



## Spicy food consumption reduces the risk of ischaemic stroke: a prospective study

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### Abstract

Previous studies revealed that consuming spicy food reduced mortality from CVD and lowered stroke risk. However, no studies reported the relationship between spicy food consumption, stroke types and dose–response. This study aimed to further explore the association between the frequency of spicy food intake and the risk of stroke in a large prospective cohort study. In this study, 50 174 participants aged 30–79 years were recruited. Spicy food consumption data were collected via a baseline survey questionnaire. Outcomes were incidence of any stroke, ischaemic stroke (IS) and haemorrhagic stroke (HS). Multivariable-adjusted Cox proportional hazard models estimated the association between the consumption of spicy food and incident stroke. Restricted cubic spline analysis was used to examine the dose–response relationship. During the median 10·7-year follow-up, 3967 strokes were recorded, including 3494 IS and 516 HS. Compared with those who never/rarely consumed spicy food, those who consumed spicy food monthly, 1–2 d/week and 3–5 d/week had hazard ratio (HR) of 0·914 (95 % CI 0·841, 0·995), 0·869 (95 % CI 0·758, 0·995) and 0·826 (95 % CI 0·714, 0·956) for overall stroke, respectively. For IS, the corresponding HR were 0·909 (95 % CI 0·832, 0·994), 0·831 (95 % CI 0·718, 0·962) and 0·813 (95 % CI 0·696, 0·951), respectively. This protective effect showed a U-shaped dose–response relationship. For obese participants, consuming spicy food  $\geq$  3 d/week was negatively associated with the risk of IS. We found the consumption of spicy food was negatively associated with the risk of IS and had a U-shaped dose–response relationship with risk of IS. Individuals who consumed spicy food 3–5 d/week had a significantly lowest risk of IS.

**Keywords:** Spicy food: Stroke: Haemorrhagic stroke: Ischaemic stroke: Prospective cohort studies

The disease burden from stroke is one of the most significant, worldwide. According to a recent study, stroke continues to be the second leading cause of death globally and the third leading cause of death and disability<sup>(1)</sup>. In 2019, 6·55 million people died from stroke globally<sup>(2)</sup>, compared with 2·19 million deaths and 45·9 million disability-adjusted life years in China<sup>(3)</sup>. It is estimated that there are approximately 2·4 million new strokes and 1·1 million stroke-related deaths in China each year, with 11·1 million stroke survivors alive at any given time<sup>(4)</sup>. Of these, 87·9 % of ischaemic stroke (IS) disability-adjusted life years and 89·5 % of haemorrhagic stroke (HS) disability-adjusted life years

are due to potentially modifiable risk factors, demonstrating the great potential for reducing the burden of stroke by reducing risk factor exposure<sup>(5)</sup>.

Spices not only enhance the flavour, aroma and colour of food and beverages but also have preventive effects on acute and chronic diseases<sup>(6–9)</sup>. Previous studies have demonstrated that spices possess antioxidant, antiviral, antihypertensive, anti-diabetic and other beneficial effects<sup>(10,11)</sup>. Several previous studies have investigated the association between spicy food and specific metabolic diseases, indicating that increased consumption of spicy food is inversely correlated with obesity<sup>(12)</sup>, hypertension<sup>(13)</sup>,

**Abbreviations:** CKB, China Kadoorie Biobank; HS, haemorrhagic stroke; HR, hazard ratio; IS, ischaemic stroke.

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diabetes<sup>(14)</sup> and serum cholesterol<sup>(15)</sup>. Additionally, the consumption of spicy food can reduce the risk of death from CVD, including stroke mortality<sup>(16–19)</sup>. A cohort study conducted in western China discovered an association between spicy food consumption and a reduced risk of stroke among individuals with lower Dietary Approaches to Stop Hypertension (DASH) scores<sup>(20)</sup>, and another study conducted by the China Kadoorie Biobank (CKB) revealed that the consumption of spicy food was independently linked to a decreased incidence of adverse cardiovascular events among Chinese adults with diabetes<sup>(21)</sup>. However, both studies were limited to a specific population, and the frequency of spicy food consumption and the incident stroke were not thoroughly examined.

Therefore, to further explore the relationship between the frequency of spicy food consumption and the risk of stroke in the general population, we prospectively followed approximately 50 000 people for 10 years in Liuzhou, China.

## Methods

### Study population

The CKB is one of the largest chronic disease cohorts in China, to investigate the impact of various lifestyle, genetic and environmental factors on the process of developing and dying from chronic diseases. The CKB study design, survey technique and demographic have all been detailed elsewhere<sup>(22,23)</sup>. The current study used data collected in Liuzhou City, one of ten areas assessed by the CKB cohort. In summary, the study included 50 174 people aged 30–79 years between August 2004 and January 2008. All investigation operations were carried out in accordance with standardised processes and with the assistance of skilled and competent experts. In this study, individuals with cancer (*n* 386), stroke (*n* 1357) and heart disease (*n* 2294) at baseline, as well as participants lost to follow-up (*n* 329), were excluded from the analysis. With follow-up through 31 December 2017, 45 908 participants were included in the overall stroke analysis (Fig. 1). The study was conducted in accordance with the guidelines of the Declaration of Helsinki, and all procedures involving participants were approved by the Ethics Committee of the University of Oxford, UK (approval number: 025–04, 3.2.2005; University of Oxford, the UK), and the Ethics Committee of the Chinese Centre for Disease Control and Prevention (approval number: 005/2004, 9.7.2004; Beijing, China)<sup>(24)</sup>. Written informed consent was obtained from all participants.

### Assessment of spicy food consumption

Spicy food intake referred to the direct consumption of fresh chilli peppers; the addition of fresh/dried chilli peppers, chilli oil/sauce/paste, curry or other 'hot' spices when cooking; or the addition of chilli oil/sauce/paste to food when eating<sup>(8)</sup>. During the baseline survey, participants were asked 'During the past month, about how often did you eat hot spicy food?' Answers include 'never/almost never', 'only occasionally', '1–2 days/week', '3–5 days/week', and '6–7 days/week'.

