Dietary intake of saturated fatty acids and mortality from cardiovascular disease in Japanese: the Japan Collaborative Cohort Study for Evaluation of Cancer Risk Study[1–3]

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ABSTRACT

Background: Prospective epidemiologic studies have generated mixed results regarding the association between saturated fatty acid (SFA) intake and risk of ischemic heart disease (IHD) and stroke. These associations have not been extensively studied in Asians.

Objective: The aim of this study was to test the hypothesis that SFA intake is associated with the risk of cardiovascular disease mortality in Japanese whose average SFA intake is low.

Design: The Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC Study) comprised 58,453 Japanese men and women who completed a food-frequency questionnaire. Participants were aged 40–79 y at baseline (1988–1990) and were followed up for 14.1 y. Associations of energy-adjusted SFA intake with mortality from stroke (intraparenchymal and subarachnoid hemorrhages and ischemic stroke) and heart diseases (IHD, cardiac arrest, and heart failure) were examined after adjustment for age, sex, and cardiovascular disease risk and dietary factors.

Results: We observed inverse associations of SFA intake with mortality from total stroke [n = 976; multivariable hazard ratio (95% CI) for highest compared with lowest quintiles: 0.69 (0.53, 0.89); P for trend = 0.004], intraparenchymal hemorrhage [n = 224; 0.48 (0.27, 0.85); P for trend = 0.03], and ischemic stroke [n = 321; 0.58 (0.37, 0.90); P for trend = 0.01]. No multivariable-adjusted associations were observed between SFA and mortality from subarachnoid hemorrhage [n = 153; 0.91 (0.46, 1.80); P for trend = 0.47] and heart disease [n = 836; 0.89 (0.68, 1.15); P for trend = 0.59].

Conclusion: SFA intake was inversely associated with mortality from total stroke, including intraparenchymal hemorrhage and ischemic stroke subtypes, in this Japanese cohort. *Am J Clin Nutr* doi: 10.3945/ajcn.2009.29146.

INTRODUCTION

A few, but not all, studies have documented an increased risk of ischemic heart disease (IHD) with intake of saturated fatty acids (SFAs) since the Seven Countries Study showed an ecologic association several decades ago (1). SFA intake is strongly correlated with blood cholesterol concentrations (2), and high blood cholesterol is a strong risk factor for IHD (3). Nonetheless, the association between SFA intake and IHD has been controversial. SFA intake has been shown to be positively associated with the risk of IHD (4, 5), and replacing SFA intake with polyunsaturated fatty acid (PUFA) intake was associated with a lower risk of IHD (6). SFA intake, however, was inversely associated with the progression of coronary atherosclerosis (7). A recent meta-analyses of cohort studies did not support an adverse effect of SFA intake on risk of IHD (8, 9).

An association of SFA intake with ischemic stroke has been less clear (10–14), even though ischemic stroke is considered an atherosclerotic disease in Western societies. This is probably because nonatherosclerotic pathophysiologic pathways, such as arteriolosclerosis, are also involved in the etiology of ischemic stroke, especially lacunar stroke in perforator areas (15). Moreover, SFA intakes (11, 16) and blood total and LDL-cholesterol concentrations (3, 17–19) have been inversely associated with the incidence of intraparenchymal hemorrhage because of its nonatherosclerotic etiology (15).

SFA intake increases blood concentrations of HDL cholesterol as well as of total and LDL cholesterols; thus, the net effect on cardiovascular outcomes could be different with that of total or

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LDL cholesterol alone. In this context, we sought to examine the association between SFA intake and mortality from stroke in a Japanese cohort. Our a priori hypothesis was that a low intake of SFAs is associated with an increased risk of mortality from stroke, primarily intraparenchymal hemorrhage, in this Japanese sample. We also hypothesized that the association of SFA intake with mortality from heart diseases (IHD, cardiac arrest, and heart failure) would be null, because the distribution of SFA intake among the Japanese is far lower than that among Americans (11, 16).

