

Red Meat Consumption and Risk of Stroke

A Meta-Analysis of Prospective Studies

Joanna Kaluza, PhD; Alicja Wolk, DMSc; Susanna C. Larsson, PhD

Background and Purpose—Prospective studies of red meat consumption and risk of stroke have provided inconsistent results. We performed a meta-analysis to summarize the evidence regarding the effects of red meat (fresh, processed, and total) consumption on stroke risk.

Methods—Studies were identified by searching the PubMed database through May 26, 2012, and by reviewing the reference lists of retrieved articles. Prospective studies that reported relative risks (RR) with 95% confidence intervals (CI) for the association between red meat consumption and risk of stroke were eligible. Results were combined using a random-effects model.

Results—Five articles including results from 6 prospective studies with 10 630 cases of stroke and 329 495 participants were included in the meta-analysis. For each serving per day increase in fresh red meat, processed meat, and total red meat consumption, the RR (95% CI) of total stroke were 1.11 (1.03–1.20), 1.13 (1.03–1.24), and 1.11 (1.06–1.16), respectively, without heterogeneity among studies ($P > 0.16$). Among 4 articles with results for stroke subtypes, the risk of ischemic stroke was positively associated with consumption of fresh red meat (RR, 1.13; 95% CI, 1.00–1.27), processed meat (RR, 1.15; 95% CI, 1.06–1.24), and total red meat (RR, 1.12; 95% CI, 1.05–1.19); no statistically significant associations were observed for hemorrhagic stroke.

Conclusion—Results from this meta-analysis indicate that consumption of fresh red meat and processed red meat as well as total red meat is associated with increased risk of total stroke and ischemic stroke, but not hemorrhagic stroke. (*Stroke*. 2012;43:2556–2560.)

Key Words: meat ■ meta-analysis ■ prospective studies ■ stroke

High consumption of red meat has been associated with increased risk of total, cardiovascular, and cancer mortality,¹ as well as with some types of cancers, including colorectal,^{2,3} pancreatic,⁴ esophageal, and stomach cancer.^{5,6} Moreover, results of studies indicated that processed meat consumption is connected with higher incidence of coronary heart disease⁷ and type 2 diabetes.^{1,7,8} Whether red meat consumption increases the risk of stroke is unclear. In a meta-analysis published by Micha et al,⁷ which was based on only 3 studies with a total of 2280 stroke cases, a positive relation between red meat consumption and stroke was observed in 1 study,⁹ but not in the other 2 studies.^{10,11} Furthermore, the authors presented results of combining the relative risk (RR) for different stroke subtypes (ischemic stroke, hemorrhagic stroke, and total stroke), which could have influenced the findings.

Clarifying the relationship between red meat consumption and stroke is relevant because of the high incidence of stroke,

the high morbidity and mortality associated with the disease, and the widespread consumption of red meat. According to the American Heart Association report, each year $\approx 795\,000$ people experience a new or recurrent stroke and every 4 minutes someone dies from the disease.¹² At the same time, in many countries red meat consumption is high and has remained at a stable level for several years. Nationally representative data collected for United States adults indicated that red meat consumption was approximately the same in surveys from 1988 to 1994 (45.5 g/d per person) and 1999 to 2004 (39.9 g/d per person), but it was lower in a survey conducted in 1994 to 1996 (32.3 g/d per person).¹³

Therefore, we conducted a systematic review and a meta-analysis of prospective studies to assess the relation between consumption of red meat (fresh red meat, processed meat, and total red meat) and the risk of total stroke and stroke subtypes. This meta-analysis includes 4.7-times more stroke cases and

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Larsson had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Kaluza, Wolk, and Larsson. Acquisition of data: Kaluza and Larsson. Analysis and interpretation of data: Larsson and Kaluza. Drafting of the manuscript: Kaluza and Larsson. Critical revision of the manuscript for important intellectual content: Kaluza, Wolk, and Larsson. Statistical analysis: Larsson. Study supervision: Wolk and Larsson.

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>2.2-times more participants compared with the previous meta-analysis.⁷ Moreover, this meta-analysis examines whether the association between red meat consumption and stroke risk differs by stroke subtypes, which could not be addressed in the previous meta-analysis.

Materials and Methods

Literature Search and Selection

We conducted a literature search through May 26, 2012, using the PubMed database (<http://www.ncbi.nlm.nih.gov/pubmed>) without language restrictions. The search term “stroke” was used in combination with “meat,” “beef,” “pork,” “veal,” “lamb,” “steak,” or “hamburger,” and with the processed meat items “ham,” “bacon,” or “sausage.” In addition, we reviewed the reference lists of retrieved articles to identify additional relevant studies.

