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# Prospective Study of Fat and Protein Intake and Risk of Intraparenchymal Hemorrhage in Women

Hiroyasu Iso, MD; Meir J. Stampfer, MD; JoAnn E. Manson, MD; Kathryn Rexrode, MD;  
Frank B. Hu, MD; Charles H. Hennekens, MD; Graham A. Colditz, MBBS;  
Frank E. Speizer, MD; Walter C. Willett, MD

**Background**—Dietary animal fat and protein have been inversely associated with a risk of intraparenchymal hemorrhage in ecological studies.

**Methods and Results**—In 1980, 85 764 women in the Nurses' Health Study cohort, who were 34 to 59 years old and free of diagnosed cardiovascular disease and cancer, completed dietary questionnaires. From these questionnaires, we calculated fat and protein intake. By 1994, after 1.16 million person-years of follow-up, 690 incident strokes, including 74 intraparenchymal hemorrhages, had been documented. Multivariate-adjusted risk of intraparenchymal hemorrhage was higher among women in the lowest quintile of energy-adjusted saturated fat intake than at all higher levels of intake (relative risk [RR], 2.36; 95% CI, 1.10 to 5.09;  $P=0.03$ ). For trans unsaturated fat, the corresponding RR was 2.50 (95% CI, 1.35 to 4.65;  $P=0.004$ ). Animal protein intake was inversely associated with risk (RR in the highest versus lowest quintiles, 0.32; 95% CI, 0.10 to 1.00;  $P=0.04$ ). The excess risk associated with low saturated fat intake was observed primarily among women with a history of hypertension (RR, 3.66; 95% CI, 1.09 to 12.3;  $P=0.04$ ), but such an interaction was not seen for trans unsaturated fat or animal protein. These nutrients were not related to risk of other stroke subtypes. Dietary cholesterol and monounsaturated and polyunsaturated fat were not related to risk of any stroke subtype.

**Conclusions**—Low intake of saturated fat and animal protein was associated with an increased risk of intraparenchymal hemorrhage, which may help to explain the high rate of this stroke subtype in Asian countries. The increased risk with low intake of saturated fat and trans unsaturated fat is compatible with the reported association between low serum total cholesterol and risk. (*Circulation*. 2001;103:856-863.)

**Key Words:** dietary fats ■ proteins ■ stroke ■ hemorrhage

Ecological studies among populations suggest that a low intake of saturated fat (mostly animal fat) and animal protein is associated with an increased risk of intraparenchymal hemorrhagic stroke, specifically intraparenchymal hemorrhage.<sup>1,2</sup> Rural Japanese with a very low mean intake of animal fat (15 g/d) and animal protein (44 g/d) had twice the incidence of intraparenchymal hemorrhage as urban Japanese, but the incidence of subarachnoid hemorrhage did not vary among populations.<sup>1,2</sup> Japanese persons living in Japan, who had an average intake of 16 g/d of saturated fat and 40 g/d animal protein, had a 3-fold higher incidence of hemorrhagic stroke<sup>3</sup> than Japanese persons living in Honolulu, who consumed a mean of 40 g/d saturated fat and 71 g/d animal protein.<sup>4</sup> The groups had similar blood pressure levels.<sup>4</sup>

An association between a low intake of saturated fat and risk of intraparenchymal hemorrhage has also been suggested

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by a higher risk for intraparenchymal hemorrhage among individuals with very low serum total cholesterol levels ( $<4.14$  mol/L) in studies of Japanese,<sup>5-7</sup> Japanese-American,<sup>8</sup> and white US men.<sup>9</sup> In the white men, the increased risk associated with low serum cholesterol levels was confined to those with hypertension.<sup>9</sup> However, no prospective study has examined the relationship between the dietary intake of animal fat and protein and the risk of intraparenchymal hemorrhage. An inverse association between animal protein intake and risk of hemorrhagic stroke was reported in a small study ( $n=34$  cases) of Japanese men living in Honolulu, but intraparenchymal and subarachnoid hemorrhages were grouped together.<sup>3</sup> Fourteen years of prospective data from the Nurses' Health Study allowed us to

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From Channing Laboratory (H.I., M.J.S., J.E.M., K.R., G.A.C., F.E.S., W.C.W.) and the Division of Preventive Medicine (J.E.M., K.R.), Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Mass; Departments of Epidemiology (M.J.S., G.A.C., W.C.W.) and Nutrition (M.J.S., F.B.H., W.C.W.), Harvard School of Public Health, Boston, Mass; and University of Miami (C.H.H.), Miami, Fla.

Tables I and II can be found Online Only at [www.circulationaha.org](http://www.circulationaha.org)

Correspondence to Meir J. Stampfer, MD, Channing Laboratory, Brigham and Women's Hospital and Harvard Medical School, 181 Longwood Avenue, Boston, MA 02115.

