Original Article

Stroke risk with vegetarian, low-animal and high-animal diets: A systematic review and meta-analysis

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Background and Objectives: Vegetarian and prudent diets are associated with several health benefits but their role in stroke epidemiology is not as clear. This study aimed to evaluate stroke risk with vegetarian, low-animal, and high-animal diets. **Methods and Study Design:** Studies reporting stroke risk with high versus low use of vegetarian or low/high-animal diets were identified by conducting literature search in Ebsco, Ovid, PubMed, Science Direct, and Web of Science databases. Relative risks (RRs) of stroke between high and low use of vegetarian, low-animal, and high-animal were pooled to achieve overall estimates. Relationship between stroke risk and increasing quantiles of dietary patterns was sought by performing metaregression analyses. **Results:** 17 studies (932545 individuals; follow-up 11.7 years [95% confidence interval (CI): 9.5, 13.9]) were included. Compared to low use, high use of vegetarian and low-animal diets was associated with lower risk of hemorrhagic stroke (RR: 0.71 [95% CI: 0.47, 0.96] and 0.82 [95% CI: 0.64, 0.99]), ischemic stroke (RR: 0.78 [95% CI: 0.66, 0.91] and 0.70 [95% CI: 0.45, 0.95]) and total stroke (RR: 0.84 [95% CI: 0.71, 0.96] and 0.72 [95% CI: 0.61, 0.83]) respectively. Dose-response analyses further supported these findings. High use of high-animal diet was associated with relatively higher risk of stroke [RR: 1.12 [95%CI: 0.94, 1.29]. In vegetarians, relative to high use of vegetables, high use of fruits posed lower risk of stroke. **Conclusions:** Stroke risk is lower with more use of a vegetarian or low-animal diet but relatively higher with more use of a high-animal diet.

Key Words: stroke, hemorrhagic, ischemic, vegetarian, vegan

INTRODUCTION

Human dietary patterns without meat are called vegetarian diets. These can be vegan (a diet totally based on plants), lacto-vegetarian, ovo-vegetarians, or lacto-ovo-vegetarian (a plant-based diet with dairy products and/or eggs).[1] Among the low-animal (prudent) diets, the most prominent is the Mediterranean diet which is characterized by high use of vegetables, legumes, fruit, nuts, and cereals; a moderate intake of fish, poultry, and wine; low use of dairy products, red meat, and sweets; and olive oil as the main lipidic source.[2] Because of the environmental concerns of farming and animal welfare, vegetarian and prudent diets are increasingly being consumed and advocated.[3] Commonly used foods vary widely in carbon dioxide and methane production. Plant-based foods contribute to these greenhouse gasses much lower than animal-based foods.[4]

The health benefits of vegetarian and low animal diets are well-reported. Many meta-analyses have found an inverse association between the vegetarian diet and diabetes,[5,6] blood pressure,[7] cardiovascular diseases,[8,9] fractures,[10] and cancer.[11-13] Prudent diets are also found to be associated with the reduced risk of several conditions including metabolic syndrome,[14] cardiovascular diseases,[15] dementia,[16] and cancer,[17] whereas the consumption of more meat in the diet is reported to be associated with chronic diseases including diabetes,[18] cardiovascular diseases,[19,20] and cancer.[21] A meta-analysis of 6 prospective studies (329495 individuals with 10630 stroke cases) found that the consumption of red meat (fresh or processed) was associated with an increased risk of ischemic but not hemorrhagic stroke.[22] The data are however inconclusive regarding the association of vegetarian and low-animal diets with stroke risk.

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Manuscript received 11 April 2022. Initial review completed 20 May 2022. Revision accepted 21 July 2022.
doi: 10.6133/apjcn.202209_31(3).0010

A large prospective cohort study of over 480000 participants who were followed for 18 years examined the stroke risk in meat eaters, fish eaters, vegetarians, and vegans and found higher risks of hemorrhagic and total stroke in vegetarians in comparison with meat-eaters.[23] Another epidemiological study found that high animal fat and cholesterol consumption were associated with a reduced risk of death from ischemic stroke.[24] A prospective cohort study of over 40000 individuals reported that daily use of green-yellow vegetables and fruits lowered the risk of mortality due to total, hemorrhagic or ischemic stroke.[25] This scenario necessitated a systematic review of this area.

In the literature, there is no review article to report the pooled risk of stroke with high versus low use of vegetarian or low-animal diet. A need for the synthesis of the outcomes of epidemiological studies stems from the inconsistencies and variabilities in the reported outcomes of these studies. The present study aimed to evaluate the risk of stroke with vegetarian and low-animal, and high-animal diets by conducting a literature survey for the identification of all relevant studies and to perform meta-analyses of relative risks (RRs) of stroke between the high and low use of a dietary pattern in order to gain refined evidence of the stroke risk modification associated with vegetarian, low-animal and high-animal diet in the general population.