### Follow-up and outcome measures

In the Liuzhou cohort of the CKB study, the vital status of each participant was identified chiefly by using linkage with the local disease and death registries and the health insurance system<sup>(25)</sup>. The primary diseases examined in this study were stroke (ICD-10: I60–I61, I63–I64), and the secondary outcomes were IS (ICD-10: I63) and HS (ICD-10: I61). Participants were enrolled from the date of enrolment until the earliest occurrence of the outcome, death (from any cause), failure to follow-up or the end date of the study (31 December 2017).

### Assessment of covariates

We obtained covariates through baseline surveys, including socio-demographic characteristics (sex, age, education level, occupation, marital status and household income), lifestyle behaviours (smoking, alcohol consumption, meat, fresh fruits, dairy products, fresh vegetables and eggs) and personal disease history (CHD, diabetes). Total physical activity can be quantified as MET hours per day, which is calculated by multiplying the MET value assigned to each activity by its duration, and then summing the results across all activities<sup>(26)</sup>. Overweight was defined as BMI  $\geq 24.0$  kg/m<sup>2</sup> and obesity as BMI  $\geq 28.0$  kg/m<sup>2</sup><sup>(27)</sup>.

### Statistical analysis

We calculated the baseline characteristics of study participants according to their frequency of spicy food consumption, categorising it into five groups. Continuous variables were described using means and standard deviations, while categorical variables were presented as percentages. Cox proportional hazard regression models were employed to estimate hazard ratios (HR) and 95% CI for the association between spicy food consumption and incident stroke. The models were adjusted for covariates: model 1 was adjusted for sex and age (30~, 40~, 50~, 60~, 70~). Model 2 was based on model 1, additionally adjusted for education background (illiterate and elementary, middle school, high school and above), household income (< 20 000 Yuan,  $\geq 20 000$  Yuan), occupation (non-retired, retired), marital status (married, widowed, separated/divorced/unmarried), BMI (underweight/normal, overweight, obesity), smoking (never smoker, ex-regular smoker/smoker), drinking (never drinker, ex-regular drinker/drinker) and total physical activity (quartile grouping) adjusted. On the basis of model 2, model 3 further adjusted for meat (daily, non-daily), fresh vegetable (daily, non-daily), fresh fruit (daily, 1–6 d/week, rarely), dairy product (1–7 d/week, rarely) and eggs intake (4–7 d/week, 1–3 d/week, rarely). Survival probability curves and log-rank tests were used to assess the survival probability of outcomes based on the frequency of spicy food consumption. Restricted cubic spline analysis was used to examine the dose–response relationship between the frequency of spicy food intake and the risk of stroke. Additionally, we conducted a stratified analysis of sex, age and BMI to further investigate this relationship. We conducted two sensitivity analyses: (I) excluding participants who experienced a stroke within a 2-year follow-up period; (II) those who self-reported having diabetes at the baseline survey were excluded. (III) Those who self-reported having

