent variables for our study were self-reported hypertension (yes/no) at baseline and CVD- and all-cause mortality. The exposure variables were energy-adjusted total PUFA, n3-PUFA and n6-PUFA intake distributed into quintiles, and fish intake grouped according to frequency of intake and method of usual preparation. Thus, fish consumption (tuna, fried fish, broiled fish, total of fried and broiled fish, and total of tuna, fried and broiled fish) was modeled as <1 time/month, 1-3 times/month, 1-3 times/week or ≥4 times/week. The following covariates were considered: age, sex, race, body mass index (BMI),

recruitment site (CHC, general population), education (<high school, high school/GED, some college, graduate), annual household income (<$15,000, ≥$15,000), smoking (≥20 cigarettes/day, <20 cigarettes/day, past smoker, never smoker), alcohol intake (current if alcohol was consumed in the last one year, past, never drinker), diabetes (yes, no), statin use (yes, no), total energy intake, and energy-adjusted intakes of saturated fatty acids (SFA), monounsaturated fatty acids (MUFA) and proteins.

Statistical analysis

To address the objectives of the current study, data from 69,559 participants were analyzed. Due to high correlations between total energy intake and macronutrient variables, we computed energy-adjusted PUFA, MUFA, SFA and protein variables by using the residual method [23,24]. One-way ANOVA (for continuous variables) and chi-square tests (for categorical variables) were used to test for the differences in the distributions of participant characteristics by quintiles of energy-adjusted total PUFA intake. Logistic regression was used to test the association between PUFA and prevalent hypertension. Due to established associations between the listed covariates and blood pressure, all factors were kept in the models without model selection steps. *P*-values for a dose-response relationship were calculated by treating the medians of each quintile of energy-adjusted PUFA as a continuous variable in the logistic regression models. To assess the potential effect of statins on the association between PUFA and hypertension, we included both PUFA and statins as main effects and their corresponding interaction term in the model and computed quintile-specific odds ratios (OR) (95% confidence intervals (CI)) using the lowest quintile of PUFA intake as the reference among statin users and non-users. In addition, we conducted separate analyses for n3- and n6-PUFA intakes to assess whether they have similar associations with hypertension.

In additional analyses with categories of fish intake considered in separate models, we used logistic regression to test the associations between fish intake and hypertension. To test whether the association between fish intake and hypertension could be due to factors other than PUFA, the models were additionally adjusted for PUFA intake.

In prospective analyses, we used Cox regression to test whether intakes of n3-PUFA, n6-PUFA and fish are associated with CVD- and all-cause mortality. Except for age which was adjusted for as the time scale variable, Cox regression models included all covariates listed for hypertension analyses.

All analyses were conducted using SAS version 9.3 (SAS Institute Inc., Cary, NC). *P*-values ≤0.05 were considered statistically significant.

Results

Table 1 shows the characteristics of included SCCS participants by quintiles of energy-adjusted PUFA. The mean (±SD) age at enrollment was 52±9 years, mean BMI was 30±8 kg/m^2, and average energy intake from PUFA was 8.0±1.8%. Statin use was reported by 16% of participants, and hypertension (54%) and current smoking (41%) were common in this cohort.

The average energy from PUFA in SCCS was 8.0% overall and without racial differences (8.0% among blacks and 8.0% among whites). The top ten contributors to PUFA intake are shown in **Supplemental Table 1**. While there was concordance in the intake level of some foods, the intake of salty snacks (0.90 g/day vs 0.76 g/day in blacks and whites, respectively) and margarine (0.75 g/day vs 1.00 g/day in blacks and whites, respectively) varied substantially by race. In addition, blacks reported higher intake of fried chicken, fried sea food and mixed rice and meat, whereas whites reported higher intake of peanut butter, fried potatoes and chicken mixed dishes. The intakes of n3- and n6-PUFA were weakly correlated (r=0.22, P<0.0001).

Association between PUFA intake and prevalent hypertension

Table 2 shows results from models that examined the association between total PUFA intake and hypertension. In the fully-adjusted model, there was a trend of decreasing odds of hypertension with increasing quintiles of PUFA intake which did not reach statistical significance (P for trend=0.14). Concordant with our *a priori* hypothesis that use of statins lowers background CVD risk making it difficult to detect effects of less potent cardiovascular interventions among statin users, we conducted separate analyses for statin users and non-users despite lack of a significant interaction between PUFA intake and statin use (P=0.12). In fully-adjusted models, there was an inverse trend (P for trend=0.05) between PUFA intake and hypertension among non-statin users but not among statin users (P for trend=0.26).