METHODS

Inclusion and exclusion criteria

For inclusion in the meta-analysis a study had to have a) prospective longitudinal cohort design; b) recruited individuals from the general population; c) a follow-up of at least 3 years; d) evaluated the risk of stroke incidence or mortality with the vegetarian, low-animal, or high-animal dietary pattern; and e) reported risk indices (hazard ratio or risk ratio) of stroke incidence or mortality between high versus low intake of a dietary pattern. Studies were excluded if they: a) evaluated the risk of stroke with a specific food or nutrient rather than a dietary pattern; b) evaluated stroke risk with whole versus refined food; c) carried out a direct comparison between dietary patterns but not the risk assessment with high vs low intake of dietary patterns; and d) case-control studies. For the present study, the outcomes of interest were the RRs of stroke (hemorrhagic, ischemic, or total) incidence or mortality between the highest quantile versus the lowest quantile of vegetarian, low-animal, or high-animal diet.

Literature search

For data acquisition, a comprehensive literature search was conducted in Ebsco, Ovid, PubMed, Science Direct and Web of Science databases using following key terms: 'diet', 'dietary pattern', 'vegetarian', 'plant-based', 'low-animal', 'prudent', 'vegetables', 'fruits', 'stroke', 'hemorrhagic', 'ischemic', 'cerebrovascular disease', 'epidemiological study', 'survey', 'longitudinal' and 'follow-up'. Additional searches included the screening of bibliographic sections of important research articles and database software corroborations. The search encompassed research articles published in the English language without the restriction of publication period.

Data analyses

Data extraction and quality assessment of the included studies were performed by 2 reviewers independently and then outputs were unified. A third reviewer was also involved in the process when necessary. The Newcastle-Ottawa Scale was used for the assessment of the quality of included studies. Publication bias assessment was performed with Begg's rank correlation test.

Random effects meta-analyses were performed with Stata software (Stata Corporation, College Station, Texas, USA) by pooling the RRs reported by the individual studies to generate weighted RRs using the DerSimonian-Laird method. The point estimates (hazard or risk ratios) were pooled interchangeably based on the following observations: a) statistical procedures of included studies for these point estimates involved either Cox proportional hazard model (15 studies), logistic regression (1 study) or Poisson regression (1 study); and b) that the incidence of stroke was relatively infrequent in these cohorts. Only multivariate RRs adjusted for several variables including age, BMI, sex, smoking status, education, energy intake, alcohol consumption, physical activity, marital status, nutritional supplements, history of diabetes mellitus, cancer and heart disease, hypertension, and hypercholesterolemia were used for the meta-analyses. To seek the relationship between the risk of stroke and ascending number of quantiles of dietary patterns, metaregression was performed using the restricted maximum likelihood method with Stata software. A p-value of <0.05 was considered to show a significant relationship.

RESULTS

Seventeen prospective longitudinal cohort studies 25-41 of 932545 participants who were followed for 11.7 years [95% confidence interval (CI): 9.5, 13.9] were included (Figure 1). These studies were of high quality. An assessment with the Newcastle-Ottawa Scale is presented in Supplementary Table 1. There was no significant publication bias according to Begg's test (Adjusted Kendall's score: 8±22.2; p=0.719; Supplementary Figure 1). Important characteristics of the included studies are given in Supplementary Table 2.

In comparison with low use, the high use of vegetarian diet was associated with a lower risk of hemorrhagic stroke (RR: 0.71 [95% CI: 0.47, 0.96]), ischemic stroke (RR: 0.78 [95% CI: 0.66, 0.91]), and total stroke (RR: 0.84 [95% CI: 0.71, 0.96]). Compared to low use, the high use of low-animal diet was also associated with a lower risk of hemorrhagic stroke (RR: 0.82 [95% CI: 0.64, 0.99]), ischemic stroke (0.70 [95% CI: 0.45, 0.95]), and total stroke (RR: 0.72 [95% CI: 0.61, 0.83]). Sensitivity analyses endorsed these outcomes. The risk of mortality from stroke was also less with high use of vegetarian/low-animal diet in comparison with the low use (Supplementary Figure 2). In comparison with low use, the high use of a high-animal diet was associated with a relatively higher risk of total stroke (RR: 1.12 [95% CI: 0.94, 1.29]) (Figure 2). In sensitivity analyses, the RR deviated from 1.05 [95% CI: 0.91, 1.18] to 1.18 [95% CI: 0.95, 1.41].

A statistically significant inverse relationship was observed between the risk of any stroke (hemorrhagic/ischemic/total) and increasing quantiles of a vegetarian