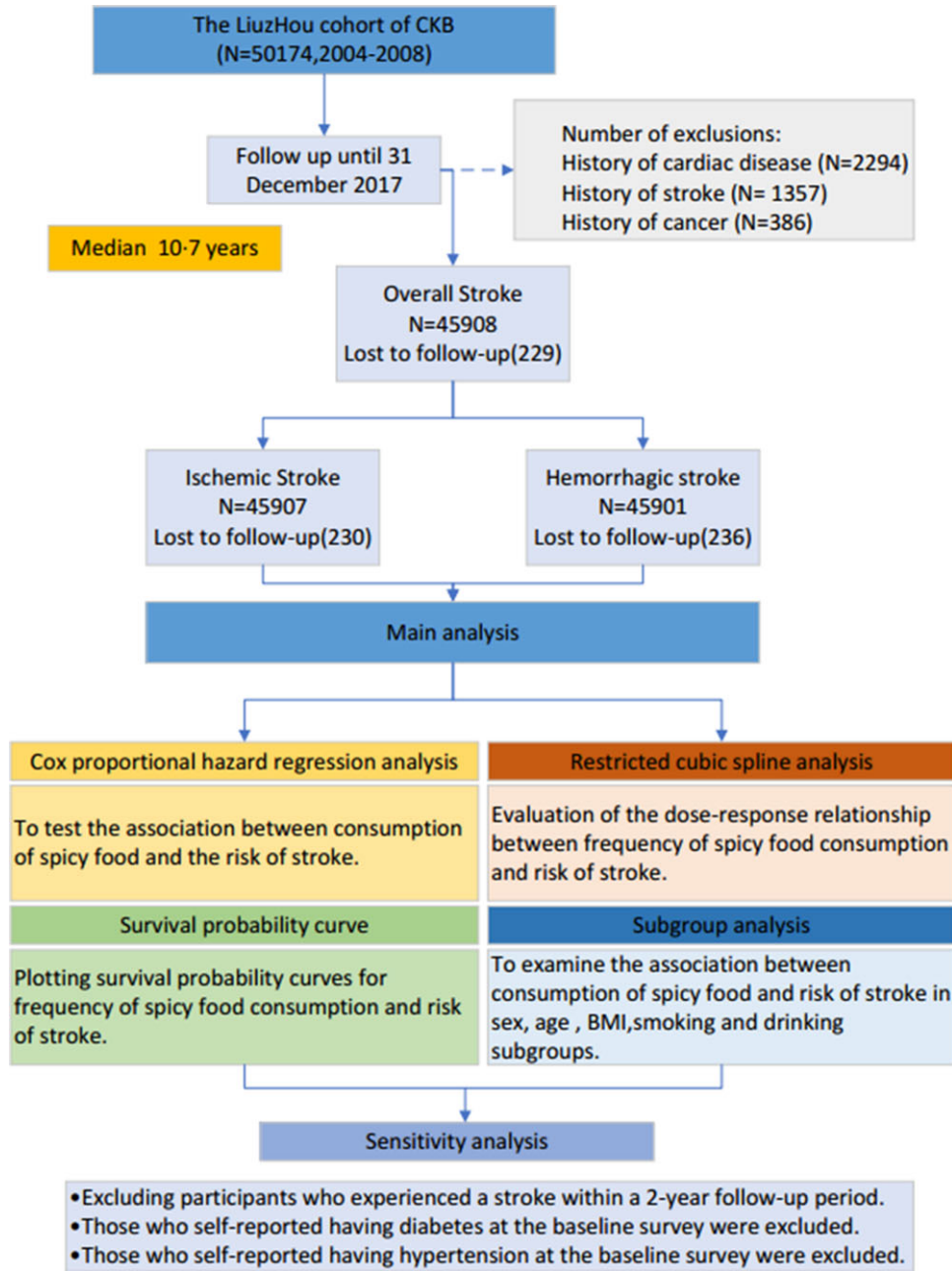


Fig. 1. Flow chart of Liuzhou cohort participants included in the analysis.

hypertension at the baseline survey were excluded. All statistical analyses were conducted using R software (version 4.2.1). All statistical significance was set at  $P < 0.05$ .

## Results

This study included a total of 45 908 participants. The mean age at baseline was 53.54 (SD 10.24) years, and 61.61 % of the participants were women. Compared with non-consumers of spicy food, individuals who regularly consumed spicy food were more likely to be women, younger, educated, not retired,

married, non-smokers, frequent drinkers and have a higher BMI (Table 1). Over an approximate follow-up period of 450 000 person-years (median duration = 10.7 years), a total of 3967 strokes, 3494 IS and 516 HS, were observed.

As shown in Table 2, participants who consumed spicy food monthly had a lower risk of stroke than those who did not consume spicy food (model 1: HR: 0.904, 95 % CI 0.832, 0.982, model 2: HR: 0.910, 95 % CI 0.836, 0.989, model 3: HR: 0.914, 95 % CI 0.841, 0.995) after adjusting for covariates. Similarly, participants who consumed spicy food 1–2 d per week had a lower risk of stroke (model 1: HR: 0.831, 95 % CI 0.726, 0.950, model 2: HR: 0.858, 95 % CI 0.749, 0.983, model 3: HR: 0.869,

**Table 1.** Distribution of baseline characteristics and frequency of spicy food consumption (Mean values and standard deviations)

Characteristics		Overall	Never/rarely	Monthly	1–2 d/week	3–5 d/week	6–7 d/week
<i>n</i>		45 908	10 329	12 574	3982	3753	15 270
Sex	Men	17 626	3859	4793	1581	1532	5861
	Women	28 282	6470	7781	2401	2221	9409
Age	Mean	53.54	57.22	54.01	51.66	50.57	51.87
	SD	10.24	10.27	10.17	10.25	9.67	9.67
Education	Illiterate and elementary	10 855	3466	3005	729	572	3083
	Middle school	15 902	3379	4261	1256	1317	5689
	High school and above	19 151	3484	5308	1997	1864	6498
Occupation	Non-retired	26 640	4996	6961	2530	2557	9596
	Retired	19 268	5333	5613	1452	1196	5674
Marital	Married	39 770	8818	10 913	3477	3294	13 268
	Widowed	3722	1112	1026	289	221	1074
	Separated/Divorced/Unmarried	2416	399	635	216	238	928
Income	<20000 Yuan	22 978	6104	6341	1653	1604	7276
	≥20000 Yuan	22 332	4058	6088	2294	2110	7782
BMI	Mean	23.77	23.42	23.62	23.61	23.87	24.13
	SD	3.16	3.12	3.06	3.06	3.12	3.27
MET	Mean	17.33	15.71	16.98	18.52	18.99	18.01
	SD	11.23	10.62	11.07	11.08	11.35	11.61
Smoking	Never smoker	30 457	7393	8540	2572	2340	9612
	Ex-regular smoker/smoker	15 451	2936	4034	1410	1413	5658
Drinking	Never drinker	15 885	5142	4325	1063	937	4418
	Ex-regular drinker/drinker	30 023	5187	8249	2919	2816	10 852
Fruit	Daily	17 828	3899	4532	1721	1361	6315
	1–6 d/week	22 774	5015	6723	1924	2003	7109
	Rarely	5306	1415	1319	337	389	1846
Meat	Daily	33 049	7166	8628	3163	2696	11 396
	Non-daily	12 859	3163	3946	819	1057	3874
Fresh vegetables	Daily	44 972	10 171	12 348	3913	3659	14 881
	Non-daily	936	158	226	69	94	389
Dairy products	1–7 d/week	19 715	4393	5521	1916	1737	6148
	rarely	26 193	5936	7053	2066	2016	9122
Egg	4–7 d/week	6665	1479	1828	584	551	2223
	1–3 d/week	30 989	6838	8521	2757	2558	10 315
	Rarely	8254	2012	2225	641	644	2732
Number of strokes in 2-year follow-up period		531	159	142	35	28	167
Number of people with diabetes excluded		3467	851	951	277	236	1152
Number of people with hypertension excluded		6487	1746	1757	487	419	2078

95% CI 0.758, 0.995) after adjusting for covariates. Similarly, participants who consumed spicy food 3–5 d per week had a lower risk of stroke (model 1: HR: 0.816, 95% CI 0.707, 0.942, model 2: HR: 0.830, 95% CI 0.717, 0.960, model 3: HR: 0.826, 95% CI 0.714, 0.956) after adjusting for covariates. Results for IS were consistent with overall stroke, but the same results were not observed for HS.

As shown in Fig. 2, as the follow-up time increases, participants who never/rarely consumed spicy food had the lowest probability of survival, followed by those with monthly consumption, 6–7 d/week consumption and 1–2 d/week consumption, and the highest probability of survival was observed in the 3–5 d/week consumption group ( $P < 0.0001$ ) (Fig. 2(a)). Similar findings were observed in incidence of IS ( $P < 0.0001$ ) (Fig. 2(b)), but there was no significant association for consumption of spicy food and incidence of HS ( $P = 0.1100$ ) (Fig. 2(c)). In addition, restricted cubic spline analysis showed that the frequency of spicy food consumption and the risk of stroke have a U-shaped dose–response relationship (Fig. 3) ( $P_{\text{nonlinear}} = 0.0003$  for overall stroke and IS). Similar findings were observed in three sensitivity analyses, which excluded

participants with stroke during a 2 years follow-up period and participants with self-reported diabetes at baseline (online Supplementary Table S1–S3).

