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Review

High Dietary Saturated Fat is Associated with a Low Risk of Intracerebral Hemorrhage and Ischemic Stroke in Japanese but not in Non-Japanese: A Review and Meta-Analysis of Prospective Cohort Studies

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***Aim*: The associations between dietary saturated fatty acids and the risks of stroke subtypes in cohort studies were examined by a meta-analysis of separate ethnic Japanese and non-Japanese cohorts, and causes of their difference were elucidated.**
***Method*: Log hazard ratio (HR) with 95% confidence interval (CI) of the highest versus the lowest saturated fat intake from cohort studies were weighed by an inverse variance method to combine HRs.**
***Results*: Five studies of intracerebral hemorrhage and 11 studies/comparisons of ischemic stroke were selected. A meta-analysis of intracerebral hemorrhage excluding subarachnoid hemorrhage showed a strong inverse association in Japanese ($n=3$, HR=0.55, 95% CI 0.32−0.94) but not in non-Japanese ($n=2$, HR=0.98, 95% CI 0.62−1.53). A meta-analysis of ischemic stroke showed a mild inverse association in Japanese ($n=4$, HR=0.82, 95% CI 0.71−0.93) but not in non-Japanese ($n=7$, HR=0.93, 95% CI 0.84−1.03). The effect size of saturated fat in reducing the risk of stroke in Japanese was stronger for intracerebral hemorrhage (45% reduction) than for ischemic stroke (18% reduction).**
***Conclusions*: In Japanese but not in non-Japanese, a diet high in saturated fat is associated with a low risk of intracerebral hemorrhage and ischemic stroke. This may be due to differences in the range of intake of saturated fat, genetic susceptibility, incidence of lacunar infarction, and/or confounding factors such as dietary proteins. An intervention study targeting Japanese will be required to verify the causality.**

Key words: Saturated fatty acid, Hemorrhagic stroke, Brain infarction, Relative risk

Introduction

The association of the intake of saturated fat (saturated fatty acids) with the risk of stroke has been a major concern in Japan[1)] because most cohort studies conducted in Japan showed an inverse association between the intake of saturated fat and the incidence of stroke or its mortality[2-7)], which is opposite to the guidelines that recommend a reduction in saturated fat intake to prevent cardiovascular disease[8)]. Three previous meta-analyses of cohort studies were conducted to examine the association between the intake of saturated fat and the risk of stroke[9-11)]. The first meta-analysis conducted in 2010, in which ischemic and hemorrhagic strokes were pooled, showed no significant association between the intake of saturated fat and the risk of stroke (n [studies]=8, relative risk [RR]=0.81, 95% confidence interval [CI] 0.62−1.05)[9)]. The second meta-analysis conducted in 2015, in which only ischemic strokes were pooled, also showed no significant association between the intake of saturated fat and the risk of ischemic stroke (n [studies/comparisons]=12/15, RR=1.02: 95% CI 0.90−1.15)[10)]. However, the third meta-analysis conducted in 2016, in

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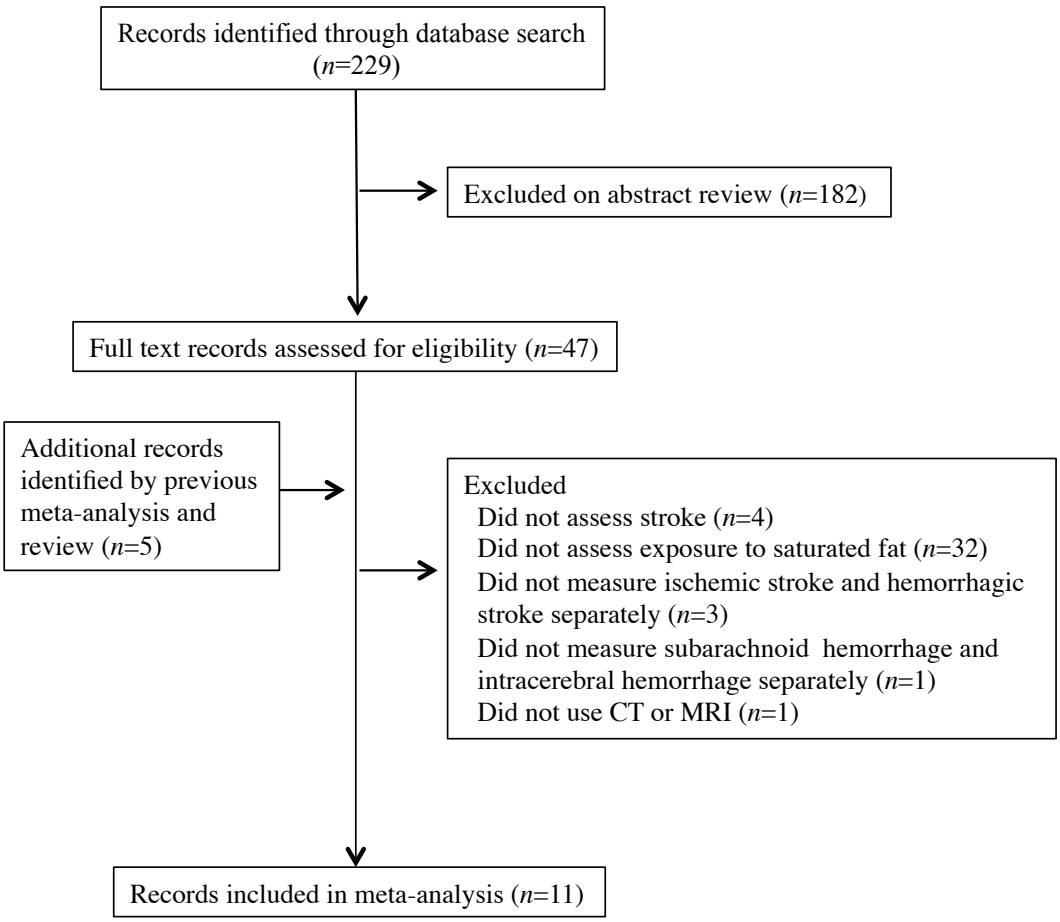


Fig. 1. Flow chart of the selection of the studies.

which ischemic and hemorrhagic strokes were pooled, showed that a high intake of saturated fat was significantly associated with a reduction in stroke morbidity and mortality (*n* [studies/comparisons] = 15/16, RR = 0.89, 95% CI 0.82−0.96)[11]. Furthermore, many confounding factors in these studies, such as stroke subtypes, ethnicities, sex, amount of fat intake, duration of observations, and body mass index (BMI), affected this association[11]. In a subgroup analysis of stroke type, the intake of saturated fat showed a stronger inverse association with the risk of hemorrhagic stroke (*n* [studies] = 6, RR = 0.76, 95% CI 0.63−0.93) than with ischemic stroke (*n* [studies] = 10, RR = 0.90, 95% CI 0.82−0.99).

Most strokes were classified as subarachnoid hemorrhage (ICD-10 code I60), intracerebral hemorrhage (ICD-10 code I61), thrombotic infarction (ICD-10 code I63.0 or I63.3), embolic infarction (ICD-10 code I63.1 or I63.4), or lacunar infarction (ICD-10 code G46)[12, 13]. Each subtype of stroke may have a different etiology. Thus, lifestyle—including dietary habits—may affect the incidence of each stroke subtype differently. Indeed, in the previous studies in which subarachnoid hemorrhage and intracerebral hemorrhage were analyzed separately, the intake of saturated fat was inversely associated with mortality in patients with intraparenchymal hemorrhage (*n* [patients] = 224, hazard ratio [HR] = 0.48, 95% CI 0.27−0.85) but not with that of subarachnoid hemorrhage (*n* [patients] = 153, HR = 0.91, 95% CI 0.46−1.80)[6]. Another study showed that the intake of saturated fat was inversely associated with the incidence of intraparenchymal hemorrhage (*n* [patients] = 894, HR = 0.61, 95% CI 0.43−0.86) but not with that of subarachnoid hemorrhage (*n* [patients] = 348, HR = 0.87, 95% CI 0.50−1.52)[7]. However, in the previous meta-analyses[9, 11], hemorrhagic stroke included cases of subarachnoid hemorrhage and intracerebral hemorrhage, and ischemic stroke (or cerebral infarction) included cases of thrombosis and embolism, by which the associations between each stroke subtypes with saturated fat may become unclear.