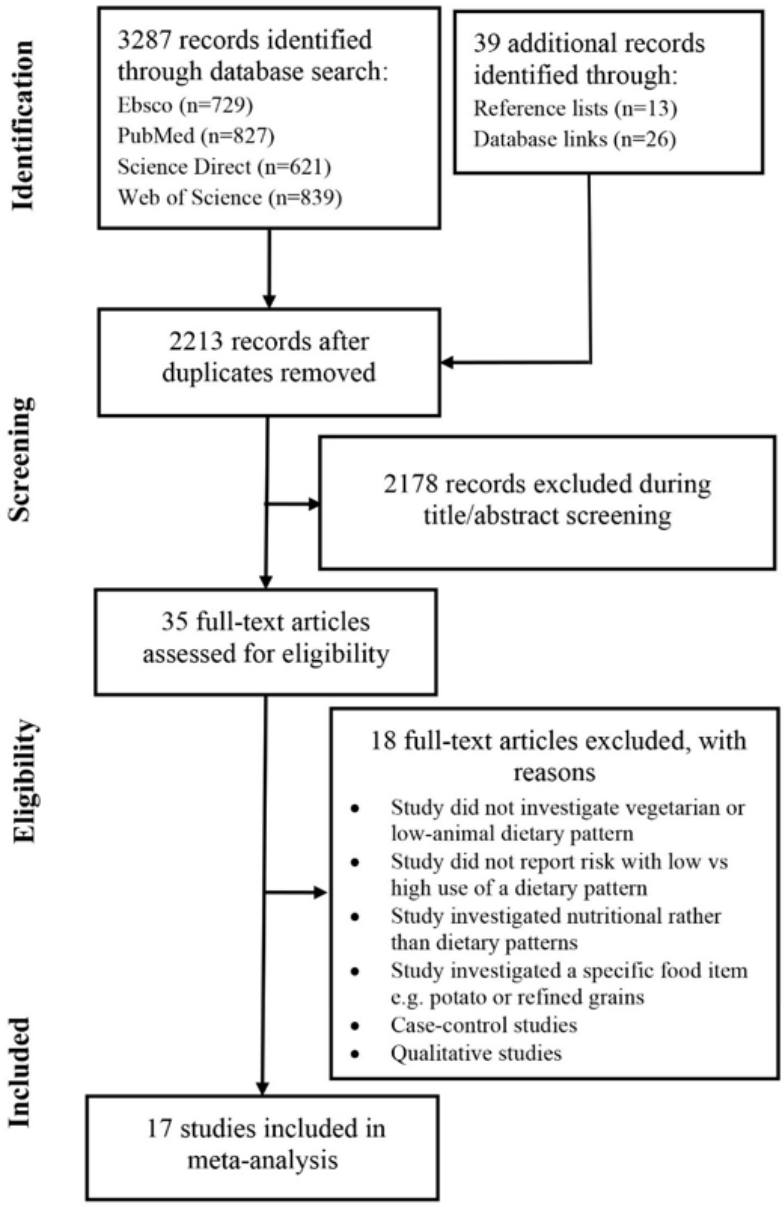

Figure 1. A flowchart of literature search output, study screening and selection process.

diet (metaregression coefficient (MC): −0.080 [−0.098, −0.061]; $p<0.0001$) or low-animal diet (MC: −0.074 [−0.095, −0.053]; $p<0.0001$). On the other hand, there was no statistically significant relationship between the risk of any stroke and the increasing quantiles of high-animal diet (MC: 0.014 [95% CI: −0.021, 0.049]; $p=0.425$) (Figure 3a-c).

Within the vegetarian group, the risk of hemorrhagic stroke was relatively lower with high use of fruits (RR 0.61 [95% CI: 0.49, 0.73]) than with high use of vegetables (RR 0.99 [95% CI: 0.79 1.18]). The risk of ischemic stroke was also lower with high fruit use (RR 0.72 [95% CI: 0.64, 0.81]) than with high use of vegetables (0.80 [95% CI: 0.63, 0.96]). Total stroke risk was lower with high fruit use (0.72 [95% CI: 0.64, 0.81]) than with high vegetable consumption (RR 0.88 [95% CI: 0.72, 1.04]) (Figure 4). Sensitivity analyses endorsed these outcomes.

DISCUSSION

We have found that the higher use of vegetarian or low-animal diet poses lower risk of ischemic, hemorrhagic, or total stroke in a dose-dependent fashion whereas the higher use of a high-animal diet was associated with a relatively higher risk of total stroke. The stroke mortality risk was also lower with high use of a vegetarian or low-animal diet. Among vegetarians, the use of higher amounts of fruits was associated with a lower risk of stroke than with high use of vegetables.

A previous meta-analysis found that high adherence to the Mediterranean diet was associated with a lower risk of stroke (RR 0.71 [95% CI: 0.57, 0.89]).[42] On the other hand, a meta-analysis of 6 prospective studies (329495 individuals; 10630 stroke cases) found that the consumption of red meat (fresh or processed) was associated with an increased risk of ischemic but not hemorrhagic stroke.[22] Another meta-analysis also found a higher risk of stroke with high meat consumption.[43] A review that combined data from 5 prospective studies (Adventist Mortality, Health Food Shoppers, Adventist Health, Heidelberg, and Oxford Vegetarian) found that mortality from ischemic heart disease was 20% lower in occasional meat eaters, 34% lower in fish-eaters, 34% lower in lacto-

