Dietary intake of saturated fatty acids and incident stroke and coronary heart disease in Japanese communities: the JPHC Study

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Title page

Dietary intake of saturated fatty acids and incident stroke and coronary heart disease in Japanese communities: The JPHC Study

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Brief title: Saturated fat and incident stroke and CHD

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Introduction

Saturated fatty acid (SFA) intake has been considered to be atherogenic, and reducing SFA intake is recommended to prevent atherosclerotic diseases.[1] Yet, recent meta-analyses have indicated that greater dietary intake of SFA *per se* may not be associated with increased risk of coronary disease[2, 3], though another meta-analysis showed that replacing SFA intake with polyunsaturated fatty acids (PUFA) intake was inversely associated with coronary events.[4] Several cohort studies, but not all, have reported an inverse association between dietary SFA and risk of ischemic stroke and/or intraparenchymal haemorrhage.[3] Thus, the role of SFA intake in the development of both coronary diseases and stroke remains under debate.

Compared with Westerners, Asian people traditionally consume less SFA-containing foods, as shown in the Seven Countries Study[5] and also in later studies.[6, 7] The low SFA intake amongst Asians has been believed to be one reason why they have lower mortality from coronary disease than Westerners. However, no prospective studies have been conducted to examine the association of dietary SFA intake with incident stroke and coronary disease in Asians, except for intraparenchymal haemorrhage.[6]

The Japan Public Health Center-based prospective (JPHC) Study is one of the

largest prospective studies in Japan, with systematic incidence registry of cardiovascular disease. An advantage of this study included enough number of population to study subtypes of stroke (ie, lacunar, large artery occlusive or embolic infarction, and subarachnoid, deep or lobar intraparenchymal haemorrhage), which is often hard to study in Western cohorts. The population is also unique in that they have very low SFA intake, and high stroke and low coronary disease incidence. Our hypotheses were that low SFA intake is associated with elevated risk of lacunar infarction and deep intraparenchymal haemorrhage, and high SFA intake with elevated risk of coronary heart disease.

Methods

Study cohort

The JPHC Study is an ongoing cohort study comprising a community-based sample of 140,420 persons (68,722 men and 71,698 women) in Japan. Details of the JPHC Study protocol were described elsewhere.[8] Briefly, the JPHC Study included two sub-cohorts based on Public Health Center areas; Cohort I (started in 1990, 5 Public Health Center areas, participants aged 40-59) and Cohort II (started in 1993, 6 PHC areas, aged 40-69); however, participants in 2 Public Health Center areas (Tokyo and Osaka) were excluded from the current study because the follow-up data were incomplete. Thus, 116,896 subjects, all residents living in the study areas at baseline, were eligible for follow-up. Participants were asked to complete self-administered questionnaires about their lifestyles and medical histories. Informed consent was obtained before participants completed the questionnaire, or sometimes from community leaders instead of individuals, as this had been in common practice for informed consent in Japan at that time. The JPHC study was approved by the institutional review boards of the National Cancer Center and the University of Tsukuba.

Baseline questionnaires

A self-administrated questionnaire was distributed to all residents living in the study areas aged 40-59 for Cohort I in 1990 and those aged 40-69 for Cohort II in 1993. The questionnaire included demographic characteristics, medical history, smoking, drinking and dietary habits. A five-year follow-up questionnaire, which includes food frequency questionnaire (FFQ), was distributed to all eligible study subjects in 1995 for Cohort I and in 1998 for Cohort II. Of these, 92,905 persons (79%) returned their follow-up questionnaire. We excluded persons who lost or refused follow-up (n=226); who had histories of myocardial infarction, angina pectoris, stroke or cancer based on the first or 5-year follow-up questionnaires or who were found in the stroke/coronary heart disease registry (n=7,964), or who did not satisfactorily complete their dietary questionnaire (n=1,114). We further excluded persons with total energy intake <1 percentile or >99 percentile (n=1,670). Ultimately, 81,931 (38,084 men and 43,847 women) were included in this study.

The FFQ in the 5-year follow-up of cohorts I and II was used to determine the dietary intake of SFA and other nutrients/foods. The FFQ included 138 food items and 4 choices for frequency of intake was offered for each item. The nutrients that each food item contained were mostly estimated by the Japan Food Table 5th version. Fatty acids were estimated by a JPHC study food table, which was largely based on the Japan Food

Table 4th version[9], since the 5th version did not include fatty acids. The intake of SFA was then calculated by multiplying the frequency scores and estimated SFA for each food, and summing across all 138 items. Validation of FFQ was tested comparing SFA determined by FFQ and that by dietary records: the Spearman's correlation coefficients between energy adjusted SFA derived from FFQ and dietary records were 0.61 amongst men and 0.60 amongst women in Cohort I[9] and 0.62 amongst men and 0.51 amongst women in Cohort II[10]. The mean intake of SFA derived from FFQ was 11-31% higher than that from dietary records. Reproducibility of FFQ was also confirmed for Cohort II at an approximately one-year interval, and was fairly good (Spearman r=0.61 amongst men and 0.53 amongst women).[10] All dietary variables were adjusted for energy intake using the nutrient residual model.[11]

Stroke and coronary heart disease registries

A total of 78 hospitals formed the register of events within the 9 PHC areas. All were major hospitals with the capability of treating patients with acute coronary heart disease, stroke or cancer events. Ninety-seven percent of strokes and 92% of myocardial infarctions in the 9 PHC areas were treated at these 78 registry hospitals. Physicians in the hospitals, PHCs, or investigators, blinded to the patients' lifestyle data, reviewed the

medical records of cohort participants at each hospital and extracted clinical information including brain images, electrocardiogram and enzymes, onto cohort-specific registration forms.

Stroke was confirmed according to the criteria of the National Survey of Stroke[12], which requires the presence of focal neurological deficits of sudden or rapid onset lasting at least 24 hours or until death. Strokes were classified according to subtypes; i.e., intraparenchymal haemorrhage (deep or lobar), subarachnoid haemorrhage, or cerebral infarction (large-artery thrombotic, lacunar or embolic).[13] Almost all registered hospitals were equipped with CT and/or MRI scans. Imaging was available for 98% of registered stroke events.

Myocardial infarction was confirmed in the medical records according to the criteria of the Monitoring Trends and Determinants of Cardiovascular Disease (MONICA) project[14], which requires typical chest pain and evidence from electrocardiogram and/or cardiac enzymes. For cases with typical prolonged chest pain (>20 minutes) but not confirmed by electrocardiograms or cardiac enzymes (11% of total myocardial infarctions), a possible myocardial infarction diagnosis was made and these were included in myocardial infarction cases. Sudden cardiac death was defined as a death of unknown origin that occurred within 1 hour from onset of event.

For analysis, only first-ever stroke (regardless of subtype) or coronary heart disease (myocardial infarction or sudden cardiac death) events during follow-up were included; recurrent events were excluded. If one person suffered both coronary heart disease and stroke, both events were included.

