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Intake of total *trans*, *trans*-18:1 and *trans*-18:2 fatty acids and risk of sudden cardiac death in women

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Abstract

Background—Total intake of *trans* fat is associated with coronary heart disease (CHD) and recent reports in primarily male populations suggest that blood levels of specific *trans* isomers may have different effects on risk, particularly risk of sudden cardiac death (SCD).

Methods—We prospectively examined the association between dietary intake of *trans* fat and SCD among 86,762 women from the Nurses' Health Study. CHD risk factors, including diet and lifestyle factors were updated via questionnaires every 2–4 years, beginning in 1980.

Results—Over 26 years, we documented 317 SCD events. In the primary analysis, we found no significant association between intake of total *trans* fat, *trans*-18:1 or *trans*-18:2 isomers and risk of SCD. Compared to the lowest quintile of intake, the relative risk (RR) (95% CI) of SCD in the highest quintile was 1.28 (0.82, 2.00) for total *trans*, 1.08 (0.64, 1.83) for *trans*-18:1 and 1.19 (0.76, 1.88) for *trans*-18:2. In a secondary pre-specified analysis, total *trans* fat was significantly related to SCD among women who reported a diagnosis of CHD prior to SCD (RR: 3.24; 95% CI: 1.42, 7.40 for the highest versus lowest quintile, P trend=0.01); however, the test for interaction was not significant (P=0.11)

Conclusions—In this large prospective cohort of women, neither dietary intake of *trans* fat, nor the individual *trans* isomers, *trans*-18:1 and *trans*-18:2, were significantly associated with risk of SCD. However, *trans* fat intake may be associated with SCD risk among women with CHD,

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suggesting that *trans* fat intake may play a greater role in SCD risk among those with clinically manifest atherosclerosis.

Introduction

Sudden cardiac death (SCD) accounts for approximately half of all CHD deaths, with over 50% of the cases occurring without any previously diagnosed CHD[1]. The majority of SCD are due to lethal ventricular arrhythmias[2,3], thus factors that influence myocardial electrical stability may influence SCD risk[4]. Fatty acids have varying effects on the propensity for arrhythmias, influenced by their structural properties, like chain length and saturation[5]. Omega-3 fatty acids, which have anti-arrhythmic properties[6], are associated with lower risk of SCD[7].

Intake of *trans* fat, mainly from hydrogenated vegetable oils, is associated with higher risk of CHD[8–10]. *Trans* fatty acids have pro-arrhythmic properties[11], which may increase risk of SCD, although this relationship is not well-established. In two recent studies, composed primarily of men, blood levels of *trans*-18:2 isomers, but not *trans*-18:1, were positively associated with risk of SCD[12,13]. Because *trans* fat may have different effects on SCD risk in women, we prospectively investigated the relationship between intake of total *trans* fat and the individual *trans*-18:1 and *trans*-18:2 isomers and risk of SCD in women.

Methods

The Nurses' Health Study Cohort

The Nurses' Health study is a prospective cohort of 121,700 registered female nurses, aged 30 to 55 y at baseline in 1976[14]. We assess information on medical history, CHD risk factors, lifestyle factors and newly diagnosed disease through self-administered questionnaires biennially. Beginning in 1980, and approximately every 4 years, participants completed a food frequency questionnaire (FFQ). For this analysis, we excluded women who did not complete the 1980 FFQ, left ≥10 food items blank or had implausible energy intake (<600 or >3500 kcal/day). We also excluded women who reported a history of stroke or cancer prior to 1980. The Institutional Review Board of Brigham and Women's Hospital approved the study protocol.

Dietary assessment

We collected information on usual diet using a FFQ administered approximately every 4 years. For each food item, a portion size was specified and participants were asked how often, on average, she had consumed that quantity over the past year. Average intake of *trans* fat and other nutrients was calculated by multiplying the frequency of consumption of each food by its nutrient content and then summing across all foods. Nutrient values were obtained from the Harvard University Food Composition Database[15], which accounts for types of margarine and fats used in cooking and baking. Intake of *trans* fat estimated from the FFQ is significantly correlated with *trans* fat concentrations in adipose tissue ($r=0.51$; $p<0.001$)[16] and RBC ($r=0.43$; $p<0.01$)[17].