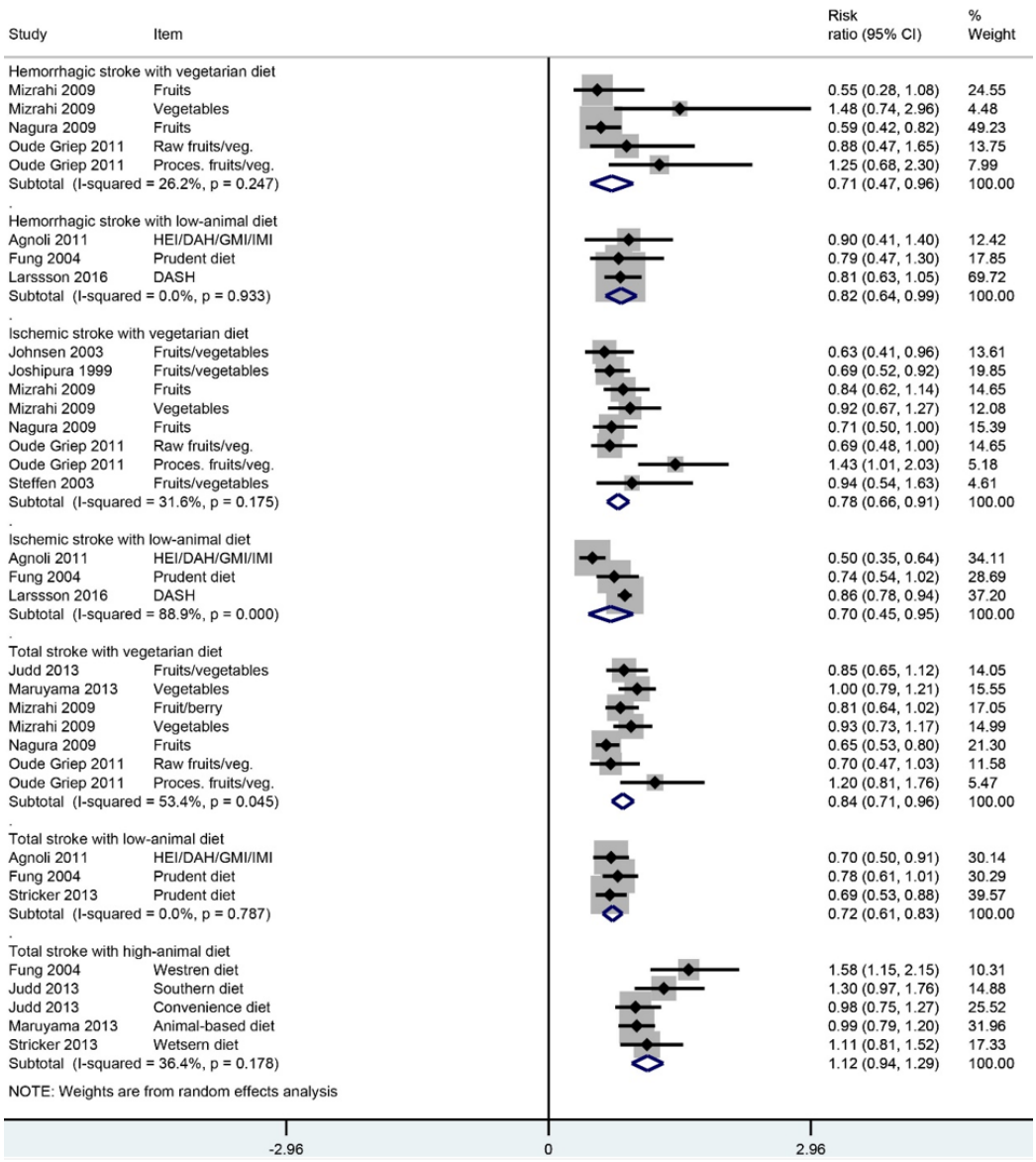

Figure 2. A forest graph showing the pooled risk ratios of stroke incidence between high vs low use of dietary patterns. DASH: dietary approach to stop hypertension; HEI: Healthy Eating Index; GMI: Greek Mediterranean Index; Italian Mediterranean Index; Proc.: processed; veg.: vegetables.

ovo-vegetarians, and 26% lower in vegans in comparison with regular meat-eaters. In this study, the stroke risk was 7% less in vegetarians than in non-vegetarians.[44] A recently published report of a large epidemiological study with 416104 participants followed for over 16 years revealed lower stroke mortality risk with higher plant protein intake (HR: 0.70 [95% CI: 0.57, 0.89]). Moreover, the authors found a 10% increased risk of stroke mortality if 3% of protein intake was substituted with animal proteins.[45] Another epidemiological study of 2 Taiwanese cohorts (13352 individuals) also found that vegetarians were at lower risk of stroke than non-vegetarians.[46]

There is a predominance of studies to find a stroke risk-reducing role of vegetarian and low-animal diets. However, contradictions do exist. In a large prospective cohort study, the EPIC-Oxford study, in which over 480000 participants were followed for 18 years, a higher risk of hemorrhagic stroke was found with the vegetarian diet in a comparison with high-animal diet (hazard ratio: 1.48 [95% CI: 1.11, 1.97]). Vegetarians in this study were found deficient in nutrients like vitamin B12, vitamin D, and some important amino acids and fatty acids.[23] Cai et al also found a higher risk of stroke with high use of vegetables and a lower risk of stroke with high use of meat.[27] Another study reported a higher risk of stroke mortality with the high intake of vegetal proteins and fats, although these outcomes were not linear across the quantiles of dietary intake. In this study, the risk of stroke mortality was lower with a higher intake of animal fats and proteins. However, in this population, only about 20% of energy was derived from animal sources in the high-animal diet group.[24]