In the present meta-analysis, we analyzed the effects of dietary saturated fats on the incidence of intracerebral (intraparenchymal) hemorrhage exclud-

Table 1. Basic characteristics of included studies

	Source	Country, region/cohort	Followup, yrs	No. (women, %)	Age, yrs	Mean or median BMI	Mean or median saturated fat intake (g/d)
1	Seino, 1997	Japan, Shibata Study	15.5	2283 (58%)	Over 40	21.5	11
2	Gillman, 1997	USA, Framingham Heart Study	20	832 (0%)	45-65	26.9	43.8
3	Iso, 2001	USA, Nurses' Health Study (NHS)	14	85764 (100%)	34-59	24.0	28
4	He, 2003	USA, Health Professional Follow Up Study (HPFS)	14	43732 (0%)	40-75	24.9	24
5	Iso, 2003	Japan, Circulatory Risk in Communities Study (CIRCS)	14	4775 (52%)	40-69	23.8	10.9
6	Sauvaget, 2004	Japan, Hiroshima and Nagasaki/Life Span Study (LSS)	14	3731 (63%)	35-89	22.3	12
7	Yamagishi, 2010	Japan, JACC study	14	58453 (61%)	40-79	22.8	14.4
8	Wallstrom, 2012	Sweden, Malmo Diet and Cancer Cohort (MDC)	13.5	8139 (0%) 12535 (100%)	44-73	26.1 (men) 25.4 (women)	16.8 (men) 16.7 (women)
9	Larsson, 2012	Sweden, Swedish Mammography Cohort (SMC)	10.4	34670 (100%)	49-83	25.0	26.9
10	Yaemsiri, 2012	USA, Women's Health Initiative Observational Study (WHI-OS)	7.6	87025 (100%)	50-79	27.2	14.5
11	Yamagishi, 2013	Japan, JPHC study	11.1	81931 (54%)	40-69	23.6	16.3

BMI, body mass index; CT, computed tomography; MRI, magnetic resonance imaging; TIA, transient ischemic attack

ing subarachnoid hemorrhage, and their confounding factors were discussed. However, there was only one cohort study of ischemic stroke in which cases of thrombosis and embolism were separately examined[7] because it might be difficult to differentiate thrombosis from embolism by computed tomography (CT) or magnetic resonance imaging (MRI). Therefore, as a reference for intracerebral hemorrhage, the association of the intake of saturated fat with the risk of ischemic stroke including cases of thrombosis and embolism was also compared.

Methods

Data Sources and Searches

The PubMed database was searched for studies published before March 3, 2016. The computer-based searches were conducted by combining search terms related to saturated fatty acids ("fat" OR "dietary fat" OR "saturated fatty acids"), diet ("diet" OR "intake"), stroke ("stroke"), and cohort study ("cohort" OR "prospective study"), and 229 articles were identified (**Fig. 1**). The reference lists of the retrieved studies and review articles were manually searched to identify any eligible

(Cont Table 1)

	Source	No. of patients, outcome	Methods of diagnosis
1	Seino, 1997	75, Incidence of cerebral infarction (exclude TIA)	Clinical images and CT
2	Gillman, 1997	61, Incidence of ischemic stroke (including atherothrombotic brain infarction and embolus; excluding TIA) 14, Incidence of hemorrhagic stroke (including subarachnoid and intracerebral)	Clinical images and CT
3	Iso, 2001	385, Incidence of ischemic stroke (including thrombotic and embolic; excluding TIA) 74, Incidence of intraparenchymal hemorrhage	Clinical images, CT, MRI, and autopsy
4	He, 2003	455, Incidence of ischemic stroke (including embolism and thrombosis) 125, Incidence of hemorrhagic stroke (including subarachnoid and intracerebral)	Criteria of the National Survey of Stroke
5	Iso, 2003	68, Incidence of intraparenchymal hemorrhage	85% were confirmed by CT and MRI
6	Sauvaget, 2004	60, Death from cerebral infarction (ICD-10 I63, I69.3)	Death certificates
7	Yamagishi, 2010	224, Death from intraparenchymal hemorrhage (ICD-10 I61) 321, Death from ischemic stroke (ICD-10 I63)	Death certificates
8	Wallstrom, 2012	401 (men), 354 (women), Incidence of ischemic stroke (ICD-10 I63 or I64)	CT, MRI, and autopsy
9	Larsson, 2012	1310, Incidence of cerebral infarction (ICD-10 I63) 233, Incidence of hemorrhagic stroke (ICD-10 I61)	Swedish hospital discharge registry and Swedish death registry
10	Yaemsiri, 2012	1049, Incidence of ischemic stroke (excluding TIA)	Criteria of the Trial of ORG 10172 Acute Stroke Trial (TOAST). Over 95% of cases were classified by brain imaging.
11	Yamagishi, 2013	894, Incidence of ischemic stroke (including large-artery thrombotic, lacunar, and embolic; excluding TIA) 1939, Incidence of intraparenchymal hemorrhage (excluding subarachnoid)	Criteria of the National Survey of Stroke. CT and MRI were available for 98% of registered stroke events.

BMI, body mass index; CT, computed tomography; MRI, magnetic resonance imaging; TIA, transient ischemic attack

resources. We included studies that met the following criteria: (1) a prospective cohort design was used to examine the association between the intake of saturated fats and the incidence or death of intracerebral hemorrhage or ischemic stroke (or cerebral infarction); and (2) CT, MRI, or autopsy findings were used for diagnosis. Studies on mortality in which stroke was classified by death certificate were also included if they were conducted since the 1980s when CT or MRI became available[14]. Both authors (M.M. and O.E.) independently performed the selection of papers.

Data Synthesis and Analysis

To calculate the risk of intracerebral hemorrhagic or ischemic stroke morbidity and mortality (the primary outcome), the log HRs of the highest versus the lowest values for cohort studies were combined by an inverse variance method. Most studies were conducted by Cox proportional hazards regression analysis, and thus the HR was used instead of RR. The odds ratios in one study[15] were assumed to approximate the same measure of HR. When effect size was expressed by a per-1-SD change, the log risk estimates were transformed assuming a normal distribution, with the comparison between the top and bottom thirds being equal to 2.18 times the log HR for a 1-SD increase[16]. SEs of the log HRs were also calculated using published confidence limits, and we transformed the SEs in the same way. These log conversions were conducted on data from the Framingham Heart Study[17]. Studies that reported HRs with different degrees of adjustment for other risk factors required the most adjustment in their estimates.