Statistical analyses

Follow-up started from completion of the 5-year questionnaire, and ended at the date of death, emigration, incident stroke or coronary heart disease event, or end of 2009 (for Cohort I) or end of 2007 (for Cohort II), whichever came first. The incidence rates of each outcome were calculated according to quintiles of energy-adjusted SFA intake. Hazard ratios (HR) with 95% confidence intervals (CI) were calculated after adjustment for age, sex, and other covariates with Cox proportional hazard models. The covariates included cohort, baseline body mass index (quintile), smoking status (never, ex-, current smoker of 1-<20, 20-<30 and 30 cigarettes/day or more) , alcohol intake (0, 1-150, 151-300, 301-450 and 451 g/wk or more), sports at leisure time (rarely, 1-3/month, 1-2/week, 3-4/week or more), walking and standing time (<1, 1-3, 3 hr/day or more), perceived mental stress (low, medium, high), employment status (non-employed or employed), total energy intake (quintile), and quintiles of energy-adjusted dietary

intakes of carbohydrate, cholesterol, vegetables, fruit, and calcium. We did not include MUFAand PUFA in the model, so the results should be interpreted as the association of SFA in exchange for the average combination of other types of fat than SFA (ie, MUFA and PUFA). We also did not include serum lipids, hypertension or diabetes, since these could be potential mediators for the relation between SFA intake and cardiovascular outcomes. The linear trend of HRs across quintiles was tested by an ordinal variable (-2, -1, 0, +1, +2) for successive quintiles. Multiplicative interactions with sex were tested using a cross-product term. The proportional hazards assumption was tested using time by SFA interaction terms and was not violated for each outcome.

We used SAS version 9.1.3 Service Pack 4 (SAS Institute Inc., Cary, NC) for the analyses. All probability values for statistical tests were two-tailed and values of $p<0.05$ were regarded as statistically significant.

Results

The average age was 56.7 years and the median SFA intake was 16.3 g. Most risk/dietary factors at baseline were correlated with energy-adjusted SFA intake as shown in Table 1. During follow-up of 81,932 persons for a mean of 11.1 years (median=9.9 years), a total of 3,192 incident strokes, including 894 intraparenchymal haemorrhages, 348 subarachnoid haemorrhages, and 1,939 ischemic strokes (871 lacunar, 403 large-artery occlusive and 563 embolic), 610 myocardial infarctions and 116 sudden cardiac deaths were registered. There were no statistical interactions between SFA and sex in relation to any cardiovascular outcomes. Therefore, we pooled men and women for further analyses.

As shown in Table 2, SFA intake was inversely associated with age-, sex-, and energy-adjusted incidence rates of total stroke, total and deep intraparenchymal haemorrhages, ischemic stroke, lacunar infarction, and total cardiovascular disease. On the other hand, SFA intake was positively associated with myocardial infarction, but not associated with subarachnoid haemorrhage or sudden cardiac death. Further adjustment for potential cardiovascular risk factors and nutrients did not change these results substantially. There was no interaction between sex and SFA intake in relation to each outcome. The sex-specific baseline characteristics, the number of each event,

multivariable HRs and p for trend were presented in Supplementary Tables S-1, S-2 and S-3.

We consider hypertension and diabetes to be on the causal pathway between SFA and cardiovascular outcomes. When we included treatment for hypertension and diabetes in the model, the results were similar for total stroke [multivariable HR for highest *vs.* lowest SFA quintiles =0.82 (0.69-0.98), p for trend=0.01], intraparenchymal haemorrhage [HR=0.63(0.45-0.89), p for trend=0.009], lacunar infarction [HR=0.81(0.57-1.14), p for trend=0.047] and myocardial infarction [HR=1.49(0.99-2.22), p for trend=0.02), but attenuated for ischemic stroke [HR=0.91(0.72-1.14), p for trend=0.25].

Discussion

We observed an inverse relationship between dietary intake of SFA and stroke, consistent with some previous studies[6, 15-18], but not all[19-22]. The major strengths of this study was the large sample size and availability of stroke subtypes, with 98% of cases diagnosed by CT/MRI imaging. We revealed that the inverse association of SFA intake with stroke incidence was mainly due to its association with the incidence of deep intraparenchymal haemorrhage and lacunar infarction. We also found the association of SFA intake with myocardial infarction was positive, the first epidemiological observation in Asia, but overall association of SFA intake with total cardiovascular disease was inverse, and was driven by its inverse association with stroke.

According to the national statistics, Japanese consumed SFA far less than Americans (mean intakes were 16-17g among Japanese in 1988-1993 *vs.* 33g and 22g for American men and women, respectively, in 1989-1991)[23, 24]. In contrast, they have much higher incidence of intraparenchymal haemorrhage and lacunar infarction.[25] This ecological association suggested that their high incidence of both intraparenchymal haemorrhage and lacunar infarction could be attributed to low SFA intake since haemorrhage and ischemia in the perforator area of the brain is reported to share a common pathological condition (i.e., cerebral small vessel pathology called

arteriolosclerosis)[26], and the presence of arteriolosclerosis has been associated with very low blood total cholesterol levels[27] attributable in part by low SFA consumption. The present finding would be consistent with previous observations that very low blood total or LDL-cholesterol[28-31], as well as low SFA intake[6, 16], were associated with increased risk of intraparenchymal haemorrhage.

We found a positive association between SFA intake and myocardial infarction incidence, primarily for men, but not for women, although there was no sex-interaction. This is compatible with the result of a previous Japanese study showing a similar sex difference in the association between LDL cholesterol and mortality from myocardial infarction.[32] Major reasons for no association amongst women in the present study would be a small number of incident myocardial infarction, but could also relate to the attenuated LDL-cholesterol levels by sex-hormones and/or the low incident rate of myocardial infarction, which might obscure the adverse coronary effect of high SFA intake. Much lower smoking rate of women may also be related.[33] The null associations in women were in line with the results of other studies such as the Nurses' Health Study[34].

The distribution of SFA intake in the present study population was significantly lower than that for US or European populations, and the cardiovascular disease profile

is also different. Therefore, we plotted SFA intake and crude incidence of or mortality from haemorrhagic stroke, ischemic stroke and coronary heart disease from the present and other published literatures[6, 17, 18, 21, 35, 36] where information on absolute amount of daily saturated fatty acid intake was available (Figure). Taken together with the other studies, there seems to be a threshold around 20g/day of SFA intake for inverse relation of SFA intake with stroke, especially with haemorrhagic stroke. There could be an optimal level of SFA intake, which should be confirmed by meta-analyses.

Haemorrhage in the perforator area and lacunar infarction in Western populations are not as common as that in Asians.[37] The present results may be extrapolated to Asian populations that share dietary habits and cardiovascular disease profiles with Japan, but not necessarily to populations who with Western lifestyles. Although there is no clinical trial evidence, we speculate that people consuming below optimal level, if any, of SFA might benefit by modestly increasing their SFA intake. However, even in Japanese, this could increase the risk of myocardial infarction especially in men. Therefore, recommendation to increase SFA intake cannot made in current Japan since both SFA intake and coronary heart disease incidence rate are increasing amongst urban Japanese men.[38, 39]

We did not include hypertension and diabetes since we consider them as

mediators of the associations, as SFA was reported to affect insulin resistance and blood pressure.[40-42] In the present study, the adjustment for treatment of hypertension and diabetes weaken the association between SFA intake and risk of ischemic stroke, suggesting that the association was mediated largely by hypertension and diabetes.