Generally, it appears that whereas high meat consumption is associated with ischemic stroke, it is not associated with hemorrhagic stroke.[22,43,47] The reason for this association may be attributed to the lipid profiles associated with meat consumption. Meat eaters usually have higher levels of total cholesterol and non-high-density lipoprotein cholesterol.[48] A meta-analysis of 23 prospective studies (1430141 participants with 7960 hemorrhagic stroke

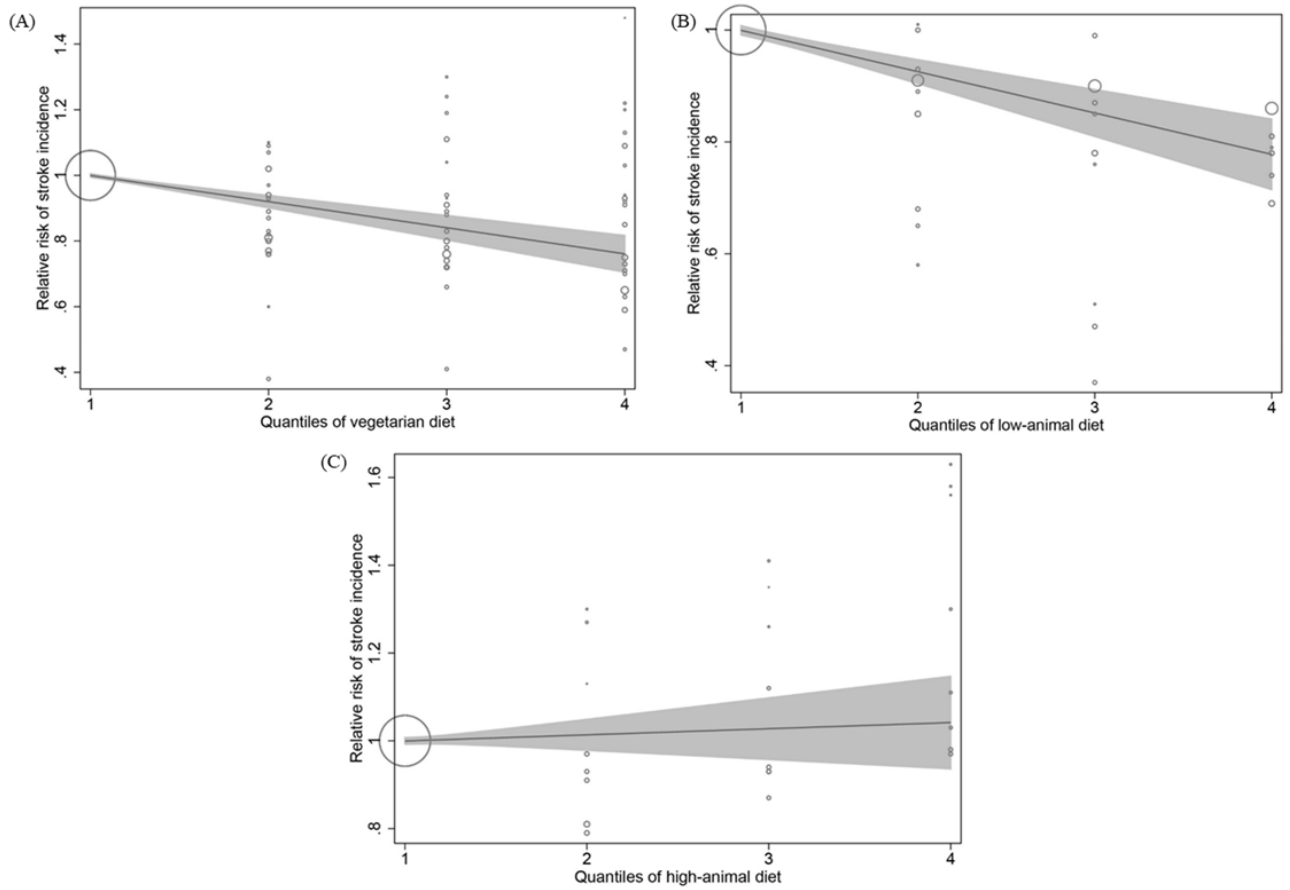

Figure 3. A forest graph showing the pooled risk ratios of stroke incidence between high vs low use of dietary patterns. DASH: dietary approach to stop hypertension.

cases) found in a high versus low comparison that total cholesterol and low-density lipoprotein (LDL)-cholesterol levels were inversely associated with hemorrhagic stroke risk.[49] However, in vegetarians, especially vegans, total cholesterol and LDL-cholesterol levels are usually found nearest to the healthy range.[48] This may explain the absence of an increased risk of hemorrhagic stroke observed in the present meta-analysis.

Research on the effects of diet on adverse health outcomes is usually affected by the controls and confounders. It is suggested that a healthy diet and lifestyle can reduce the human, social and economic burden of cardiovascular and cerebrovascular diseases.[50,51] Healthy dietary habits are usually conjoined with many other positive behaviors, thereby confounding the effects of each other.[52] In a case-control study of over 13000 stroke cases from 32 countries, reduction in stroke risk was associated with the use of vegetables and fruits along with the adherence to recommended physical activity.[53] Pannizza et al[54] who examined the association between the Healthy Eating Index-2015 (HEI-2015) and CVD, cancer, and all-cause mortality in a multiethnic cohort of over 215000 individuals found that the higher HEI-2015 scores were associated with reduced all-cause mortality and the risk of mortality due to CVD and cancer. They suggested that increasing the intake of fruits and vegetables, whole grains, monounsaturated and polyunsaturated fatty acids while reducing the use of refined grains, sodium, and saturated fats can improve healthy survival.