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investigate the relationship between animal fat and protein intake and the incidence of stroke. Our a priori hypothesis was that a low intake of animal fat and protein increase the risk of intraparenchymal hemorrhage and that this relationship is most pronounced in hypertensive women.

## Methods

The Nurses' Health Study began in 1976, when 121 700 female registered nurses (98% white) living in 11 states completed questionnaires about their lifestyle and medical history, including previous cardiovascular disease, cancer, diabetes, hypertension, and high serum cholesterol concentration. Every 2 years, follow-up questionnaires are sent to these women to update their exposure variables and to identify any newly diagnosed major illnesses.

### Ascertainment of Diet

In 1980, we collected information on usual dietary intake using a semiquantitative food-frequency questionnaire.<sup>10</sup> For each of 61 food items, a commonly used unit or portion size was specified, and each woman was asked how often, on average, during the previous year she had consumed that amount of the item. Nine responses were possible, ranging from "almost never" to "six or more times per day." The average daily intake of nutrients was calculated by multiplying the frequency of the consumption of each item by the nutrient content and totaling the nutrient intake for all food items. Nutrient intakes were adjusted for total energy intake.<sup>10</sup> The correlations between nutrient intakes assessed from four 1-week diet records and from a subsequent questionnaire were 0.59 for saturated fat, 0.56 for monounsaturated fat, 0.48 for polyunsaturated fat, 0.61 for cholesterol, and 0.47 for total protein.<sup>10</sup> A total of 98 462 women returned the 1980 dietary questionnaire. We excluded women who left  $\geq 10$  items blank or who had implausible total food intakes and those who had a history of cancer, angina, myocardial infarction, coronary revascularization, stroke, or other cardiovascular diseases in 1980; 85 764 women remained for the analyses.

### Ascertainment of Stroke

Women who reported a nonfatal stroke on a follow-up questionnaire were asked for permission to review their medical records. The 18.4% of nonfatal strokes for which confirmatory information was obtained by telephone or letter but for which no medical records were available were regarded as probable. Fatal strokes were initially ascertained from reports from relatives or postal authorities and a search of the National Death Index.<sup>11</sup> They were then documented by medical records and/or death certificates. Mortality follow-up was  $>98\%$  complete.<sup>11</sup> The 22.3% of fatal strokes confirmed by telephone, letter, or death certificate, but for which no medical records were available, were regarded as probable. Medical records were reviewed by physicians blinded to dietary and other risk factors.

Strokes were confirmed from medical records according to the criteria of the National Survey of Stroke,<sup>12</sup> which require a constellation of neurological deficits of sudden or rapid onset lasting  $\geq 24$  hours or until death; events were further subclassified as subarachnoid hemorrhages, intraparenchymal hemorrhages, ischemic strokes (thrombotic or embolic), or strokes of undetermined type. Results from CT scans, MRIs, or autopsy were available for 88% of intraparenchymal hemorrhages, 81% of subarachnoid hemorrhages, and 94% of ischemic strokes. Furthermore, complete inter-rater concordance was achieved when tested in a systematic sample of 100 strokes.<sup>13</sup> Strokes were regarded as incident if they occurred after the date of return of the 1980 questionnaires but before June 1, 1994. Only confirmed and probable strokes were considered in the analyses of total stroke. For analyses of intraparenchymal hemorrhage and other specific types of stroke, only confirmed cases were included. For the end point of intraparenchymal hemorrhage, we also conducted analyses excluding women with subcortical hematoma, which is commonly caused by arteriovenous malformation, and those with concurrent subdural hematoma and cerebral infarction, because these end points have different pathogenetic mechanisms.

## Statistical Analyses

The analyses were based on incidence rates of stroke during 14 years of follow-up (1980 to 1994). For each woman, person-months of follow-up were allocated according to 1980 exposure variables and were updated according to information on biennial follow-up questionnaires until death or an end point (stroke) was reached or until May 31, 1994. From the 1980 questionnaire, we used information on the intake of fat, protein, and selected foods; the consumption of n3 polyunsaturated fatty acids; and regular exercise. We present findings based on the 1980 dietary variables without updating because we were most interested in the long-term effects of the intake of fat and protein on risk of stroke. Updating the intakes of these nutrients using the 1984, 1986, and 1990 questionnaires yielded generally similar associations with risk of stroke. Height was ascertained in 1976. Information on usual aspirin use was updated in 1982, 1984, and 1988, and data on alcohol intake were updated in 1984, 1986, and 1990. All other exposure variables (ie, body mass index, menopausal status, postmenopausal hormone use, and histories of hypertension, diabetes, high cholesterol levels, and the use of multivitamin and vitamin E supplements) were updated on each follow-up questionnaire.