SUBJECTS AND METHODS

Study cohort

The Japan Collaborative Cohort Study for Evaluation of Cancer Risk Sponsored by Ministry of Education, Culture, Sports, Science and Technology of Japan (JACC Study) is an ongoing cohort study that comprised a nationwide community-based sample of 110,792 persons (46,465 men and 64,327 women) aged 40–79 y during the baseline period (1988–1990), from 45 communities of Japan, as described elsewhere in detail (20). Participants completed self-administered questionnaires about their lifestyles and medical histories of previous cardiovascular disease or cancer. The subjects, measurements, and statistical analyses were basically the same as in a recent JACC publication (21). Briefly, we excluded persons who reported a history of heart disease, stroke, or cancer at baseline and those with incomplete answers for the foods making a major contribution to SFA intake in the dietary questionnaire. Participants from 11 communities were also excluded because the complete version of the food-frequency questionnaire (FFQ) was not distributed in these communities. As a result, we included 23,024 men and 35,429 women from 34 communities. Informed consent was obtained before participants completed the questionnaire or sometimes from community leaders instead of individuals, because this had been a common practice for informed consent in Japan at that time. The JACC Study protocol was approved by the institutional review board of the University of Tsukuba and the Osaka University School of Medicine.

Mortality surveillance

In each community, investigators conducted a systematic review of death certificates through the end of 2003, except for 3 communities where the follow-up had ended in 1999. In Japan, registration of death is legally required and is believed to be followed across Japan. Thus, all deaths that occurred in the cohort were ascertained by death certificates from a public health center, except for subjects who died after they had moved from their original community, in which case the subject was censored. We used the underlying cause of death coded with the *International Statistical Classification of Diseases and Related Health Problems–10th Revision* (ICD-10) (22) to identify mortality endpoints: I60-I69 for total stroke, I60 for subarachnoid hemorrhage, I61 for intraparenchymal hemorrhage, I63 for ischemic stroke, I20-I25 for IHD, I21 for myocardial infarction, I46-49 for cardiac arrest, I50 for heart failure, and I00-I99 for total cardiovascular disease. The date of moving from the community was verified by population-register sheets. Four percent of participants (n = 2472) moved from their original communities during follow-up.

Baseline questionnaire

The FFQ included 33 food items and 5 choices for frequency of intake offered for each item (23). The amount of SFA that each food item contained was estimated based on the *Japan Food Table, fourth version*. The intake of SFA was then calculated by multiplying the frequency scores by the estimated SFA intake from each food and summing across all 33 items as validated previously (23). Intakes of SFA and of vegetables, fruit, ω-3 (n−3) and ω-6 (n−6) PUFAs, and cholesterol were adjusted for energy intake by using the nutrient residual model (24). The quintiles of energy-adjusted SFA intake were 1.6 to <6.9, 6.9 to <8.5, 8.5 to <9.8, 9.8 to <11.3, and 11.3–25.3 g/d and were underestimated by 36.7% according to the validation study that compared them with dietary records in a subsample (n = 85, mostly female; median: 9.5 compared with 15.0 g/d) (23). Spearman's correlation coefficient between SFAs derived from the FFQ and dietary records was 0.50 (23).

Statistical analyses

The mortality rates of each outcome were calculated according to quintiles of energy-adjusted SFA intake. Hazard ratios (HRs) with 95% CIs were calculated after adjustment for age, sex, and other potential risk factors with Cox proportional hazards models. The risk factors included baseline body mass index, history of hypertension or diabetes, smoking status, alcohol intake, perceived mental stress, walking, sports, educational level, total energy intake, and energy-adjusted intakes of cholesterol, ω-3 and ω-6 PUFAs, vegetables, and fruit as in a previous publication (23). Because animal protein intake was highly correlated with SFA intake (Spearman's r = 0.73), we also present HRs with further adjustment for energy-adjusted animal protein intake. The linear trend of HRs across the quintiles was tested by an ordinal variable for successive quintiles. Multiplicative interactions with sex were tested by using a cross-product term.

