Red Meat Consumption and the Risk of Stroke: A Dose–Response Meta-analysis of Prospective Cohort Studies

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Background: Prospective studies of red meat consumption and risk of stroke have provided inconsistent results. We aimed to assess this association by conducting a meta-analysis of prospective cohort studies. *Methods:* Relevant studies were identified by searching PubMed and EMBASE through April 1, 2013. Summary relative risks (RR) and the corresponding 95% confidence intervals (CIs) were estimated by random-effect or fixed-effect models. *Results:* Seven prospective cohort studies were included in the analyses, involving 2,079,236 subjects and 21,730 strokes cases. Total red meat consumption was associated with total stroke (RR = 1.14, 95% CI 1.05-1.24), cerebral infarction (RR = 1.13, 95% CI 1.0-1.28), and ischemic stroke (RR = 1.22, 95% CI 1.01-1.46). A significant association was found between consumption of processed red meat and total stroke (RR = 1.17, 95% CI 1.09-1.27). Consumption of fresh red meat was significantly associated with total stroke (RR = 1.13, 95% CI 1.04-1.22) and ischemic stroke (RR = 1.15, 95% CI 1.03-1.29). However, no evidence suggests that any type of meat was associated with hemorrhagic stroke. Also, no association was found between consumption of processed red meat and ischemic stroke (RR = 1.15, 95% CI .98-1.36) and between consumption of fresh red meat and cerebral infarction (RR = 1.06, 95% CI [.94, 1.20]). A significant risk for total stroke could be observed when the consumption of total red meat was above 50 g/day, processed red meat was just above 0 g/day, and fresh red meat was above 70 g/day. *Conclusion:* Our findings indicate that high consumption of red meat, especially processed red meat, will increase the risk of stroke. **Key Words:** Meat—stroke—prospective studies—meta-analysis—dose–response.

Introduction

As the global population aging process accelerates, stroke brings great harm to middle aged and elderly people, which aggravates the patient's family and results in socioeconomic burden. According to the American Heart Association report, each year 795,000 people experience a new or recurrent stroke and every 4 minutes someone dies from the disease.[1] Owing to the high incidence and high mortality of stroke, the medical community ranks it as 1 of 3 top diseases that threatens human health, along with coronary heart disease and cancer.[2-4]

Strokes can be classified into 2 major categories: ischemic and hemorrhagic, and ischemic stroke is the predominant type accounting for 87% of all cases.[5] Ischemic stroke can also be divided into 2 main types: thrombotic and embolic. Thrombotic stroke is clinically referred to as cerebral thrombosis or cerebral infarction, and this type of event is responsible for almost 50% of

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all strokes. Owing to the category difference between cerebral infarction and ischemic stroke, it can be inferred that some factors that can cause ischemic stroke do not necessarily cause cerebral infarction, so stroke can also be divided into 3 types: cerebral infarction, hemorrhagic stroke, and ischemic stroke.

Meat consumption accounts for a large part of the diet and meat acts as a major source of protein, fat, and energy for humans. However, the 2005 U.S. Dietary Guidelines for Americans recommend that consumption of red and processed meat should be moderated.[6] Such recommendations are in large part derived from epidemiological evidence that high consumption of red meat was associated with increased risk of type 2 diabetes, digestive system disease, cancer, and cardiovascular disease.[7-10] Recently, red meat consumption as a potential risk for stroke has been studied in 2 observational studies.[11,12] However, sufficient evidence for direct relationships between red meat consumption and stroke has been lacking to support more quantitative recommendations about specific consumption levels of meats.

Accordingly, we performed 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, which could not be addressed in the previous meta-analysis.

Subjects and Methods

Search Strategy

We performed a meta-analysis on the basis of guidance of Meta-analysis of Observational Studies in Epidemiology. We performed a comprehensive literature search on PubMed database through April 1, 2013, by using key words such as "meat," "red meat," "processed meat," "meat products," "beef," "pork," "lamb," "steak," "mutton," "cardiovascular disease," "hemorrhagic stroke," "ischemic stroke," "mortalities," "risk," "death," "fatal," and "incidence" (Fig 1). In addition, we reviewed the reference lists of published articles to identify additional relevant studies. To obtain additional data or main results for the meta-analysis, we contacted authors of primary studies (Table 1).[13-19]