The relative risk of stroke was defined as the incidence of stroke among women in various categories for intake of nutrients and foods, divided by the corresponding rate among women in the lowest category of intake. Relative risks with 95% confidence intervals (95% CI) were adjusted for age in 5-year categories and for smoking status in 5 categories (never, former, current 1 to 14 cigarettes/d, current 15 to 24/d, and current 25+/d), and tests for a linear trend across the dietary categories were conducted using median variables of each dietary category. We conducted stratified analyses by history of hypertension to assess effect modification. To adjust simultaneously for other cardiovascular risk factors, we used pooled logistic regression over the seven 2-year intervals.<sup>14</sup>

## Results

Among the 85 764 women followed for 14 years, we documented 690 incident cases of stroke that occurred during 1 164 577 person-years of follow-up; the strokes included 74 intraparenchymal hemorrhages, 129 subarachnoid hemorrhages, 385 ischemic strokes, and 102 unclassified strokes. Saturated fat intake was positively associated with smoking, diabetes, and overweight and inversely associated with vigorous exercise, alcohol intake, use of multivitamin and vitamin E supplements, and intakes of n3 polyunsaturated fat and calcium (Table 1). Intake of trans unsaturated fat had similar associations for all of these variables except diabetes, with which it had no relation. Animal protein intake was positively associated with hypertension, diabetes, overweight, vigorous exercise, use of multivitamin and vitamin E supplements, and intakes of n3 polyunsaturated fat and calcium and inversely associated with smoking and alcohol intake.

In analyses adjusted for age and smoking, women in the lowest quintile for saturated fat had a greater risk of intraparenchymal hemorrhage than those with higher intakes (Table 2), but the association was nonlinear. A similar relation was observed for trans unsaturated fat intake. We observed a modest, nonsignificant trend toward a lower risk of intraparenchymal hemorrhage with increased intake of monounsaturated fat, probably due to the high correlation with saturated fat intake ( $r=0.81$ ). These relations were not altered appreciably after adjustment for total energy intake and other cardiovascular risk factors. Intakes of cholesterol, polyunsaturated fat, and total fat were not significantly associated with risk of intraparenchymal hemorrhage. There was no signifi-

**TABLE 1. Baseline Characteristics and Risk Factors in a Cohort of 85 764 Women in 1980, According to the Intake of Saturated Fat, Trans Unsaturated Fat, and Animal Protein**

	Saturated fat			Trans unsaturated fat			Animal protein		
	Lowest	Intermediate	Highest	Lowest	Intermediate	Highest	Lowest	Intermediate	Highest
Mean age, y	46.9	46.0	45.8	47.2	45.8	45.7	45.8	46.0	46.9
Women with potential risk indicators, %*									
Current smoking	26.6	27.1	33.3	28.5	28.4	29.9	33.0	27.7	25.6
Hypertension	17.2	15.3	15.0	16.1	15.7	15.5	14.2	15.0	18.1
Diabetes	1.8	2.1	2.4	2.2	2.1	2.2	1.2	0.0	3.3
High cholesterol levels	6.7	5.1	4.3	5.5	5.1	5.3	4.6	4.9	6.4
Body mass index $\geq 29$ kg/m <sup>2</sup>	12.3	14.0	15.0	11.1	13.9	15.6	11.1	12.4	18.3
Current hormone use in postmenopausal women	34.2	36.3	39.2	36.1	38.2	35.8	34.5	38.3	36.6
Vigorous exercise†	49.6	44.2	34.0	52.8	44.4	36.5	39.5	44.9	49.0
Alcohol intake $\geq 25$ g/d	13.0	6.4	2.9	13.7	6.2	2.6	12.2	6.5	3.1
Multivitamin use	37.5	33.9	31.3	41.5	33.5	27.9	30.7	33.9	38.2
Vitamin E use	16.7	12.1	11.8	19.4	11.7	9.3	11.6	12.7	15.3
Aspirin use $\geq 1$ /wk	33.2	35.4	33.2	31.9	35.7	34.7	34.7	34.8	33.4
Percentage in highest quintile of nutrients									
Saturated fat	...	...	...	7.4	22.7	26.6	5.6	21.5	30.6
Trans unsaturated fat	12.0	20.6	26.6	...	...	...	25.9	21.6	10.4
Animal protein	16.2	16.9	29.9	28.2	20.3	10.3	...	...	...
n3 Polyunsaturated fatty acids	33.3	18.1	9.5	35.7	18.4	8.7	2.6	11.8	56.0
Calcium	24.6	16.1	18.0	31.9	18.8	10.6	6.8	18.7	35.7

The women were divided into 5 groups for each nutrient according to intake. Lowest denotes the first quintile; intermediate, the third quintile; and highest, the fifth quintile.

\*Age-adjusted by the 5-year age categories of the age distribution of the cohort.

†Sweat-producing exercise at least once a week.

cant relation between these fat intakes and risk of subarachnoid hemorrhage or ischemic stroke (Tables I and II, available at [www.circulationaha.org](http://www.circulationaha.org)).