Figure 4 shows the results of the subgroup analysis. Regarding overall stroke, the HR for individuals consuming spicy food 3–5 d/week was 0.767 (95% CI 0.620, 0.949) for men, compared with those who never/rarely consumed spicy food. In addition, the HR for individuals consuming spicy food 1–2 d/week was 0.796 (95% CI 0.653, 0.971) for women compared with those counterparts. For participants under 60 years old, the HR for consuming spicy food monthly, 3–5 d per week, were 0.785 (95% CI 0.681, 0.904) and 0.632 (95% CI 0.507, 0.788), respectively, compared with participants who never/rarely consumed spicy food. For participants ≥ 60 years of age, the HR for consuming spicy food 1–2 d per week was 0.810 (95% CI 0.671, 0.977) compared with those who never/rarely consumed spicy food. For underweight/normal and obese participants, the HR for consuming spicy food 3–5 d per week were 0.758 (95% CI 0.600, 0.950) and 0.593 (95% CI 0.387, 0.911), respectively, compared with those who never/rarely consumed spicy food. Among participants who smoked, the HR

**Table 2.** HR for stroke and subtypes adjusted for frequency of spicy food consumption (Hazard ratios and 95 % confidence intervals)

	Never/rarely	Monthly		1–2 d/week		3–5 d/week		6–7 d/week		
		HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI	
<b>Overall Stroke</b>										
No. of events	1206	1063		263		223		1212		
No. of person years	106 123-60	130 406-40		41 329-63		39 454-12		156 893-90		
Model 1	Ref	0.904*	0.832, 0.982	0.831**	0.726, 0.950	0.816**	0.707, 0.942	1.028	0.948, 1.115	
Model 2	Ref	0.910*	0.836, 0.989	0.858*	0.749, 0.983	0.830*	0.717, 0.960	1.013	0.932, 1.102	
Model 3	Ref	0.914*	0.841, 0.995	0.869*	0.758, 0.995	0.826*	0.714, 0.956	1.005	0.924, 1.093	
<b>IS</b>										
No. of events	1082	943		224		194		1051		
No. of person years	106 575-10	130 803-50		41 462-16		39 577-40		157 450-30		
Model 1	Ref	0.901*	0.825, 0.984	0.799**	0.692, 0.924	0.804**	0.689, 0.938	1.007	0.923, 1.097	
Model 2	Ref	0.907*	0.830, 0.991	0.823**	0.711, 0.953	0.814**	0.696, 0.951	0.991	0.907, 1.083	
Model 3	Ref	0.909*	0.832, 0.994	0.831*	0.718, 0.962	0.813**	0.696, 0.951	0.988	0.904, 1.080	
<b>HS</b>										
No. of events	135	143		37		30		171		
No. of person years	111 062-40	134 558-90		42 350-03		40 361-59		161 723-10		
Model 1	Ref	1.052	0.830, 1.332	0.988	0.685, 1.425	0.905	0.607, 1.349	1.215	0.965, 1.530	
Model 2	Ref	1.065	0.837, 1.354	1.036	0.715, 1.500	0.907	0.602, 1.365	1.190	0.938, 1.510	
Model 3	Ref	1.054	0.828, 1.341	1.050	0.725, 1.521	0.900	0.598, 1.354	1.197	0.942, 1.519	

HR, hazard ratio; IS, ischaemic stroke; HS, haemorrhagic stroke.  
*P* < 0.05 \*  
*P* < 0.01 \*\*  
*P* < 0.001 \*\*\*

Spicy food consumption reduces the risk of ischemic stroke



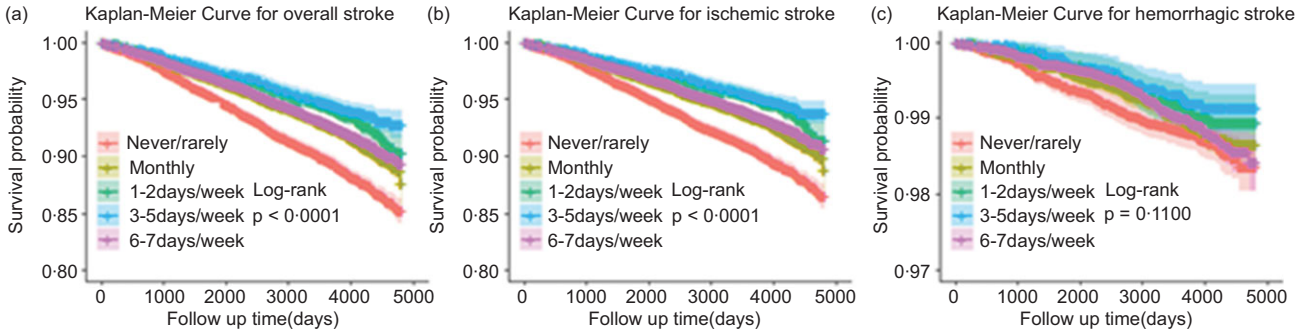


Fig. 2. Survival probability curves between the frequency of spicy food consumption and the risk of stroke occurrence.

