

## Review

## Saturated Fat Intake and Cardiovascular Disease in Japanese Population

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The evidence for the impact of saturated fat intake on cardiovascular disease remains inconsistent. One reason for this inconsistency may be the large difference in the distribution of saturated fat intake between the East and West. In this review, we focus on the published literature on this topic among Japanese population. Three studies have examined the link between saturated fat intake and intraparenchymal hemorrhage, consistently showing an inverse association. However, the association for ischemic stroke is less clear, although it is generally inverse. As for myocardial infarction, the findings in Japanese studies are inconsistent, as are those of Western studies. The JPHC study, however, found a positive association, the first report in Asia. Taken together with the results of the JPHC and Western studies, a saturated fat intake of around 20 g/day (approximately 10% of total energy) may be optimal, which corresponds to 200 g of milk a day and 150 g of meat every other day.

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The amount of dietary intake of saturated fatty acids is an important determinant of the blood cholesterol level<sup>1, 2</sup>. Correspondingly, a high blood cholesterol level raises the risk of myocardial infarction<sup>3</sup>. Some studies, mainly from Western countries, have shown that high cholesterol levels are also associated with an increased risk of ischemic stroke<sup>4</sup>. The 'lower the better' cholesterol hypothesis was subsequently accepted and quickly spread nationwide in Japan, although the Seven Countries Study showed that the association between blood cholesterol and mortality from coronary heart disease is prominent only among populations with high blood cholesterol levels, such as in Northern Europe and the United States, and not among populations with low blood cholesterol levels, such as in Japan<sup>5</sup>. This hypothesis has also been applied to stroke, although the epidemiological evi-

dence is lacking.

On the other hand, Yoshio Komachi, a pioneer Japanese cardiovascular epidemiologist, observed a far higher incidence of intraparenchymal hemorrhage in Akita, in northeastern Japan, where the population cholesterol levels were very low in the era of the 1960-70's, compared with that observed among Osaka residents, whose cholesterol levels were relatively high<sup>6</sup>. He observed that the lifestyles of the Akita people at that time were characterized by the consumption of traditional Japanese foods, including a large amount of rice and salt and a small amount of animal products, as well as heavy agricultural work. In general, among the traditional Akita farmers, lean, poor-looking middle-aged men suffered from stroke. Based on this observation, Komachi hypothesized that the association between the blood cholesterol level and cardiovascular disease may not be linear and that a very low cholesterol level also has an adverse effect on the incidence of stroke.

This hypothesis has long been under debate and became widely familiar in 1989 according to the results of a cohort study in Akita (presently a part of

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**Table 1.** Summary of Japanese studies regarding saturated fat intake and cardiovascular disease

Study	Population	Events	Endpoint	Category	Median values of saturated fat in each category		Hazard ratio (95%CI) of highest vs lowest categories	Reference
					Lowest category (g/d)	Highest category (g/d)		
Intraparenchymal hemorrhage								
CIRCS	4,775	67	Incidence	Quartiles	5	17	0.30 (0.12-0.71)	Iso H, et al., 2003 <sup>12</sup> .
JACC	58,453	224	Mortality	Quintiles	9	20	0.48 (0.27-0.85)	Yamagishi K, et al., 2010 <sup>15</sup> .
JPHC	81,931	894	Incidence	Quintiles	10	25	0.61 (0.43-0.86)	Yamagishi K, et al., 2013 <sup>16</sup> .
Ischemic stroke								
Shibata Study	2,283	75	Incidence	Quartiles	7	15	0.68 (0.21-2.26)	Seino F, et al., 1997 <sup>13</sup> .
LSS	3,731	60	Mortality	Tertiles	7	21	0.58 (0.28-1.20)	Sauvaget C, et al., 2004 <sup>14</sup> .
JACC	58,453	321	Mortality	Quintiles	9	20	0.58 (0.37-0.90)	Yamagishi K, et al., 2010 <sup>15</sup> .
JPHC	81,931	1,939	Incidence	Quintiles	10	25	0.84 (0.67-1.06)	Yamagishi K, et al., 2013 <sup>16</sup> .
Myocardial infarction								
JACC	58,453	330	Mortality	Quintiles	9	20	0.85 (0.56-1.29)	Yamagishi K, et al., 2010 <sup>15</sup> .
JPHC	81,931	610	Incidence	Quintiles	10	25	1.39 (0.93-2.08)	Yamagishi K, et al., 2013 <sup>16</sup> .
NIPPON DATA90	7,819	72	Mortality	Quintiles	1.2-4.7 %E 1.4-5.2 %E	7.0-13.0 %E 7.7-13.8 %E	M 0.92 (0.73-1.16) F 1.34 (1.02-1.74)	Nakamura Y, et al. 2013 <sup>17</sup> .