In cross-sectional analyses restricted to n3-PUFA (**Supplemental Table 2**), there was a non-significant inverse trend (P for trend=0.09) between n3-PUFA intake and hypertension in non-statin users and a significant positive trend in statin users (P for trend=0.04). Compared to the lowest quintile, the OR (95% CI) for the highest quintile of PUFA intake was 0.94 (0.88-1.00) in non-statin users and 1.14 (0.97-1.33) in statin users. We observed, a significant inverse trend between n6-fatty acids intake and hypertension in non-statin users (P for trend=0.04) but not in statin users (P for trend=0.57) (**Supplemental Table 3**). The OR (95% CI) for the 5th quintile compared to the lowest quintile of n6-PUFA intake was 0.92 (0.84-1.00) in non-statin users and 1.10 (0.93-1.30) in statin users.

Association between fish intake and prevalent hypertension

In unadjusted cross-sectional analyses using fish as the exposure variable, consumption of broiled fish showed an inverse association with hypertension (P for trend<0.05). The association for broiled fish (OR=0.91; 95% CI: 0.82-1.00) remained marginally significant after adjusting for confounders (**Supplemental Table 4**). None of the other fish intake categories showed significant associations with prevalent hypertension (Supplemental Table 4).

Association between PUFA intake and CVD- and all-cause mortality

During a median (25th, 75th percentile) follow-up of 6.4 (4.7, 8.0) years, 6,396 of the participants (n=69,559) died, with 2,023 deaths from CVD. As shown in **Table 3**, there was suggestion of an inverse association between n3-PUFA and risk of CVD mortality but no statistically significant association in either non-statin users or users (P for trend>0.05 for

both statin groups). On the other hand, there was a significant inverse trend between n3-PUFA intake and all-cause mortality in non-statin users (*P* for trend=0.04) but not in statin users (*P* for trend=0.73). In analyses restricted to n6-PUFA (**Table 4**), there was a significant inverse association between n6-PUFA intake and CVD- (*P* for trend=0.03) and all-cause (*P* for trend=0.01) mortality in non-statin users but not in statin users (*P* for trend>0.05).

Association between fish intake and CVD- and all-cause mortality

As shown in **Table 5**, fish consumption was inversely associated with all-cause mortality among non-statin users but not statin users. Among non-statin users, significant trends ($P<0.05$) were observed for all types of fish except tuna. In fully adjusted models with fish intake (fried or broiled or tuna combined) of less than once per month as the referent, the HRs (95% CIs) for all-cause mortality were 0.96 (0.87-1.05), 0.90 (0.82-0.98) and 0.87 (0.77-0.98) for intakes of 1-3 times/month, 1-3 times/week and ≥4 times/week, respectively (*P* for trend=0.05). Corresponding associations for CVD mortality as the outcome are shown in **Supplemental Table 5**. As for all-cause mortality, inverse associations between fish consumption and CVD mortality were only observed among non-statin users but most of the associations did not attain statistical significance.

Discussion

The results of this study raise the possibility of a benefit of fish and n3- and n6-PUFA intake on hypertension and CVD- and all-cause mortality among individuals not on treatment with statins. Except for n3-PUFA and hypertension, we did not observe significant trends in the associations between PUFA or fish intake with regard to hypertension or mortality, overall and in separate cross-sectional analyses of n3- and n6-PUFA among statin users. This observation is consistent with recent randomized clinical trials showing null associations for the effects of PUFA on cardiovascular outcomes [6].

Prior studies showed that elevated intake of PUFA is associated with reduced blood pressure [25-30]. For example, a cross-sectional study (n=4,033) by Grimsgaard *et al* [27] showed an inverse association between linoleic acid intake and blood pressure. Findings from a 17-year prospective study (n=787) by Livingstone *et al* [29] also showed an inverse association between PUFA intake and both systolic and diastolic blood pressure. Similarly, a small clinical trial (n=157) conducted in Norway showed that elevated intake of eicosapentaenoic and docosahexaenoic acid was associated with reduced diastolic and systolic blood pressure [25]. However, use of statins was not reported in these studies. Consistent with findings from the Genetics of Lipid-Lowering Drugs and Diet Network study [30], the current study indicates that elevated n3- and n6-PUFA intake is associated with decreased odds for hypertension but mainly among non-statin users.