"Red meat" was defined as unprocessed beef, pork and lamb except for poultry, fish and eggs; "processed meat" was mainly processed red meat such as bacon, baloney, salami, hot dog, and luncheon meats except for fish and eggs; "total red meat" was defined as the total of these 2 categories.[20,21] When possible, we conducted a linear dose–response analysis of stroke risk per increment in consumption of 100 g/day for red meat and 50 g/day for processed meat using generalized least-squares trend estimation analysis developed by Greenland and Longnecker.[22]

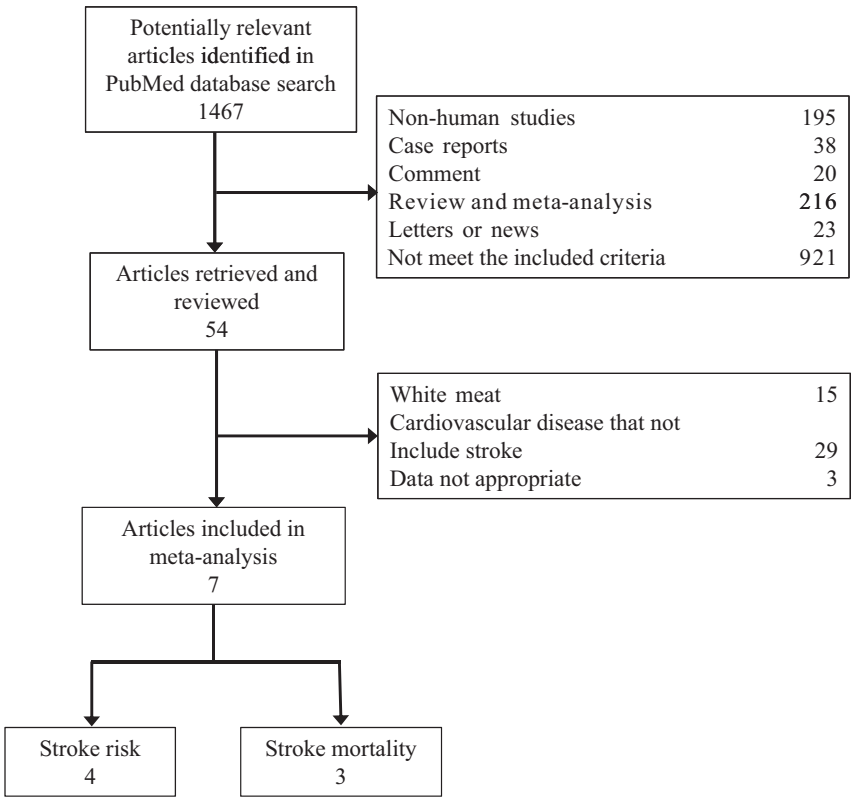

Figure 1. *Literature searched and selection of studies in the meta-analysis.*

Table 1. *Characteristics of observational studies of the relation between red meat intake and risk of stroke included in the meta-analysis*