As supplemental analyses, we ran substitution models to examine whether replacing SFA with PUFA, monounsaturated fatty acid (MUFA), or carbohydrate would still be associated with an increased risk of mortalities from IHD and stroke. The model simultaneously included total energy (kcal/d), protein (% of energy), PUFA (% of energy), MUFA (% of energy), carbohydrate (% of energy), alcohol (% of energy), and other cardiovascular disease risk factors.

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 2-tailed, and P values < 0.05 were considered statistically significant.

RESULTS

As shown in **Table 1**, most risk factors at baseline correlated with energy-adjusted SFA intake. During a median follow-up of 58,453 persons for 14.1 y, we documented 976 deaths due to stroke—including 224 intraparenchymal hemorrhages, 153 subarachnoid hemorrhages, and 321 ischemic strokes—and 420 IHDs, 330 myocardial infarctions, 107 cardiac arrests, and 309 heart failures. Because no interactions with sex were observed for the association of SFA intake with any mortality endpoint, we combined men and women for further analyses.

TABLE 1
Baseline cardiovascular disease risk factors and select dietary variables in a cohort of 23,024 men and 35,429 women according to quintile of saturated fatty acid (SFA) intake[1]

	Quintile of SFA intake (g/d)[2]					
	2.5 to <11.0	11.0 to <13.4	13.4 to <15.4	15.4 to <17.9	17.9–40.0	*P* value[3]
Men						
Median SFA intake (g/d)[2]	9.2	12.2	14.4	16.5	20.3	
Number at risk	5076	4573	4194	4157	5024	
Age at baseline (y)[4]	55.2 ± 9.7	55.7 ± 9.8	55.7 ± 9.6	56.5 ± 10.1	56.5 ± 10.3	<0.001
Mean BMI (kg/m^2)	22.7	22.8	22.8	22.6	22.5	<0.001
History of hypertension (%)	22.1	21.3	18.6	17.4	15.3	<0.001
History of diabetes (%)	5.6	5.6	6.3	5.7	7.4	<0.001
Current smoker (%)	60.0	53.8	52.4	51.2	51.6	<0.001
Current drinker (%)	83.1	80.5	76.5	72.8	62.6	<0.001
Sports ≥1 h/wk (%)	26.3	28.7	29.6	34.6	36.9	<0.001
Walking ≥1 h/d (%)	51.1	51.6	50.8	48.2	47.1	<0.001
College or higher education (%)	14.0	16.1	16.9	20.2	24.9	<0.001
High perceived mental stress (%)	22.5	21.9	24.3	25.3	28.2	<0.001
Mean energy intake (kcal/d)	1607	1698	1699	1657	1592	<0.001
Dietary cholesterol (mg/d)	164	226	250	271	302	<0.001
MUFAs (g/d)	6.2	8.5	9.7	10.7	12.4	<0.001
PUFAs (g/d)	6.4	7.9	8.4	8.8	9.2	<0.001
ω-3 PUFAs (g/d)	1.2	1.6	1.7	1.8	1.9	<0.001
ω-6 PUFAs (g/d)	5.1	6.3	6.7	7.0	7.2	<0.001
Animal protein intake (g/d)	17	23	26	29	34	<0.001
Plant protein intake (g/d)	27	30	30	29	28	<0.001
Vegetable intake (g/d)	70	87	95	102	108	<0.001
Fruit intake (g/d)	90	108	125	131	143	<0.001
Women						
Median SFA intake (g/d)[2]	9.4	12.3	14.4	16.5	19.8	
Number at risk	6614	7118	7497	7534	6666	
Age at baseline (y)[4]	58.0 ± 9.9	56.8 ± 9.9	56.2 ± 9.7	55.8 ± 9.6	54.5 ± 9.8	<0.001
Mean BMI (kg/m^2)	23.2	23.1	23.0	22.9	22.6	<0.001
History of hypertension (%)	22.2	20.5	22.0	19.5	18.2	<0.001
History of diabetes (%)	2.9	3.0	3.5	3.6	4.1	<0.001
Current smoker (%)	6.7	4.6	3.7	3.7	5.6	<0.001
Current drinker (%)	23.2	23.7	23.2	23.0	24.4	0.28
Sports ≥1 h/wk (%)	17.5	20.6	23.8	25.2	28.4	<0.001
Walking ≥1 h/d (%)	54.5	53.8	51.3	50.1	48.2	<0.001
College or higher education (%)	7.2	8.6	10.1	11.8	15.7	<0.001
High perceived mental stress (%)	20.1	19.9	20.6	21.8	22.0	0.005
Mean energy intake (kcal/d)	1309	1352	1347	1348	1283	<0.001
Dietary cholesterol (mg/d)	165	223	248	273	287	<0.001
MUFAs (g/d)	6.5	8.7	9.7	10.8	11.9	<0.001
PUFAs (g/d)	6.5	7.8	8.1	8.4	8.2	<0.001
ω-3 PUFAs (g/d)	1.3	1.6	1.7	1.8	1.8	<0.001
ω-6 PUFAs (g/d)	5.2	6.2	6.3	6.6	6.4	<0.001
Animal protein intake (g/d)	17	24	27	30	33	<0.001
Plant protein intake (g/d)	27	27	27	26	24	<0.001
Vegetable intake (g/d)	87	101	109	113	114	<0.001
Fruit intake (g/d)	124	144	152	155	157	<0.001