In our prospective analyses, we observed a trend of decreasing risks of CVD-and all-cause mortality with increasing PUFA intake among non-statin users but not in statin users. While earlier randomized controlled trials showed that elevated PUFA intake is associated with lower cardiovascular risk [1,2], more recent large clinical trials have failed to demonstrate a cardiovascular benefit from n3-fatty acids [5-7]. However, as summarized in a recent review

[10], post-hoc analyses of these trials suggest protective effects from n3-fatty acids only among non-statin users, a finding consistent with results from the current study. If our findings of differential effects in statin vs. nonstatin users hold true in large studies, the recent dramatic increase in use of statins may in part explain null results from the more recent studies [11,12,15,31]. As suggested by the investigators of the Outcome Reduction with an Initial Glargine Intervention study, concomitant use of statins may substantially lower the background cardiovascular risk such that the benefit from less potent interventions may not be apparent or is difficult to detect because of small effect size when the background risk is reduced by statins [6]. As suggested in a recent comprehensive review of trials on statins and n3-fatty acids [10], an alternative explanation for the null results for PUFA among statin users is that the benefits of fatty acids, particularly n3-fatty acids, could be reduced by statins which are hypothesized to interfere with the metabolism of n3-fatty acids. Regardless of the mechanism through which statins may modify effects of PUFA, the current study suggests a benefit from higher PUFA or fish intake among non-statin users but not among statin users, supporting the hypothesis that higher intake of PUFA may not offer additional cardiovascular benefit in the context of statin therapy or in populations with high intakes of PUFA. However, the finding that both fish and PUFA intake are associated with lower risk of CVD- and all-cause mortality and possibly hypertension among non-statin users, makes PUFA a viable option for primary prevention of CVD in individuals where statin use is not indicated e.g., because statins are not available as in the case of developing countries, or CVD risk is increased but the risk score is still below the prevailing cut-point for indicating statin therapy (e.g., <7.5% in the American Heart Association/American College of Cardiology 2013/2014 guidelines) or in patients who cannot tolerate statins.

The exact mechanisms through which PUFA may reduce blood pressure remain to be fully elucidated. Evidence from intervention studies indicate that elevated PUFA intake attenuates vascular response to angiotensin II and norepinephrine [32,33], augments production of nitric oxide [34], reduces sub-clinical inflammation [35], improves vascular function [36], and improves arterial compliance [35]. It has also been hypothesized that increased PUFA intake reduces the production of thromboxane A_2 and increases the production of prostaglandin I_3 (prostacyclin) [26]. The net effect is a reduction of peripheral vascular resistance and blood pressure, which could translate into reduced mortality.

Concordant with findings from previous studies [28,37], we observed a trend of decreasing odds of hypertension with increasing intake of broiled fish and indication of a similar trend with tuna consumption but not with fried or total fish consumption. Findings from the Multi-Ethnic Study of Atherosclerosis cohort showed an inverse association between non-fried fish consumption and subclinical atherosclerosis but not with fried fish consumption [38]. If partially hydrogenated oils are used to fry fish, increased fried fish consumption could lead to increased intake of *trans*-fats which have been associated with increased risk of CVD and mortality [24,38-40]. Indeed, the American Heart Association recommends limiting the consumption of fried fish because added fat and the associated *trans*-fats could negate the benefits derived from fish consumption [41].

The main strength of the current study is the large population of blacks and whites (n=69,559) that provided ample statistical power to investigate the association between

PUFA and fish intake and hypertension. The study population is one of generally low income, a risk factor for CVD, in an area of the country with elevated CVD risk [22], with large numbers of statin users and non-users, thus enhancing the study's ability to assess the effects of PUFA on hypertension and mortality according to statin use.