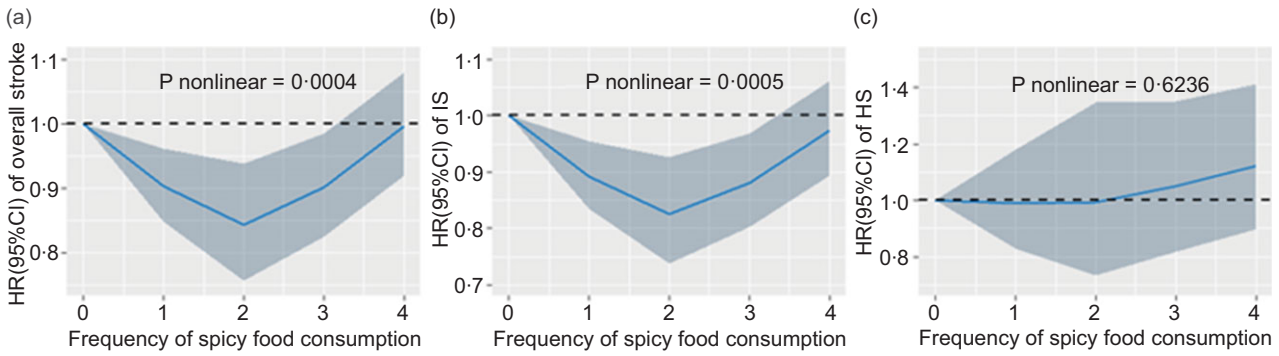


Fig. 3. Dose-response relationship between the frequency of spicy food consumption and the risk of stroke, 0: never/rarely, 1:1: monthly, 2:1-2 d/week, 3:3 d/week and 4:6-7 d/week

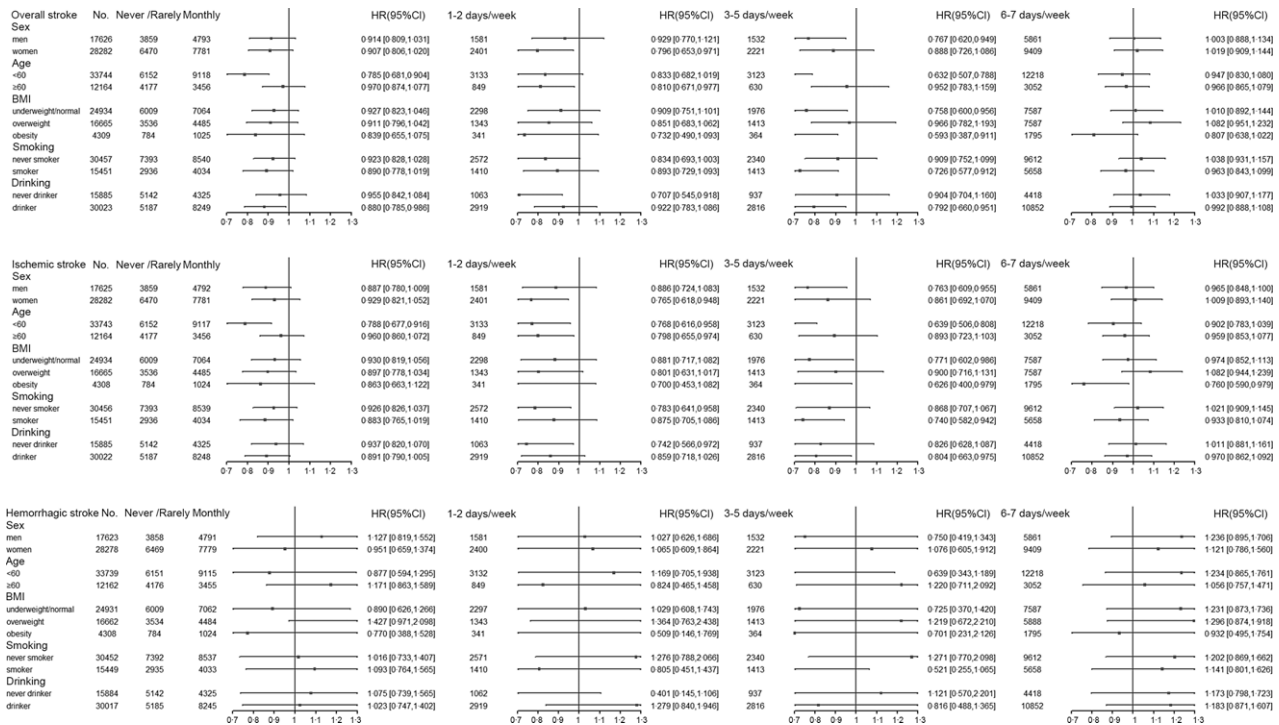


Fig. 4. Subgroup analysis of strokes.

for eating spicy food 3-5 d per week was 0.726 (95 % CI 0.577, 0.912) compared with those who never or rarely ate spicy food. Among participants who never drank alcohol, the HR for eating

spicy food 1-2 d per week was 0.707 (95 % CI 0.545, 0.918) compared with those who never or rarely ate spicy food. In contrast, among participants who drank alcohol, the HR for

those who ate spicy food monthly and those who ate spicy food 3–5 d per week was 0.880 (95 % CI 0.785, 0.986) and 0.792 (95 % CI 0.660, 0.951), respectively.

In the case of IS, the HR for consuming spicy food 3–5 d/week was 0.763 (95 % CI 0.609, 0.955) for men compared with those who never/rarely consumed spicy food, and 0.765 (95 % CI 0.618, 0.948) for women who consumed 1–2 d/week compared with those who never/rarely consumed spicy food. The HR for monthly, 1–2 d per week and 3–5 d per week consumption of spicy food were 0.788 (95 % CI 0.677, 0.916), 0.768 (95 % CI 0.616, 0.958) and 0.639 (95 % CI 0.506, 0.808), respectively, for participants aged < 60 years compared with those who never/rarely consumed spicy food. The HR for participants aged  $\geq$  60 years who consumed spicy foods 1–2 d per week was 0.798 (95 % CI 0.655, 0.974) compared with those who never/rarely consumed spicy food. The HR for consumption of spicy food 3–5 d per week was 0.771 (95 % CI 0.602, 0.986) for participants who were underweight/normal weight compared with those who never/rarely consumed spicy food. The HR for obese participants consuming spicy food 3–5 d per week and 6–7 d per week compared with those who never/rarely consumed spicy food were 0.626 (95 % CI 0.400, 0.979) and 0.760 (95 % CI 0.590, 0.979), respectively. Among never-smoking participants, the HR for eating spicy food 1–2 d per week was 0.783 (95 % CI 0.641, 0.958) compared with participants who never or rarely ate spicy food. In contrast, among participants who smoked, the HR (95 % CI) for those who ate spicy food 3–5 d per week was 0.740 (95 % CI 0.582, 0.942). Among participants who never drank alcohol, the HR for eating spicy food 1–2 d per week was 0.742 (95 % CI 0.566, 0.972) compared with participants who never or rarely ate spicy food. In contrast, among participants who drank alcohol, the HR for those who ate spicy food 3–5 d per week was 0.804 (95 % CI 0.663, 0.975).