Lower intake of animal protein tended to be associated with a higher age- and smoking-adjusted risk of intraparenchymal hemorrhage (Table 2). When we examined intakes of specific amino acids, the relative risks in the highest versus the lowest quintile of amino acid intake, after controlling for age and smoking, were 0.56 (95% CI, 0.27 to 1.14;  $P=0.09$  for trend) for methionine, 0.59 (95% CI, 0.28 to 1.22;  $P=0.04$ ) for tryptophan, 0.69 (95% CI, 0.33 to 1.46;  $P=0.13$  for trend) for aspartate, and 0.41 (95% CI, 0.18 to 0.90;  $P=0.02$  for trend) for glutamate. These associations were not appreciably altered after adjustment for total energy intake and other cardiovascular risk factors. Intake of vegetable protein was not associated with risk of intraparenchymal hemorrhage. There was no significant relation between total protein intake and risk of subarachnoid hemorrhage or ischemic stroke (Tables I and II).

The higher risk of intraparenchymal hemorrhage in the lowest quintile of saturated fat intake was somewhat attenuated but remained significant after further adjustment for intakes of cholesterol, specific types of fat, and protein (Table 3). The multivariate relative risk of the lowest quintile compared with all higher levels of intakes was 2.36 (95% CI, 1.10 to 5.09;  $P=0.03$ ). When we excluded secondary hemorrhages related to use of thrombolytic agents ( $n=4$ ) or

steroids ( $n=1$ ) and "atypical cases" with subcortical hematoma ( $n=1$ ) or hemorrhage accompanied by subdural hematoma ( $n=3$ ) or concurrent cerebral infarction ( $n=1$ ), the excess risk in the lowest quintile of saturated fat intake was more pronounced. The multivariate relative risk of the lowest quintile compared with all higher levels of intakes was 2.87 (95% CI, 1.23 to 6.47;  $P=0.01$ ). We further examined the risk of primary intraparenchymal hemorrhage in each of the 2 lowest deciles of saturated fat compared with all higher levels of intake (not shown in tables). The multivariate relative risk was 3.08 (95% CI, 1.09 to 8.74) for the lowest decile and 2.72 (95% CI, 1.13 to 6.54) for the second lowest decile ( $P=0.02$  for trend).

The significant excess risk of intraparenchymal hemorrhage in the lowest quintile of trans unsaturated fat intake persisted after further adjustment for intakes of cholesterol and specific types of fat and protein (Table 3); the relative risk of the lowest quintile compared with all higher levels of intakes was 2.50 (95% CI, 1.35 to 4.65;  $P=0.004$ ). The multivariate relative risk of primary intraparenchymal hemorrhage was 2.73 (95% CI, 1.20 to 6.21) for the lowest decile and 2.53 (95% CI, 1.19 to 5.39) for the second lowest decile ( $P=0.006$  for trend).

An inverse relation between animal protein and risk of intraparenchymal hemorrhage also remained significant after further adjustment for intakes of cholesterol, specific types of fat, and vegetable protein (Table 3). The association was

**TABLE 2. Relative Risk (95% CI) of Intraparenchymal Hemorrhage in a Cohort of 85 764 Women From 1980 to 1994, According to Quintiles of Calorie-Adjusted Intake of Dietary Fat, Cholesterol, and Protein**