As far as we know, this is the first study to examine the association between SFA intake and stroke subtypes. In addition, this is the first study to examine the association between SFA intake and risk of myocardial infarction amongst Asians. Other strengths of this study include the prospective cohort design, systematic registration of stroke and coronary heart disease incidence, high availability of CT/MRI imaging for stroke diagnosis, reasonable number of events for statistical power, and multiple adjustments for relevant confounders. Limitations of this study, however, warrant discussion. First, the use of a FFQ inevitably leads to SFA misclassification, although the FFQ was validated by dietary records. Random misclassification of SFA would typically attenuate observed associations. Second, persons with low SFA intake in the present study were older (women), leaner (men), more hypertensive, less diabetic (men), less active, more likely to be current smokers and drinkers (men) and to have fruit (women). Although we adjusted for a number of covariates, there would still be a potential residual confounding by other dietary and/or socioeconomic factors. Third, the

present study was not sufficient to prove the causality. The effects of increasing or decreasing SFA intake on the incidence of different types of cardiovascular disease should be evaluated ideally by randomized controlled trial.

In conclusion, we found an inverse association of dietary intake of SFA with risk of stroke, primarily for deep intraparenchymal haemorrhage and lacunar infarction, and a positive association with risk of myocardial infarction among Japanese.

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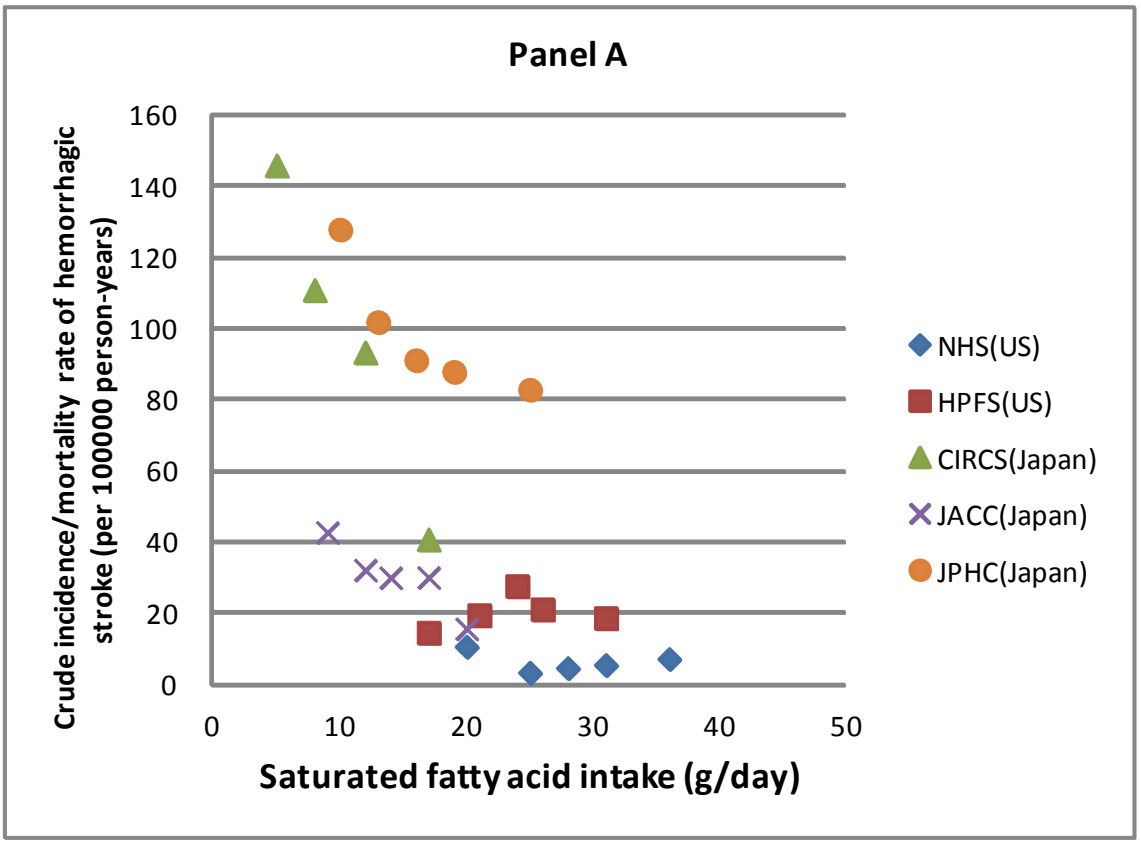
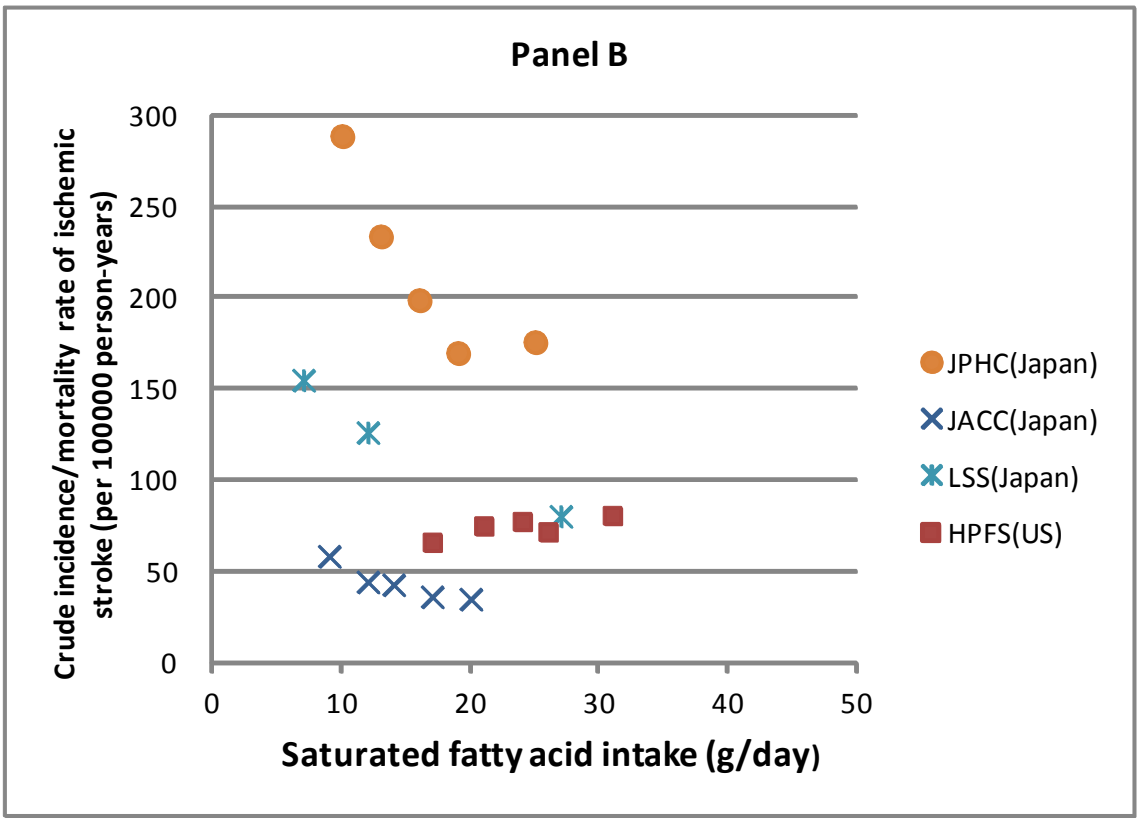
Conflict of interest: none declared.