## Discussion

The study estimates the associations between the consumption of spicy food and the risk of stroke. We found the consumption of spicy food was negatively associated with the risk of IS and had a U-shaped dose–response relationship with the risk of IS. In addition, individuals who consumed spicy food 3–5 d/week had a significantly lowest risk of IS. For obese participants, consuming spicy food  $\geq$  3 d per week was inversely associated with the risk of IS.

In this study, the proportion of people who ate spicy food 6–7 d/week was 33.26 % (15270/45908), lower than the proportion in Hunan Province (99.4 %,  $n$  50 192) but higher than the proportion in Zhejiang Province (2.7 %,  $n$  1276)<sup>(28)</sup>. The reasons may be due to the subtropical monsoon climate, which is rainy and humid and more suitable for spicy food<sup>(29)</sup>. For example, previous meta-analysis of four prospective cohort studies from the USA, Italy, Iran and China found that regular consumption ( $\geq$  1 d/week) of spicy food was associated with a 12 % reduction in the risk of all-cause mortality and was negatively associated with the risk of death from ischaemic heart disease<sup>(30)</sup>. In a prospective cohort study of 22 160 people from western China

with a mean follow-up of 45.5 months, the consumption of spicy food appeared to be associated with a lower risk of stroke only in those with lower DASH scores<sup>(20)</sup>. Another CKB cohort of 26 163 diabetic patients with a median follow-up of 8.5 years found that the consumption of spicy food was independently associated with a reduced incidence of adverse cardiovascular events in Chinese adults with diabetes<sup>(21)</sup>. The results of these two studies are consistent with our finding. The probable cause is the action of capsaicin.

The transient receptor potential capsaicin 1 receptor (TRPV1), also known as the capsaicin receptor, is widely distributed in tissues such as the brain, cardiovascular system, vascular endothelial cells and macrophages. It is a non-selective cation channel with a preference for  $\text{Ca}^{2+}$ <sup>(31)</sup>. Activation of TRPV1 by dietary capsaicin may directly reduce stroke events through its anti-atherogenic effects. For example, activation of TRPV1 induced autophagy through the APM-activated protein kinase signalling pathway, thereby inhibiting foam cell formation in vascular smooth muscle cells<sup>(32)</sup>. This process also involved the activation of other signalling pathways, including the divalent cation calcium ( $\text{Ca}^{2+}$ )/phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt)/endothelial nitric oxide synthase (eNOS)/nitric oxide (NO)/rescue of SIRT1 and inhibition of the NF- $\kappa$ B signalling pathway<sup>(33–36)</sup>. Meanwhile, TRPV1 also reduces mitochondrial reactive oxygen species (ROS) production through the protein kinase A (PKA)/uncoupling protein 2 (UCP2) pathway<sup>(37)</sup>. Activation of these pathways helps to inhibit the inflammatory response of endothelial cells and promotes vasodilation and angiogenesis, thereby slowing the progression of atherosclerosis. In addition, TRPV1 can also regulate the expression of atp-binding cassette transporter A1 and LDL-related protein 1, reduce the increase in cholesterol efflux and decrease in uptake in cells, thereby delaying the generation of plaques<sup>(38)</sup>. However, prolonged or repeated application of capsaicin may induce channel dephosphorylation of calmodulin phosphatase and channel phosphorylation of PKA, thereby causing desensitisation of TRPV1, resulting in insensitivity of TRPV1 to capsaicin<sup>(39,40)</sup>. This may explain why eating spicy food 6–7 d per week did not prevent stroke and why the dose–response relationship was U-shaped.

Eating spicy food 1–2 d/week was negatively associated with stroke in women, while men needed to eat 3–5 d/week, which may be related to the action of sex hormones in women. Previous studies have found that oestradiol exerts a protective effect against atherosclerosis by preventing monocytes from adhering to the vascular system, inhibiting the recruitment of inflammatory cells, promoting cholesterol efflux from endothelial cells and decreasing the number of vascular endothelial cell-derived foam cells<sup>(41,42)</sup>. It may be that oestrogen and capsaicin work together in women to exert a protective effect against IS even when they eat less spicy food. We found a significant negative association between eating spicy food and IS in people aged < 60 years. A person's energy expenditure is most stable between the ages of 20 and 50 and does not begin to decline until after age 60<sup>(43)</sup>. This difference could influence how their bodies process and respond to the bioactive compounds in spicy food, such as capsaicin. Further research is needed to determine the underlying mechanisms behind this discrepancy.



Obesity is an independent risk factor for stroke<sup>(44)</sup>. The HR for stroke increased by 1.18 (1.14, 1.22) for every 5 kg/m<sup>2</sup> increase in BMI<sup>(45)</sup>. An imbalance of adipokines, caused by the production of pro-inflammatory adipokines from visceral adipose tissue, is one of the causes of atherosclerosis induced by obesity<sup>(46)</sup>. Capsaicin successfully reduced adipokine production and modulated macrophage behaviour in the adipose tissue of mice with obesity by activating TRPV1 channels to induce Ca<sup>2+</sup> influx and inhibiting the down-regulation of TRPV1 expression<sup>(47,48)</sup>. Population studies have shown that capsaicin controls obesity by increasing energy expenditure, promoting fat oxidation, reducing fat formation, suppressing appetite and enhancing satiety<sup>(49)</sup>. A nationwide prospective study involving 12 970 Chinese adults revealed a negative association between chilli intake and the risk of overweight/obesity<sup>(12)</sup>. Furthermore, our study confirmed that consuming spicy food  $\geq 3$  d/week provided protection against IS in individuals with a BMI  $\geq 28.0$ , indicating that individuals with obesity may benefit from increasing their intake of spicy food to reduce the risk of IS.