We acknowledge a number of limitations. First, we cannot rule out inaccuracies resulting from self-reported information on hypertension and dietary intake values. Second, due to a high prevalence of undiagnosed hypertension in the USA [42], many participants with hypertension are likely to have been misclassified as non-hypertensive potentially shifting the association between PUFA intake and hypertension towards the null. On the other hand, the questionnaire used to record dietary intake has been extensively validated in the SCCS population and other populations in the USA [19,22]. Third, we did not adjust for *trans*-fat intake because those data are not available in SCCS. Since t*rans*-fat intake is associated with both PUFA and adverse cardiovascular outcomes [24,39], we suspect that we may have underestimated the association between PUFA intake and hypertension. Fourth, because of the cross-sectional nature of the analyses on hypertension, we cannot be sure that hypertension itself did not influence dietary consumption, including PUFA intake, or that the collected dietary data, which concerned consumption in the year prior to entry into the SCCS, reflects dietary habits prior to the onset of hypertension. Nevertheless, any misclassifications of dietary exposure categories are more likely to be non-differential and therefore more likely to mask than to falsely generate effects between PUFA or fish intake and hypertension or mortality.

Conclusions

Our results suggest that consumption of PUFA or fish may be beneficial for hypertension and cardiovascular- and all-cause mortality in the absence of statin therapy. This may suggest that use of PUFA or fish is valuable for primary CVD prevention but may not add survival benefits to patients already treated with statins. More studies are warranted to confirm these findings. In the interim, the potential benefit of PUFA and fish consumption in primary prevention of CVD should be considered in discussions with patients who are not candidates for statin therapy but are at increased risk for hypertension and mortality.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

MUFA	Monounsaturated fatty acids.
PUFA	Polyunsaturated fatty acids.
SCCS	Southern Community Cohort Study.
SFA	Saturated fatty acids.

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Highlights

- Whether intake of polyunsaturated fats adds to benefits from statins is uncertain.
- Intake of polyunsaturated fat did not add benefits on mortality among statin users.
- Intake of polyunsaturated fat protected against mortality among non-statin users.
- Both n3- and n6-PUFA were beneficial among non-statin users.
- Fish intake was also beneficial on mortality but only among non-statin users.

Table 1

Characteristics of Southern Community Cohort Study participants by quintiles of energy-adjusted PUFA.

		Quintiles of energy-adjusted PUFA					*P* value*
		1 (n=13,856)	2 (n=13,896)	3 (n=13,932)	4 (n=13,973)	5 (n=13,902)	
Age, mean (SD), y		52.2 (8.8)	52.4 (8.9)	52.1 (8.7)	51.9 (8.6)	51.9 (8.5)	< 0.001
Sex, No. (%), female		7871 (56.8)	8125 (58.5)	8047 (57.8)	8308 (59.5)	9247 (66.5)	< 0.001
Race, No. (%), white		4294 (31.0)	4523 (32.5)	4548 (32.6)	4603 (32.9)	4456 (32.1)	0.005
Education, No. (%)							
	< high school	4420 (31.9)	4057 (29.2)	3926 (28.2)	3714 (26.6)	3360 (24.2)	< 0.001
	High school/GED	5546 (40.0)	5374 (38.7)	5425 (38.9)	5423 (38.8)	5340 (38.4)	
	Some college	2395 (17.3)	2656 (19.1)	2731 (19.6)	2935 (21.0)	3101 (22.3)	
	Graduate	1495 (10.8)	1809 (13.0)	1850 (13.3)	1901 (13.6)	2101 (15.1)	
Income, No. (%), <15,000/y		8285 (59.8)	7566 (54.4)	7550 (54.2)	7427 (53.2)	7127 (51.3)	< 0.001
Recruitment site, No. (%), CHC		12245 (88)	12123 (87)	12230 (88)	12298 (88)	12280 (88)	0.02
Smoking, No. (%)							
	≥ 20 cigarettes/day	2281 (16.5)	2064 (14.9)	1987 (14.3)	1988 (14.2)	1800 (12.9)	< 0.001
	< 20 cigarettes/day	4035 (29.1)	3732 (26.9)	3764 (27.0)	3647 (26.1)	3242 (23.3)	
	Past	2844 (20.5)	3148 (22.7)	3137 (22.5)	3264 (23.4)	3502 (25.2)	
	Never	4696 (33.9)	4952 (35.6)	5044 (36.2)	5074 (36.3)	5358 (38.5)	
Alcohol intake, No. (%)							
	Current	8396 (60.6)	7831 (56.4)	7763 (55.7)	7467 (53.4)	6878 (49.5)	< 0.001
	Past	3586 (25.9)	4091 (29.4)	4287 (30.8)	4504 (32.2)	4812 (34.6)	
	Never	1874 (13.5)	1974 (14.2)	1882 (13.5)	2002 (14.3)	2212 (15.9)	
BMI (kg/m^2), No. (%)							
	< 18.5	199 (1.4)	163 (1.2)	192 (1.4)	173 (1.2)	147 (1.1)	< 0.001
	18.5-24.9	4009 (28.9)	3565 (25.7)	3400 (24.4)	3262 (23.3)	2728 (19.6)	
	25.0-29.9	4161 (30.0)	4191 (30.2)	4191 (30.1)	4202 (30.1)	3976 (28.6)	
	30.0-34.9	2820 (20.4)	2997 (21.6)	3017 (21.7)	3039 (21.7)	3271 (23.5)	
	≥ 35.0	2667 (19.2)	2980 (21.4)	3132 (22.5)	3297 (23.6)	3780 (27.2)	
Systolic BP, mean (SD), mm Hg		134 (21)	135 (20)	135 (21)	134 (20)	134 (21)	0.34
Diastolic BP, mean (SD), mm Hg		82 (12)	83 (12)	83 (12)	83 (12)	83 (12)	0.61