Studies were included in the meta-analysis if the following criteria were met: (1) had a prospective design; (2) the exposure studied was fresh red meat, processed meat, and/or total red meat consumption; (3) the outcome of interest was stroke and stroke subtypes; and (4) reported RR with 95% confidence intervals (CI). If data were duplicated in >1 study, then we included the study with the largest number of stroke cases.

Data Extraction

The following data were extracted from each study: first author’s last name, publication year, country where the study was performed, name of cohort study, study period, number of cases and cohort size, sex and age, type and categories of red meat consumption, stroke subtypes, covariates adjusted for in the analysis, and RR with 95% CI of total strokes and stroke subtypes for each category of meat consumption or for a 1 serving per day increase in consumption. Study selection and data extraction were conducted independently by 2 investigators (J.K. and S.C.L.), with disagreements resolved by consensus.

Statistical Analysis

We transformed the reported RR and corresponding standard errors (derived from the CI) to their natural logarithms to stabilize the variances and to normalize the distributions. Because the majority of the studies provided results in servings (or frequency), rather than in grams, of red meat consumption, we used the results for servings per day. For 2 studies^{14,15} that provided results in grams per day, we used the original data to estimate the RR with 95% CI for a 1 serving per day increase in red meat consumption. We combined the results for a 1 serving per day increase in consumption of red meat using a random-effects model, which takes into account both within-study and between-study variabilities.^{16,17} If the study only provided results by categories of red meat consumption, then we estimated the RR with corresponding 95% CI for a 1 serving per day increase in red meat consumption using the method proposed by Greenland and Longnecker¹⁸ and Orsini et al.¹⁹ The median or mean level of red meat consumption for each consumption category was assigned to the corresponding RR. When the median or mean consumption per category was not reported, we assigned the midpoint of the upper and lower boundaries in each category as the average consumption. If the upper boundary of the highest category was not provided, then we assumed that it had the same amplitude as the previous category.

We conducted a sensitivity analysis in which 1 study at the time was removed and the rest were analyzed to assess the influence on single studies on the overall estimates. Furthermore, we conducted analyses stratified by geographic region and stroke subtypes (ischemic and hemorrhagic strokes). If the study presented results separately for intracerebral hemorrhage and subarachnoid hemorrhage, then we combined the results for the 2 subtypes. Statistical heterogeneity among studies was assessed using the I^2 statistics.²⁰ We considered 2 cut points for the I^2 values: <30% (no or marginal between-study heterogeneity), 30% to 75% (mild heterogeneity), and >75% (notable heterogeneity). Test for publication bias was based

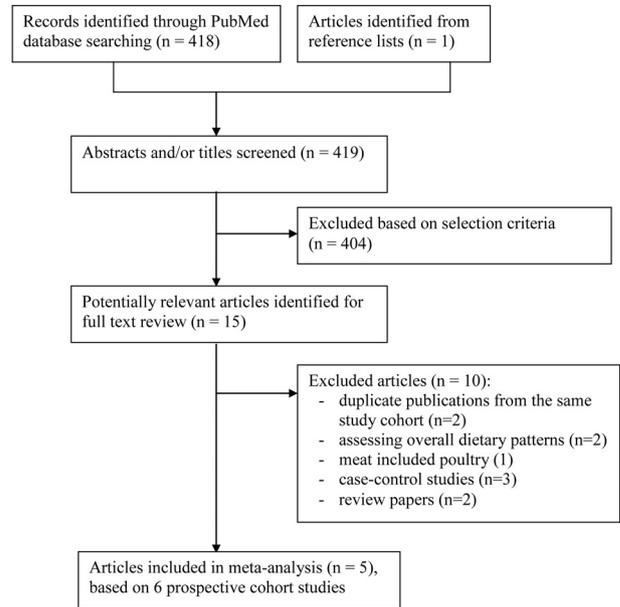


Figure 1. Flow chart of study selection.

on Egger test.¹⁷ All statistical analyses were performed with Stata (StataCorp). P values were 2-sided and $P < 0.05$ was considered statistically significant.