A sensitivity analysis (secondary outcome) was

Table 2. Detailed characteristics of the included studies

	Source	Method	Outcome measures	Adjustment factors
1	Seino, 1997	FFQ	Hazard ratio by Cox proportional hazard regression model	Sex, age, diastolic blood pressure, atrial fibrillation
2	Gillman, 1997	24-hour recall	Cumulative incidence rate (per 1000) by Mantel-Haenszel methods and relative risk by Cox proportional hazard regression model	Age, systolic blood pressure, cigarette smoking, glucose intolerance, BMI, physical activity index, left ventricular hypertrophy, and intake of energy, alcohol, and fruits and vegetables
3	Iso, 2001	FFQ	Relative risk by logistic regression model	Age, smoking status, time interval, BMI, alcohol intake, menopausal status and postmenopausal hormone use, vigorous exercise, usual aspirin use, multivitamin use, vitamin E use, n-3 fatty acid intake, calcium intake, and histories of hypertension, diabetes, and high cholesterol levels, and total energy intake
4	He, 2003	FFQ	Relative risk by Mantel-Haenszel methods and Cox proportional hazard regression model	BMI, physical activity, history of hypertension, smoking status, aspirin use, multivitamin use, consumption of alcohol, potassium, fiber, vitamin E, fruit and vegetables, total energy intake, hypercholesterolemia, polyunsaturated fatty acids, mono-unsaturated fatty acids, and trans fatty acids
5	Iso, 2003	24-hour recall	Relative risk by Cox proportional hazard regression model	Age, sex, quartiles of total energy intake, BMI, hypertension category, diabetes, serum total cholesterol, smoking status, ethanol intake, and menopausal status
6	Sauvaget, 2004	24-hour recall	Relative hazard by Cox proportional hazard regression model	Sex, age, radiation dose, city, BMI, smoking status, alcohol habits, and medical history of hypertension and diabetes
7	Yamagishi, 2010	FFQ	Hazard ratio by Cox proportional hazard regression model	Age, sex, history of hypertension and diabetes, smoking status, alcohol consumption, BMI, mental stress, walking, sports, educational level, and dietary intakes of total energy, cholesterol, n-3 and n-6 polyunsaturated fatty acids, vegetables, and fruit
8	Wallstrom, 2012	FFQ	Hazard ratio by Cox proportional hazard regression model	Age, method version, total energy intake, season, BMI class, smoking category, education, alcohol category, systolic blood pressure, antihypertensive treatment, antihyperlipidemic treatment, leisure time physical activity (quartiles), and quintiles of energy-adjusted dietary fiber
9	Larsson, 2012	FFQ	Relative risk by Cox proportional hazard regression model	Age, smoking status and pack-years of smoking, education, BMI, total physical activity, history of hypertension, history of diabetes, aspirin use, family history of myocardial infarction, intakes of alcohol, protein, and dietary fiber, intakes of total fat, and quintiles of cholesterol
10	Yaemsiri, 2012	FFQ	Hazard ratio by Cox proportional hazard regression model	Age, race, education, family income, years as a regular smoker, hormone replacement therapy use, total MET-hours per week, alcohol intake, history of coronary disease, history of atrial fibrillation, history of diabetes, aspirin use, use of antihypertensive medication, use of cholesterol-lowering medication, BMI, systolic blood pressure, and total energy intake
11	Yamagishi, 2013	FFQ	Hazard ratio by Cox proportional hazard regression model	Age, sex, energy intake, cohort, cigarette smoking status, alcohol intake, BMI, sports during leisure time, walking and standing times, perceived mental stress, energy-adjusted dietary intakes of carbohydrate, protein, cholesterol, vegetables, fruit, and calcium

BMI, body mass index; FFQ, food-frequency questionnaire

Table 3. Hazard ratio and 95% CI of the risk of intracerebral hemorrhage by intake of saturated fat for race, sex, BMI, mean saturated fat intake, and followup duration

Outcome	Studies (n)	HR	95% CI		*P* value	*I*-squared
Hemorrhagic stroke	5	0.69	0.48	1.00	0.048	58.1
Race						
Japanese	3	0.55	0.32	0.94	0.03	68.6
Non-Japanese	2	0.98	0.62	1.53	0.91	37.9
Sex						
Women	2	0.98	0.62	1.53	0.91	37.9
Men	0					
Mixed	3 (all Japanese)	0.55	0.32	0.94	0.03	68.6
BMI						
< 24	3 (all Japanese)	0.55	0.32	0.94	0.03	68.6
≥ 24	2	0.98	0.63	1.53	0.91	37.9
Mean saturated fat intake						
< 25 g/d	3 (all Japanese)	0.55	0.32	0.94	0.03	68.6
≥ 25 g/d	2	0.98	0.63	1.53	0.91	37.9
Follow-up duration						
< 14 years	2 (1 Japanese)	0.93	0.58	1.45	0.74	53.5
≥ 14 years	3 (2 Japanese)	0.51	0.35	0.75	0.001	24.1

BMI, body mass index; CI, confidence interval; HR, hazard ratio

conducted to detect any potential bias including that for ethnicity (Japanese, non-Japanese), sex, BMI, amount of saturated fat intake, and follow-up duration. Publication bias was assessed using funnel plots and Egger's test. A quantitative measure of inconsistency across individual studies was assessed by the *I*-square statistic[18]. A small *I*-square value is interpreted as meaning that the effect size is comparable across studies, whereas a large *I*-square value is interpreted as meaning that the effect size varies substantively across studies[19].

Because our goal was to report on the dispersion of effects as function of a covariate (we assumed that the true effect size might be different from study to study by the effect of confounders), the random-effects model was used. However, when the number of samples was two, a fixed-effect model was used because we were not concerned with dispersion in the observed effects and a summary based on two studies would yield a more precise estimate of the true effect than either study alone[20]. The data were analyzed using Comprehensive Meta-Analysis Software Version 2.0 (Biostat, Eaglewood, NJ, USA).

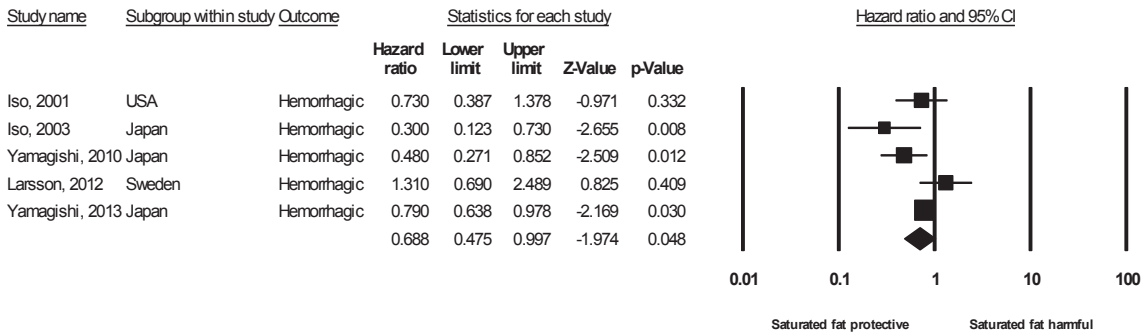
Results

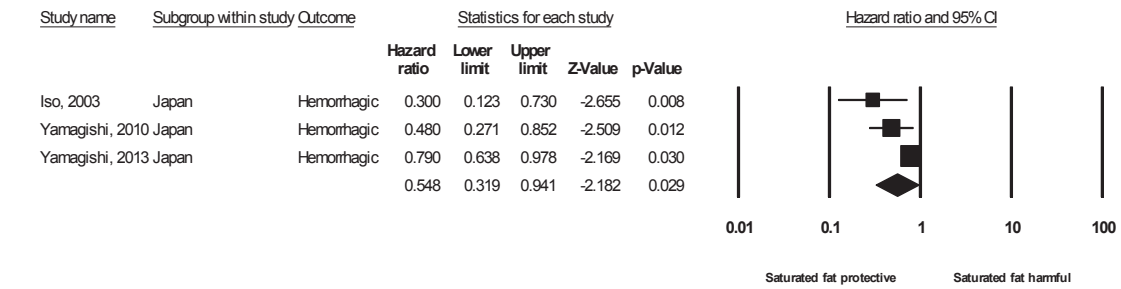
Study Selection

In total, 11 studies were selected[3-7, 15, 17, 21-24] (**Fig. 1**). The Honolulu Heart Program study, the Caerphilly Prospective Study, and the European Prospective Investigation into Cancer and Nutrition were excluded because they only investigated total stroke (hemorrhagic and ischemic strokes were not separately analyzed)[25-27]. The Ni-Hon-San Study was excluded because the diagnoses of intracranial hemorrhage and thromboembolic stroke were based on the clinical image and not on CT or MRI[2]. Summaries of the included studies are shown in **Table 1** (basic characteristics) and **Table 2** (detailed characteristics).

Intracerebral hemorrhage was analyzed in 5 studies[4, 6, 7, 15, 24]. Because subarachnoid hemorrhage was included as hemorrhagic stroke in the Framingham Heart Study and the Health Professionals Follow-Up Study[17, 21], these two studies were excluded from our analysis, despite the fact that they were included in the previous meta-analyses[9-11].