CI stands for confidence interval, %E for percent energy, M for male, F for female.

the Circulatory Risk in Communities Study, CIRCS)<sup>7</sup> and a cohort study in the United States (Multiple Risk Factor Intervention Trial, MRFIT)<sup>4</sup>, which independently showed an inverse association between a low total cholesterol level and the risk of intraparenchymal hemorrhage. As a result of these reports, the National Heart, Lung and Blood Institute (NHLBI) held an international conference on low blood cholesterol in 1990 to review and discuss existing data on the U-shaped relationship between the total cholesterol level and cardiovascular disease collected from cohort studies worldwide<sup>8</sup>. Since then, the inverse association between the total or low-density lipoprotein (LDL) cholesterol levels and intraparenchymal hemorrhage has been repeatedly replicated in meta-analyses and cohort studies<sup>3</sup>.

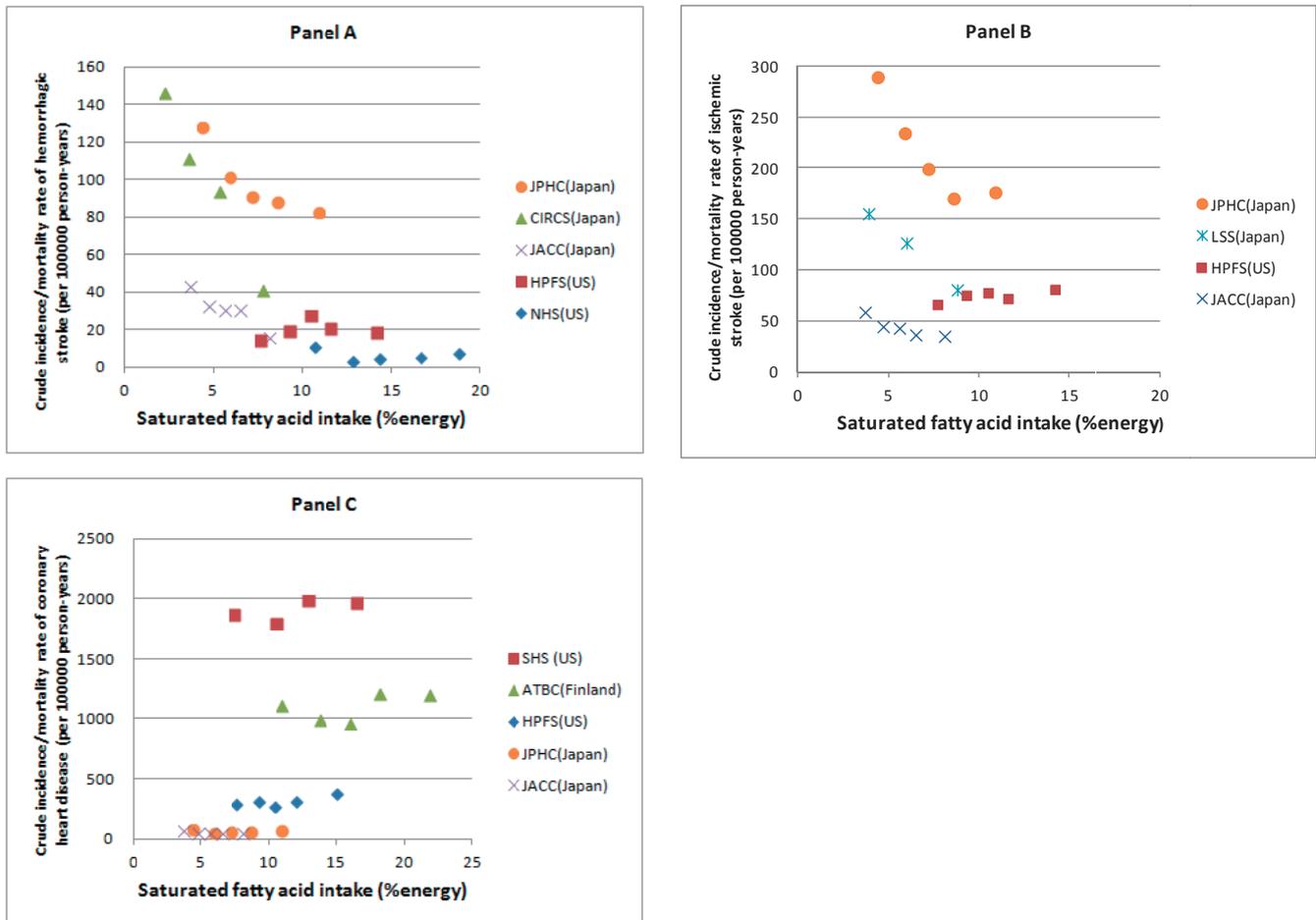
A similar hypothesis was recently tested with respect to the association between saturated fat intake and the risk of cardiovascular disease. Several studies have found a positive association between saturated fat intake and myocardial infarction, and the new Japanese guidelines recommend a dietary pattern involving <7% energy from saturated fat<sup>9</sup>, although the positive association is not clear in meta-analyses<sup>10, 11</sup>. As for cerebral infarction, some studies have demonstrated an inverse association, while others have shown null associations<sup>11</sup>. In contrast, most studies have

documented an inverse association between saturated fat intake and the risk of intraparenchymal hemorrhage<sup>11</sup>.

However, considering that the range of saturated fat intake is significantly different between Western countries and Asia, it is inappropriate to directly apply the results of these meta-analyses to Japan, as they include many Western studies. Therefore, we focused on six cohort studies of Japanese population<sup>12-17</sup>. A summary of these studies is presented in **Table 1**.

In the CIRCS, the authors followed up 4,775 residents in Akita, Ibaraki, Osaka and Kochi for 14 years and found a strong inverse association between the level of saturated fat intake estimated according to the 24-hour dietary recall method and the risk of intraparenchymal hemorrhage<sup>12</sup>. In addition, the authors compared these results with those of the Nurses' Health Study (NHS)<sup>18</sup> and found a similar inverse association, although the range of saturated fat intake was far different between the two studies. That is, the median value of saturated fat intake in the highest category of the CIRCS was 17 g/day, while that in the lowest category of the NHS was 20 g/day, indicating the absence of overlap in the distribution of saturated fat intake between the two populations.