		Quintiles of energy-adjusted PUFA					*P* value*
		1 (n=13,856)	2 (n=13,896)	3 (n=13,932)	4 (n=13,973)	5 (n=13,902)	
Statin use, No. (%)		2236 (16.1)	2272 (16.4)	2242 (16.1)	2170 (15.5)	2305 (16.6)	0.18
Diabetes, No. (%)		2612 (18.9)	2784 (20.0)	2781 (20.0)	2925 (20.9)	3357 (24.1)	< 0.001
MI/CABG, No. (%)		984 (7.1)	935 (6.7)	900 (6.5)	879 (6.3)	940 (6.8)	0.07
Stroke/ TIA, No. (%)		905 (6.5)	886 (6.4)	860 (6.2)	843 (6.0)	850 (6.1)	0.41
Hypertension, No. (%)		7487 (54.0)	7648 (55.0)	7443 (53.4)	7447 (53.3)	7669 (55.2)	0.002
Total energy, mean (SD), kcal/day		2532 (2181)	2458 (1561)	2562 (1255)	2625 (1023)	2614 (813)	< 0.001
Carbohydrates, mean (SD), g/day**		241 (78)	276 (69)	285 (58)	285 (50)	276 (46)	< 0.001
Proteins, mean (SD), g/day**		63 (16)	80 (16)	88 (17)	94 (18)	98 (19)	< 0.001
Saturated fat, mean (SD), g/day**		18.0 (5.9)	23.9 (5.4)	26.8 (5.4)	28.8 (5.2)	30.2 (5.2)	< 0.001
MUFA, mean (SD), g/day**		21.3 (5.4)	29.1 (4.5)	33.3 (4.7)	36.7 (4.8)	40.6 (5.4)	< 0.001
Tuna intake, No. (%)							
	< once/month	6084 (43.9)	4770 (34.3)	4103 (29.5)	3601 (25.8)	3443 (24.8)	< 0.001
	1-3 times/month	5442 (39.3)	5837 (42.0)	5751 (41.3)	5547 (39.7)	4947 (35.6)	
	1-3 times/week	2009 (14.5)	2926 (21.1)	3687 (26.5)	4250 (30.4)	4350 (31.3)	
	≥ 4 times/week	321 (2.3)	363 (2.6)	391 (2.8)	575 (4.1)	1162 (8.4)	
Fried fish intake, No. (%)							
	< once/month	5006 (36.1)	3749 (27.0)	3185 (22.9)	2849 (20.4)	2594 (18.7)	< 0.001
	1-3 times/month	5835 (42.1)	5952 (42.8)	5717 (41.0)	5283 (37.8)	4925 (35.4)	
	1-3 times/week	2548 (18.4)	3725 (26.8)	4485 (32.2)	5156 (36.9)	5194 (37.4)	
	≥ 4 times/week	467 (3.4)	470 (3.4)	545 (3.9)	685 (4.9)	1189 (8.6)	
Broiled fish intake, No. (%)							
	< once/month	7397 (53.4)	6523 (46.9)	6116 (43.9)	5853 (41.9)	5606 (40.3)	< 0.001
	1-3 times/month	4333 (31.3)	4602 (33.1)	4487 (32.2)	4328 (31.0)	4050 (29.1)	
	1-3 times/week	1825 (13.2)	2427 (17.5)	2926 (21.0)	3306 (23.7)	3462 (24.9)	
	≥ 4 times/week	301 (2.2)	344 (2.5)	403 (2.9)	486 (3.5)	784 (5.6)	
Broiled/fried fish intake, No. (%)							
	< once/month	3689 (26.6)	2612 (18.8)	2231 (16.0)	1974 (14.1)	1793 (12.9)	< 0.001
	1-3 times/month	5360 (38.7)	4978 (35.8)	4444 (31.9)	3973 (28.4)	3606 (25.9)	
	1-3 times/week	3986 (28.8)	5367 (38.6)	6082 (43.7)	6528 (46.7)	6256 (45.0)	