[1] All values are age-adjusted means or percentages unless otherwise indicated. MUFAs, monounsaturated fatty acids; PUFAs, polyunsaturated fatty acids.
[2] Energy-adjusted values were derived by using a nutrient residual model. Ranges and median values for SFA were divided by an underestimation rate of 63.3%.
[3] *P* values for overall differences between quintiles based on ANCOVA.
[4] Values are unadjusted means ± SDs.

The HRs of death from cardiovascular diseases, according to dietary SFA intake, are shown in **Table 2**. SFA was inversely associated with age- and sex-adjusted risks of total stroke, intraparenchymal hemorrhage, and ischemic stroke. These associations remained statistically significant after further adjustment for potential cardiovascular disease risk factors and nutrients: HR (95% CI) for the highest compared with the lowest quintile = 0.69 (0.53, 0.89) for total stroke, 0.48 (0.27, 0.85) for intraparenchymal hemorrhage, and 0.58 (0.37, 0.90) for ischemic stroke. Mortality from intraparenchymal hemorrhage had the lowest HR for the highest compared with the lowest SFA intake quintile. No associations were observed for subarachnoid hemorrhage [HR (95%

TABLE 2
Multivariate hazard ratios (HRs) (and 95% CIs) for mortality from stroke, ischemic heart disease, cardiac arrest, and heart failure and total cardiovascular disease according to quintiles of saturated fatty acid (SFA) intake in 23,024 men and 35,429 women combined