Nutrient/Stroke Category	Quintiles of Intake					P for Trend
	1	2	3	4	5	
<b>Total fat</b>						
Median, g/d	52	63	70	77	87	
No. of women	18	14	12	14	16	
Age and smoking-adjusted RR	1.0	0.84 (0.42–1.67)	0.70 (0.34–1.44)	0.82 (0.41–1.64)	0.94 (0.48–1.83)	0.93
Multivariate RR	1.0	0.85 (0.42–1.72)	0.69 (0.33–1.45)	0.81 (0.40–1.67)	0.92 (0.45–1.88)	0.77
<b>Saturated fat</b>						
Median, g/d	20	25	28	31	36	
No. of women	25	8	11	13	17	
Age and smoking-adjusted RR	1.0	0.30 (0.13–0.65)	0.47 (0.23–0.94)	0.49 (0.25–0.96)	0.70 (0.38–1.30)	0.38
Multivariate RR	1.0	0.30 (0.14–0.68)	0.47 (0.23–0.95)	0.52 (0.26–1.02)	0.73 (0.39–1.39)	0.42
<b>Monosaturated fat</b>						
Median, g/d	20	25	29	32	38	
No. of women	20	14	10	17	13	
Age and smoking-adjusted RR	1.0	0.66 (0.33–1.29)	0.42 (0.20–0.87)	0.82 (0.43–1.55)	0.61 (0.30–1.22)	0.32
Multivariate RR	1.0	0.64 (0.32–1.27)	0.38 (0.17–0.81)	0.73 (0.37–1.44)	0.53 (0.25–1.12)	0.13
<b>Polyunsaturated fat</b>						
Median, g/d	4.5	6.0	7.2	8.6	11.1	
No. of women	19	12	15	17	11	
Age and smoking-adjusted RR	1.0	0.68 (0.33–1.39)	0.93 (0.48–1.82)	0.99 (0.52–1.89)	0.74 (0.36–1.51)	0.70
Multivariate RR	1.0	0.69 (0.33–1.42)	0.96 (0.48–1.90)	0.99 (0.51–1.93)	0.69 (0.33–1.48)	0.59
<b>Trans unsaturated fat</b>						
Median, g/d	2.5	3.3	3.9	4.6	5.7	
No. of women	27	8	10	16	13	
Age and smoking-adjusted RR	1.0	0.37 (0.17–0.81)	0.38 (0.19–0.78)	0.71 (0.39–1.29)	0.55 (0.28–1.05)	0.20
Multivariate RR	1.0	0.36 (0.16–0.80)	0.35 (0.17–0.73)	0.64 (0.33–1.21)	0.48 (0.24–0.96)	0.11
<b>Cholesterol</b>						
Median, g/d	212	275	322	371	465	
No. of women	12	15	19	16	12	
Age and smoking-adjusted RR	1.0	1.34 (0.63–2.85)	1.71 (0.83–3.51)	1.35 (0.63–2.89)	1.03 (0.45–2.35)	0.98
Multivariate RR	1.0	1.36 (0.63–2.93)	1.68 (0.83–3.51)	1.38 (0.64–2.98)	1.04 (0.46–2.38)	0.98
<b>Animal protein</b>						
Median, g/d	42.7	52.9	60.4	68.2	81.6	
No. of women	21	15	14	12	12	
Age and smoking-adjusted RR	1.0	0.75 (0.39–1.45)	0.67 (0.33–1.33)	0.56 (0.27–1.16)	0.58 (0.28–1.19)	0.08
Multivariate RR	1.0	0.73 (0.38–1.44)	0.66 (0.33–1.33)	0.53 (0.24–1.13)	0.47 (0.20–1.11)	0.06
<b>Vegetable protein</b>						
Median, g/d	9.5	11.9	13.8	16.0	19.7	
No. of women	18	12	10	19	15	
Age and smoking-adjusted RR	1.0	0.70 (0.33–1.48)	0.55 (0.25–1.22)	1.09 (0.57–2.12)	0.78 (0.38–1.62)	0.88
Multivariate RR	1.0	0.71 (0.34–1.47)	0.57 (0.26–1.24)	1.08 (0.56–2.09)	0.81 (0.40–1.63)	0.96

The multivariate models included the following: age (5-year categories), smoking status (5 categories), time interval, body mass index (5 categories), alcohol intake (4 categories), menopausal status and postmenopausal hormone use, vigorous exercise (yes vs no), usual aspirin use (<1/wk, 1–2/wk, 3–6/wk, 7–14/wk, and 15+/wk), multivitamin use (yes vs no), vitamin E use (yes vs no), n3 fatty acid intake (quintile), calcium intake (quintile), and histories of hypertension, diabetes, and high cholesterol levels (yes vs no) and total energy intake (quintile).

slightly stronger after exclusion of secondary or atypical hemorrhage.

The excess risk of intraparenchymal hemorrhage in the lowest quintile of saturated fat intake was seen primarily

among women with a history of hypertension (Table 4). The multivariate relative risk in the lowest quintile compared with all other levels of intake was 3.66 (95% CI, 1.09 to 12.3; P=0.04) among hypertensives and 1.73 (95% CI, 0.62 to



**TABLE 3. Multivariate Relative Risk (95% CI)\* of Intraparenchymal Hemorrhage After Additional Adjustment for Dietary Cholesterol, Fat, and Protein in a Cohort of 85 764 Women from 1980 to 1994, According to Quintiles of Calorie-Adjusted Dietary Saturated Fat, Trans Unsaturated Fat, and Animal Protein**