Ten studies were included in the analysis of ischemic stroke, of which 7 studies were described as evaluating ischemic stroke[6, 7, 15, 17, 21-23], whereas that in 3 studies was described as evaluating cerebral infarction[3, 5, 24]. The definition of ischemic stroke (but not cerebral infarction) may include both cerebral infarction and transient ischemic attack (TIA), which is an acute episode of temporary neurologic dysfunction that results from focal ischemia and is not associated with acute tissue infarction (episode disappears within 24 hours after onset). The inclusion of TIA in ischemic stroke may lead to misclassification and biased results in epidemiological research[28]. However, all 7 studies, in which the outcomes of ischemic stroke were reported, excluded TIAs[6, 7, 15, 17, 21-23]. Thus, we





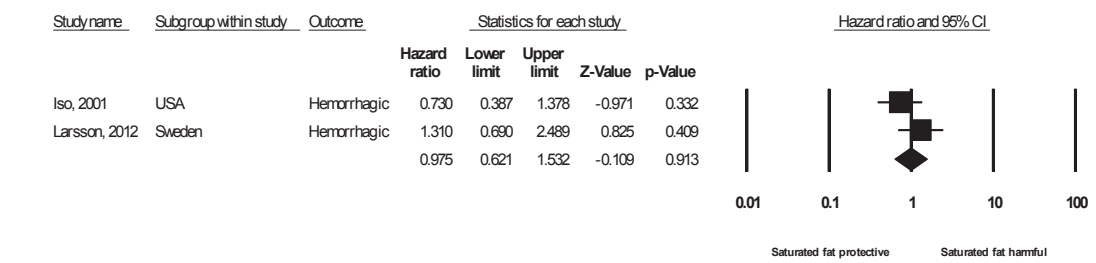


Fig. 2. Forest plot of the hazard ratio for saturated fat and the risk of intracerebral hemorrhage in total (A), Japanese (B), and non-Japanese (C) populations. A summary of the hazard ratios is shown in the last row of the forest plot data (◆). CI, confidence interval

considered ischemic stroke and cerebral infarction to be the same, and 10 studies were included in the present analysis. The Swedish Malmo Diet and Cancer Cohort study, in which ischemic stroke was separately analyzed in men and women, was counted as two comparisons[23].

Primary Outcome

A high intake of saturated fat was significantly associated with a reduction in the risk of both intracerebral hemorrhage (*n* [studies] = 5, HR = 0.69, 95% CI 0.48–1.00) and ischemic stroke (*n* [studies] = 11, HR = 0.89, 95% CI 0.82–0.96) (**Table 3** and **Fig. 2A** for

Table 4. Hazard ratio and 95% CI of risk of ischemic stroke by intake of saturated fat for race, sex, BMI, mean saturated fat intake, and follow-up duration

Outcome	Studies (n)	HR	95% CI		*P* value	*I*-squared
Ischemic stroke	11	0.89	0.82	0.96	0.004	38.9
Race						
Japanese	4	0.82	0.71	0.93	0.003	19.0
Non-Japanese	7	0.93	0.84	1.03	0.172	41.7
Sex						
Women	4	1.04	0.90	1.21	0.586	5.0
Men	3	0.85	0.74	0.97	0.018	35.9
Mixed	4 (all Japanese)	0.82	0.71	0.93	0.003	19.0
BMI						
< 24	4 (all Japanese)	0.82	0.71	0.93	0.003	19.0
≥ 24	7	0.93	0.84	1.03	0.172	41.7
Mean saturated fat intake						
< 25 g/d	8 (4 Japanese)	0.92	0.83	1.02	0.111	43.3
≥ 25 g/d	3	0.85	0.75	0.96	0.010	36.2
Follow-up duration						
< 14 years	5 (1 Japanese)	0.96	0.86	1.07	0.441	27.2
≥ 14 years	6 (3 Japanese)	0.79	0.70	0.90	0.000	11.2

BMI, body mass index; CI, confidence interval; HR, hazard ratio

intracerebral hemorrhage, **Table 4** and **Fig. 3A** for ischemic stroke). The effect size in intracerebral hemorrhage (HR = 0.69) was larger than that in ischemic stroke (HR = 0.89).

Secondary Outcome of Intracerebral Hemorrhage

In the 5 studies examined, all 3 Japanese studies showed a significant inverse association[4, 6, 7], whereas the 2 non-Japanese studies showed no association[15, 24]. Therefore, in the subgroup meta-analysis of intracerebral hemorrhage, a high intake of saturated fat in Japanese was strongly associated with a reduction in the risk of intracerebral hemorrhage (*n* [studies] = 3, HR = 0.55, 95% CI 0.32 − 0.94)[4, 6, 7], whereas this inverse association was not observed in non-Japanese (*n* [studies] = 2, HR = 0.98, 95% CI 0.62 − 1.53)[15, 24] (**Table 3**, **Fig. 2B, C**).

The characteristics of all of the Japanese studies included mixed sex (women and men), the BMI values were < 24 kg/m^2, and the mean intake of saturated fat was < 25 g/day. In contrast, the non-Japanese studies were of women only, the BMI values were ≥ 24 kg/m^2, and the mean intake of saturated fat was ≥ 25 g/day. Thus, when a subgroup analysis was conducted according to sex, BMI, and the mean intake of saturated fat, the same studies used in a subgroup analysis of the Japanese and non-Japanese were selected. Therefore, in the studies of mixed sex (women and men), with BMI values of < 24 kg/m^2, and mean intake of saturated fat of < 25 g/day, a strong inverse association was observed between the intake of saturated fat and the risk of intracerebral hemorrhage (**Table 3**). Studies over a follow-up period of ≥ 14 years, in which 2 Japanese studies were included, showed an inverse association between the intake of saturated fat and the risk of intracerebral hemorrhage (*n* [studies] = 3, HR = 0.51, 95% CI 0.35 − 0.75) (**Table 3**). The longer follow-up period may detect a higher incidence of stroke, which most often occurs in elderly adults.

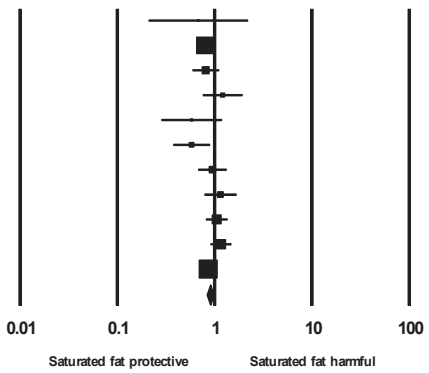
Secondary Outcomes of Ischemic Stroke

In 4 Japanese studies, the 2 more recent studies showed that a high intake of saturated fat was associated with a reduction in the risk of ischemic stroke[6, 7], whereas the other 2 older studies did not show a significant association[3, 5]. In 7 non-Japanese studies, one study of men showed that a high intake of saturated fat was associated with a reduction in the risk of ischemic stroke[17], but the other 6 studies/comparisons did not show a significant association[15, 21-24]. In a subgroup meta-analysis of ischemic stroke, a high intake of saturated fat by Japanese was associated with a reduction in the risk of ischemic stroke (*n* [studies] = 4, HR = 0.82, 95% CI 0.71 − 0.93), whereas this association was not observed in non-Japanese (*n* [studies] = 7, HR = 0.93, 95% CI 0.84 − 1.03) (**Table 4**, **Fig. 3B, C**).

The characteristics of all of the Japanese studies included mixed sex (women and men) and BMI values of < 24 kg/m^2, whereas those of the non-Japanese studies analyzed women or men separately and included

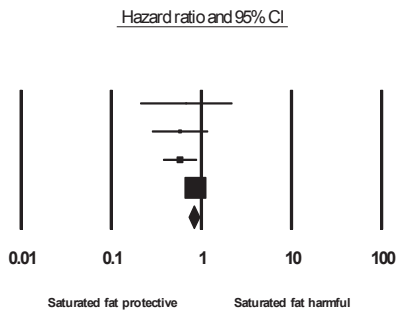
A) Total

Study name	Subgroup within study	Outcome	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value
Seino, 1997	Japan	Ischemic	0.680	0.207	2.231	-0.636	0.525
Gillman, 1997	USA	Ischemic	0.795	0.678	0.932	-2.831	0.005
Iso, 2001	USA	Ischemic	0.810	0.583	1.126	-1.255	0.209
He, 2003	USA	Ischemic	1.210	0.747	1.961	0.774	0.439
Sauvaget, 2004	Japan	Ischemic	0.580	0.280	1.201	-1.467	0.142
Yamagishi, 2010	Japan	Ischemic	0.580	0.372	0.905	-2.402	0.016
Wallstrom (men), 2012	Sweden	Ischemic	0.950	0.669	1.349	-0.287	0.774
Wallstrom (women), 2012	Sweden	Ischemic	1.150	0.777	1.703	0.698	0.485
Larsson, 2012	Sweden	Ischemic	1.050	0.802	1.374	0.356	0.722
Yaemsiri, 2012	USA	Ischemic	1.160	0.896	1.503	1.124	0.261
Yamagishi, 2013	Japan	Ischemic	0.860	0.744	0.995	-2.031	0.042
			0.888	0.819	0.963	-2.871	0.004