Author	Location/study type/ follow-up years	No. of participants/ follow-up years/age	Meat type	Stroke type	RR for strokes	Dose	Adjustment
Bernstein	United States Prospective cohort Men/21 years Women/26 years	1,397 total strokes, 829 ISs, 165 IC, 53 HS Men 43,150 Age 40-75 years	Total red meat (men)	Total stroke HS IS	1.28 (1.02-1.61) 1.07 (.55-2.08) 1.31 (.97-1.77)		Age, BMI, cigarette smoking, physical exercise, parental history of early myocardial infarction, menopausal status, total energy, cereal fiber, trans fat, fruit and vegetables, other protein sources
			Total red meat (women)	Total stroke HS IS	1.19 (1.0-1.41) 1.30 (.72-2.34) 1.16 (.92-1.48)		
		2,633 total strokes, 1,383 ISs, 235 ICHs, 240 HS Women 84,010 Age 30-55 years	Processed red meat (men)	Total stroke HS IS	1.27 (1.03-1.55) 1.47 (.80-2.72) 1.31 (1.00-1.71)		
			Processed red meat (women)	Total stroke HS IS	1.10 (.95-1.27) .94 (.56-1.57) 1.07 (.87-1.31)		
			Fresh red meat (men)	Total stroke HS IS	1.11 (.88-1.39) .70 (.36-1.37) 1.23 (.91-1.67)		
			Fresh red meat (women)	Total stroke HS IS	1.19 (1.02-1.40) .93 (.54-1.60) 1.30 (1.03-1.63)		
Larsson (man)	Sweden Prospective cohort 10.1 years	2,409 incident cases of stroke (1,849 CIs, 350 HSs, and 210 unspecified strokes (40,291) Age 45-79 years	Total red meat	Total stroke CI HS	1.15 (1.00-1.33) 1.06 (.90-1.25) 1.57 (1.09-2.25)	Total red meat <62.5 62.5-88.3 88.4-110.3 110.4-136.1 ≥ 136.2	Age, smoking status, pack-years of smoking, education, BMI, total physical activity, histories of diabetes and hypertension, aspirin use, family history of myocardial infarction, and intakes of total energy, alcohol, fish, fruits, and vegetables
			Fresh red meat	Total stroke CI HS	1.07 (.93-1.24) 1.02 (.87-1.20) 1.27 (.90-1.80)	Fresh red meat and processed red meat <33.5 33.5-50.4 50.5-67.1 67.2-83.1 >83.1	
			Processed meat	Total stroke HS	1.23 (1.07-1.40) 1.39 (.97-1.99)		
Larsson (woman)	Sweden Prospective cohort 10.4 years	1,680 incident cases of stroke comprising 1,310 CIs, 154 intracerebral hemorrhages, 79 subarachnoid hemorrhages, and 137 unspecified strokes (34,670) Age 49-83 years	Total red meat	Total stroke CI IS	1.12 (.95-1.32) 1.22 (1.01-1.46) .74 (.45-1.12)	Total red meat <36.5 36.5-53.6 53.7-68.3 68.4-85.9 ≥86.0	Age, smoking status and pack-years of smoking, education, BMI, total physical activity, history of diabetes, history of hypertension, aspirin use, family history of myocardial infarction, and intakes of total energy, alcohol, coffee, fish, fruits, and vegetables
			Fresh red meat	Total stroke CI HS	1.07 (.91-1.23) 1.12 (.93-1.34) .85 (.54-1.34)	Fresh red meat and processed red meat <16.5 16.5-29.0 29.1-36.4 36.5-48.7 ≥ 48.8	
			Processed meat	Total stroke HS	1.18 (1.00-1.38) .91 (.6,1.39)		

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Table 1. (*continued*)

Author	Location/study type/ follow-up years	No. of participants/ follow-up years/age	Meat type	Stroke type	RR for strokes	Dose	Adjustment
He ka	United States Prospective cohort 14 years	455 ISs, 125 hemorrhagic stokes, and 145 strokes of unknown type (51,529) Age 40-75 years	Total red meat	Total stroke HS	1.58 (.55-4.55) .97 (.60-1.55)		BMI, physical activity, history of hypertension, smoking status, aspirin use, multivitamin use, consumption of alcohol, potassium, fiber, and vitamin E, total fruits and vegetables, total energy intake, and hypercholesterolemia
Mortality							
Takata	China Prospective cohort 11.2 years	4,210 deaths 803,265 women and 334,281 men Age 40-70 years	Red meat (women) Red meat (men)	HS IS HS IS	.57 (.37-.87) .84 (.55-1.28) .71 (.43-1.20) 1.22 (.69-2.15)		Age, total caloric intake, income, occupation, education, comorbidity index, physical activity level, total vegetable intake, total fruit intake, fish intake, red meat or poultry intake where appropriate, smoking history, consumption of alcohol
Sauvage	Japan Prospective cohort 16 years	1,462 stroke deaths 15,350 men and 24,999 women Mean age 56	Red meat Processed red meat	Total stroke Total stroke	1.01 (.73-1.38) .90 (.61-1.33)	Total red meat fresh and processed red meat 0 14.3 28.6-57.1 ≥ 100	City, radiation dose, self-reported BMI, smoking status, alcohol habits, education level, history of diabetes, or hypertension
Sirin Yaemsiri	United States and Columbia Prospective cohort 8 years	1,049 ISs (663,041) Age 50-79 years	Total red meat Red meat	Total stroke IS	.95 (.75-1.23) 1.13 (.95-1.34)		Age and race, education, family income, smoke, 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, and total energy intake, vitamin E, fruits and vegetable intake (quintiles), fiber

Abbreviations: BMI, body mass index; CI, cerebral infarction; HR, hazard risk; HS, hemorrhagic stroke; IS, ischemic stroke; RR, relative risk.
RRs include RR/HR (Song/Knekt: RR, Wedick/Nettleton: HR).