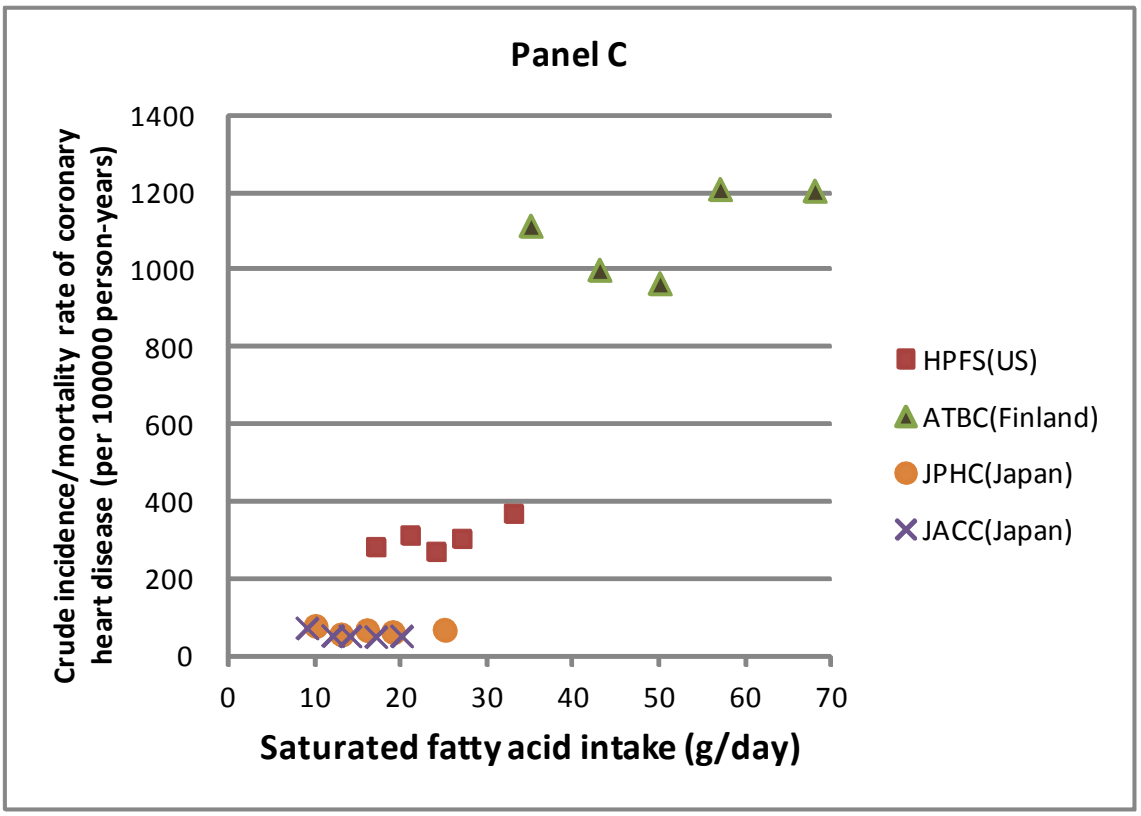
Figure legend

Comparison of the association of saturated fatty acid intake with crude incidence/mortality rates (per 100,000 person-years) of haemorrhagic stroke (Panel A), ischemic stroke (Panel B) and coronary heart disease/myocardial infarction (Panel C). NHS: Nurses' Health Study[16], ages 34-59, US; HPFS: Health Professional Follow-up Study[21, 35], ages 40-75, US; CIRCS: Circulatory Risk in Communities Study[6], ages 40-69, Japan; JPHC; Japan Public Health-based Cohort Study (this study), ages 45-74, Japan; JACC; Japan Collaborative Cohort Study[18], ages 40-79, Japan; LSS: Life Span Study[17], ages 35-89, Japan; ATBC: Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study[36], ages 50-69, Finland. The JACC and LSS were mortality studies, which made large difference in crude event rates with JPHC Study. The other studies as well as JPHC Study were incidence studies. The ATBC was an intervention study for male smokers. Note that characteristics of study population (eg, age range) varied by study.

Figure


Panel A
Crude incidence/mortality rate of hemorrhagic stroke (per 100000 person-years)
160
140
120
100
80
60
40
20
0
0
10
20
30
40
50
Saturated fatty acid intake (g/day)
NHS(US)
HPFS(US)
CIRCS(Japan)
JACC(Japan)
JPHC(Japan)


Panel B
Crude incidence/mortality rate of ischemic stroke (per 100000 person-years)
300
250
200
150
100
50
0
0
10
20
30
40
50
Saturated fatty acid intake (g/day)
JPHC(Japan)
JACC(Japan)
LSS(Japan)
HPFS(US)


Panel C
Crude incidence/mortality rate of coronary heart disease (per 100000 person-years)
1400
1200
1000
800
600
400
200
0
0
10
20
30
40
50
60
70
Saturated fatty acid intake (g/day)
HPFS(US)
ATBC(Finland)
JPHC(Japan)
JACC(Japan)

Appendix

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Table 1. Baseline cardiovascular risk factors and selected dietary variables in a cohort of 38,084 men and 43,847 women according to quintiles of saturated fatty acid (SFA) intake.