	Quintile of SFA intake (g/d)[1]					
Mortality endpoint	2.5 to <11.0	11.0 to <13.4	13.4 to <15.4	15.4 to <17.9	17.9–40.0	*P* for trend
Person-years	147,057	148,710	149,314	148,995	145,920	
Total stroke (*n*)	245	213	193	177	148	
Absolute rate[2]	1.67	1.43	1.29	1.19	1.01	
HR (95% CI)[3]						
Model 1[4]	1.0	0.90 (0.75, 1.08)	0.86 (0.71, 1.03)	0.76 (0.63, 0.93)	0.66 (0.53, 0.80)	<0.001
Model 2[5]	1.0	0.90 (0.74, 1.09)	0.89 (0.72, 1.10)	0.80 (0.64, 1.00)	0.69 (0.53, 0.89)	0.004
Intraparenchymal hemorrhage (*n*)	63	48	45	45	23	
Absolute rate[2]	0.43	0.32	0.30	0.30	0.16	
HR (95% CI)						
Model 1	1.0	0.78 (0.54, 1.14)	0.77 (0.52, 1.12)	0.75 (0.51, 1.10)	0.39 (0.24, 0.63)	<0.001
Model 2	1.0	0.87 (0.58, 1.29)	0.89 (0.58, 1.36)	0.90 (0.57, 1.42)	0.48 (0.27, 0.85)	0.03
Subarachnoid hemorrhage (*n*)	29	46	28	30	20	
Absolute rate[2]	0.20	0.31	0.19	0.20	0.14	
HR (95% CI)						
Model 1	1.0	1.59 (1.00, 2.53)	0.98 (0.58, 1.64)	1.05 (0.63, 1.75)	0.77 (0.44, 1.36)	0.14
Model 2	1.0	1.77 (1.08, 2.89)	1.12 (0.64, 1.98)	1.22 (0.68, 2.20)	0.91 (0.46, 1.80)	0.47
Ischemic stroke (*n*)	86	66	64	54	51	
Absolute rate[2]	0.58	0.44	0.43	0.36	0.35	
HR (95% CI)						
Model 1	1.0	0.79 (0.58, 1.09)	0.81 (0.59, 1.13)	0.65 (0.47, 0.92)	0.62 (0.44, 0.88)	0.004
Model 2	1.0	0.74 (0.53, 1.04)	0.79 (0.55, 1.14)	0.63 (0.42, 0.93)	0.58 (0.37, 0.90)	0.01
Ischemic heart disease (*n*)	108	80	79	76	77	
Absolute rate[2]	0.73	0.54	0.53	0.51	0.53	
HR (95% CI)						
Model 1	1.0	0.76 (0.57, 1.02)	0.79 (0.59, 1.06)	0.73 (0.55, 0.99)	0.76 (0.56, 1.01)	0.08
Model 2	1.0	0.83 (0.61, 1.13)	0.93 (0.68, 1.28)	0.89 (0.63, 1.24)	0.93 (0.65, 1.35)	0.86
Myocardial infarction (*n*)	88	65	64	53	60	
Absolute rate[2]	0.60	0.44	0.43	0.36	0.41	
HR (95% CI)						
Model 1	1.0	0.76 (0.55, 1.05)	0.79 (0.57, 1.08)	0.63 (0.45, 0.88)	0.72 (0.52, 1.00)	0.03
Model 2	1.0	0.82 (0.58, 1.14)	0.92 (0.65, 1.31)	0.74 (0.50, 1.10)	0.85 (0.56, 1.29)	0.40
Cardiac arrest (*n*)	29	22	19	21	16	
Absolute rate[2]	0.20	0.15	0.13	0.14	0.11	
HR (95% CI)						
Model 1	1.0	0.77 (0.44, 1.34)	0.71 (0.40, 1.26)	0.74 (0.42, 1.31)	0.59 (0.32, 1.09)	0.12
Model 2	1.0	0.73 (0.41, 1.31)	0.64 (0.34, 1.21)	0.69 (0.36, 1.34)	0.50 (0.23, 1.10)	0.11
Heart failure (*n*)	77	61	46	65	60	
Absolute rate[2]	0.52	0.41	0.31	0.44	0.41	
HR (95% CI)						
Model 1	1.0	0.83 (0.59, 1.16)	0.66 (0.46, 0.95)	0.91 (0.65, 1.26)	0.87 (0.62, 1.22)	0.62
Model 2	1.0	0.88 (0.62, 1.25)	0.75 (0.50, 1.11)	1.01 (0.69, 1.48)	0.99 (0.64, 1.52)	0.83
Total cardiovascular disease (*n*)	507	424	383	392	346	
Absolute rate[2]	3.45	2.85	2.57	2.63	2.37	
HR (95% CI)						
Model 1	1.0	0.86 (0.76, 0.98)	0.82 (0.72, 0.94)	0.82 (0.72, 0.93)	0.74 (0.65, 0.85)	<0.001
Model 2	1.0	0.89 (0.78, 1.02)	0.89 (0.77, 1.03)	0.89 (0.77, 1.04)	0.82 (0.69, 0.97)	0.05

[1] Energy-adjusted values were derived by using a nutrient residual model. Ranges and median values for SFA were divided by an underestimation rate of 63.3%.