The outcomes of the present study have public health implications. Stroke is a major public health problem to cause mortality and disability. Any preventive measure that can be taken to reduce the burden of the disease will benefit society as well as healthcare. Plant-based and prudent diets have proven benefits in reducing the incidence of cardiovascular and cerebrovascular diseases whereas higher intake of meat is found to be associated with an increased risk of several diseases. Because the consumption of plant-based diets is also associated with reduced risks of several other conditions including diabetes, and cancer, these have the potential for preventing or reducing comorbidities. Additionally, the use of plant-based diets can also help in mitigating climate change-related health risks and can benefit efforts devoted to tackling climate change.

In this meta-analysis of 17 prospective epidemiological studies with over 930000 participants who were followed for approximately 12 years, stroke risk was lower with high use of vegetarian and low-animal diets but was relatively higher with high use of high-animal diet. Higher use of fruits was found to pose a lower risk of stroke than with higher use of vegetables. Thus, the use of vegetarian and low-animal diets, especially fruit-rich diets appear to confer benefits in stroke prevention.

AUTHOR DISCLOSURES

The authors declare no conflict of interest.

This work was supported by Heilongjiang Provincial Natural Science Foundation Project (LH2021H065).

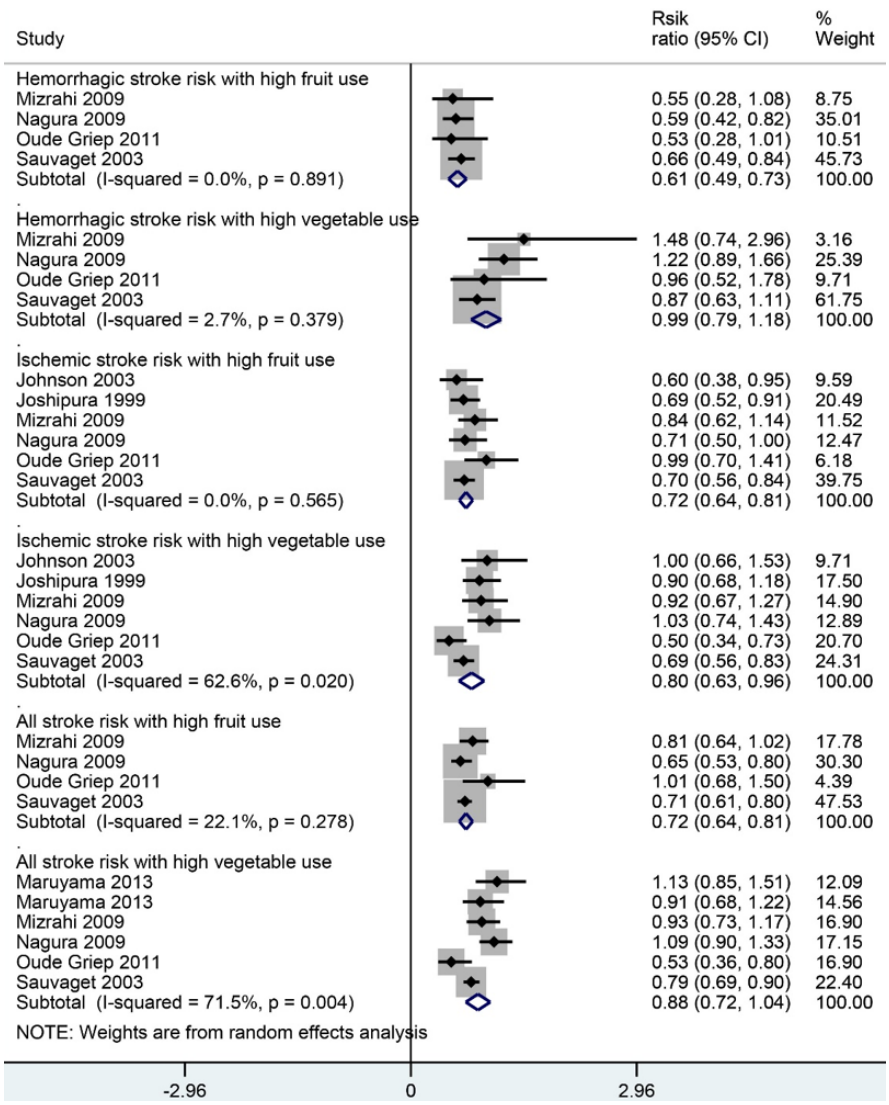

Figure 4. A forest graph showing the pooled risk ratios of stroke incidence between high vs low use of vegetables and fruits.