Assessment of Medical History, Anthropometric Data, and Lifestyle Factors

On the baseline questionnaire, we collected information on weight, height, smoking status, parental history of MI, menopausal status, use of medications (aspirin and hormone therapy), dietary supplements, physical activity and personal history of CHD and other diseases. This information, with the exception of height and parental history, has been updated on biennial follow-up questionnaires. Details on the validity of the questionnaire has been reported elsewhere[18–20].

Ascertainment of sudden death

Details for the classification of SCD have been described elsewhere[3]. Briefly, cardiac deaths were considered sudden if the death or cardiac arrest occurred within 1 hour of symptom onset as documented by medical records or through reports from next of kin. We included unwitnessed deaths that could have occurred within 1 hour of symptom onset and that had autopsy findings consistent with SCD in our analysis (n=36). To increase the specificity for an "arrhythmic death", we excluded women with evidence of circulatory collapse (hypotension, exacerbation of congestive heart failure or neurologic dysfunction) before disappearance of the pulse, based on the definition of Hinkle and Thaler[2]. This rigorous definition of SCD is highly specific for arrhythmic death and systematically excludes most unwitnessed deaths and deaths during sleep. In a secondary analysis, we included unwitnessed deaths and deaths that occurred during sleep where the participant was documented to be symptom free when last observed within the preceding 24 hours and where circumstances suggested that the death could have been sudden (n=104).

Statistical analysis

For each woman, person-months of follow-up were calculated from the date of return of the 1980 questionnaire until date of death or June 1, 2006, whichever came first. We postulated that if dietary *trans* fat influenced the risk of SCD, the mechanism of action would most likely be through pro-arrhythmic effects, thus most recent diet most likely influences risk. In primary analysis, we used the most recent diet prior to event[21], where 1980 diet was used for the 1980–1984 follow-up period, and 1984 diet was used for the 1984–1986 follow-up period, and so on. Because dietary *trans* fat may influence SCD risk through more long-term mechanisms related to atherogenesis, in secondary analysis we used the cumulative average of the diet to represent long-term effects and reduce random measurement error[21]. Because participants may change their diet after diagnosis of intermediate conditions, we stopped updating dietary information in the cumulative average estimate after new diagnoses of nonfatal MI, nonfatal stroke, coronary revascularization, angina, diabetes, hypertension, hypercholesterolemia or transient ischemic attack.

We used Cox proportional hazards models to estimate the relative risk across quintiles of *trans* fat intake. Models were adjusted for age (in months) and calendar year and adjusted for calories (continuous), smoking (5 categories), BMI (<25, 25–29.9, 30+ kg/m^2), family history of CHD (no, prior to 60 years, 60 years or older), menopausal status, use of postmenopausal hormones (current, past, never), aspirin use (<1, 1–6, 7+/week), multivitamin and vitamin E supplements, moderate to vigorous activity (hours/week), alcohol intake (0, 0.1–4.9, 5–14.9 and 15+ g/day), intake of fatty acids (long-chain omega-3, alpha-linolenic and ratio of polyunsaturated to saturated) (in quintiles) and diagnosis of CHD, stroke, diabetes, hypertension and hypercholesterolemia. All variables were included as time-varying covariates. We conducted tests for linear trend by assigning the median value to each quintile and modeling this variable as a continuous variable.

To estimate the impact of substituting a specific percentage of energy from *trans* fat for the same percentage of energy from carbohydrates, we modeled intake of *trans* fat, protein and all major types of fat (saturated, monounsaturated, and omega-6 and omega-3 polyunsaturated fats) as continuous variables simultaneously in the model. To estimate the relative risk of substituting energy from *trans* fat for another fatty acid, we used the difference between the regression coefficients from the same model and calculated the 95% CIs by using the covariance of the regression coefficients[22].

In pre-specified secondary analysis, we explored whether the relation between *trans* fat and SCD differed according to presence or absence of CHD (angina, MI, or coronary

revascularization), age (<60, ≥60 y) and intake of alpha-linolenic acid. To test formally for interaction, we modeled the cross-product term between *trans* fat and the variable of interest (CHD, age or alpha-linolenic acid) and used a likelihood ratio test, comparing models with and without the interaction term. For all stratified analyses, we used the most recent dietary intake. All statistical analysis was performed using SAS software, version 9.1.3 (SAS Institute Inc, Cary NC). This work was funded by grants from the NIH and American Heart Association. The authors are solely responsible for the design, conduct and analyses of the study and the drafting and editing of the manuscript, and its final contents.