Inclusion Criteria

Studies were included if these (1) had a prospective cohort design; (2) defined the exposure factors as consumption of red meat, processed meat, or fresh meat (unprocessed meat); (3) regarded different types of stroke as primary outcome indicators; (4) presented hazard risk (HR), relative risk (RR), or odds radio (OR) estimates with 95% confidence intervals (CIs); and (5) regulated all participants as middle aged and elderly people.

Exclusion Criteria

Studies were excluded if they (1) used other languages except for English; (2) were repetitive articles or data; and (3) were articles such as comment, letter, review, editorial, and animal studies.

Data Extraction and Quality Evaluation

The following data were extracted from each study: author's name, publication year, the experiment design, study location, age range or mean age of the participants, gender, number of cases and cohort size, length of follow-up, exposure range, RR with 95% CI of total strokes and stroke subtypes for each category of meat consumption. If the exposure factors included all types of total meat, we selected only related information on total red meat and red meat types. If the studies contained total stroke, stroke types, strokes morbidity, and mortality, we chose only the number of cases, the largest sample, and the amount of information of the most complete data. Study selection and data extraction were conducted independently by 2 investigators (Yang and Pan), with disagreements resolved by consensus.

We used the Newcastle–Ottawa Scale's 9-star system to evaluate the study quality. The scoring system summarized 9 aspects of each study: representativeness of the exposed cohort, selection of the unexposed cohort, ascertainment of exposure, outcome of interest not present at the start of study, control for important factors or additional factors, outcome assessment, follow-up time long enough for outcomes to occur, and adequacy of follow-up of cohorts. Therefore, the full score was 9 stars, and a study with 7 awarded stars was defined as a high-quality study.[23]

Statistical Analysis

All analyses were performed using Stata, version 11.0 (StataCorp, College Station, TX). The extracted RRs with 95% CI (highest compared to lowest red meat consumption) were computed from adjusted RRs, HRs, and ORs (HR and OR were directly considered as RR) to measure the association between red meat consumption and the risk of strokes.

Heterogeneity between the studies was assessed using Q and I^2 statistics. Because multiple factors such as participants, outcome indicators, and methodology may affect the outcomes, we needed to do a heterogeneity test, and if the heterogeneity was significant, we needed to explore its source. For the Q statistic, a P value less than .10 was considered statistically significant for heterogeneity. For the I^2 statistic, heterogeneity was interpreted as absent (I^2 = 0%-25%), low (I^2 = 25.1%-50%), moderate (I^2 = 50.1%-75%), or high (I^2 = 75.1%-100%); if I^2 was 50% or above, we need to choose a random-effect model to indicate the obvious heterogeneity.[24,25]

A quantified dose–response relationship between total red meat, processed red meat, fresh meat consumption, and incidence of strokes was examined on the basis of the principle of Greenland and Longnecker.[22] The analysis used data from each category of average consumption, number of cases and person years, and adjusted RR with 95% CI. Forest plots and funnel plots were used to examine the overall effect and to assess the publication bias.[26,27]

Results

Literature Search and Study Characteristic

There were total 1467 citations identified through the primary search. All studies were adjusted for age, smoking, fish, fruits, vegetables, body mass index, and disease history. Moreover, most studies also presented results on total energy consumption, physical activity, education level, and alcohol. After the Newcastle–Ottawa Scale's 9-star system analyses, the included articles reached 7 stars, and the 7 identified investigations were prospective cohorts. These studies were conducted in the United States (3 articles),[13,16,19] Sweden (2 articles),[14,15] China (1 article),[18] and Japan (1 article).[17] A total of 2,079,236 unique individuals including 21,730 stroke cases were involved (Table 1). The holistic heterogeneity was low (I^2 = 0%-54.5%) and there was no indication of a publication bias, either from Egger's test (P = .780) or from Begg's test (P > .05 for both tests).

Total Red Meat Consumption and Strokes

The meta-analysis of total red meat intake and total stroke risk was based on 4 prospective cohort studies. In the highest versus lowest model, we found that the summary RR was 1.14 (95% CI 1.05-1.24). The heterogeneity test result showed no heterogeneity (I^2 = 0, P = .504) (Fig 2, A). The RR between total red meat consumption and cerebral infarction was 1.13 (95% CI 1.0-1.28), and the heterogeneity test result suggests there was no statistical significance (I^2 = 19.8%, P = .264) (Fig 2, B). The RR between total red meat and hemorrhagic stroke was 1.18 (95% CI .93-1.50); the results of the heterogeneity test indicate that the heterogeneity was moderate among the studies (Fig 2, C). The RR between total red meat and ischemic stroke was 1.22 (95% CI 1.01-1.46). The heterogeneity test conducted showed no heterogeneity among the studies (I^2 = 0%, P = .534) (Fig 2, D).