Our study has several strengths. It was prospective cohort study with a median follow-up time of 10.7 years, a large sample size and a low rate of loss to follow-up, adjusted for known and potential confounders, including socio-demographic characteristics (sex, age, etc.), lifestyle (smoking, alcohol consumption, etc.) and dietary factors (meat, eggs, etc.). Several limitations should be acknowledged in our study. First, the use of FFQ for assessing spicy food intake may introduce potential inaccuracies in quantifying actual consumption, as the FFQ primarily captured frequency rather than precise quantities consumed. Furthermore, we were unable to directly account for variations in the amount of spicy food consumed per body weight, particularly between men and women, due to data limitations. Additionally, spiciness is a subjective perception, making it challenging to establish precise causal relationships. In addition, our study did not directly investigate salt intake, which is a dietary factor associated with stroke risk, nor did it further investigate the effects of egg and meat consumption on CVD. In conclusion, further research is warranted to explore the mechanisms underlying the potential effects of capsaicin on stroke risk, considering these limitations.

### Conclusions

Spicy food consumption was negatively associated with the risk of IS in a southern Chinese population, with a U-shaped dose–response relationship with risk of IS. However, there was no significant association observed between the consumption of spicy food and the incidence of HS. The consumption of spicy food  $\leq 5$  d/week was associated with a reduced risk of IS, showing the strongest protective effect in frequency of 3–5 d/week consumption. Obesity people may benefit from a higher frequency of consuming spicy food. More future research is needed to reveal the protective mechanisms of spicy food.

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The authors declare that there is no conflict of interest.

### Supplementary material

For supplementary material referred to in this article, please visit <https://doi.org/10.1017/S0007114524000229>

### References

1. Feigin VL, Stark BA, Johnson CO, *et al.* (2021) Global, regional, and national burden of stroke and its risk factors, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Neurol* **20**, 795–820.
2. Roth GA, Mensah GA, Johnson CO, *et al.* (2020) Global Burden of Cardiovascular Diseases and Risk Factors, 1990–2019: update from the GBD 2019 study. *J Am Coll Cardiol* **76**, 2982–3021.
3. Ma Q, Li R, Wang L, *et al.* (2021) Temporal trend and attributable risk factors of stroke burden in China, 1990–2019: an analysis for the Global Burden of Disease Study 2019. *Lancet Public Health* **6**, e897–e906.
4. Wang W, Jiang B, Sun H, *et al.* (2017) Prevalence, incidence and mortality of stroke in China: results from a nationwide population-based survey of 480 687 adults. *Circulation* **135**, 759–771.
5. Feigin VL, Nichols E, Alam T, *et al.* (2019) Global, regional, and national burden of neurological disorders, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* **18**, 459–480.
6. Jiang TA (2019) Health benefits of culinary herbs and spices. *JAOAC Int* **102**, 395–411.
7. O'Neill J, Brock C, Olesen AE, *et al.* (2012) Unravelling the mystery of capsaicin: a tool to understand and treat pain. *Pharmacol Rev* **64**, 939–971.
8. Chan WC, Millwood IY, Kartsonaki C, *et al.* (2021) Spicy food consumption and risk of gastrointestinal-tract cancers: findings from the China Kadoorie Biobank. *Int J Epidemiol* **50**, 199–211.
9. Li Q, Cui Y, Jin R, *et al.* (2017) Enjoyment of spicy flavor enhances central salty-taste perception and reduces salt intake and blood pressure. *Hypertension* **70**, 1291–1299.
10. Singh N, Rao AS, Nandal A, *et al.* (2021) Phytochemical and pharmacological review of *Cinnamomum verum* J. Presl-a