Results

The median intake of *trans*-18:1 isomers was 1.1% of energy [interquartile range (IQR): 0.8%, 1.7%] while the median intake of *trans*-18:2 isomers was 0.20% of energy (IQR: 0.15%, 0.26%). The median intake (IQR) of *trans* fat during the first half of follow-up (1980–1994) was 1.7% (1.3%, 2.3%) of total energy, but only 1.2% (0.9%, 1.5%) during the second half of follow-up (1994–2006).

Women who consumed higher amounts of *trans* fat tended to consume greater amounts of all other types of fat, with the exception of the omega-3 fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) (table 1). Women with higher *trans* fat intake were less likely to report a diagnosis of hypercholesterolemia, take vitamin supplements and exercise and more likely to smoke.

Over 26 years of follow up, we documented 317 cases of sudden cardiac death. Using the simple update method, *trans* fat intake was positively associated with risk of SCD after adjusting for age and total energy (*P*-trend=0.01) but this association was attenuated and no longer significant after adjustment for CHD risk factors (table 2). Findings were similar when we used the cumulative average of *trans* fat intake (multivariate RR: 1.23; 95%CI: 0.81, 1.87). These results were not materially altered when deaths that occurred during sleep or otherwise were unwitnessed and symptom free within 24 hours of death were included (multivariate RR: 1.00; 95%CI: 0.67, 1.48).

When modeled as a continuous variable, the replacement of 2% of energy of carbohydrates with *trans* fat was not significantly associated with risk of SCD after adjustment for CHD risk factors (Table 3). Results were similar for the isocaloric substitution of most major fat subtypes for *trans* fat. A nonsignificant trend toward higher risk of SCD was seen with the substitution of omega-3 fatty acids (ALA, EPA and DHA) with *trans* fat; for each 1% energy, the relative risk of SCD with *trans* fat was 1.74 (95%CI: 0.83, 3.67). The results were similar in the first and last halves of the study follow-up period. The relative risk of SCD for the substitution of 2% of energy of carbohydrates with *trans* fat was 1.35 (95%CI: 0.65, 2.79) from 1980–1994 and 0.97 (95%CI: 0.50–1.90) from 1994–2006.

One potential explanation for the lack of a significant association may be the reduction in *trans* fat in the food supply throughout follow-up. Therefore we estimated the relative risk comparing more extreme intakes of *trans* fat. Compared to women with <1% of energy from *trans* fat, the risk of SCD among women with ≥3% of energy from *trans* fat (4% of the population) was higher, although not statistically significant (multivariate RR: 1.55; 95%CI: 0.80, 3.01).

We found a significant positive association between dietary intake of the *trans*-18:1 isomer and risk of SCD after adjustment for age and total energy (*P*-trend=0.01), which was attenuated after adjustment for CHD risk factors (table 4). Dietary intake of the *trans*-18:2 isomer was not associated with risk of SCD. For each 0.25% of total energy increment, intake of *trans*-18:1 fat was associated with an adjusted relative risk of 1.00 (95%CI: 0.94, 1.07) while

intake of *trans*-18:2 fat was associated with an adjusted relative risk of 1.28 (95%CI: 0.89, 1.83).

In secondary analyses, total *trans* fat intake was significantly associated with risk of SCD even after adjustment for CHD risk factors among the sub-group of women with clinically diagnosed CHD (Table 5). In this subgroup, women in the highest quintile of *trans* fat intake had a relative risk of SCD of 3.24 (95% CI, 1.42, 7.40) compared to women in the lowest quintile of intake. The relative risk for the substitution of 1% of energy from omega-3 fat for *trans* fat was 5.70 (95%CI: 1.30, 25.0). In contrast, *trans* fat intake was not associated with risk of SCD among women without a history CHD (Table 5). The statistical power to detect an interaction by history of CHD was limited, with only 100 cases among women with prior CHD (*P*-interaction=0.11). We found no evidence for interactions between *trans* fat intake and age (*P*-interaction=0.31) or intake of alpha-linolenic acid (*P*-interaction=0.45).

Discussion

In this large prospective cohort of women, neither intake of *trans* fat, nor the individual *trans* isomers, *trans*-18:1 and *trans*-18:2, were significantly associated with risk of SCD. Total *trans* fat intake was associated with a three-fold elevated SCD risk among women with a prior history of CHD, after adjustment for classic CHD risk factors and other important dietary variables; however, the interaction was not significant and this analysis is limited by the small numbers of women with a prior history of CHD in this generally healthy cohort.