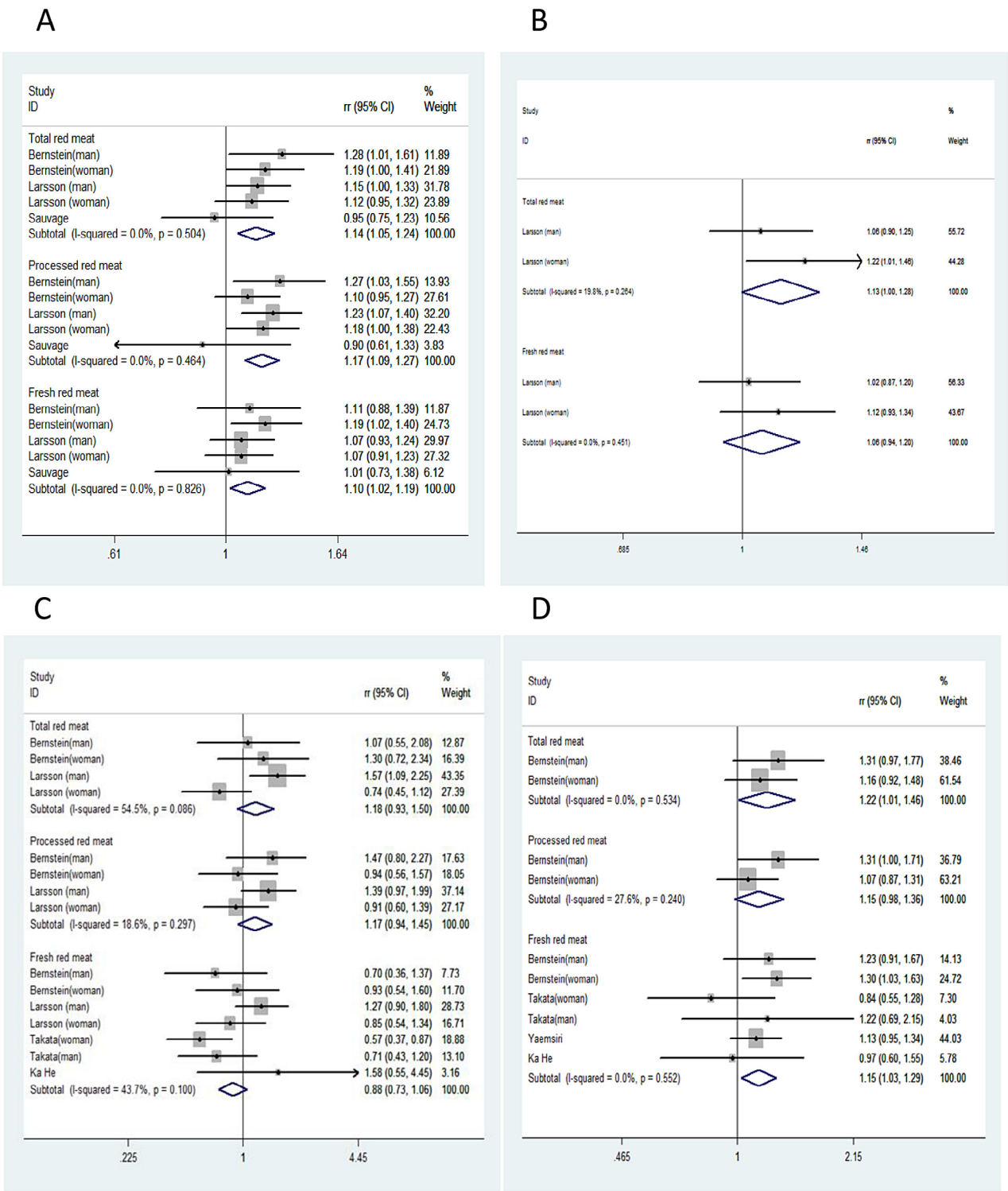

Figure 2. *(A) Estimates of red meat consumption and risk of total stroke. (B) Estimates of red meat consumption and risk of cerebral infarction. (C) Estimates of red meat consumption and hemorrhagic stroke risk. (D) Estimates of red meat consumption and ischemic stroke risk. Squares indicate study-specific risk estimates (the size of the square reflects the study statistical weight, i.e., inverse of variance); horizontal lines indicate 95% CI; diamonds indicate summary relative risk estimate with its corresponding 95% CI. Abbreviation: CI, confidence interval.*