Nutrient/Stroke Category	Quintiles of Intake					P for Trend†
	1	2	3	4	5	
<b>Saturated fat‡</b>						
Intraparenchymal hemorrhage						
No.	25	8	11	13	17	
Multivariate RR	1.0	0.35 (0.14–0.86)	0.54 (0.20–1.41)	0.63 (0.22–1.83)	1.05 (0.32–3.39)	0.83 (0.03)
Primary intraparenchymal hemorrhage§						
No.	23	7	9	13	12	
Multivariate RR	1.0	0.30 (0.12–0.80)	0.48 (0.14–1.19)	0.53 (0.17–1.62)	0.55 (0.15–1.99)	0.43 (0.01)
<b>Trans unsaturated fat‡</b>						
Intraparenchymal hemorrhage						
No.	27	8	10	16	13	
Multivariate RR	1.0	0.37 (0.16–0.84)	0.53 (0.23–1.22)	0.57 (0.26–1.27)	0.43 (0.17–1.10)	0.15 (0.004)
Primary intraparenchymal hemorrhage§						
No.	24	7	8	14	11	
Multivariate RR	1.0	0.37 (0.15–0.89)	0.30 (0.12–0.73)	0.56 (0.24–1.30)	0.40 (0.15–1.08)	0.13 (0.005)
<b>Animal protein</b>						
Intraparenchymal hemorrhage						
No.	21	15	14	12	12	
Multivariate RR	1.0	0.66 (0.32–1.38)	0.53 (0.23–1.22)	0.38 (0.15–1.00)	0.32 (0.10–1.00)	0.04 (0.14)
Primary intraparenchymal hemorrhage§						
No.	20	11	13	9	11	
Multivariate RR	1.0	0.49 (0.22–1.11)	0.48 (0.20–1.16)	0.27 (0.10–0.79)	0.26 (0.08–0.88)	0.03 (0.04)

\*Adjusted for factors cited in the footnotes of Tables 1 and 2, and intakes (quintile) of cholesterol, monosaturated fat, polyunsaturated fat (linoleic acid), vegetable protein, and 2 of the 3 intakes of saturated fat, trans unsaturated fat, or animal protein.

†Test for the lowest quintile vs the other higher quintiles is in parentheses.

‡The multivariate relative risk of intraparenchymal hemorrhage in the lowest quintile compared with all higher levels of saturated fat intake was 2.36 (95% CI, 1.10–5.09;  $P=0.03$ ) and that of primary intraparenchymal hemorrhage was 2.82 (95% CI, 1.23–6.47;  $P=0.01$ ). The respective relative risks according to trans unsaturated fat intake were 2.50 (95% CI, 1.35–4.65;  $P=0.004$ ) and 2.61 (95% CI, 1.34–5.07;  $P=0.005$ ), respectively.

§Secondary hemorrhage due to drug treatment and hemorrhage with subcortical hematoma, subdural hematoma, and cerebral infarction were excluded.

4.87;  $P=0.30$ ) among nonhypertensives. Such an interaction was not evident for trans unsaturated fat or animal protein intake.

We also evaluated foods that contributed importantly to intakes of saturated fat, trans unsaturated fat, or animal protein (data not shown). Women who almost never ate hard cheese were at a significantly higher risk of intraparenchymal hemorrhage than women who ate this food at least once a month, and similar inverse trends were seen for beef, pork, or lamb as a side dish; fish; ice cream; cookies; eggs; cottage cheese; and margarine. Consumption of beef, pork, or lamb as a main dish; chicken; skim or whole milk; hamburger; or white bread was not related to risk of intraparenchymal hemorrhage, and butter intake was positively associated with risk.

## Discussion

### Intake of Fat and Protein and Stroke Risk

In this large prospective study, women in the lowest quintile of either dietary saturated fat or trans unsaturated fat intake had an  $\approx 2.5$ -fold increased risk of intraparenchymal hemor-

rhage compared with women in higher quintiles, and animal protein intake was inversely associated with the risk. As hypothesized a priori, the excess risk associated with low saturated fat intake was seen primarily among women with a history of hypertension, but such an interaction was not evident for trans unsaturated fat or animal protein intake.

Our findings among American women are consistent with epidemiological observations comparing Japan and the United States. Japan has a 2-fold higher stroke mortality rate than the United States.<sup>15</sup> In one cross-cultural study, Japanese living in Japan had a 3-fold higher incidence of hemorrhagic stroke than Japanese living in America.<sup>3</sup> In 1965 through 1970, the intake of saturated fat among Japanese living in Japan was only 20% to 25% that of Japanese living in American and of American whites; the corresponding proportion for animal protein was  $\approx 60\%$ .<sup>4</sup> The intake of trans unsaturated fat among Japanese in Japan was only 5% that of American whites in 1959 through 1964.<sup>16</sup> In a rural Japanese population, the incidence of intraparenchymal hemorrhage declined by 65% between 1964 through 1968 and 1969 through 1973, with a concurrent increase in dietary meat fat from an average of 3 g/d to 12 g/d.<sup>2</sup>; in this rural Japanese

**TABLE 4. Multivariate Relative Risk (95% CI)\* of Intraparenchymal Hemorrhage After Additional Adjustment for Dietary Cholesterol, Fat, and Protein in a Cohort of 85 764 Women From 1980 to 1994, According to Quintiles of Calorie-Adjusted Intake of Dietary Saturated Fat, Trans Unsaturated Fat, and Animal Protein, Stratified by a History of Hypertension**