B) Japanese

Study name	Subgroup within study	Outcome	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value
Seino, 1997	Japan	Ischemic	0.680	0.207	2.231	-0.636	0.525
Sauvaget, 2004	Japan	Ischemic	0.580	0.280	1.201	-1.467	0.142
Yamagishi, 2010	Japan	Ischemic	0.580	0.372	0.905	-2.402	0.016
Yamagishi, 2013	Japan	Ischemic	0.860	0.744	0.995	-2.031	0.042
			0.816	0.713	0.934	-2.958	0.003



C) Non-Japanese

Study name	Subgroup within study	Outcome	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value
Gillman, 1997	USA	Ischemic	0.795	0.678	0.932	-2.831	0.005
Iso, 2001	USA	Ischemic	0.810	0.583	1.126	-1.255	0.209
He, 2003	USA	Ischemic	1.210	0.747	1.961	0.774	0.439
Wallstrom (men), 2012	Sweden	Ischemic	0.950	0.669	1.349	-0.287	0.774
Wallstrom (women), 2012	Sweden	Ischemic	1.150	0.777	1.703	0.698	0.485
Larsson, 2012	Sweden	Ischemic	1.050	0.802	1.374	0.356	0.722
Yaemsiri, 2012	USA	Ischemic	1.160	0.896	1.503	1.124	0.261
			0.932	0.841	1.031	-1.365	0.172

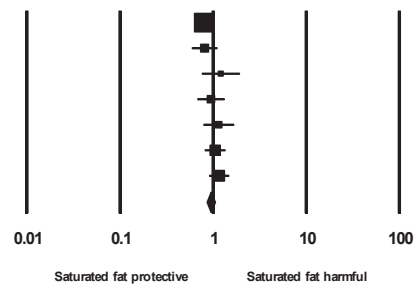


Fig. 3. Forest plot of the hazard ratio for saturated fat and the risk of ischemic stroke in total (A), Japanese (B), and non-Japanese (C) populations. A summary of the hazard ratios is shown in the last row of the forest plot data (◆). CI, confidence interval

patients with BMI values of ≥24 kg/m^2. Thus, when subgroup analyses were conducted according to sex, BMI, and the mean intake of saturated fat, the analysis of mixed sex and patients with BMI values of <24 kg/m^2 revealed an inverse association between the intake of saturated fat and the risk of ischemic stroke (**Table 4**).

In an analysis in 7 non-Japanese studies, a subgroup meta-analysis in 3 studies of men showed that a high intake of saturated fat was associated with a reduction in the risk of ischemic stroke (*n* [studies]=3, HR=0.85, 95% CI 0.74−0.97)[17, 21, 23], whereas in the 4 studies of women, this association was not observed (*n* [studies]=4, HR=1.04, 95% CI 0.90−1.21)[15, 22-24] (**Table 4**).

The studies in which the mean intake of saturated fat was ≥25 g/day were all in non-Japanese. However, a subgroup meta-analysis of studies in which the mean intake of saturated fat was ≥25 g/day showed that a high intake of saturated fat was associated with a reduction in the risk of ischemic stroke (*n* [studies]=3, HR=0.85, 95% CI 0.75−0.96)[15, 17, 24] (**Table 4**).

Three of the 6 studies in which the follow-up period was ≥14 years were Japanese. A meta-analysis of these 6 studies showed that a high intake of saturated fat was associated with a reduction in the risk of ischemic stroke (*n* [studies]=6, HR=0.79, 95% CI 0.70−0.90)[3, 5, 6, 15, 17, 21] (**Table 4**).

Publication Bias

A statistical analysis (Egger's test) indicated that there was no publication bias regarding studies that investigated the association between the intake of saturated fat and the risks of hemorrhagic and ischemic stroke (*P*=0.517, 0.866, respectively), and funnel plots had a symmetrical appearance (by visual inspection) (**Fig. 4A, B**).

Discussion

Association between Dietary Saturated fat Intake and Risk of Stroke Differs between Ethnic Japanese and Non-Japanese

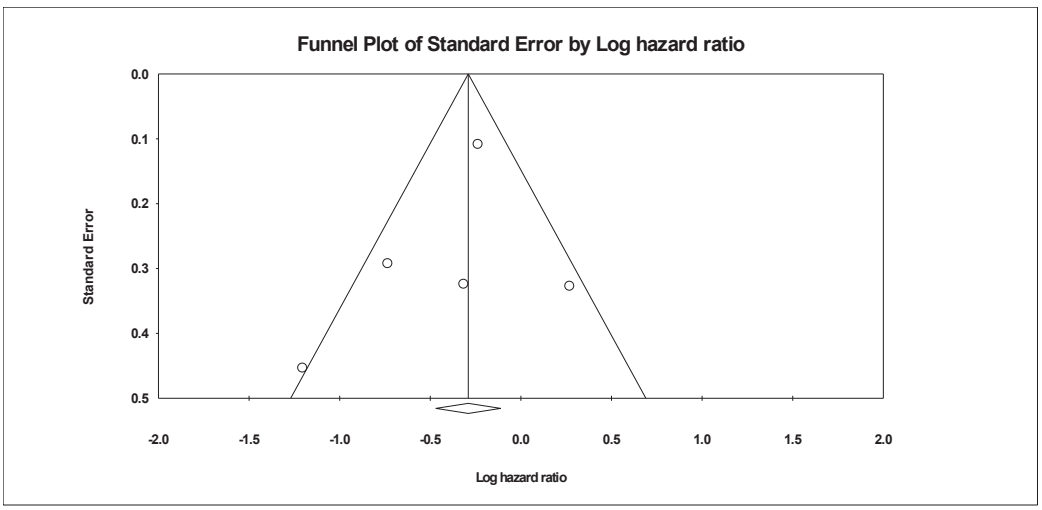
In this meta-analysis, we focused on the risk of intracerebral hemorrhage, for which dietary saturated fat may have a substantial effect. For intracerebral hemorrhage, our meta-analysis of 3 studies targeting ethnic Japanese showed a strong inverse association (HR=0.55, 95% CI 0.32−0.94), whereas that of 2 studies targeting non-Japanese did not show any such association (HR=0.98, 95% CI 0.62−1.53). Similarly to intracerebral hemorrhage, for ischemic stroke, our meta-analysis of 4 studies targeting Japanese showed a mild inverse association (HR=0.82, 95% CI 0.71−0.93), whereas that of 7 studies targeting non-Japanese did not show any association (HR=0.93, 95% CI 0.84−1.03). The effect size of saturated fat to reduce the incidence of stroke in Japanese was stronger for intracerebral hemorrhage (45% reduction) than for ischemic stroke (18% reduction). However, because the genetic and environmental characteristics of Japanese and Caucasian individuals are different (e.g., Japanese have a lower BMI, a higher incidence of stroke, longer longevity, and eat less saturated fat and more soy protein and fish), if these characteristics in Japanese were selected in a sensitivity analysis, a strong inverse association between saturated fat intake and the risk of stroke might be observed. It is known that along with saturated fat, the intake of animal protein, fish oils, sodium, potassium, dairy calcium, and alcohol, and smoking, are also associated with the risk of stroke[29], and they become confounding factors when examining the effects of saturated fat on the risk of stroke between Japanese and non-Japanese.