Processed Red Meat Consumption and Stroke

Four prospective cohort studies were included in the highest model versus the lowest model; the meta-analysis of processed red meat intake and total stroke risk yielded a summary RR of 1.17 (95% CI 1.09-1.27). No heterogeneity was detected (I^2 = 0%, P = .464) (Fig 2, A). The RR between processed red meat consumption and hemorrhagic stroke was 1.15 (95% CI .92-1.44). The heterogeneity test performed (I^2 = 18.6, P = .297) (Fig 2, C) indicated that there was no significant heterogeneity among the studies. The RR between processed red meat and ischemic stroke was 1.15 (95% CI .98-1.36). Low heterogeneity was detected (I^2 = 27.6%, P = .24) (Fig 2, D).

Fresh Red Meat and Strokes

Five prospective cohort studies of fresh red meat distinction were included in the meta-analysis. In the highest model versus the lowest model, the summary RR was 1.13 (95% CI 1.04-1.22), and heterogeneity was absent (I^2 = 0%, P = .826) (Fig 2, A). The risk between fresh red meat and cerebral infarction was 1.06 (95% CI .94-1.20). No heterogeneity was detected (I^2 = 0%, P = .451) (Fig 2, B). The RR between fresh red meat and hemorrhagic stroke was .88 (95% CI .73-1.06). Low heterogeneity was detected (I^2 = 43.7%, P = .1) (Fig 2, C).The RR between fresh red meat and ischemic stroke was 1.15 (95% CI 1.03-1.29). No heterogeneity was detected (I^2 = 0, P = .552) (Fig 2, D).

Dose–Response Meta-analysis

Three studies were combined to conduct the dose–response meta-analysis on red meat consumption and total stroke. The dose–response analysis indicated that there was no risk for total stroke if the total red meat consumption was below 50 g/day; however, if the total red meat consumption was above 50 g/day, a significant risk could be observed (Fig 3, A). The consumption of processed red meat was suggested to be significantly associated with higher risk of total stroke if the dose was above 0 g/day (Fig 3, B). There was no risk for total stroke if the consumption of processed red meat was below 70 g/day; however, consumption of processed red meat above 70 g/day was related to total risk significantly (Fig 3, C).[22]

Publication Bias

Begg and Egger tests indicated no evidence of publication bias with regard to total red meat consumption in relation to the risk of total stroke (Fig 4).

Discussion

This meta-analysis of 7 prospective studies, including a large number of stroke cases, showed that there is a potential association between red meat consumption and stroke. Consumption of total red meat was associated with