Nutrient/Stroke Category	Quintiles of Intake					P for Trend†
	1	2	3	4	5	
<b>Saturated fat‡</b>						
With a history of hypertension						
No.	14	2	5	5	4	
Multivariate RR	1.0	0.17 (0.04–0.85)	0.50 (0.11–2.21)	0.37 (0.06–2.19)	0.22 (0.13–1.72)	0.10 (0.04)
Without a history of hypertension						
No.	11	6	6	8	13	
Multivariate RR	1.0	0.54 (0.17–1.71)	0.63 (0.17–2.34)	0.89 (0.22–3.58)	2.41 (0.54–10.7)	0.12 (0.30)
<b>Trans unsaturated fat‡</b>						
With a history of hypertension						
No.	12	3	4	5	6	
Multivariate RR	1.0	0.46 (0.12–1.76)	0.47 (0.09–2.64)	0.59 (0.15–2.33)	0.46 (0.10–2.05)	0.36 (0.16)
Without a history of hypertension						
No.	15	5	6	11	7	
Multivariate RR	1.0	0.38 (0.13–1.12)	0.30 (0.10–0.95)	0.68 (0.24–1.95)	0.37 (0.10–1.45)	0.28 (0.04)
<b>Animal protein</b>						
With a history of hypertension						
No.	9	5	5	3	8	
Multivariate RR	1.0	0.65 (0.19–2.28)	0.59 (0.15–2.31)	0.25 (0.05–1.37)	0.47 (0.09–2.64)	0.37 (0.31)
Without a history of hypertension						
No.	12	10	9	9	4	
Multivariate RR	1.0	0.66 (0.26–1.68)	0.50 (0.17–1.48)	0.43 (0.13–1.46)	0.18 (0.05–0.95)	0.05 (0.31)

\*Adjusted for factors cited in the footnotes of Tables 1 and 2 and intakes (quintile) of cholesterol, monosaturated fat, polyunsaturated fat (linoleic acid), vegetable protein, and 2 of the 3 intakes of saturated fat, trans unsaturated fat, or animal protein.

†Test for the lowest quintile vs the other higher quintiles is in parentheses.

‡The multivariate relative risk of intraparenchymal hemorrhage in the lowest quintile compared with all higher levels of saturated fat intake was 3.66 (95% CI, 0.9–12.3; P=0.04) among hypertensives and 1.73 (95% CI, 0.62–4.87; P=0.30) among nonhypertensives. The respective relative risk according to trans unsaturated fat intake was 2.05 (95% CI, 0.74–5.69; P=0.17) and 2.42 (95% CI, 1.10–5.31; P=0.03).

population, the incidence of subarachnoid hemorrhage was low and did not change substantially.<sup>2</sup> National statistics show that age-adjusted mortality from total stroke declined by 29% between 1965 and 1975. This period saw a doubling of the intake of meat and saturated fat and a 36% increase in animal protein intake.<sup>17</sup> In the present study, the median animal protein intake in the lowest quintile of 43 g/d corresponded to the current mean consumption among Japanese living in Japan (≈40 g/d).<sup>18</sup> The mean saturated fat intake in the lowest decile in the present study (17 g/d) was similar to the mean intake in Japan (16 g/d).<sup>18</sup>

The limitations of the present study warrant discussion. First, it is possible that women who had a low intake of saturated fat, trans unsaturated fat, and animal protein were at a higher risk for intraparenchymal hemorrhage due to other health habits and behaviors. This likelihood was reduced by the multivariate adjustment for a wide variety of potential confounding variables, including traditional cardiovascular risk factors, hormone and vitamin use, physical activity, usual aspirin use, alcohol intake, dietary fat and cholesterol intake, and total energy intake, which only had a small effect on the associations observed. In this cohort, <2% drank ≥45 g of

alcohol per day, and the results were essentially the same when these heavy drinkers were excluded (data not shown).

Second, the relation of either saturated or trans unsaturated fat with risk of intraparenchymal hemorrhage was highest in the lowest quintile of the nutrients and lowest in the second quintile but then rose again with intake through the third to fifth quintiles. This shape of the relation may weaken support for a causal interpretation. However, a rise in the higher quintiles was compatible with random variation and became smaller when we examined primary intraparenchymal hemorrhage and then further restricted the analysis to women with a history of hypertension. Furthermore, the excess risk of intraparenchymal hemorrhage with the lowest 2 deciles of saturated fat and trans unsaturated fat intake was graded. Because low intakes of these 2 types of fat are associated with low serum total cholesterol levels,<sup>19,20</sup> the present findings are compatible with the reported association between serum total cholesterol and risk: risk was increased among persons with very low serum cholesterol levels (≤4.14 mmol/L [160 mg/dL]), and plateaued at higher cholesterol levels.<sup>8,9</sup>

Third, measurement errors in assessing nutrient intake are inevitable, but in this prospective study, any errors are likely

nondifferential and would have tended to attenuate associations with saturated fat, trans unsaturated fat, and animal protein toward the null.