Our nonsignificant results for dietary intake appear at odds with the previously published literature on biomarkers of *trans* fat and SCD risk. In a population-based case-control study, RBC concentration of *trans*-18:2 isomers, but not *trans*-18:1, was positively associated with risk of SCD (odds ratio for IQR = 3.1; 95%CI: 1.7, 5.4)[13]. In the Cardiovascular Health Study, higher plasma levels of *trans*-18:2 isomers were associated with a doubling in risk (odds ratio for IQR = 2.3; 95%CI: 1.3, 4.3) while plasma *trans*-18:1 was inversely associated with risk of SCD[12]. Finally, in an autopsy study, adipose levels of *trans*-18:1 isomers were inversely associated with SCD while adipose levels of *trans*-18:2 isomer were not associated with SCD risk; however, the number of cases was small (n=66)[23].

There are several potential explanations for our apparent disparate results regarding dietary intake compared to previous studies using biomarkers. First, the *trans*-18:2 isomer, which was associated with SCD in previous studies, comprises a minority of *trans* fat in diet, and many of the same food sources contain both *trans* isomers. Our ability to discriminate fully between intake of *trans*-18:1 and 18:2 isomers from our dietary questionnaire may be limited. Additionally, the level of *trans* fats in the cell membranes, such as RBC, is determined by many factors including dietary intake, absorption and metabolism. Biomarkers may approximate better the true biologic effect of *trans* fat, thus dietary assessment of intake may underestimate the true association.

Secondly, prior studies of *trans* fat and risk of SCD were conducted in primarily male populations[13] or in older populations where the majority of participants had a history of CHD[12]. Therefore, the underlying disease process in the majority of these cases is most likely CHD, which may not be the case in this younger population of women, where the prevalence of underlying CHD is typically lower[3, 24–26]. The association between *trans* fat and SCD was statistically significant in secondary analyses among women with prior CHD, which supports the possibility that *trans* fat intake plays a greater role in SCD risk in the setting of CHD.

A third potential explanation for the null association may be the lower level of *trans* fat intake in this population. When we looked at a more extreme comparison of *trans* fat intake (≥3% v. <1% of energy), the risk of SCD was higher than in the quintile analysis. After a reduction of

trans fat in the food supply of Costa Rica, the relationship between *trans* fat and nonfatal MI was no longer significant[27]. The effect of *trans* fat may be even greater in countries like Iran, where average *trans* fat intake was estimated at 4.2% of energy[28]. Future research is needed on the association between *trans* fat and SCD in countries where intake remains high.

Additional limitations of this study warrant discussion. Although we attempted to control for potential confounding variables, the possibility of residual confounding remains. We had more cases of SCD than prior studies, however, the numbers of SCD in this study were lower than the number of CHD events in studies reporting positive associations between *trans* fat and total CHD[8–10], and therefore our power to detect modest associations and examine interactions was limited. However, the association between *trans* fat and SCD for a substitution of 2% of energy from *trans* fat (RR=1.20; 95%CI: 0.52, 1.91) was similar to the association with risk of CHD (RR=1.23, 95%CI: 1.11 to 1.37)[29]. The selective nature of this cohort, US female registered nurses, may limit the generalizability of these findings, although the high level of education and health interest of these participants, and the accuracy of reported dietary information has been well documented[30]. Another strength is the repeated assessment of diet, which captured the changes in *trans* fat in the food supply over time.

Conclusion

In conclusion, we found no significant association between *trans* fatty acid intake and risk of SCD among a large-prospective cohort of women. However, higher dietary intake of *trans* fat may be associated with an increased risk of SCD among women with established coronary heart disease. Future research is needed to determine whether differences in study results are due to gender differences, other clinical characteristics of participants, or differences in exposure level or endogenous *trans*-fat metabolism.