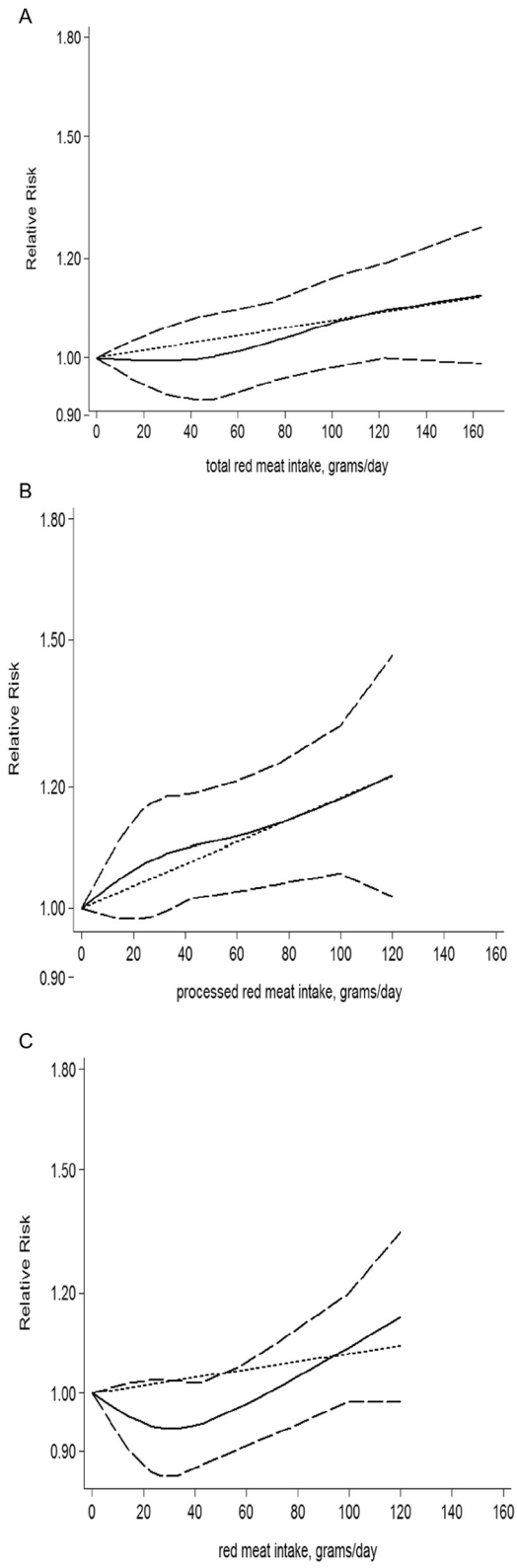

Figure 3. *Dose–response analysis. (A) Dose–response analysis of stroke risk and total red meat intake by per increment of 100 g/day for red meat, and 50 g/day for processed meat. (B) Processed red meat and total stroke risk dose–response analysis. (C) Fresh red meat and total stroke dose–response analysis. The solid line and the long dashed line represent the estimated relative risk and its 95% CI; the short dashed line represents the linear relationship. Abbreviation: CI, confidence interval.*

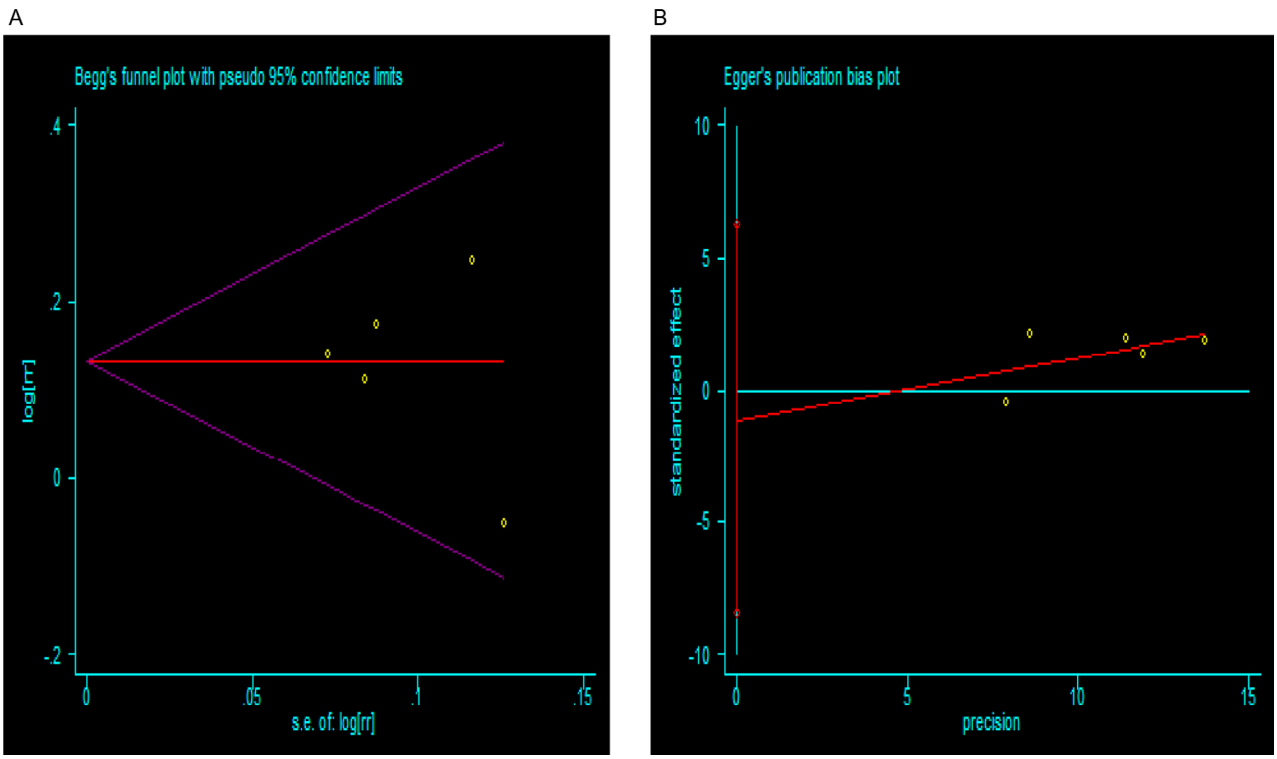

Figure 4. *Analysis of publication bias about total red meat and total stroke. (A) Begg's funnel plots to detect potential publication bias about total red meat and total stroke. (B) Egger's funnel plots to detect potential publication bias about total red meat and total stroke.*