[2] Absolute rate is presented per 1000 person-years.

[3] HRs for each outcome were calculated by using a Cox proportional hazards model.

[4] Adjusted for age and sex.

[5] Adjusted as for model 1 and for a history of hypertension and diabetes, smoking status, alcohol consumption, BMI, mental stress, walking, sports, educational level, and dietary intakes of total energy, cholesterol, ω-3 and ω-6 polyunsaturated fatty acids, vegetables, and fruit.

CI) for the highest compared with the lowest quintile = 0.91 (0.46, 1.80), *P* for trend = 0.47] and heart diseases [IHD, cardiac arrest and heart failure pooled, HR = 0.89 (0.68, 1.15), *P* for trend = 0.59].

Further adjustment for animal protein did not change the stroke results materially: HRs for the highest compared with the lowest quintile = 0.67 (0.49, 0.92), *P* for trend = 0.01 for total stroke; 0.45 (0.22, 0.89), *P* for trend = 0.048 for intraparenchymal

hemorrhage; and 0.56 (0.32, 0.97), *P* for trend = 0.046 for ischemic stroke (data not shown in the tables).

SFA intake was consistently inversely associated with stroke mortality in substitution models; replacement of SFA by increasing MUFA, PUFA, or carbohydrate intakes was significantly or nonsignificantly positively associated with stroke mortality. The HRs of each nutrient (MUFA, PUFA, or carbohydrate) for which 1% of energy was substituted for SFA were as follows: 1.06 (0.89, 1.27), 1.19 (1.09, 1.30), and 1.05 (0.98, 1.13), respectively. We found no protective effects on IHD when SFA was replaced with MUFA, PUFA, or carbohydrates; the respective HRs were 0.95 (0.74, 1.23), 1.02 (0.89, 1.16), and 1.00 (0.91, 1.11) (data not shown in the tables).

DISCUSSION

In this large community-based prospective cohort study, SFA intake was inversely associated with mortality from stroke. This inverse association was similarly observed for intraparenchymal hemorrhage and ischemic stroke, but not for subarachnoid hemorrhage. Indeed, decreasing SFA intake by increasing PUFA was significantly positively associated with stroke mortality in the JACC Study. It is consistent with the previous JACC finding that dietary intake of PUFA was not associated with stroke mortality (21).

It is well known that a greater intake of SFA increases the blood total cholesterol concentration (2), and blood total and LDL-cholesterol concentrations are inversely associated with risk of intraparenchymal hemorrhage (3, 17–19, 25–27). Inverse associations of dietary SFA intake with intraparenchymal hemorrhage have been consistently observed in previous studies of Japanese (16) and Americans (11). Therefore, an inverse association between SFA intake and mortality from intraparenchymal hemorrhage in this study was not surprising.