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Table I

Selected characteristics* across quintiles of *trans* fatty acid intake among women in the Nurses' Health Study in 1994

	Quintiles of total *trans* fat (% energy)				
	Q1	**Q2**	**Q3**	**Q4**	**Q5**
Range, (%energy)	<0.97	0.97–1.27	1.28–1.61	1.62–2.12	>2.12
Median, (% energy)	0.77	1.12	1.43	1.83	2.55
Age, mean (SD), y	61 (7)	61 (7)	60 (7)	60 (7)	60 (7)
Current smokers (%)	10	13	14	15	15
Reported diagnosis of					
Hypertension (%)	36	37	37	38	37
Diabetes (%)	6.0	6.5	6.7	6.4	7.2
High cholesterol (%)	51	49	47	46	45
Prior CHD (%)	9	8	8	8	8
BMI (kg/m^2)	25.6	26.4	26.8	26.9	27.0
Family history of MI before age 60 (%)	14	14	13	13	11
Post-menopausal (%)	83	83	82	82	80
Aspirin use, ≥ 7 times/week (%)	12	11	11	10	9
Vitamin supplement use					
Vitamin E (%)	36	28	23	19	14
Multivitamin (%)	49	43	39	33	26
Moderate to vigorous physical activity (hours/week)	4.5	3.6	3.2	2.9	2.6
Nutrient intake					
Alcohol (g/day)	6.0	5.6	4.9	4.3	3.7
Total fat (% energy)	23.9	28.7	31.3	33.6	36.9
Saturated fat (% energy)	7.6	9.7	10.8	11.7	12.9
Monounsaturated fat (% energy)	9.4	11.2	12.2	13.1	14.8
Polyunsaturated fat (% energy)	4.5	5.1	5.4	5.7	6.2
Omega-3 fat (% energy)	0.16	0.12	0.11	0.09	0.07
Alpha-linolenic acid (% energy)	0.44	0.48	0.50	0.51	0.53
Trans fat (% energy)					
trans-18:1 isomer	0.55	0.87	1.13	1.49	2.25
trans-18:2 isomer	0.12	0.18	0.22	0.26	0.31

*All characteristics are age-standardized with the exception of age

Table II

Relative risks (95% confidence intervals) of sudden cardiac death according to total *trans* fatty acid intake

	Quintiles of total *trans* fat (% energy)					P - trend
Total *trans* (median intake, % energy)	0.77	1.12	1.43	1.83	2.55	
Cases	69	77	59	61	51	
Person-years	443,754	443,149	444,421	446,960	450,507	
Age and calorie adjusted	*1.0 (ref)*	1.33 (0.96–1.85)	1.15 (0.81–1.63)	1.48 (1.03–2.12)	1.65 (1.11–2.45)	0.01
Multivariate adjusted 1	*1.0 (ref)*	1.15 (0.83–1.60)	0.90 (0.63–1.28)	1.02 (0.71–1.48)	0.95 (0.63–1.43)	0.95
Multivariate adjusted 2	*1.0 (ref)*	1.27 (0.91–1.79)	1.02 (0.70–1.48)	1.18 (0.80–1.74)	1.18 (0.76–1.83)	0.64
Multivariate adjusted 3	*1.0 (ref)*	1.27 (0.90–1.79)	1.04 (0.72–1.52)	1.26 (0.85–1.87)	1.28 (0.82–2.00)	0.36

Multivariate adjusted 1: Adjusted for age, calories, smoking, BMI, parental history of MI, menopausal status, use of postmenopausal hormones, aspirin use, multivitamin and vitamin E supplements, physical activity and alcohol intake.

Multivariate adjusted 2: Adjusted for multivariate 1 plus intake of omega-3 fatty acid, alpha-linolenic fatty acids and ratio of polyunsaturated to saturated fatty acids

Multivariate adjusted 3: Adjusted for multivariate 2 plus diagnosis of CHD, stroke, diabetes, high blood pressure or high cholesterol

Table III

Relative risks (95% CI) of sudden cardiac death associated with the isocaloric substitution of energy of major types of fat with *trans* fat intake

	RR (95% CI)*
Intake of *trans* fat for:	
Carbohydrates (2%)†	1.20 (0.75–1.91)
Saturated fat (2%)†	1.22 (0.74–2.00)
Monounsaturated fat (2%)†	1.20 (0.72–2.01)
Total polyunsaturated fat (2%)†	1.37 (0.83–2.28)
omega-3 fat (1%)‡	1.74 (0.83–3.67)
omega-6 fat (1%)‡	1.11 (0.84–1.46)

*Model adjusted for age, calories, smoking, BMI, parental history of MI, menopausal status, use of postmenopausal hormones, aspirin use, multivitamin and vitamin E supplements, physical activity, alcohol intake and diagnosis of stroke, diabetes, high blood pressure or high cholesterol

†From a single model including linear terms for all types of fat (saturated, monounsaturated, polyunsaturated, and *trans*), protein, and total energy intake. The relative risk is for a substitution of 2% of total energy.