total stroke, cerebral infarction, and ischemic stroke. There was a significant association between processed red meat consumption and total stroke. Fresh red meat consumption was significantly associated with total stroke and ischemic stroke. However, no statistically significant associations were observed for hemorrhagic stroke. Also, no association was observed between consumption of processed red meat and ischemic stroke and between consumption of fresh red meat and cerebral infarction. A significant risk for total stroke could be observed when the consumption of the total red meat was above 50 g/day, processed red meat consumption was just above 0 g/day, and fresh red meat was above 70 g/day.

The mechanism why much red meat consumption leads to stroke may be explained by several potential biochemical views. Red meat contains abundant heme iron, and heme iron can contribute to endogenous formation of N-nitroso compounds,[28] which has been linked to cardiovascular disease and stroke in epidemiological studies.[29,30] In experimental studies, nitrates and their by-products have been suggested to promote atherosclerosis and vascular dysfunction[31] and to reduce insulin secretion,[32,33] all of which may contribute to increase the risk of stroke. And oxidative stress and DNA damage caused by iron are also thought to be risk factors for stroke.[34,35] In addition, red meat contains high amounts of saturated fatty acids and cholesterol, which have been shown to have adverse effects on serum lipid profiles and subsequently may increase the risk of stroke.[36-38]

High consumption of red meat has been suggested to negatively impact on human health, but too less red meat consumption is also harmful. Red meat has been long established as an important dietary source of protein and essential nutrients including iron, zinc, and vitamin B12.[39,40] As described above, red meat is a major source of heme iron. Iron is vital for many cellular processes in the body and, as a component of hemoglobin, is essential to maintaining adequate transport of oxygen in the blood.[28] Iron-deficiency anemia is the most common nutritional deficiency worldwide, being particularly prevalent among children and young women.[41] And anemia is known to be one of the causes of stroke.[42] All in all, moderate consumption of red meat as part of a balanced diet may positively influence nutrient intake, whereas too less red meat consumption will not be beneficial for human long-term health.

The strength of our study lies in a large sample size (2,079,236 subjects and 21,730 strokes cases) and no significant evidence of publication bias. Furthermore, all the original studies included in this meta-analysis were high-quality research and had a prospective cohort design. In addition, we used the nonlinear curve fitting method to analyze the dose–response, which is more accurate and credible.

Although we have tried our best to get more precise conclusions, there still exist several limitations. First, most of population data were obtained from questionnaires, while different questionnaire designs had some loopholes. During the implementation of the questionnaire, the number of participants was so large that the questionnaire was difficult to spread, and thus questionnaire quality was not guaranteed. Second, lifestyle plays an important role. Unhealthy lifestyle such as smoking, alcohol, physical inactivity, and overeating salty foods may affect the reliability of the results. These confounding factors tend to exaggerate the risk between red meat and stroke.[43,44] Next, some diseases like heart diseases, diabetes mellitus, and hypertension will increase the risk of stroke. Heart disease patients are prone to have thrombus, which may cause a stroke; diabetes patients not only are prone to develop blood lipid metabolic disorders, which aggravate atherosclerosis, but also are prone to suffer from hypertension, which is a risk factor for stroke. A sudden change in the blood pressure of hypertensive patients will lead to a stroke.[45-47] Lastly, during the long follow-up, the participants may have changed their diets. The participants may have adjusted to a healthy diet structure in which the red meat consumption was reduced. All in all, these potential factors are likely to impact the results.

Conclusion

In summary, our meta-analysis supports that the consumption of fresh red meat, processed red meat, and total red meat has a significant association with risk for total stroke and ischemic stroke except for hemorrhagic stroke. However, the association between red meat and cerebral infarction has not been clearly confirmed. In addition, the dose–response analysis demonstrates that the consumption of processed red meat and total red meat rather than fresh red meat is consistently associated with the risk of stroke in a nonlinear fashion. These results indicate that high consumption of red meat, especially processed red meat will increase the risk of stroke.

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