Difference in the Range of Intake of Saturated Fat May be a Cause of Differential Effects of Saturated Fat on the Risk of Stroke between Ethnic Japanese and Non-Japanese

The difference in the risk of stroke in response to dietary saturated fat observed between ethnic Japanese and non-Japanese may be due to a difference in the range of the amount of saturated fat intake, as previously suggested by Iso *et al.*[4] and Yamagishi *et al.*[7]. Under this hypothesis, the effect of saturated fat on the risk of stroke was non-linear: in the range of a low intake of saturated fat, the relationship was linear (decrease), but in the range of a high intake of saturated fat, the relationship plateaued. We also plotted the intake of saturated fat and the crude incidence/mortality rates of intracerebral hemorrhage in studies used in our meta-analysis on the basis of saturated fat weight (**Fig. 5A**) or the percent of total energy intake (en %) (**Fig. 5B**). The results were similar to those of previous studies[4, 7]. If we assumed that the dose-dependent effects of saturated fat on the risk of intracerebral hemorrhage applied to both Japanese and non-Japanese, the incidence/mortality rates would appear to reach a plateau around 20 g/day or 8 en %, respectively. However, this is not conclusive because there were no groups with a high intake of saturated fat in the Japanese nor groups with a low intake of saturated fat in the non-Japanese.

A similar plot was conducted for ischemic stroke (**Fig. 6**). In contrast to intracerebral hemorrhage, there was a substantial overlap in the groups with low intake of saturated fat between ethnic Japanese and non-Jap-

A) Intracerebral hemorrhage



B) Ischemic stroke

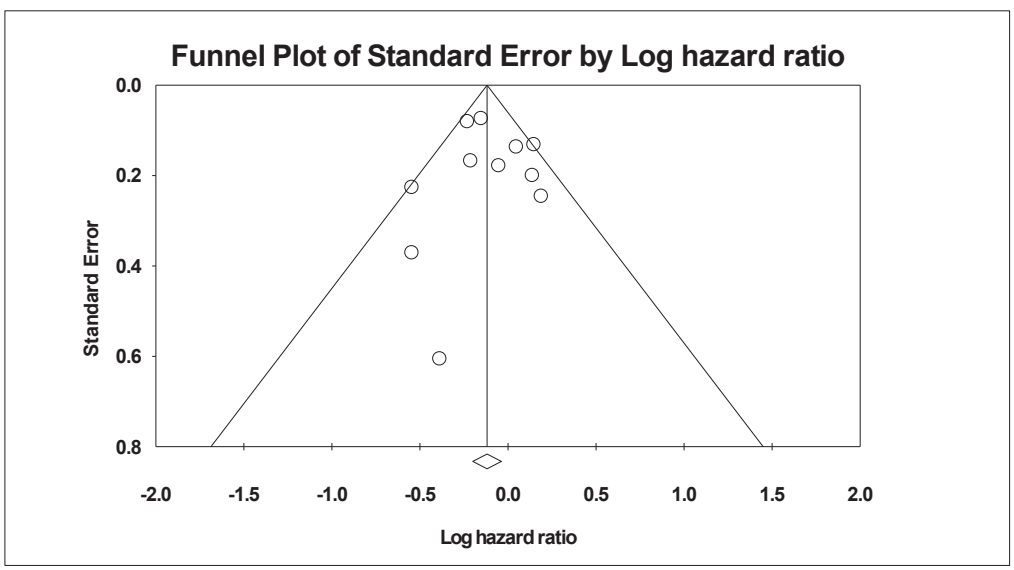


Fig. 4. Funnel plot of the standard error by the log hazard ratio for intracerebral hemorrhage (A) and ischemic stroke (B)

anese. On the basis of saturated fat weight (**Fig. 6A**) or en % (**Fig. 6B**), an increased incidence/mortality of ischemic stroke in the group with a low intake of saturated fat was observed in the Japanese (JPHC, LSS, and JACC studies) but not in the non-Japanese (MDC-M, MDC-W, and WHI-OS studies). This suggested that the increased incidence/mortality of ischemic stroke in the group with a low intake of saturated fat might be specific to ethnic Japanese, in which lacunar stroke is predominant (see the last section of the Discussion).

Does a Genetic Difference Affect the Risk of Stroke in Response to Dietary Saturated Fat?

Studies on second-generation ethnic Japanese living in the US might provide a clue to whether the favorable effects of saturated fats on intracerebral hem-

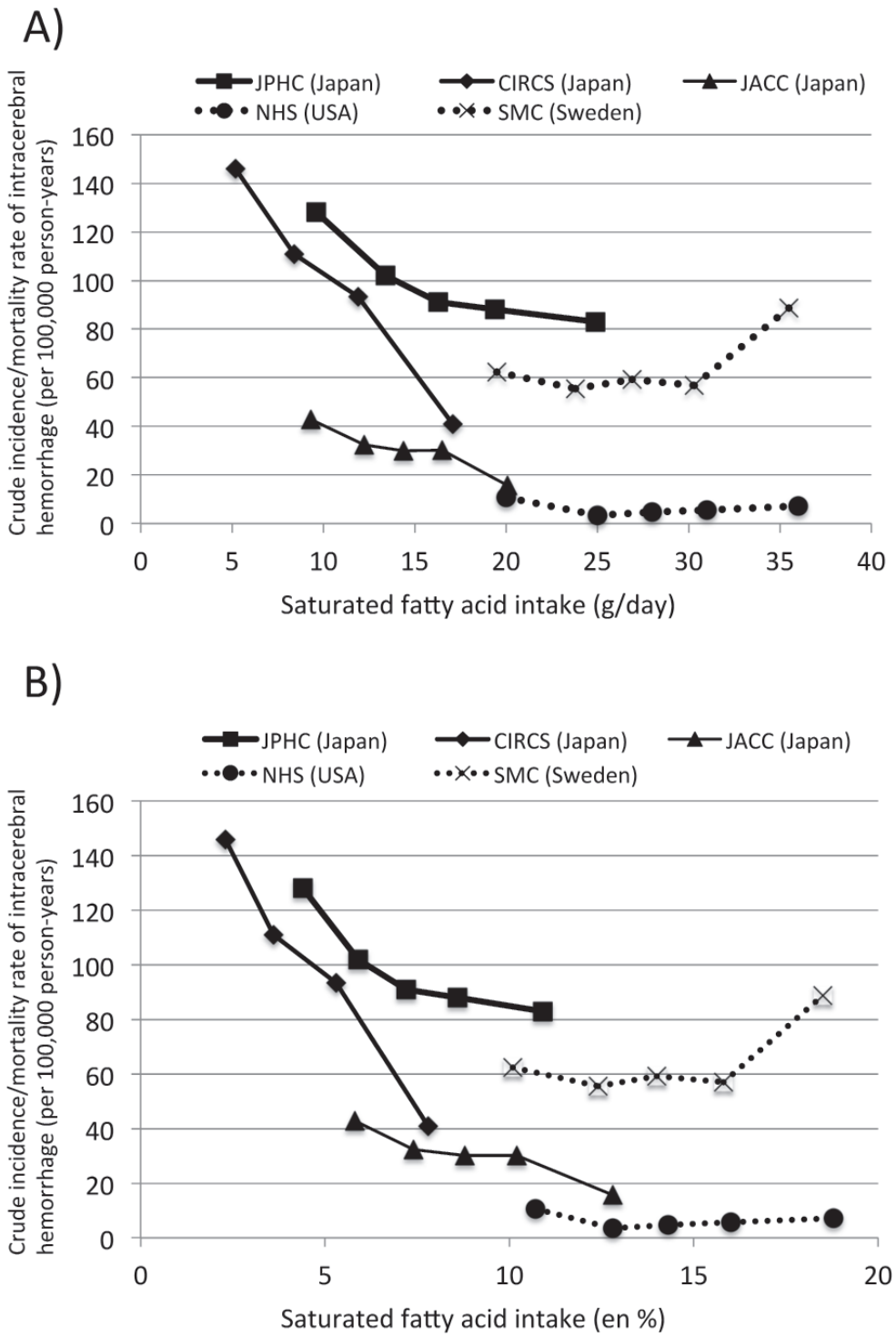


Fig. 5. Comparison of the effects of the dose of saturated fat on crude incidence/mortality rates (per 100 000 person-years) of intracerebral hemorrhage in studies used in this meta-analysis, expressed as the weight of saturated fat intake per day (A) and the percent of total energy intake (en %) of saturated fat (B). JPHC: Japan Public Health-based Cohort Study[7], CIRCS: Circulatory Risk in Communities Study[4], JACC: Japan Collaborative Cohort Study[6], NHS: Nurses' Health Study[15], SMC: Swedish Mammography Cohort[24]. The JACC was a mortality study. Note that the crude incidence/mortality rates were not adjusted by age and confounders; therefore, these rates should not be compared between studies.