	Quintiles of energy-adjusted PUFA					*P* value*
	1 (n=13,856)	**2 (n=13,896)**	**3 (n=13,932)**	**4 (n=13,973)**	**5 (n=13,902)**	
≥ 4 times/week	821 (5.9)	939 (6.8)	1175 (8.4)	1498 (10.7)	2247 (16.2)	
Tuna/broiled/fried fish intake, No. (%)						
< once/month	2407 (17.4)	1490 (10.7)	1198 (8.6)	999 (7.1)	904 (6.5)	< 0.001
1-3 times/month	4882 (35.2)	3851 (27.7)	3192 (22.9)	2633 (18.8)	2277 (16.4)	
1-3 times/week	5394 (38.9)	7062 (50.8)	7623 (54.7)	7710 (55.2)	6950 (50.0)	
≥ 4 times/week	1173 (8.5)	1493 (10.7)	1919 (13.8)	2631 (18.8)	3771 (27.1)	
Tuna/broiled/fried fish intake, mean (SD), servings/day	0.24 (0.38)	0.29 (0.39)	0.33 (0.41)	0.38 (0.43)	0.48 (0.54)	< 0.001
PUFA, mean (SD), g/day**	12.2 (2.5)	17.0 (0.9)	19.8 (0.8)	22.6 (0.9)	27.1 (2.8)	--
PUFA, mean (sd), % total energy	6.1 (1.6)	7.2 (1.2)	7.9 (1.0)	8.6 (0.9)	10.1 (1.2)	--

BP, blood pressure; CABG, coronary artery bypass graft; CHC, community health centers; MI, myocardial infarction; MUFA, Monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; TIA, transient ischemic attack.

* *P* values are from one-way ANOVA tests for continuous variables and Chi-square tests for categorical variables.

** Adjusted for total energy intake

Table 2

The association between energy-adjusted total polyunsaturated fat intake and prevalent hypertension.

Model *	Quintiles of polyunsaturated fat intake					*P* for trend
	1 (reference)	2	3	4	5	
Overall						
Unadjusted	1.00	1.04 (0.99, 1.09)	0.98 (0.93, 1.02)	0.97 (0.93, 1.02)	1.05 (1.00, 1.10)	0.54
Fully adjusted	1.00	1.02 (0.96, 1.08)	0.95 (0.89, 1.02)	0.94 (0.87, 1.02)	0.95 (0.87, 1.04)	0.14
Statin use						
Yes	1.00	1.15 (0.98, 1.34)	1.01 (0.86, 1.18)	1.09 (0.92, 1.28)	1.13 (0.96, 1.34)	0.26
No	1.00	1.00 (0.94, 1.06)	0.94 (0.88, 1.01)	0.92 (0.85, 1.00)	0.93 (0.85, 1.02)	0.05

* Values are reported as odds ratios (95% confidence intervals) and are from a model that included age, sex, race, BMI, recruitment site, education, income, smoking, alcohol consumption, total energy, energy-adjusted polyunsaturated fat (PUFA), saturated fat, monounsaturated fat and proteins, diabetes, PUFA, statin use and the interaction between PUFA and statin use.