	Quintiles of SFA intake‡					
	0.8-11.7	11.8-14.8	14.9-17.7	17.8-21.5	21.6-96.7	p-value†
Men and women						
Median SFA intake‡, g/day	9.6	13.4	16.3	19.4	24.9	
Number at risk	16,386	16,386	16,387	16,386	16,386	
Age at baseline*, y	57.5(7.7)	56.9(7.7)	56.6(7.8)	56.4(7.8)	55.9(7.9)	<0.001
Body mass index, kg/m^2	23.5(3.1)	23.6(3.1)	23.6(3.1)	23.5(3.1)	23.6(3.2)	0.005
Systolic blood pressure¶,	133(18)	131(17)	130(17)	130(17)	129(17)	<0.001
Diastolic blood pressure¶,	79(11)	78(11)	78(11)	78(11)	77(10)	<0.001
Treatment for hypertension, %	21.9	20.0	19.2	18.4	17.9	<0.001
Treatment for diabetes, %	2.2	2.6	3.0	3.3	3.8	<0.001
Serum cholesterol¶, mg/dl	203(36)	206(36)	207(35)	208(35)	209(34)	<0.001
Treatment for HC, %	5.7	5.6	5.5	4.5	4.3	<0.001
Current smoker, %	28.9	25.4	23.6	22.7	22.4	<0.001
Current drinker, %	51.2	45.8	41.8	39.7	36.2	<0.001
Sports ≥3 times/wk, %	7.3	8.9	11.2	12.0	14.1	<0.001
Walking/standing ≥3 h/day, %	68.3	65.8	64.9	62.6	61.8	<0.001
High perceived mental stress,	17.1	18.1	17.4	17.8	17.4	0.19
Non-employed, %	6.3	6.7	7.8	8.2	8.7	<0.001
Mean energy intake, Kcal/day	1,956(732)	2,029(688)	2,038(672)	2,037(653)	2,057(742)	<0.001
Dietary cholesterol, mg/day	198(146)	275(165)	313(183)	345(205)	388(285)	<0.001
Protein, g/day	61(29)	72(30)	76(30)	79(31)	81(35)	<0.001
Carbohydrate, g/day	289(101)	286(88)	275(80)	260(72)	232(76)	<0.001
MUFA, g/day	13.6(7.8)	19.5(9.2)	22.5(10.3)	25.4(11.4)	30.8(16.3)	<0.001
ω-3 PUFA, g/day	2.7(1.7)	3.4(2.0)	3.5(1.9)	3.6(1.9)	3.4(1.8)	<0.001
ω-6 PUFA, g/day	7.4(3.9)	9.2(4.5)	9.9(4.5)	10.5(4.6)	11.2(5.5)	<0.001
Salt, mg/day	11.9(6.8)	13.2(6.5)	13.1(6.3)	12.9(5.9)	12.2(5.8)	<0.001
Calcium, mg/day	389(219)	497(246)	553(264)	602(297)	750(545)	<0.001
Vegetable intake, g/day	212(192)	242(188)	239(172)	230(155)	206(148)	<0.001
Fruit intake, g/day	231(254)	251(226)	242(207)	219(184)	172(160)	<0.001
Meat intake, g/day	28(27)	49(37)	63(46)	78(54)	103(85)	<0.001
Dairy intake, g/day	59(80)	122(109)	171(140)	221(183)	379(431)	<0.001

HC: hypercholesterolemia, SFA: saturated fatty acids; MUFA: monounsaturated fatty acids; PUFA: polyunsaturated fatty acids

Age and sex-adjusted means (unadjusted standard deviations), or age and sex-adjusted percentages presented unless otherwise indicated.

* Sex-adjusted mean

† p values for overall difference among quintiles based on analysis of covariance

‡ Energy-adjusted values by nutrient residual model.

¶ Only available for subsample (8,765 men and 16,047 women)

Table 2. Age, sex and energy-adjusted and multivariate adjusted hazard ratios and 95% confidence intervals of incident cardiovascular outcomes according to quintiles of saturated fatty acids intake, JPHC Study, 1993-2008.

	Men and Women					
	Quintiles of SFA intake (g/day)†					
	Q1	Q2	Q3	Q4	Q5	Trend p
Median intake, g/d	9.6	13.4	16.3	19.4	24.9	
Person-years	179,635	182,406	182,672	182,019	180,991	
Total stroke (n)	817	695	594	540	546	
Age, sex, energy-adjusted HR	1.0	0.91(0.82-1.00)	0.83(0.75-0.93)	0.80(0.72-0.90)	0.86(0.77-0.96)	<0.001
Multivariable HR (95%CI)	1.0	0.98(0.88-1.10)	0.90(0.79-1.03)	0.83(0.71-0.97)	0.77(0.65-0.93)	0.002
Intraparenchymal hemorrhage (n)	230	186	167	161	150	
Age, sex, energy-adjusted HR	1.0	0.85(0.70-1.03)	0.80(0.66-0.98)	0.81(0.66-1.00)	0.79(0.64-0.98)	0.04
Multivariable HR (95%CI)	1.0	0.92(0.74-1.14)	0.84(0.65-1.07)	0.76(0.57-1.01)	0.61(0.43-0.86)	0.005
Deep intraparenchymal hemorrhage	172	138	125	114	114	
Age, sex, energy-adjusted HR	1.0	0.84(0.67-1.05)	0.80(0.64-1.01)	0.77(0.60-0.98)	0.80(0.62-1.02)	0.06
Multivariable HR (95%CI)	1.0	0.91(0.71-1.17)	0.85(0.64-1.13)	0.75(0.54-1.05)	0.67(0.45-0.99)	0.04
Lobar intraparenchymal hemorrhage	52	42	39	42	31	
Age, sex, energy-adjusted HR	1.0	0.86(0.57-1.29)	0.84(0.56-1.29)	0.95(0.63-1.44)	0.74(0.47-1.17)	0.33
Multivariable HR (95%CI)	1.0	0.93(0.59-1.46)	0.85(0.51-1.43)	0.81(0.45-1.45)	0.49(0.24-1.02)	0.07
Subarachnoid hemorrhage (n)	64	78	63	68	75	
Age, sex, energy-adjusted HR	1.0	1.13(0.81-1.57)	0.87(0.61-1.24)	0.91(0.64-1.29)	1.00(0.70-1.41)	0.57
Multivariable HR (95%CI)	1.0	1.17(0.81-1.68)	0.91(0.59-1.39)	0.93(0.58-1.50)	0.87(0.50-1.52)	0.45
Ischemic stroke (n)	520	427	364	309	319	
Age, sex, energy-adjusted HR	1.0	0.90(0.79-1.02)	0.85(0.74-0.97)	0.78(0.67-0.90)	0.86(0.74-0.99)	0.006
Multivariable HR (95%CI)	1.0	0.98(0.85-1.13)	0.94(0.80-1.11)	0.85(0.70-1.03)	0.84(0.67-1.06)	0.08
Lacunar Infarction (n)	224	216	167	126	138	
Age, sex, energy-adjusted HR	1.0	1.04(0.86-1.26)	0.88(0.72-1.08)	0.71(0.57-0.89)	0.83(0.67-1.03)	0.002
Multivariable HR (95%CI)	1.0	1.15(0.93-1.41)	0.97(0.76-1.25)	0.75(0.55-1.01)	0.75(0.53-1.07)	0.02
Large artery occlusive infarction (n)	111	81	71	73	67	
Age, sex, energy-adjusted HR	1.0	0.80(0.60-1.07)	0.78(0.58-1.06)	0.87(0.65-1.18)	0.86(0.63-1.18)	0.56
Multivariable HR (95%CI)	1.0	0.83(0.60-1.14)	0.80(0.55-1.16)	0.89(0.58-1.35)	0.81(0.49-1.34)	0.55
Embolic infarction (n)	155	116	102	90	100	
Age, sex, energy-adjusted HR	1.0	0.83(0.65-1.06)	0.82(0.64-1.05)	0.79(0.61-1.03)	0.95(0.73-1.22)	0.59
Multivariable HR (95%CI)	1.0	0.92(0.71-1.20)	0.96(0.70-1.30)	0.94(0.65-1.34)	1.04(0.69-1.58)	0.84
Myocardial infarction (n)	142	104	125	115	124	
Age, sex, energy-adjusted HR	1.0	0.85(0.66-1.09)	1.17(0.92-1.49)	1.20(0.93-1.54)	1.41(1.10-1.81)	<0.001
Multivariable HR (95%CI)	1.0	0.90(0.68-1.18)	1.24(0.92-1.67)	1.24(0.88-1.75)	1.39(0.93-2.08)	0.046
Sudden cardiac death (n)	43	24	13	19	17	
Age, sex, energy-adjusted HR	1.0	0.64(0.39-1.06)	0.40(0.21-0.75)	0.65(0.37-1.12)	0.64(0.36-1.13)	0.18
Multivariable HR (95%CI)	1.0	0.53(0.30-0.93)	0.29(0.14-0.60)	0.42(0.19-0.92)	0.39(0.15-0.99)	0.06
Total cardiovascular disease (n)	996	812	724	664	671	
Age, sex, energy-adjusted HR	1.0	0.88(0.80-0.97)	0.86(0.78-0.94)	0.84(0.76-0.93)	0.90(0.82-1.00)	0.03
Multivariable HR (95%CI)	1.0	0.94(0.85-1.05)	0.91(0.81-1.03)	0.86(0.75-0.98)	0.82(0.69-0.96)	0.01