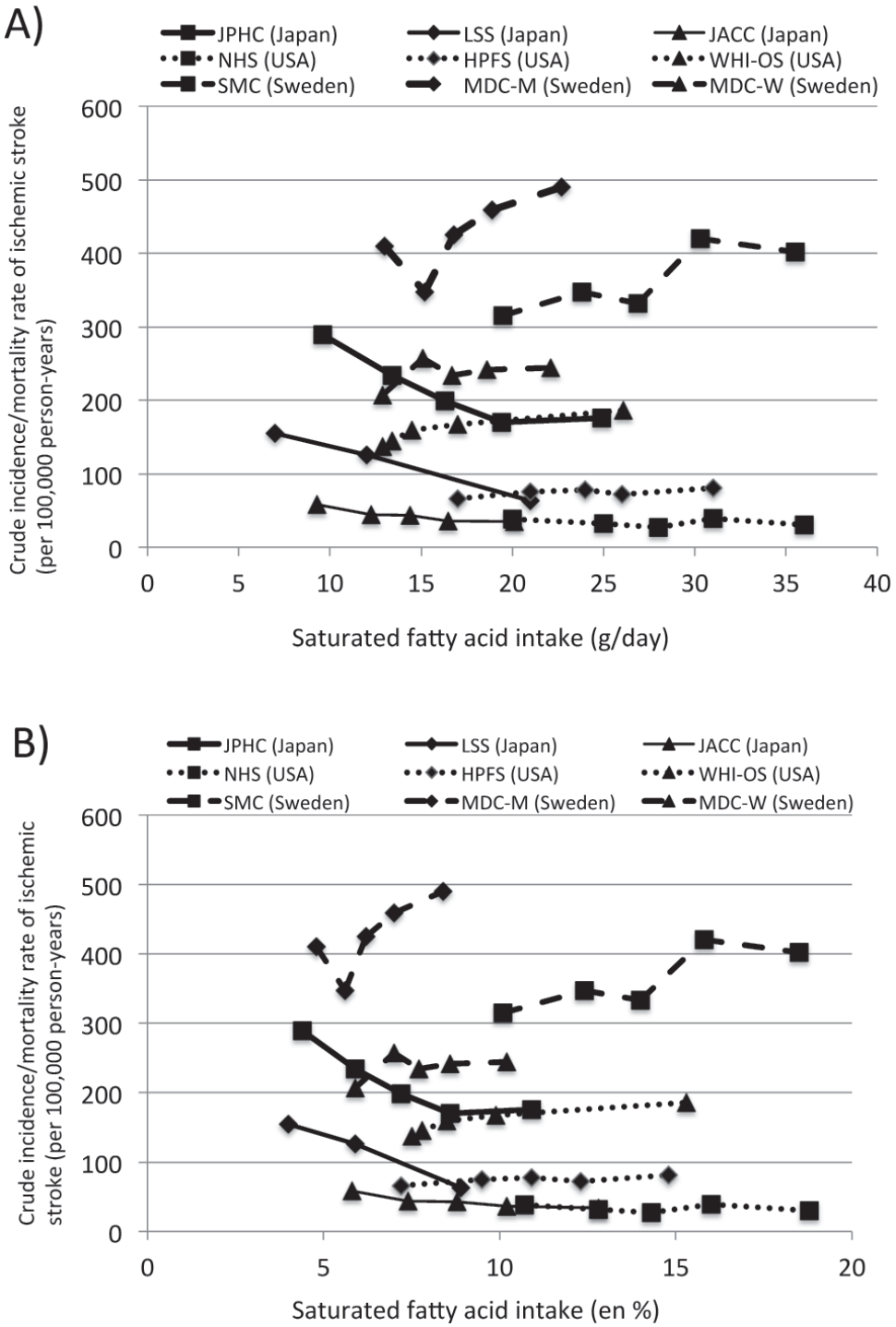


Fig. 6. Comparison of the effects of the dose of saturated fat on crude incidence/mortality rates (per 100 000 person-years) of ischemic stroke in the studies used in this meta-analysis, expressed as the weight of saturated fat intake per day (A) and the percent of total energy intake (en %) of saturated fat (B). JPHC: Japan Public Health-based Cohort Study[7], LSS: Hiroshima and Nagasaki/Life Span Study[5], JACC: Japan Collaborative Cohort Study[6], NHS: Nurses' Health Study[15], HPFS: Health Professional Follow Up Study[21], WHI-OS: Women's Health Initiative Observational Study[22], SMC: Swedish Mammography Cohort[24], MDC: Malmo Diet and Cancer Cohort[23]. The JACC was a mortality study. The MDC had two studies; men (MDC-M) and women (MDC-W). The Shibata study was not included because the actual incidence of ischemic stroke was not reported[3]. The Framingham Heart Study was not included because the absolute amount of saturated fat intake was not reported[17]. Note that the crude incidence/mortality rates were not adjusted by age and confounders; therefore, these rates should not be compared between studies.

orrhage and ischemic stroke in Japanese were due to genetic or environmental factors, because these Japanese individuals tend to consume a large amount of saturated fat. Two studies answered this question, but they were excluded from the meta-analysis because the Honolulu Heart Program investigated total stroke[25] and because the diagnoses of intracranial hemorrhage and thromboembolic stroke in the Ni-Hon-San Study were made based on the clinical findings only and not CT or MRI[2]. In addition, the number of participants in these cohort studies might be too small (7088 men in the Honolulu Heart Program; 7895 men in the Ni-Hon-San Study) to detect the effects of different doses of saturated fat intake on the risk of stroke. Furthermore, both studies used a 24-hour recall nutrition survey rather than a food-frequency questionnaire (FFQ). A 24-hour recall nutrition survey is less suitable than FFQ to estimate habitual intakes in nutrition. However, these 2 studies are worthwhile for examining the genetic differences in the risk of total stroke because both intracerebral hemorrhage and ischemic stroke in ethnic Japanese showed a similar response to saturated fats in our analysis.

The Honolulu Heart Program began in the early 1960s among men of Japanese ancestry who resided on the island of Oahu[25, 30]. They found intake of saturated fat in these men was related inversely to stroke mortality during 10 years of surveillance[25]. However, the relationship was not linear: a marked increase in stroke death was observed in the group with the lowest saturated fat intake (<10 g/day), but no substantial difference in stroke death was observed in the groups with other levels of saturated fat intake (>10 g/day)[25]. Although the mean intake of saturated fat in these men was 31.8±15.4 g/day (12.3±4.0% as a percentage of calories)[30], which is higher than that of most Japanese living in Japan (median intake of saturated fat, 16.3 g/day)[7] and that of male non-Japanese living in the US (24 g/day)[21], this data suggested that in Japanese, similar to non-Japanese, intake of over 10 g of saturated fat did not substantially affect the risk of stroke.

The Ni-Hon-San Study was begun in 1965 on men residing in Hiroshima and Nagasaki, Japan and in Japanese-American men residing in Hawaii and San Francisco in whom the difference in genetic factors is minimized but the variation in environmental and lifestyle factors is large[2]. As part of the Ni-Hon-San Study, the stroke incidence of Japanese was compared in the Japan and Hawaii cohorts[2]. The age-adjusted incidence of total stroke among the Japanese living in Japan was 2.7 times greater than that of the Japanese living in Hawaii[2]. The combination of the animal protein and saturated fat intake was significantly inversely associated with the incidence of total stroke among the Japanese living in Hawaii, and this association was also suggested among the Japanese living in Japan[2]. The total calorie, animal protein, and saturated fat intakes were larger in the Japanese living in Hawaii than in those living in Japan (the age-adjusted mean saturated fat intake of the Japanese living in Hawaii was 55 g/day, whereas that of the Japanese living in Japan was 18 g/day), and the distribution of participants in the group in Hawaii with a low saturated fat intake was very low (1.3% in the group with intake of <5 g/day vs. 4.1% in the group with intake of 5−14 g/day)[2]. Among Japanese living in the US, an inverse association was observed between the intake of saturated fat and the risk of stroke. However, non-Japanese living in the US did not show this inverse association (as estimated by other studies), suggesting that a reduction in stroke incidence in response to saturated fat in the range of high saturated fat intake might be observed in ethnic Japanese.