Results

Study Characteristics

The detailed steps of our literature search are shown in Figure 1. Six studies were excluded for the following reasons: case-control study; review paper; assessing overall dietary pattern; or total meat included poultry. We identified 7 articles, based on 8 prospective studies, that investigated the relationship between fresh red meat, processed meat, and/or total red meat consumption and stroke risk.^{9–11,14,15,21,22} Two^{9,11} studies were excluded because data from those cohorts had been reanalyzed with longer follow-up and more stroke cases and published once again;²¹ only the latest publication²¹ was included in this meta-analysis. Hence, the present meta-analysis included results from 6 independent prospective studies (published in 5 articles).^{10,14,15,21,22}

The eligible studies were published between 2003 and 2012, and included a total of 10 630 stroke cases and 329 495 participants (Supplementary Table 1). Data about subtypes of stroke were presented in 4 articles^{14,15,21,22} and contained 6420 cases of ischemic stroke and 1276 cases of hemorrhagic stroke. Two studies were conducted in Europe, 3 (published in 2 articles) were conducted in the United States, and 1 was conducted in Japan. Two studies provided results for red meat consumption in grams per day, 3 in servings per day, and 1 in frequency (how often). In 2 articles, stroke events were identified using The International Classification of Diseases 10th revision,^{14,15} in which strokes were classified as ischemic stroke (International Classification of Diseases 10th revision code I63), hemorrhagic strokes (International Classification of Diseases 10th revision codes I60 and I61), and unspecified strokes (I64). Bernstein et al²¹ classified strokes according to criteria in the National Survey of Stroke. Yaemsiri et al²² identified incident cases of ischemic stroke through self-

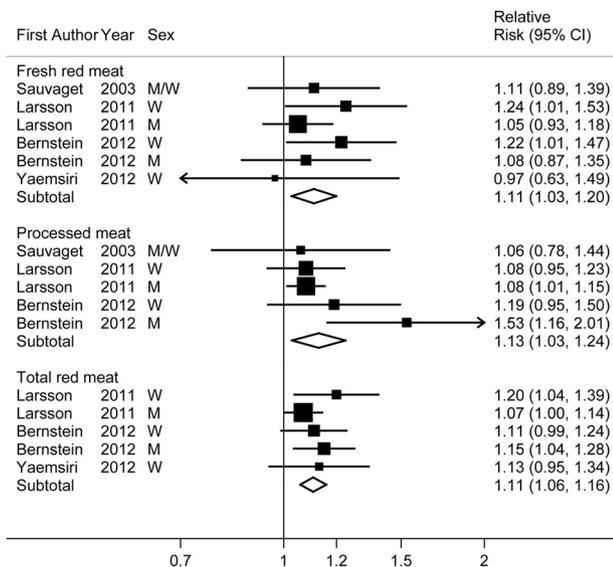


Figure 2. Relative risks of total incident stroke and stroke mortality for a 1 serving per day increase in fresh red meat, processed meat, and total red meat consumption. One serving equals \approx 50 g of processed meat and 100 to 120 g of fresh red meat and total red meat. Squares represent study-specific relative risk estimates (size of the square reflects the study-specific statistical weight, ie, the inverse of the variance). Horizontal lines represent 95% confidence interval (CI). Diamonds represent summary relative risk estimates with 95% CI. Tests for heterogeneity: fresh red meat, $Q=3.35$; $P=0.65$; $I^2=0\%$; processed meat, $Q=6.43$; $P=0.17$; $I^2=37.8\%$; and total red meat, $Q=2.80$; $P=0.59$; $I^2=0\%$.

reports; however, $>95\%$ of the cases were classified based on brain imaging and the Trial of ORG 10172 Acute Stroke Trial (TOAST) classification. In the study by Sauvaget et al,¹⁰ stroke deaths were ascertained by linkage to the nationwide family registration system of Japan and were coded according to the International Classification of Diseases 9th revision codes.

All studies provided RR and 95% CI that were adjusted for age, body mass index, and alcohol consumption. Moreover, almost all studies further controlled for smoking, physical activity, history of diabetes, history of hypertension, energy intake, and fruit and vegetable consumption.

Red Meat Consumption and Stroke

The RR (95% CI) of total stroke for an increment of 1 serving per day in red meat consumption are shown in Figure 2. The summary RR estimates showed that fresh red meat, processed meat, and total red meat consumption were associated with a statistically significant 11% to 13% increase in stroke risk, without heterogeneity among studies (all P for heterogeneity >0.16).