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Supplementary table 1. Newcastle–Ottawa scale for assessment of quality of cohort studies[†]

NOS criteria	Representativeness of exposed cohort?	Selection of non-exposed cohort?	Ascertainment of exposure	Demonstration that outcome of interest was not present at start
NOC criteria from the perspective of the present study	Representative of general population	Same population	Study database, regional mortality/ hospital discharge database	Absence of stroke at baseline
Sauvaget 2003 [17]	★	★	★	★
Agnoli 2011 [18]	★	★	★	★
Cai 2007 [19]	★	★	★	★
Fung 2004 [20]	★	★	★	★
Gillman 1995 [21]	★	★	★	★
Johnsen 2003 [22]	★	★	★	★
Joshipura 1999 [23]	★	★	★	★
Judd 2013 [24]	★	★	★	★
Kinjo 1999 [25]	★	★	★	★
Larssson 2016 [26]	★	★	★	★
Maruyama 2013 [27]	★	★	★	★
Mizrahi 2009 [28]	★	★	★	★
Nagura 2009 [29]	★	★	★	★
Oude Griep 2011 [30]	★	★	★	★
Shimazu 2007 [31]	★	★	★	★
Steffen 2003 [32]	★	★	★	★
Stricker 2013 [33]	★	★	★	★

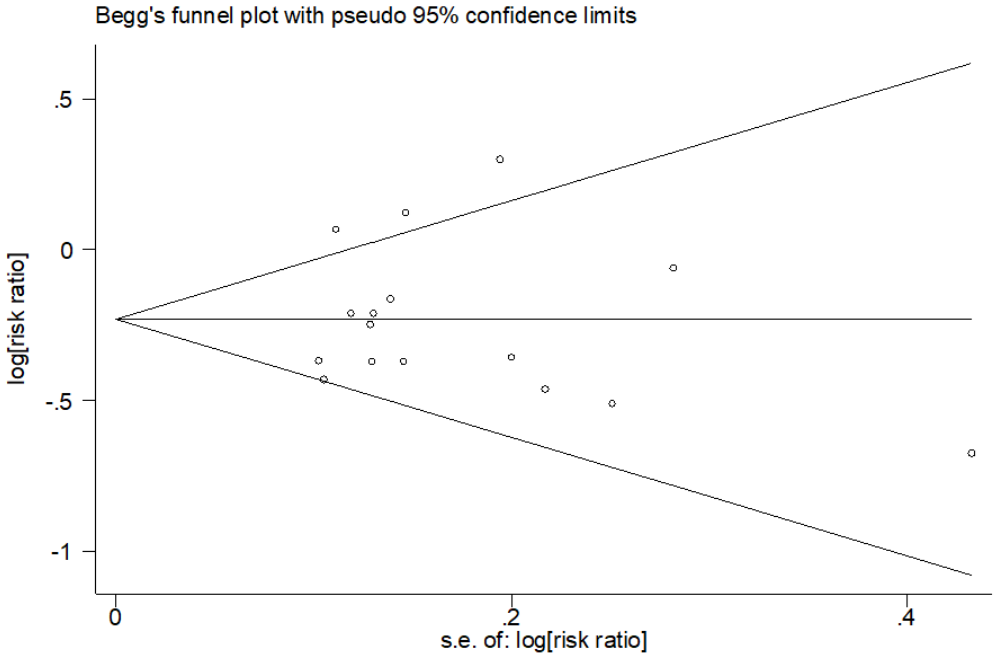
NOS criteria	Comparability of cohorts on basis of design or analysis	Study controls for at least 3 additional risk factors?	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohort
NOC criteria from the perspective of the present study	Low vs high use of dietary patterns	Age, gender, physical exercise, obesity, morbidity	Record linkage	At least 5 years	Follow-up completion rate
Sauvaget 2003 [17]	★	★	★	★	
Agnoli 2011 [18]	★	★	★	★	★
Cai 2007 [19]	★	★	★	★	★
Fung 2004 [20]	★	★	★	★	
Gillman 1995 [21]	★	★	★	★	
Johnsen 2003 [22]	★	★	★	★	
Joshipura 1999 [23]	★	★	★	★	★
Judd 2013 [24]	★	★	★	★	★
Kinjo 1999 [25]	★	★	★	★	
Larssson 2016 [26]	★	★	★	★	
Maruyama 2013 [27]	★	★	★	★	
Mizrahi 2009 [28]	★	★	★	★	
Nagura 2009 [29]	★	★	★	★	
Oude Griep 2011 [30]	★	★	★	★	
Shimazu 2007 [31]	★	★	★	★	
Steffen 2003 [32]	★	★	★	★	★
Stricker 2013 [33]	★	★	★	★	★

[†]Each asterisk represents if individual criterion within the subsection was fulfilled.