Taken together with these two studies of Japanese living in the US, although there were groups with high saturated fat intake among the Japanese living in Hawaii, it is not clear whether the Japanese showed a plateau or a decrease in the range of high saturated fat intake.

After the submission of this manuscript, the association between the intake of saturated fat and the risk of total stroke was reported in a large prospective study (The Prospective Urban Rural Epidemiology [PURE] study) in 18 countries from 5 continents[31]. This study included the Asian countries of Bangladesh, China, India, Malaysia, and Pakistan, which are characterized by middle- or low-income subjects and a dietary pattern of a higher carbohydrate/lower fat intake, and thus, groups with a lower intake of saturated fat were included in the analysis. Unexpectedly, the effect of saturated fat intake on the risk of stroke was linear (decreased) in the range of high saturated fat intake. From the lowest to highest quintile, the median intake of saturated fat was 2.8, 4,9, 7.1, 9.5, and 13.2 en%, and the HRs for the incidence of stroke were 1, 1.10, 1.01, 0.93, and 0.79, respectively (trend $P=0.0498$). These data suggested that in ethnic Asians, a higher intake of saturated fat might reduce the risk of stroke linearly. A further analysis that separates ethnic and stroke subtypes in this cohort may clarify this finding.

Intervention Study

Cohort studies could not lead to the conclusion that dietary saturated fat exerts an inhibitory effect on the risk of stroke in Japanese. To prove causality, intervention studies are required, but no such studies have examined the effects of increasing or decreasing the

saturated fat intake on the risk of stroke in Japanese. Only one intervention study examined the incidence of hemorrhagic and ischemic stroke in non-Japanese. This was a large randomized controlled trial of 48,835 postmenopausal women of 50 to 79 years of age who participated in the Women's Health Initiative Dietary Modification Trial[32]. Women were randomly assigned to an intervention or comparison group in a free-living setting. The intervention group received intensive behavior modification designed to reduce the total fat intake to 20% of calories and increase the vegetable/fruit intake to 5 servings/day and the grain intake to at least 6 servings/day for 8.1 years. By year 6, the mean saturated fat intake decreased by 2.9% of the energy intake in the intervention group; thus the total saturated fat intake became 9.5% of the energy intake. However, this diet had no significant effect on the incidence of hemorrhagic stroke (HR, 0.90; 95% CI, 0.66−1.22) or ischemic stroke (HR, 1.01; 95% CI, 0.86−1.18). These data support the results of a cohort study of non-Japanese in whom a lower saturated fat intake did not increase the risks of hemorrhagic or ischemic stroke.

Animal Studies

The stroke-prone spontaneously hypertensive rat (SHRSP) is a unique genetic model of stroke, especially of hemorrhage and lacunar infarction, due to its severe hypertension[33]. Stroke is prevented in SHRSPs by improving their diet through such means as sodium restriction and potassium supplementation and by feeding them diets containing proteins, some amino acids and fatty acids, and dietary fiber[34]. As for dietary fats, SHRSPs fed a high-fat/cholesterol diet (20% suet, 5% cholesterol, and 2% cholic acid, in wt/wt) did not show an increased lifespan but did show a reduced incidence of cerebral lesions in comparison to SHRSPs fed a normal laboratory stock diet[35]. SHRSPs fed a milk-fat rich diet (20% milk fat, in wt/wt) did not show an increased lifespan but did show a reduced incidence of cerebrovascular disease in comparison to SHRSPs fed a regular stock diet (Funahashi SP diet including 4.5% crude fat in wt/wt)[36]. The mean survival time of SHRSPs fed various dietary oils was longest in rats fed a diet high in saturated fatty acids under a 10% (wt/wt) oil-fed condition with 1% NaCl solution[37]. Under this same condition with a 0.25% NaCl solution, the mean survival duration was longest in SHRSPs that were fed butter in comparison to those fed perilla-lard, lard, margarine, or hydrogenated soy[38]. Specific fats may also affect the lifespan of SHRSPs. The addition of 1% (wt/wt) palmitoleic acid (C16:1) delayed the development of stroke in salt-loaded SHRSPs relative to the addition of 1% (wt/wt) palmitic, 1% oleic, or 1% linolenic acids, possibly by maintaining the integrity of the vascular smooth muscle cells[34, 39]. Undecylenic acid (C11:1) also prolonged the lifespan in salt-loaded SHRSPs[34].

However, these studies did not examine the effect size of dietary fat to delay the onset of stroke relative to those of protein and carbohydrate. Under *ad libitum* or iso-energy feeding conditions, when the amount of a specific macronutrient is changed to examine its effects, the amounts of the other macronutrients are obligatorily changed. Thus, it is difficult to examine the specific effects of one macronutrient. To discern the macronutrients responsible for an increased incidence of stroke, the amount of one macronutrient was fixed, and the effect of different ratios of the other two macronutrients on stroke incidence was compared. It was found that the proportion of protein in the diet, but not that of carbohydrate or fat, was a primary determinant of the onset of stroke[40]. In a further study, peptides in milk protein, but not fat, might be responsible for delaying the onset of stroke[41]. The amount of protein was a key to the favorable effects of dietary fats. When the protein proportion was low (10% of total calories), increasing dietary fat might delay the onset of stroke[40], whereas when the protein proportion was high (20% of total calories), increasing dietary fat did not delay the onset of stroke[40, 41].

Animal experiments suggest that the amount of protein may influence the effects of saturated fat on the risk of stroke. Japanese eat less protein than non-Japanese; thus, increasing their saturated fat intake may reduce their risk of stroke.

Possible Reasons for the Reduction in Risk of Ischemic Stroke by Saturated Fatty Acids in Japanese

Cerebral infarction (or ischemic stroke), ICD-10 code I63, includes infarction due to both thrombosis (mostly due to arteriosclerosis) and embolism (mostly due to heart disease). The etiologies of heart diseases (valvular disease, myocardial infarction, bacterial endocarditis, and atrial fibrillation) might be different from those of thrombosis due to atherosclerosis. Thus, the risk factors may differ in cerebral infarction caused by thrombosis and embolism.

Pathologically, cerebral arteries are affected by atherosclerosis and arteriolosclerosis[29]. Atherosclerosis is observed typically in large arteries such as the carotid arteries and basal cerebral arteries and is characterized by lipid accumulation with proliferative changes leading to plaque formation (a cause of infarction due to thrombosis)[29]. In contrast, arteriolosclerosis is observed in small penetrating arterioles in basal ganglia of the brain and is characterized by the necrosis or apoptosis of smooth muscle cells within the media, leading to

the formation of microaneurysms (a cause of intracerebral hemorrhage) and/or fibrous proliferative changes (a cause of lacunar stroke)[42]. The major risk factors for atherosclerosis include dyslipidemia, diabetes mellitus, hypertension, and smoking, whereas the main risk factor for arteriolosclerosis is hypertension[29]. Thus, it is conceivable that the etiology of intracerebral hemorrhage and lacunar stroke might be the same. Cerebral infarction found in Japan is more commonly related to arteriolosclerosis in the small intraparenchymal vessels rather than to atherosclerosis of the circle of Willis and its major branches[43, 44]. In a recent study in Japan[7], among 520 patients with ischemic stroke, 224 experienced lacunar infarction, 155 embolic infarction, and 111 large-artery occlusive infarction, and the intake of saturated fat was inversely associated with the incidence of lacunar infarction (trend $P=0.02$) but not that of embolic infarction (trend $P=0.74$) and large-artery occlusive infarction (trend $P=0.55$). In epidemiological studies, cerebral infarction included lacunar infarction, the etiology of which is similar to that of intracerebral hemorrhage. This may cause a dietary saturated fat-induced reduction in the risk of ischemic stroke and hemorrhage in Japanese.

Conclusion

The results of this review and meta-analysis suggested that in ethnic Japanese, a diet high in saturated fat is associated with a low risk of intracerebral hemorrhage and ischemic stroke. However, this favorable effect of saturated fat was not observed in non-Japanese. This may be due to differences in the range of intake of saturated fat, genetic susceptibility, the incidence of lacunar infarction, and/or confounding factors such as intake of dietary protein, vitamins, and minerals, which may be associated with dietary saturated fat. An intervention study in Japanese may clarify this important issue.

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