In a sensitivity analysis in which 1 study at the time was excluded and the rest were analyzed, the RR of stroke for each 1 serving per day increment of total red meat consumption ranged from 1.10 (95% CI, 1.04–1.15) when excluding the Swedish Mammography Cohort¹⁴ to 1.14 (95% CI, 1.07–1.22) when excluding the Cohort of Swedish Men.¹⁵ For fresh red meat, the corresponding RR ranged from 1.09 (95% CI, 1.00–1.19) when excluding the Nurses' Health Study²¹ to 1.16 (95% CI, 1.04–1.28) when excluding the Cohort of

Swedish Men.¹⁵ For processed red meat, excluding 1 of the studies at a time resulted in RR that ranged from 1.09 (95% CI, 1.03–1.15) when excluding the Health Professionals Follow-Up Study²¹ to 1.18 (95% CI, 1.02–1.37) when excluding the Cohort of Swedish Men.¹⁵ Hence, none of the individual studies alone accounted for the observed associations. Excluding the Japanese study,¹⁰ which was the only study with stroke mortality as the outcome and the only that did not adjust for physical activity and fruit and vegetable consumption, did not change the results materially (RR, 1.11 and 95% CI, 1.02–1.21 for fresh red meat; RR, 1.14 and 95% CI, 1.03–1.28 for processed meat).

When we stratified the analysis by geographic region, positive associations of fresh red meat, processed meat, and total red meat consumption with risk of stroke were observed in studies conducted in Europe (Sweden) and in the United States, but not in Japan (only 1 study). For example, for total red meat, the RR of stroke for an increase of 1 serving per day in consumption were 1.11 (95% CI, 1.00–1.24) for the 2 studies in Sweden and 1.13 (95% CI, 1.06–1.21) for the 3 United States studies.

In analyses by stroke subtypes, the risk of ischemic stroke was significantly increased for each serving per day increase in fresh red meat (RR, 1.13; 95% CI, 1.00–1.27), processed meat (RR, 1.15; 95% CI, 1.06–1.24), and total red meat consumption (RR, 1.12; 95% CI, 1.05–1.19), without heterogeneity among studies ($P>0.34$). There was no significant association between hemorrhagic stroke and consumption of fresh red meat (RR, 1.08; 95% CI, 0.84–1.39), processed meat (RR, 1.16; 95% CI, 0.92–1.46), or total red meat (RR, 1.13; 95% CI, 0.94–1.35).

We found no evidence of publication bias. The P values based on Egger test were 0.76 for fresh red meat, 0.26 for processed meat, and 0.09 for total red meat.

Discussion

This meta-analysis of 6 prospective studies, including a large number of stroke cases, showed that fresh red meat, processed meat, and total red meat consumption are significantly positively associated with risk of total stroke and ischemic stroke. Increased consumptions of 1 serving per day of fresh red meat, processed meat, and total red meat were associated with 11%, 13%, and 11% higher risk of total stroke, respectively.

There are several potential mechanisms by which red meat consumption may increase the risk of stroke. Red meat is a source of saturated fatty acids and cholesterol. Some studies have indicated that a high intake of saturated fatty acids increases plasma total cholesterol levels and low-density lipoprotein cholesterol and triglycerides,^{23–25} which could increase the risk of stroke. Moreover, red meat is a source of heme iron. It is well-known that iron is a redox-active metal that catalyzes the formation of hydroxyl free radicals in the Fenton reaction. High doses of iron may lead to oxidative stress, a state with increased peroxidation of lipids,^{26–28} protein modification, and DNA damage.^{28–30} If continued for a long time, oxidative stress induced by iron may lead to the development of many diseases, such as cardiovascular disease,^{31,32} type 2 diabetes,^{33–35} atherosclerosis,^{36,37} neurological disorders,^{38,39} and chronic inflammation.⁴⁰ According to

Liang et al,⁴¹ intake of high amounts of iron (>161 mg/wk vs <100 mg/wk) was related to higher risk of ischemic stroke. Moreover, processed meat contains sodium and nitrite preservatives, which can contribute to increased risk of cardiovascular disease, type 2 diabetes, and other diseases. Dietary sodium significantly increases blood pressure⁴² and may also lead to impaired arterial compliance and cause vascular stiffness.⁴³ Results from a meta-analysis of 10 prospective studies showed that high dietary sodium (salt) intake was associated with a significant 23% increased risk of stroke.⁴⁴ Nitrites and their products promote atherosclerosis and vascular dysfunction,⁴⁵ and they also reduced and impaired insulin secretion.^{46,47} A stronger association between red meat consumption and stroke risk is expected for processed meat than for fresh red meat because processed meat is a source of sodium and nitrite preservatives. It should be noted that the serving size for processed meat is usually smaller than for fresh red meat, which is eaten as a main dish. This may explain the similar risk estimates for 1 serving per day of processed meat and fresh red meat consumption.