A previous meta-analysis of randomized clinical trials for cholesterol lowering in individuals at a high risk of coronary disease found an increased risk of fatal stroke (odds ratio for treated versus control, 2.64; 95% CI, 1.42 to 4.92) in 3 trials using clofibrate.<sup>21</sup> Because intraparenchymal hemorrhage is more likely to be fatal than ischemic stroke, this excess risk may have been due to intraparenchymal hemorrhage.<sup>21</sup> Two recent meta-analyses of statin treatment trials showed a significant reduction of nonfatal stroke, but results for fatal stroke were inconclusive; the overall odds ratios for treatment versus control were 1.17 (95% CI, 0.69 to 1.67)<sup>22</sup> and 0.77 (95% CI, 0.57 to 1.04).<sup>23</sup> Type of stroke was not distinguished.

### Potential Mechanisms for Increased Risk of Intraparenchymal Hemorrhage

Intraparenchymal hemorrhage is caused by the rupture of microaneurysms resulting from the arterionecrosis (fibrinoid necrosis or lipohyalinosis) of small intracerebral penetrating arterioles (diameter, 100 to 200  $\mu\text{m}$ ) from the basal ganglia, thalamus, and brain stem.<sup>24</sup> Hypertension is a major cause of arterionecrosis. Penetrating arteries are more vulnerable to arterionecrosis than small arteries in subcortical regions because they have larger lumens relative to their wall thickness, sustain higher wall stress, and are liable to injure cell membranes.<sup>25</sup>

In hypertensive rats, a diet-induced increase in serum cholesterol from very low to moderate levels was associated with a reduction in arterionecrosis<sup>26</sup> and fewer strokes.<sup>27</sup> Hypertensive patients with ischemic cerebral infarction and extracerebral atherosclerosis had higher serum cholesterol levels and less arterionecrosis than hypertensive patients without cerebral infarction.<sup>25</sup> Also, neonatal rat cardiomyocytes depleted of cholesterol were more prone to anoxia because cholesterol depletion increases permeability and ion fluxes across the membranes of cardiomyocytes, which may lead to cell death.<sup>28</sup> In addition to a possible direct effect on vascular walls, low serum cholesterol levels may prevent atherosclerosis in carotid arteries and large cerebral arteries in the circle of Willis, which in turn exposes the distal penetrating arteries to higher wall stress and may enhance arterionecrosis in the presence of systematic hypertension.<sup>25</sup> Several observational and experimental studies<sup>29–31</sup> suggest that low intakes of saturated fat and trans unsaturated fat reduce platelet aggregability, which may enhance the chance of bleeding in the presence of arterionecrosis. These findings suggest that low intakes of saturated fat and trans unsaturated fat, which contribute to low serum total cholesterol concentrations<sup>19,20</sup> and/or reduced platelet aggregation, may lead to the development of intraparenchymal hemorrhage.

Stroke-prone spontaneously hypertensive rats fed a diet high in animal protein, specifically sulfur amino acids, had a delayed onset of hypertension and fewer strokes.<sup>32</sup> These experiments followed observations<sup>33</sup> that stroke-prone hypertensive rats fed a Japanese commercial diet had a 3-fold higher incidence of stroke than those fed an American diet.

The main difference between the 2 diets was in the concentrations of methionine; they were not significantly different in fat, fiber, minerals, or vitamins. Those findings were similar to the present findings for specific amino acids. The inverse association of dietary animal protein and urinary sulfur amino acids with blood pressure levels in humans<sup>34</sup> also suggest that the apparent protective effect of animal protein on the risk of intraparenchymal hemorrhage might be due, in part, to the attenuation of high blood pressures.

### Dietary Patterns and Public Health Implications

In the present study, women with a high incidence of intraparenchymal hemorrhage reported only rare consumption of meat as a side dish, fish, ice cream, cookies, eggs, cottage cheese, and margarine, which resulted in low intakes of saturated fat, trans unsaturated fat, and animal protein. Vegetarians generally consume little saturated fat,<sup>35</sup> but there are no reports of excess risk of intraparenchymal hemorrhage among such groups. Low mortality rates from total stroke among vegetarians<sup>36</sup> may limit the statistical power to assess these associations. Vegetarian diets consumed by choice, rather than because of poverty, are characterized by a high intake of fruits and vegetables, which may contribute to lower blood pressure levels and lower risk of overall stroke.<sup>36</sup>

Because lowering serum cholesterol by medication and dietary modification has been effective for the primary prevention of coronary heart disease in the United States and Europe, overall reductions of animal fat intake and trans unsaturated fat are warranted in Western countries.<sup>37,38</sup> However, a very low intake of animal fat and protein, as consumed by large populations in Asia and by some persons in Western countries, may not be optimal for the primary prevention of cardiovascular disease.

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