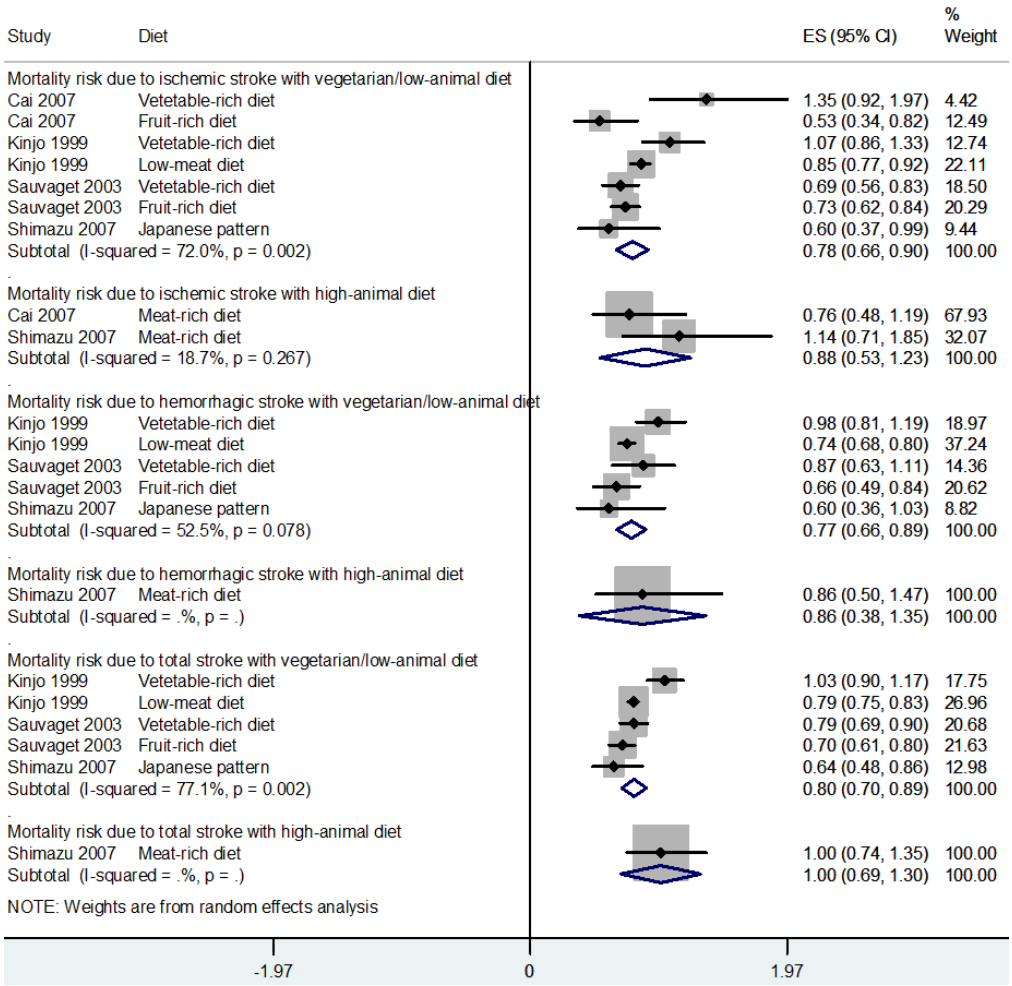
Supplementary table 2. Important characteristics of the included studies

Study identity	Name of study	Participants	Follow-up (years)	Age (years)	% Females	BMI (kg/m^2)	% Smokers	% Hypertensive	% Diabetic
Sauvaget 2003 [17]	Life Span Study	14966	16	56	60	22	32	23	9
Agnoli 2011 [18]	EPICOR	47021	7.9	50±8	69	26±4	27	37	
Cai 2007 [19]	SWHS	18766	5.7	54±10	100	24±4.1	4		
Fung 2004 [20]	NHS	121700	14		100	24.7±2.4	24	20	
Gillman 1995 [21]	832	Framingham	20	56		26.5			
Johnsen 2003 [22]	DCH	54506	3.1	56±4	54	26±4	54	47	1.8
Joshipura 1999 [23]		114279	8	48	66	24.7	20	19	
Judd 2013 [24]	REGARDS	30239	5.7		62				
Kinjo 1999 [25]		265070	15						
Larssson 2016 [26]	CSM-SMC	74404	11.9	60±10	46		24	21	6
Maruyama 2013 [27]	JACC	26598	12.6		58			19	6.3
Mizrahi 2009 [28]	FMCHE	3932	24	52	52	26.4	26	16	3
Nagura 2009 [29]	JACC	59485	13	56	58	22.5	25	20	4.5
Oude Griep 2011 [30]	MORGEN	20069	10.3	41±11	64	25±4	40		
Shimazu 2007 [31]	ONHI	40547	7	60±10	47	23.5±3.3	53	24	
Steffen 2003 [32]	ARIC	11940	11	54±1		27.2±1.1	26	32	
Stricker 2013 [33]	EPIC-NL	40011	13	49±12	57	25.7±4	62		1.4

CSM-SMC: Cohort of Swedish Men-Swedish Mammography Cohort; DCH: Diet: Cancer: and Health study; FMCHE: Finnish Mobile Clinic Health Examination Survey; GMI: Greek Mediterranean index; IMI: Italian Mediterranean index; NHS: Nurses; Health Study; ONHI: Ohsaki National Health Insurance (NHI) Cohort study; SWHS: Shanghai Women's Health Study.



Supplementary figure 1. A funnel plot corresponding to the Begg's test of publication bias.



Supplementary figure 2. A forest graph showing the pooled relative risks of stroke mortality between high vs low use of dietary patterns.