Multivariable model includes age, sex, energy intake, cohort, cigarette smoking status, alcohol intake, body mass index, sports at leisure time, walking and standing time, perceived mental stress, energy-adjusted dietary intakes of carbohydrate, protein, cholesterol, vegetables, fruit, and calcium.

†SFA intake was energy-adjusted by nutrient residual model.

Table S-1. Sex-specific baseline cardiovascular risk factors and selected dietary variables in a cohort of 38,084 men and 43,847 women according to quintiles of saturated fatty acid (SFA) intake.

	Quintiles of SFA intake‡					
	0.8-11.7	11.8-14.8	14.9-17.7	17.8-21.5	21.6-96.7	p-value†
Men						
Median SFA intake‡, g/day	9.5	13.3	16.2	19.4	24.8	
Number at risk	11,291	9,130	7,206	5,697	4,760	
Age at baseline*, y	56.4(7.6)	56.2(7.7)	56.2(7.8)	56.6(7.8)	56.7(7.8)	<0.001
Body mass index, kg/m^2	23.4(3.0)	23.5(2.9)	23.6(3.0)	23.6(3.0)	23.8(3.1)	<0.001
Systolic blood pressure¶,	135(18)	132(17)	131(17)	130(18)	130(17)	<0.001
Diastolic blood pressure¶,	80(10)	79(11)	79(11)	79(11)	78(10)	<0.001
Treatment for hypertension, %	20.2	18.2	18.0	16.4	17.1	<0.001
Treatment for diabetes, %	2.8	3.3	3.9	4.6	5.4	<0.001
Serum cholesterol¶, mg/dl	191(34)	197(35)	198(35)	197(34)	201(34)	<0.001
Treatment for HC, %	3.5	3.3	3.3	2.6	2.9	0.009
Current smoker, %	52.0	47.9	45.5	43.7	40.8	<0.001
Current drinker, %	84.1	77.1	70.8	63.2	55.8	<0.001
Sports ≥3 times/wk, %	8.0	9.7	12.0	12.8	15.0	<0.001
Walking/standing ≥3 h/day, %	66.9	62.9	61.3	57.1	55.9	<0.001
High perceived mental stress,	17.5	18.7	18.3	18.5	17.7	0.13
Non-employed, %	7.1	8.0	9.5	10.9	10.7	<0.001
Mean energy intake, Kcal/day	2,190(709)	2,228(693)	2,208(721)	2,163(721)	2,181(826)	<0.001
Dietary cholesterol, mg/day	230(150)	308(179)	343(212)	371(247)	421(346)	<0.001
Protein, g/day	66(29)	77(31)	80(32)	82(33)	85(37)	<0.001
Carbohydrate, g/day	300(101)	294(89)	283(85)	265(78)	240(83)	<0.001
MUFA, g/day	15.1(7.8)	21.1(9.5)	24.3(11.1)	27.1(12.8)	33.0(18.6)	<0.001
ω-3 PUFA, g/day	2.7(1.7)	3.4(2.0)	3.6(2.0)	3.6(2.0)	3.4(1.8)	<0.001
ω-6 PUFA, g/day	7.7(3.8)	9.6(4.4)	10.3(4.7)	10.8(5.0)	11.6(6.0)	<0.001
Salt, mg/day	12.2(6.6)	13.4(6.4)	13.4(6.4)	13.1(6.2)	12.4(6.0)	<0.001
Calcium, mg/day	396(212)	504(238)	554(272)	600(328)	771(607)	<0.001
Vegetable intake, g/day	192(173)	218(166)	219(154)	212(149)	196(150)	<0.001
Fruit intake, g/day	179(214)	199(185)	200(179)	185(159)	151(139)	<0.001
Meat intake, g/day	38(29)	61(41)	77(53)	90(65)	116(99)	<0.001
Dairy intake, g/day	67(82)	130(115)	175(156)	225(222)	400(492)	<0.001
Women						
Median SFA intake‡, g/day	10.0	13.6	16.4	19.5	25.0	
Number at risk	5,095	7,256	9,181	10,689	11,626	
Age at baseline*, y	59.3(7.7)	57.7(7.7)	56.9(7.7)	56.4(7.8)	55.8(7.9)	<0.001
Body mass index, kg/m^2	23.6(3.3)	23.6(3.3)	23.6(3.2)	23.4(3.2)	23.5(3.2)	<0.001
Systolic blood pressure¶,	132(18)	130(17)	129(18)	129(17)	129(18)	<0.001
Diastolic blood pressure¶,	77(11)	77(10)	77(10)	77(10)	76(10)	0.009
Treatment for hypertension, %	23.1	21.6	20.3	20.1	19.1	<0.001
Treatment for diabetes, %	2.2	2.2	2.2	2.3	2.6	0.10
Serum cholesterol¶, mg/dl	209(35)	212(35)	212(34)	214(34)	214(34)	<0.001
Treatment for HC, %	7.3	7.4	7.3	6.3	6.0	<0.001
Current smoker, %	5.9	4.9	4.3	4.2	5.1	<0.001
Current drinker, %	16.9	17.7	16.7	17.5	15.0	<0.001
Sports ≥3 times/wk, %	6.6	8.2	10.6	11.4	13.4	<0.001
Walking/standing ≥3 h/day, %	67.4	68.3	67.9	66.5	65.3	<0.001
High perceived mental stress,	16.9	17.3	16.5	17.3	17.2	0.58
Non-employed, %	7.0	5.8	6.3	6.3	7.0	0.007
Mean energy intake, Kcal/day	1,683(649)	1,848(617)	1,889(594)	1,909(596)	1,924(693)	<0.001
Protein, g/day	56(28)	68(29)	72(29)	75(29)	78(33)	<0.001
Carbohydrate, g/day	277(100)	279(85)	269(75)	254(69)	226(73)	<0.001
Dietary cholesterol, mg/day	169(126)	245(137)	287(152)	321(177)	361(254)	<0.001
MUFA, g/day	12.7(7.6)	18.1(8.7)	21.0(9.5)	24.0(10.5)	29.1(15.1)	<0.001
ω-3 PUFA, g/day	2.6(1.8)	3.3(1.9)	3.5(1.9)	3.6(1.9)	3.4(1.7)	<0.001
ω-6 PUFA, g/day	7.1(4.2)	8.9(4.4)	9.6(4.3)	10.2(4.4)	10.8(5.2)	<0.001
Salt, mg/day	11.5(7.0)	13.0(6.7)	12.9(6.2)	12.7(5.7)	12.0(5.7)	<0.001
Calcium, mg/day	381(233)	491(255)	553(258)	601(279)	738(517)	<0.001
Vegetable intake, g/day	232(225)	265(210)	256(183)	245(157)	219(147)	<0.001
Fruit intake, g/day	289(314)	300(259)	279(221)	251(192)	200(166)	<0.001
Meat intake, g/day	21(19)	40(28)	52(36)	67(46)	93(78)	<0.001
Dairy intake, g/day	52(74)	114(102)	168(126)	216(158)	366(403)	<0.001