Table 3

The association between energy-adjusted n3 polyunsaturated fat intake and CVD- and all-cause mortality

Model*	Quintiles of n3 fatty acid intake					*P* for trend
	1 (reference)	2	3	4	5	
CVD mortality						
Statin users	1.00	1.10 (0.82, 1.47)	0.94 (0.69, 1.27)	0.97 (0.72, 1.30)	0.90 (0.66, 1.23)	0.35
Non-users	1.00	0.93 (0.80, 1.09)	0.89 (0.76, 1.04)	0.85 (0.73, 1.01)	0.93 (0.78, 1.10)	0.57
All-cause mortality						
Statin users	1.00	1.04 (0.87, 1.26)	1.13 (0.94, 1.36)	1.05 (0.87, 1.27)	1.06 (0.87, 1.28)	0.73
Non-users	1.00	0.99 (0.91, 1.07)	0.90 (0.83, 0.98)	0.91 (0.84, 1.00)	0.90 (0.82, 1.00)	0.04

*Values are reported as hazard ratios (95% confidence intervals) and are computed from a model that included sex, race, BMI, recruitment site, education, income, smoking, alcohol consumption, total energy, energy-adjusted n3-PUFA, saturated fat, monounsaturated fat and proteins, diabetes, statin use and the interaction between n3-PUFA and statin use.

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Table 4

The association between energy-adjusted n6 polyunsaturated fat intake and CVD- and all-cause mortality

Model*	Quintiles of n6 fatty acid intake					*P* for trend
	1 (reference)	2	3	4	5	
CVD mortality						
Statin users	1.00	0.65 (0.48, 0.89)	0.88 (0.65, 1.19)	0.77 (0.56, 1.07)	0.80 (0.57, 1.12)	0.48
Non-users	1.00	0.83 (0.70, 0.98)	0.74 (0.61, 0.90)	0.80 (0.65, 0.98)	0.72 (0.57, 0.93)	0.03
All-cause mortality						
Statin users	1.00	0.92 (0.76, 1.11)	1.07 (0.88, 1.29)	1.00 (0.82, 1.22)	0.96 (0.78, 1.19)	0.90
Non-users	1.00	0.86 (0.78, 0.94)	0.82 (0.74, 0.91)	0.85 (0.75, 0.95)	0.80 (0.70, 0.92)	0.01

*Values are reported as hazard ratios (95% confidence intervals) and are computed from a model that included sex, race, BMI, recruitment site, education, income, smoking, alcohol consumption, total energy, energy-adjusted n6-PUFA, saturated fat, monounsaturated fat and proteins, diabetes, statin use and the interaction between n6-PUFA and statin use.

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Table 5

The association between fish intake and all-cause mortality in the Southern Community Cohort study.

Model*	Frequency of fish intake				*P* for trend
	<1/month	1-3/month	1-3/week	≥4/week	
Fried					
Statin users	1.00	1.02 (0.88, 1.17)	1.03 (0.88, 1.20)	1.00 (0.71, 1.40)	0.92
Non-users	1.00	0.97 (0.91, 1.04)	0.91 (0.84, 0.98)	0.84 (0.72, 0.97)	0.02
Broiled					
Statin users	1.00	1.03 (0.90, 1.17)	0.99 (0.84, 1.16)	0. 80 (0.53, 1.21)	0.28
Non-users	1.00	0.92 (0.86, 0.98)	0.97 (0.90, 1.04)	0.82 (0.68, 0.98)	0.05
Tuna					
Statin users	1.00	1.17 (1.02, 1.35)	1.21 (1.03, 1.41)	1.07 (0.77, 1.49)	0.66
Non-users	1.00	0.96 (0.90, 1.02)	0.99 (0.92, 1.07)	0.96 (0.83, 1.11)	0.79
Fried/Broiled					
Statin users	1.00	0.97 (0.82, 1.14)	0.99 (0.84, 1.16)	0.90 (0.69, 1.17)	0.53
Non-users	1.00	0.94 (0.87, 1.01)	0.89 (0.82, 0.96)	0.80 (0.71, 0.91)	0.002
Fried/Broiled/Tuna					
Statin users	1.00	1.00 (0.80, 1.24)	1.07 (0.88, 1.31)	1.00 (0.78, 1.28)	0.95
Non-users	1.00	0.96 (0.87, 1.05)	0.90 (0.82, 0.98)	0.87 (0.77, 0.98)	0.05

*Values are reported as hazard ratios (95% confidence intervals) and are computed from a model that included sex, race, BMI, recruitment site, education, income, smoking, alcohol consumption, total energy, energy-adjusted saturated fat, monounsaturated fat and proteins, diabetes, fish intake, statin use and the interaction between fish intake and statin use.