This meta-analysis was based on data from large cohort studies. The prospective design minimizes the potential concern of differential recall bias, which could be a problem in case-control studies with retrospective information about exposures. By combining the results from several studies with a large number of cases, we had higher statistical power in our analyses and could detect weaker relations than in the individual studies. A limitation of any meta-analysis of observational studies is that confounding from other risk factors may have affected the results. The 5 studies from Sweden and the United States, which all observed a positive association between total red meat consumption and stroke risk, adjusted for major potential confounders such as age, smoking, body mass index, physical activity, history of diabetes, history of hypertension, total energy intake, and alcohol, fruit, and vegetable consumption. However, the possibility that residual confounding may have influenced the findings cannot be entirely excluded. Another limitation is that red meat consumption was self-reported through questionnaires, which will inevitably lead to some misclassification of exposure. Nevertheless, because information about red meat consumption was obtained before the diagnosis of stroke, any misclassification is most likely to lead to an attenuation of the true association between red meat consumption and stroke risk. The serving sizes for red meat and processed meat consumption may differ between studies and between individuals, which could have influenced the results. As a meta-analysis of published studies, we cannot rule out that publication bias may have affected our results, although we found no evidence of such bias in the present meta-analysis. Moreover, it should be emphasized that the structure of red meat consumption, ie, quantity, frequency, and dietary patterns in the United States, Sweden and Japan, is different. According to Food and Agriculture Organization of the United Nations statistics, annual consumption (in kg per person per year) of beef in the Americans and Swedes compared with the Japanese is higher, ≈ 4.8 -times and ≈ 2.7 -times, respectively, and consumption of pork is higher 2.2-times and 1.7 times,⁴⁸ which may have resulted in the

difference in intake of some nutrients such as heme iron, saturated fatty acids, and cholesterol. With regard to dietary patterns, studies among United States and Swedish women have shown that red meat consumption is correlated with consumption of refined grains, full-fat dairy products, and sweets or soft drinks.^{9,49} In a Japanese population, meat consumption correlated with consumption of fish and deep-fried foods or tempura.⁵⁰

In conclusion, results from this meta-analysis indicate that both fresh red meat and processed meat consumption may increase the risk of stroke. This finding is of great public health importance because of the widespread consumption of red meat and the high morbidity and mortality associated with stroke. Whether the association between red meat consumption and stroke risk is limited to ischemic stroke warrants further study.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table 1. Characteristics of prospective cohort studies included in the meta-analysis

Reference	Country; study name (follow-up)	No. of cases (cohort size)	Sex, baseline age	Type of meat consumption: highest vs. lowest category	Stroke subtypes	RR (95% CI) for total strokes	P for trend	Adjustments				
Incidence												
Larsson et al. ¹	Sweden; Swedish Mammography Cohort (1997-2008)	1,680 total strokes, 1,310 ISs, 154 ICHs, 79 SAHs (34,670)	W, 49-83 y	Total red meat: ≥86.0 vs. <36.5 g/d	Total stroke	1.12 (0.95-1.32)	0.12	Age, smoking status, pack-years of smoking, education, BMI, total physical activity, history of diabetes, history of hypertension, aspirin use, family history of myocardial infraction, intake of energy, alcohol, coffee, fish, fruit, vegetables				
					IS	1.22 (1.01-1.46)	0.04					
					ICH	0.59 (0.34-1.04)	0.09					
				Fresh red meat: ≥48.8 vs. <16.5 g/d	SAH	1.02 (0.48-2.16)	0.48					
					Total stroke	1.07 (0.91-1.23)	0.31					
					IS	1.12 (0.93-1.34)	0.15					
				Processed meat: ≥41.3 vs. <12.1 g/d	ICH	0.83 (0.48-1.42)	0.29					
					SAH	0.90 (0.42-1.91)	0.91					
					Total stroke	1.18 (1.00-1.38)	0.25					
					IS	1.24 (1.04-1.49)	0.15					
									ICH	0.71 (0.42-1.18)	0.20	
									SAH	1.53 (0.73-3.20)	0.27	