In contrast, reports on the association of SFA intake or blood cholesterol with risk of ischemic stroke have been less consistent. Whereas several (3, 18, 19, 28, 29), but not all (25, 27, 30–32), studies have found positive associations between serum total or LDL cholesterol and ischemic stroke, dietary studies have shown significantly (10) or nonsignificantly (13) inverse or null (11, 12, 14) associations between SFA and ischemic stroke. Notably, a recent Japanese study reported a significant positive association of serum LDL cholesterol with large-artery occlusive infarction, but none with lacunar infarction and even an inverse association with cardioembolic infarction (33). A pathologic study of Japanese showed that serum blood cholesterol concentrations were high among fatal cases of large-artery occlusive stroke decedents, intermediate among lacunar stroke decedents, and low among intraparenchymal hemorrhage decedents (15). Ischemic stroke is considered to be an atherosclerotic disease because a large proportion of cases are large-artery occlusive infarctions in Western countries; however, in Asia, most ischemic strokes are lacular infarctions in perforator areas. We speculated that SFA may play different roles in intracranial large arteries as opposed to intracranial small vessels, and hemorrhage and ischemia in perforator areas may have a common pathophysiologic etiology, that is, very low blood cholesterol concentrations lead to angionecrosis in intracerebral arterioles through disappearance of medial smooth muscle cells and increased fragility of the vascular wall (15). Low intakes of SFAs may lower blood HDL cholesterol (34) and total and LDL cholesterols, which could partly explain the inverse association between SFA intake and stroke. This also explains in part the null association between SFA intake and IHD because the net effect of these lipids on risk of IHD could be cancelled. Adverse effects of SFAs other than on LDL cholesterol (eg, lipoproteins, blood pressure, insulin sensitivity, thrombosis, inflammation, or vascular function) have not yet been conclusive (35).

The strengths of this study include its prospective cohort design, a reasonable number of events for statistical power, multiple adjustments for multiple relevant confounders, and evaluation of an important but understudied population (ie, Japanese). The limitations of this study warrant discussion. First, we used an FFQ with only 33 food items to identify SFA intake and death certificates to define events. Diet misclassification will attenuate findings toward the null in this prospective study; outcome misclassification would also attenuate findings toward the null, because this misclassification was unlikely to be related to baseline SFA intake. Second, the exclusion of missing dietary information may affect generalizability, although it may not greatly affect the present results as discussed previously (21). Third, the possibility of residual confounding by unmeasured or incompletely adjusted stroke risk factors also applies to this study. Fourth, we did not include MUFA intake in the multivariate models because it was highly correlated with both SFA and animal protein intakes (Spearman's r = 0.82 and 0.85, respectively). Nevertheless, when we included energy-adjusted MUFA intakes in model 2, the association between SFA and total stroke was attenuated to some extent, probably because of multicolinearity [HR for the highest compared with the lowest SFA quintiles: 0.75 (95% CI: 0.53, 1.05), *P* for trend = 0.10]. Because MUFAs did not show a strong association in this model (*P* for trend =0.37), we believe that our findings were mainly explained by SFA rather than by MUFA intakes. Last, this study was conducted among Japanese, so extrapolation to other populations should be made with caution.

Assuming that the inverse association between SFA and stroke mortality is causal, it would nevertheless be inappropriate to recommend an increased consumption of SFA-containing products to the general Japanese population, because it might increase population levels of total cholesterol and the risk of IHD. Replacing SFA with PUFA had no benefit on the prevention of IHD, which contrasts with a recent pooling project of Americans and Europeans (6). Application of discrepant results to public health practice must be cautious. We believe that this discrepancy could be explained in part by a low distribution of SFA intake among Japanese. The median SFA intake, albeit underestimated by ≈37%, was very low (9.4 g/d). It is well known that the SFA intake is far lower in Japan than in Western countries; for example, the median intake of SFAs for the highest quartile of a Japanese rural population (1970–1980s) was 17 g/d (16) lower than that for the lowest quartile of intake in the Nurses' Health Study in 1980 (20 g/d) (11). These findings indicated almost no overlap of SFA intakes between the 2 populations.

In conclusion, we found an inverse association of dietary SFA intake with stroke mortality, for both ischemic stroke and intraparenchymal hemorrhage, in this Japanese population with low SFA intakes.

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The authors' responsibilities were as follows—KY and HI: developed the study hypothesis; KY: conducted the analysis and drafted the manuscript; and HI, HY, NT, CD, SK, AY, YI, and AT: critically revised the manuscript. None of the authors had a personal or financial conflict of interest.

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APPENDIX A

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