HC: hypercholesterolemia, SFA: saturated fatty acids; MUFA: monounsaturated fatty acids; PUFA: polyunsaturated fatty acids

Age-adjusted means (unadjusted standard deviations), or age-adjusted percentages presented unless otherwise indicated.

* Unadjusted mean

† p values for overall difference among quintiles based on analysis of covariance

‡ Energy-adjusted values by nutrient residual model.

¶ Only available for subsample (8,765 men and 16,047 women)

Table S-2. Age and energy-adjusted and multivariate adjusted hazard ratios and 95% confidence intervals of incident cardiovascular outcomes according to quintiles of saturated fatty acids intake, JPHC Study, 1993-2008, men.

	Men					
	Quintiles of SFA intake (g/day)†					
	Q1	Q2	Q3	Q4	Q5	Trend p
Median intake, g/d	9.6	13.4	16.3	19.4	24.9	
Person-years	122,701	99,655	77,954	60,793	50,786	
Total stroke (n)	622	456	329	245	218	
Age, sex, energy-adjusted HR	1.0	0.90(0.80-1.02)	0.84(0.73-0.96)	0.78(0.68-0.91)	0.82(0.71-0.96)	0.003
Multivariable HR (95%CI)	1.0	1.00(0.88-1.15)	0.94(0.80-1.10)	0.85(0.70-1.03)	0.80(0.63-1.01)	0.03
Intraparenchymal hemorrhage (n)	170	120	91	65	56	
Age, sex, energy-adjusted HR	1.0	0.87(0.69-1.10)	0.85(0.66-1.09)	0.77(0.58-1.02)	0.79(0.58-1.06)	0.08
Multivariable HR (95%CI)	1.0	0.96(0.74-1.25)	0.91(0.67-1.24)	0.76(0.52-1.11)	0.64(0.41-1.01)	0.04
Deep intraparenchymal hemorrhage	127	90	71	41	47	
Age, sex, energy-adjusted HR	1.0	0.87(0.66-1.14)	0.88(0.66-1.18)	0.65(0.46-0.93)	0.89(0.63-1.24)	0.17
Multivariable HR (95%CI)	1.0	1.00(0.74-1.35)	1.02(0.72-1.46)	0.73(0.46-1.14)	0.85(0.51-1.41)	0.29
Lobar intraparenchymal hemorrhage	39	25	18	21	9	
Age, sex, energy-adjusted HR	1.0	0.80(0.48-1.32)	0.74(0.42-1.29)	1.07(0.63-1.81)	0.54(0.26-1.12)	0.24
Multivariable HR (95%CI)	1.0	0.77(0.44-1.35)	0.62(0.31-1.22)	0.74(0.35-1.57)	0.29(0.10-0.82)	0.04
Subarachnoid hemorrhage (n)	38	38	24	11	13	
Age, sex, energy-adjusted HR	1.0	1.22(0.78-1.92)	0.99(0.59-1.65)	0.58(0.30-1.14)	0.82(0.44-1.54)	0.12
Multivariable HR (95%CI)	1.0	1.42(0.86-2.34)	1.21(0.65-2.26)	0.71(0.31-1.65)	0.95(0.37-2.43)	0.49
Ischemic stroke (n)	413	296	214	168	147	
Age, sex, energy-adjusted HR	1.0	0.88(0.76-1.02)	0.82(0.70-0.97)	0.80(0.67-0.96)	0.83(0.69-1.00)	0.03
Multivariable HR (95%CI)	1.0	0.98(0.83-1.15)	0.92(0.75-1.13)	0.89(0.70-1.13)	0.85(0.63-1.13)	0.21
Lacunar Infarction (n)	176	147	91	67	57	
Age, sex, energy-adjusted HR	1.0	1.03(0.82-1.28)	0.82(0.63-1.05)	0.76(0.57-1.00)	0.76(0.56-1.02)	0.01
Multivariable HR (95%CI)	1.0	1.12(0.87-1.43)	0.89(0.66-1.21)	0.80(0.55-1.16)	0.72(0.46-1.13)	0.06
Large artery occlusive infarction (n)	83	59	38	45	37	
Age, sex, energy-adjusted HR	1.0	0.88(0.63-1.23)	0.73(0.50-1.07)	1.07(0.75-1.54)	1.04(0.70-1.53)	0.54
Multivariable HR (95%CI)	1.0	0.92(0.63-1.33)	0.74(0.46-1.17)	1.04(0.63-1.72)	0.91(0.49-1.69)	0.93
Embolic infarction (n)	128	81	70	47	49	
Age, sex, energy-adjusted HR	1.0	0.78(0.59-1.02)	0.86(0.65-1.16)	0.72(0.52-1.01)	0.89(0.64-1.23)	0.41
Multivariable HR (95%CI)	1.0	0.89(0.65-1.21)	1.04(0.73-1.49)	0.88(0.57-1.37)	1.03(0.62-1.72)	0.92
Myocardial infarction (n)	117	81	89	77	75	
Age, sex, energy-adjusted HR	1.0	0.87(0.65-1.15)	1.22(0.92-1.60)	1.31(0.98-1.75)	1.51(1.13-2.02)	0.002
Multivariable HR (95%CI)	1.0	0.90(0.66-1.23)	1.25(0.89-1.76)	1.30(0.88-1.93)	1.41(0.88-2.26)	0.06
Sudden cardiac death (n)	36	18	8	11	13	
Age, sex, energy-adjusted HR	1.0	0.62(0.35-1.09)	0.35(0.16-0.76)	0.59(0.30-1.16)	0.82(0.43-1.55)	0.55
Multivariable HR (95%CI)	1.0	0.50(0.27-0.95)	0.25(0.10-0.62)	0.41(0.16-1.03)	0.54(0.18-1.57)	0.27
Total cardiovascular disease (n)	770	548	423	326	297	
Age, sex, energy-adjusted HR	1.0	0.88(0.79-0.98)	0.87(0.77-0.98)	0.84(0.74-0.96)	0.91(0.79-1.04)	0.12
Multivariable HR (95%CI)	1.0	0.96(0.85-1.09)	0.95(0.82-1.10)	0.89(0.75-1.06)	0.86(0.70-1.06)	0.12

Multivariable model includes age, sex, energy intake, cohort, cigarette smoking status, alcohol intake, body mass index, sports at leisure time, walking and standing time, perceived mental stress, energy-adjusted dietary intakes of carbohydrate, protein, cholesterol, vegetables, fruit, and calcium.