In the Shibata Study<sup>13</sup> and Life Span Study (LSS)<sup>14</sup>, albeit statistically non-significant, an inverse



**Fig 1.** Comparison of the association between the proportion of saturated fat relative to the total energy intake and the crude incidence/mortality rates (per 100,000 person-years) of intraparenchymal hemorrhage (Panel A), ischemic stroke (Panel B) and coronary heart disease/myocardial infarction (Panel C)

NHS: Nurses' Health Study<sup>18</sup>, ages 34-59, women only, US; HPFS: Health Professional Follow-up Study<sup>19, 20</sup>, ages 40-75, men only, US; CIRCS: Circulatory Risk in Communities Study<sup>12</sup>, ages 40-69, men:women=48:52, Japan; JPHC; Japan Public Health Center-based Prospective Study<sup>16</sup>, ages 45-74, men:women=46:54, Japan; JACC; Japan Collaborative Cohort Study<sup>15</sup>, ages 40-79, men:women=39:61, Japan; LSS: Life Span Study<sup>14</sup>, ages 35-89, men:women=38:62, Japan; ATBC: Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study<sup>22</sup>, ages 50-69, male smokers only, Finland; SHS: Strong Heart Study<sup>21</sup>, ages 47-79, men:women=36:64, US. The JACC and LSS were mortality studies, the other studies were incidence studies. The ATBC was an intervention study for male smokers. Note that the characteristics of the study population (e.g., age range, gender proportion) varied in each study.

association was observed between saturated fat intake and the incidence or mortality of ischemic stroke. In the Japan Collaborative Cohort (JACC) Study, a strong inverse association was noted between saturated fat intake and mortality from both ischemic stroke and intraparenchymal hemorrhage<sup>15</sup>.

In the Japan Public Health Center-based Prospective Study (JPHC Study), a large community-based cohort of 81,931 Japanese men and women, we found an inverse association between saturated fat intake and the risk of incident intraparenchymal hemorrhage and ischemic stroke; the hazard ratio [95% confidence

interval] for the highest quintile (around 24.9 g/day) versus the lowest quintile (around 9.6 g/day) was 0.61 ([0.43-0.86],  $p$  for trend = 0.005) for intraparenchymal hemorrhage and 0.84 ([0.67-1.06],  $p=0.08$ ) for ischemic stroke<sup>15</sup>. These associations were more prominent for lesions in perforating artery areas (i.e., cases of deep intraparenchymal hemorrhage and lacunar infarction). In contrast, we found a positive association between saturated fat intake and myocardial infarction (hazard ratio [confidence interval]=1.39 [0.93-2.08] for the highest versus lowest quintiles,  $p$  for trend=0.046), the first epidemiological observa-

tion in Asia. A similar positive association was also identified among women in the NIPPON DATA90 study<sup>17</sup>.

The distribution of saturated fat intake in the Japanese population is significantly lower than that observed in the US or European populations, and the profile of cardiovascular disease differs among these groups. The differential rates of stroke and myocardial infarction observed between Asian and Western countries may be explained partly (but not completely) by the difference in saturated fat intake. In the JPHC paper<sup>16</sup>, we plotted the absolute amount of saturated fat intake and the crude incidence or mortality of intraparenchymal hemorrhage, ischemic stroke and coronary heart disease based on the published literature. In **Fig. 1** in the present paper, we plotted the proportion of saturated fat relative to the total energy intake instead of the absolute amount based on the published literature<sup>12, 14-16, 18-22</sup>. Consequently, there appears to be a threshold for saturated fat intake of around 7.5% to 10% of the total energy for the inverse relationship between saturated fat intake and the risk of stroke, especially with respect to intraparenchymal hemorrhage, consistent with that observed for the absolute amount of energy (15 to 20 g/day assuming a total energy intake of 1,800 kcal)<sup>16</sup>. As shown in the table, the distribution of saturated fat intake among Japanese is around 7 g (3.5% energy) to 20 g (10% energy). To date, the inverse association has only been confirmed in this distribution, and there is no evidence of a beneficial impact of a saturated fat intake of >20 g/day in Japan, a level above which the risk of myocardial infarction may begin to increase, taken together with the results of the JPHC and Western studies. These observations suggest that a saturated fat intake of around 20 g/day may be optimal, although this finding should be confirmed in meta-analyses. An example of 20 g of saturated fat is the consumption of 200 g of milk a day and 150 g of meat every other day.

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### Conflicts of Interest

None declared.

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