‡From a single model including linear terms for all types of fat (saturated, monounsaturated, omega-3 polyunsaturated, omega-6 polyunsaturated, and *trans*), protein, and total energy intake. The relative risk is for a substitution of 1% of total energy.

Table IV

Relative risks (95% confidence intervals) of sudden cardiac death according to intake of 18:1 and 18:2-*trans* fat isomers

	Quintiles of intake of *trans* fat isomers (% energy)					
	Q1	**Q2**	**Q3**	**Q4**	**Q5**	**P - trend**
18:1 *trans* (median intake, % energy)	0.58	0.87	1.13	1.52	2.24	
Cases	72	68	68	57	52	
Person-years	443,498	443,143	444,225	446,820	451,108	
Age and calorie adjusted	*1.0 (ref)*	1.12 (0.80–1.56)	1.24 (0.88–1.74)	1.34 (0.93–1.93)	1.70 (1.14–2.53)	0.01
Multivariate adjusted*	*1.0 (ref)*	1.05 (0.74–1.48)	1.13 (0.79–1.61)	1.11 (0.75–1.65)	1.22 (0.78–1.90)	0.38
Multivariate adjusted* + 18:2 *trans*	*1.0 (ref)*	0.97 (0.66–1.41)	1.03 (0.68–1.55)	1.00 (0.63–1.58)	1.08 (0.64–1.83)	0.71
18:2 *trans* (median intake, % energy)	0.11	0.16	0.20	0.24	0.33	
Cases	65	60	68	59	65	
Person-years	446,631	445,697	445,314	444,973	446,179	
Age and calorie adjusted	*1.0 (ref)*	0.95 (0.67–1.35)	1.10 (0.78–1.55)	1.00 (0.70–1.42)	1.10 (0.78–1.56)	0.53
Multivariate adjusted*	*1.0 (ref)*	1.03 (0.72–1.48)	1.23 (0.86–1.76)	1.16 (0.79–1.70)	1.22 (0.84–1.79)	0.27
Multivariate adjusted* + 18:1 *trans*	*1.0 (ref)*	1.03 (0.72–1.49)	1.23 (0.83–1.82)	1.15 (0.75–1.76)	1.19 (0.76–1.88)	0.45

*Model adjusted for age, calories, smoking, BMI, parental history of MI, menopausal status, use of postmenopausal hormones, aspirin use, multivitamin and vitamin E supplements, physical activity, alcohol intake, intake of omega-3 fatty acid, alpha-linolenic fatty acids and ratio of polyunsaturated to saturated fatty acids and diagnosis of stroke, diabetes, high blood pressure or high cholesterol

Table V

Relative risks (95% confidence intervals) of sudden cardiac death according to *trans* fat intake stratified by history of nonfatal CHD before event

Total *trans* (median intake, % energy)	**Quintiles of total *trans* fat (% energy)**					**P - trend**
	0.77	**1.12**	**1.43**	**1.83**	**2.55**	
Prior history of CHD						
Cases	23	27	18	15	17	
Person-years	46,732	38,520	32,875	26,127	19,251	
Age and calorie adjusted	*1.0 (ref)*	1.38 (0.78–2.45)	1.31 (0.70–2.47)	1.59 (0.80–3.15)	3.07 (1.52–6.23)	0.004
Multivariate adjusted*	*1.0 (ref)*	1.78 (0.96–3.31)	1.53 (0.76–3.08)	1.90 (0.87–4.15)	3.24 (1.42–7.40)	0.01
No prior history of CHD						
Cases	46	50	41	46	34	
Person-years	397,022	404,630	411,546	420,833	431,256	
Age and calorie adjusted	*1.0 (ref)*	1.25 (0.83–1.87)	1.12 (0.73–1.71)	1.51 (0.98–2.31)	1.41 (0.87–2.30)	0.12
Multivariate adjusted*	*1.0 (ref)*	1.04 (0.69–1.58)	0.84 (0.53–1.32)	1.01 (0.64–1.61)	0.86 (0.50–1.47)	0.60

*Multivariate adjusted: Model adjusted for age, calories, smoking, BMI, parental history of MI, menopausal status, use of postmenopausal hormones, aspirin use, multivitamin and vitamin E supplements, moderate to vigorous activity, alcohol intake, intake of omega-3 fatty acid, alpha-linolenic fatty acids and ratio of polyunsaturated to saturated fatty acids and diagnosis of stroke, diabetes, high blood pressure or high cholesterol