- versatile spice used in food and nutrition. *Food Chem* **338**, 127773.
11. Nilius B & Appendino G (2013) Spices: the savory and beneficial science of pungency. *Rev Physiol Biochem Pharmacol* **164**, 1–76.
  12. Shi Z, Riley M, Taylor AW, *et al.* (2017) Chilli consumption and the incidence of overweight and obesity in a Chinese adult population. *Int J Obes (Lond)* **41**, 1074–1079.
  13. Wang H, Chen L, Shen D, *et al.* (2021) Association between frequency of spicy food consumption and hypertension: a cross-sectional study in Zhejiang Province, China. *Nutr Metab (Lond)* **18**, 70.
  14. Zhao Z, Li M, Li C, *et al.* (2020) Dietary preferences and diabetic risk in China: a large-scale nationwide internet data-based study. *J Diabetes* **12**, 270–278.
  15. Xue Y, He T, Yu K, *et al.* (2017) Association between spicy food consumption and lipid profiles in adults: a nationwide population-based study. *Br J Nutr* **118**, 144–153.
  16. Lv J, Qi L, Yu C, *et al.* (2015) Consumption of spicy foods and total and cause specific mortality: population based cohort study. *BMJ* **351**, h3942.
  17. Yang L, Sun J, Zhao M, *et al.* (2022) Chili pepper intake and all-cause and disease-specific mortality. *Int J Vitam Nutr Res* **93**(4), 378–384.
  18. Spence JD (2019) Chili pepper consumption and cardiovascular mortality. *J Am Coll Cardiol* **74**, 3150–3152.
  19. Bonaccio M, Di Castelnuovo A, Costanzo S, *et al.* (2019) Chili pepper consumption and mortality in Italian adults. *J Am Coll Cardiol* **74**, 3139–3149.
  20. Chen L, Tang W, Wu X, *et al.* (2023) Eating spicy food, Dietary Approaches to Stop Hypertension (DASH) Score, and their interaction on incident stroke in Southwestern Chinese aged 30–79: a prospective cohort study. *Nutrients* **15**, 1222.
  21. Li Q, Chang M, Lai R, *et al.* (2023) Potential benefits of spicy food consumption on cardiovascular outcomes in patients with diabetes: a cohort study of the China Kadoorie Biobank. *Nutrition* **112**, 112062.
  22. Chen Z, Chen J, Collins R, *et al.* (2011) China Kadoorie Biobank of 0.5 million people: survey methods, baseline characteristics and long-term follow-up. *Int J Epidemiol* **40**, 1652–1666.
  23. Li LM, Lv J, Guo Y, *et al.* (2012) The China Kadoorie Biobank: related methodology and baseline characteristics of the participants. *Zhonghua Liu Xing Bing Xue Za Zhi* **33**, 249–255.
  24. Hou L, Li S, Zhu S, *et al.* (2023) Lifetime cumulative effect of reproductive factors on stroke and its subtypes in postmenopausal Chinese women: a prospective cohort study. *Neurology* **100**, e1574–e1586.
  25. Chen Z, Lee L, Chen J, *et al.* (2005) Cohort profile: the Kadoorie Study of Chronic Disease in China (KSCDC). *Int J Epidemiol* **34**, 1243–1249.
  26. Bennett DA, Du H, Bragg F, *et al.* (2019) Physical activity, sedentary leisure-time and risk of incident type 2 diabetes: a prospective study of 512 000 Chinese adults. *BMJ Open Diabetes Res Care* **7**, e000835.
  27. Chen C & Lu FC (2004) The guidelines for prevention and control of overweight and obesity in Chinese adults. *Biomed Environ Sci* **17**, 1–36.
  28. Sun D, Lv J, Chen W, *et al.* (2014) Spicy food consumption is associated with adiposity measures among half a million Chinese people: the China Kadoorie Biobank study. *BMC Public Health* **14**, 1293.
  29. Wang S, Cheng L, He S, *et al.* (2019) Regional pungency degree in China and its correlation with typical climate factors. *J Food Sci* **84**, 31–37.
  30. Ofori-Asenso R, Mohsenpour MA, Nouri M, *et al.* (2021) Association of spicy chilli food consumption with cardiovascular and all-cause mortality: a meta-analysis of prospective cohort studies. *Angiology* **72**, 625–632.
  31. Reyes-Escogido Mde L, Gonzalez-Mondragon EG & Vazquez-Tzompantzi E (2011) Chemical and pharmacological aspects of capsaicin. *Molecules* **16**, 1253–1270.
  32. Li BH, Yin YW, Liu Y, *et al.* (2014) TRPV1 activation impedes foam cell formation by inducing autophagy in oxLDL-treated vascular smooth muscle cells. *Cell Death Dis* **5**, e1182.
  33. Randhawa PK & Jaggi AS (2017) TRPV(1) channels in cardiovascular system: a double edged sword? *Int J Cardiol* **228**, 103–113.
  34. Wang Y, Cui L, Xu H, *et al.* (2017) TRPV1 agonism inhibits endothelial cell inflammation via activation of eNOS/NO pathway. *Atherosclerosis* **260**, 13–19.
  35. Hollis M & Wang DH (2013) Transient receptor potential vanilloid in blood pressure regulation. *Curr Opin Nephrol Hypertens* **22**, 170–176.
  36. Zhang MJ, Zhou Y, Chen L, *et al.* (2016) Impaired SIRT1 promotes the migration of vascular smooth muscle cell-derived foam cells. *Histochem Cell Biol* **146**, 33–43.
  37. Munjuluri S, Wilkerson DA, Souch G, *et al.* (2021) Capsaicin and TRPV1 channels in the cardiovascular system: the role of inflammation. *Cells* **11**, 18.
  38. Ma L, Zhong J, Zhao Z, *et al.* (2011) Activation of TRPV1 reduces vascular lipid accumulation and attenuates atherosclerosis. *Cardiovasc Res* **92**, 504–513.
  39. Mohapatra DP & Nau C (2005) Regulation of Ca<sup>2+</sup>-dependent desensitization in the vanilloid receptor TRPV1 by calcineurin and cAMP-dependent protein kinase. *J Biol Chem* **280**, 13424–13432.
  40. Iftinca M, Defaye M & Altier C (2021) TRPV1-targeted drugs in development for human pain conditions. *Drugs* **81**, 7–27.
  41. Bolego C, Cignarella A, Staels B, *et al.* (2013) Macrophage function and polarization in cardiovascular disease: a role of estrogen signaling? *Arterioscler Thromb Vasc Biol* **33**, 1127–1134.
  42. Gasbarrino K, Di Iorio D & Daskalopoulou SS (2022) Importance of sex and gender in ischaemic stroke and carotid atherosclerotic disease. *Eur Heart J* **43**, 460–473.
  43. Pontzer H, Yamada Y, Sagayama H, *et al.* (2021) Daily energy expenditure through the human life course. *Science* **373**, 808–812.
  44. Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration (BMI Mediated Effects), Lu Y, Hajifathalian K, *et al.* (2014) Metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke: a pooled analysis of 97 prospective cohorts with 1.8 million participants. *Lancet* **383**, 970–983.
  45. Lu Y, Hajifathalian K, Ezzati M, *et al.* (2014) Metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke: a pooled analysis of 97 prospective cohorts with 1.8 million participants. *Lancet* **383**, 970–983.
  46. Lovren F, Teoh H & Verma S (2015) Obesity and atherosclerosis: mechanistic insights. *Can J Cardiol* **31**, 177–183.
  47. Zhang LL, Yan Liu D, Ma LQ, *et al.* (2007) Activation of transient receptor potential vanilloid type-1 channel prevents adipogenesis and obesity. *Circ Res* **100**, 1063–1070.
  48. Hsu CL & Yen GC (2007) Effects of capsaicin on induction of apoptosis and inhibition of adipogenesis in 3T3-L1 Cells. *J Agric Food Chem* **55**, 1730–1736.
  49. Whiting S, Derbyshire E & Tiwari BK (2012) Capsaicinoids and capsinoids. A potential role for weight management? A systematic review of the evidence. *Appetite* **59**, 341–348.