Larsson et al. ²	Sweden; Cohort of Swedish Men (1997-2008)	2,409 total strokes, 1,849 ISs, 350 HSs (40,291)	M, 45-79 y	Total red meat:	Total stroke	1.15 (1.00-1.33)	0.10	Age, smoking status, pack-years of smoking, education, BMI, total physical activity, history of diabetes, history of hypertension, aspirin use, family history of myocardial infraction, intake of energy, alcohol, fish, fruit, vegetables
				≥136.2 vs. <62.5 g/d	IS	1.06 (0.90-1.25)	0.53	
					HS	1.57 (1.09-2.25)	0.06	
				Fresh red meat:	Total stroke	1.07 (0.93-1.24)	0.77	
				≥83.1 vs. <33.5 g/d	IS	1.02 (0.87-1.20)	0.63	
					HS	1.27 (0.90-1.80)	0.26	
				Processed meat:	Total stroke	1.23 (1.07-1.40)	<0.01	
				≥57.1 vs. <20.1 g/d	IS	1.18 (1.01-1.38)	0.03	
					HS	1.39 (0.97-1.99)	0.15	
Bernstein et al. ³	US; Health Professionals Follow-Up Study (1986-2008)	1,397 total strokes, 829 ISs, 165 ICHs, 53 SAHs (43,150)	M, 40-75 y	Total red meat: median	Total stroke	1.28 (1.02-1.61)	0.01	Age, time period (type of study), BMI, smoking status, physical exercise, parental history of early myocardial infraction, menopausal status (in women), multivitamin use, vitamin E supplement use, aspirin use, intake of energy, alcohol, transfat, fruit and vegetables, other protein sources
				2.29 vs. 0.30 servings/d				
				Fresh red meat: median	Total stroke	1.11 (0.88-1.39)	0.51	
	1.11 vs. 0.14 servings/d							
	Processed red meat: median	Total stroke	1.27 (1.03-1.55)	<0.01				
	0.71 vs. 0.03 servings/d							
US; Nurses' Health Study (1980-2006)		2,633 total strokes, 1,383 ISs, 235 ICHs, 240 SAHs (84,010)	W, 30-55 y	Total red meat: median	Total stroke	1.19 (1.00-1.41)	0.07	
				1.92 vs. 0.44 servings/d	IS	1.22 (1.01-1.47)*	0.03	

					HS	1.19 (0.77-1.86)*	0.44	
				Fresh red meat: median	Total stroke	1.19 (1.02-1.40)	0.04	
				1.08 vs. 0.28 servings/d	IS	1.27 (1.06-1.53)*	0.05	
					HS	0.83 (0.55-1.27)*	0.57	
				Processed red meat: median	Total stroke	1.10 (0.95-1.27)	0.13	
				0.64 vs. 0.05 servings/d	IS	1.15 (0.98-1.35)*	0.03	
					HS	1.13 (0.76-1.67)*	0.25	
Yaemsiri et al. ⁴	US; Women's Health Initiative Observational Study (1994/98-2005)	1,049 ISs (87,025)	W, 50-79 y	Total red meat: per 1 serving/day	IS	1.13 (0.95-1.34)	no data	Age, race, education, family income, years as a regular smoker, hormone replacement therapy use, total metabolic equivalent task hours per week, alcohol intake, history of coronary heart disease, history of atrial fibrillation, history of diabetes, aspirin use, use of antihypertensive medication, use of cholesterol-lowering medication, BMI, systolic blood pressure, total energy intake, dietary vitamin E, fruits and vegetable intake, fiber intake
				Fresh red meat: per 1 serving/day	IS	0.97 (0.63-1.48)	no data	
Mortality								
Sauvaget et al. ⁵	Japan; Hiroshima/Nagasaki Life Span	1462 total stroke deaths, (40,349; M 15,350, W	M/W, mean 54/58 y	Fresh red meat: almost daily vs. never	Total stroke	1.01 (0.73-1.38)	0.86	Age, birth cohort, sex, city, radiation dose, BMI, smoking status, alcohol habits, education level, history of diabetes, or

Study	24,999)	Processed red meat:	Total stroke	0.90 (0.61-1.33)	0.81	hypertension
(1980/81-1996)		almost daily vs. never				

*Pooled RR and 95% CI for men and women.

†Follow-up ended in various part of communities in 1999, 2003, and 2008.

Abbreviations: BMI, body mass index; IS, ischemic stroke; SAH, subarachnoid hemorrhage; ICH, intracerebral hemorrhage; HS, hemorrhagic strokes; M, men; W, women

Reference

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4. Yaemsiri S, Sen S, Tinker L, Rosamond W, Wassertheil-Smoller S, He K: Trans fat, aspirin, and ischemic stroke in postmenopausal women. *Ann Neurol*. 2012;doi:10.1002/ana.23555. In press.
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