†SFA intake was energy-adjusted by nutrient residual model.

Table S-3. Age and energy-adjusted and multivariate adjusted hazard ratios and 95% confidence intervals of incident cardiovascular outcomes according to quintiles of saturated fatty acids intake, JPHC Study, 1993-2008, women.

	Women					
	Quintiles of SFA intake (g/day)†					
	Q1	Q2	Q3	Q4	Q5	Trend p
Median intake, g/d	9.6	13.4	16.3	19.4	24.9	
Person-years	56,933	82,751	104,718	121,226	130,205	
Total stroke (n)	195	239	265	295	328	
Age, sex, energy-adjusted HR	1.0	0.93(0.77-1.13)	0.86(0.71-1.03)	0.85(0.71-1.03)	0.92(0.77-1.11)	0.23
Multivariable HR (95%CI)	1.0	0.95(0.77-1.17)	0.84(0.67-1.06)	0.77(0.60-1.00)	0.72(0.53-0.97)	0.02
Intraparenchymal hemorrhage (n)	60	66	76	96	94	
Age, sex, energy-adjusted HR	1.0	0.82(0.58-1.16)	0.77(0.55-1.09)	0.87(0.63-1.21)	0.82(0.59-1.15)	0.38
Multivariable HR (95%CI)	1.0	0.86(0.58-1.26)	0.73(0.47-1.12)	0.70(0.44-1.13)	0.58(0.33-1.00)	0.05
Deep intraparenchymal hemorrhage	45	48	54	73	67	
Age, sex, energy-adjusted HR	1.0	0.79(0.52-1.19)	0.73(0.49-1.08)	0.87(0.60-1.27)	0.77(0.53-1.14)	0.35
Multivariable HR (95%CI)	1.0	0.75(0.48-1.18)	0.60(0.36-0.98)	0.62(0.36-1.07)	0.47(0.25-0.90)	0.03
Lobar intraparenchymal hemorrhage	13	17	21	21	22	
Age, sex, energy-adjusted HR	1.0	1.00(0.49-2.07)	1.03(0.51-2.06)	0.92(0.46-1.85)	0.94(0.47-1.88)	0.78
Multivariable HR (95%CI)	1.0	1.35(0.61-3.02)	1.38(0.57-3.33)	1.04(0.39-2.82)	0.92(0.29-2.85)	0.75
Subarachnoid hemorrhage (n)	26	40	39	57	62	
Age, sex, energy-adjusted HR	1.0	1.08(0.66-1.77)	0.84(0.51-1.39)	1.08(0.68-1.72)	1.11(0.70-1.76)	0.69
Multivariable HR (95%CI)	1.0	1.00(0.59-1.70)	0.75(0.41-1.36)	0.88(0.46-1.69)	0.75(0.36-1.59)	0.44
Ischemic stroke (n)	107	131	150	141	172	
Age, sex, energy-adjusted HR	1.0	0.97(0.75-1.26)	0.94(0.73-1.20)	0.80(0.62-1.03)	0.95(0.75-1.22)	0.29
Multivariable HR (95%CI)	1.0	0.99(0.75-1.31)	0.96(0.70-1.31)	0.79(0.55-1.13)	0.82(0.54-1.23)	0.20
Lacunar Infarction (n)	48	69	76	59	81	
Age, sex, energy-adjusted HR	1.0	1.15(0.79-1.66)	1.07(0.74-1.54)	0.75(0.51-1.10)	1.01(0.70-1.45)	0.32
Multivariable HR (95%CI)	1.0	1.22(0.81-1.83)	1.08(0.68-1.71)	0.67(0.39-1.14)	0.75(0.41-1.38)	0.11
Large artery occlusive infarction (n)	28	22	33	28	30	
Age, sex, energy-adjusted HR	1.0	0.61(0.35-1.07)	0.77(0.46-1.27)	0.58(0.34-0.99)	0.61(0.36-1.03)	0.09
Multivariable HR (95%CI)	1.0	0.67(0.36-1.23)	0.91(0.48-1.72)	0.74(0.35-1.59)	0.69(0.28-1.69)	0.56
Embolic infarction (n)	27	35	32	43	51	
Age, sex, energy-adjusted HR	1.0	1.04(0.63-1.73)	0.81(0.48-1.35)	0.99(0.61-1.60)	1.15(0.72-1.85)	0.67
Multivariable HR (95%CI)	1.0	0.98(0.57-1.68)	0.80(0.43-1.49)	1.01(0.52-1.99)	1.09(0.50-2.40)	0.82
Myocardial infarction (n)	25	23	36	38	49	
Age, sex, energy-adjusted HR	1.0	0.75(0.42-1.32)	0.99(0.59-1.66)	0.95(0.57-1.58)	1.20(0.73-1.95)	0.29
Multivariable HR (95%CI)	1.0	0.85(0.46-1.57)	1.14(0.60-2.18)	1.01(0.49-2.08)	1.18(0.51-2.69)	0.62
Sudden cardiac death (n)	7	6	5	8	4	
Age, sex, energy-adjusted HR	1.0	0.70(0.24-2.11)	0.50(0.16-1.60)	0.73(0.26-2.04)	0.36(0.10-1.25)	0.15
Multivariable HR (95%CI)	1.0	0.46(0.14-1.55)	0.25(0.06-1.04)	0.29(0.06-1.28)	0.14(0.02-0.97)	0.06
Total cardiovascular disease (n)	226	264	301	338	374	
Age, sex, energy-adjusted HR	1.0	0.90(0.75-1.07)	0.85(0.71-1.01)	0.86(0.72-1.02)	0.92(0.78-1.09)	0.27
Multivariable HR (95%CI)	1.0	0.91(0.75-1.10)	0.83(0.67-1.03)	0.77(0.60-0.98)	0.72(0.54-0.95)	0.01

Multivariable model includes age, sex, energy intake, cohort, cigarette smoking status, alcohol intake, body mass index, sports at leisure time, walking and standing time, perceived mental stress, energy-adjusted dietary intakes of carbohydrate, protein, cholesterol, vegetables, fruit, and calcium.

†SFA intake was energy-adjusted by nutrient residual model.