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Predictive role of modifiable factors in stroke: an umbrella review

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ABSTRACT

Background A growing number of meta-analyses reviewed the existing associations between modifiable factors and stroke. However, the methodological quality of them and quality of evidence remain to be assessed by validated tools. Thus, this umbrella review was conducted to consolidate evidence from systematic reviews and meta-analyses of cohort studies investigating the association between modifiable factors and incidence of stroke.

Methods PubMed, Web of Science, Embase, Wanfang and China National Knowledge Infrastructure databases for systematic reviews and meta-analyses of cohort studies from inception until March 2021. Assess the methodological quality of systematic reviews 2 was used to evaluate the methodological quality of each included published meta-analysis. Excess significance test was used to investigate whether the observed number of studies (O) with nominally significant results ('positive' studies, $p<0.05$) was larger than the expected number of significant results (E). Statistically significant ($p<0.05$) associations were rated into five levels (strong, highly suggestive, suggestive, weak and no) using specific criteria. Sensitivity analyses were performed.

Results 2478 records were identified through database searching. At last, 49 meta-analyses including 70 modifiable factors and approximately 856 801 stroke cases were included in the present review. The methodological quality of three meta-analyses was low, while others were critically low. Evidence of walking pace was strong. High suggestive evidence mainly included total meat, processes meat, chocolate, sodium, obesity, pulse pressure, systolic blood pressure, diastolic blood pressure, sleep duration and smoking. Suggestive evidence mainly included dietary approaches to stop hypertension (DASH) diet, vitamin C, magnesium, depression and particulate matter 2.5. After sensitivity analyses, evidence of DASH diet, magnesium and depression turned to weak. No publication bias existed, except only one study which could be explained by reporting bias.

Discussion Diet with rich macronutrients and micronutrients, healthy dietary patterns and favourable physical, emotional health and environmental management should be promoted to decrease the burden of stroke.

PROSPERO registration number CRD42021249921.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This umbrella review is the first synthesis of systematic reviews and meta-analyses of cohort studies to consider the associations between modifiable factors and stroke.
- ⇒ The quality of evidence about the associations between modifiable factors and stroke was assessed and rated into five levels (strong, highly suggestive, suggestive, weak and no) using specific criteria in this review.
- ⇒ The qualities of included meta-analyses were low as they did not meet the standards of assess the methodological quality of systematic reviews 2, such as they did not establish a protocol a priori and did the report justify any significant deviations from the protocol, which can lead to potential bias in the results of meta-analyses.
- ⇒ Since only evidence derived from systematic reviews and meta-analyses of cohort studies was included in our umbrella review, evidence from original studies was beyond our scope of discussion.

INTRODUCTION

Stroke is a serious health condition that causes disability and death. According to the Global Burden of Diseases, Injuries, and Risk Factors Study, stroke became the second leading cause of disability-adjusted life-years worldwide in 2019.[1] The incidence of a stroke increases rapidly with age, doubling every decade after 55 years of age. Patients suffering from stroke often need intensive healthcare and may experience several issues that increase their economic burden seriously.[2] Thus, immediate need to implement preventative strategies is of great importance to public health all over the world.

A growing number of evidences demonstrated genetic and environmental factors may contribute to the risk of stroke.[3 4] Among them, modifiable factors including diet and lifestyles were reported that appropriate and effective changes in them could prevent people from stroke, which are widely accepted by the public.[5 6] Recently, meta-analyses were conducted to explore the associations between modifiable factors and stroke. Some meta-analyses of prospective studies demonstrated higher adherence to Mediterranean and dietary approaches to stop hypertension (DASH) diet may were associated with a decreased risk of stroke.[7 8] Dietary factors such as dairy calcium, high dietary flavonoid intake, fish, soy, nut, tea, moderate coffee and chocolate consumption may lower the risk of stroke,[9–13] while high salt intake, consumption of fresh red meat, processed red meat as well as total red meat and heavy alcohol intake were associated with increased risk of stroke.[14 15] Besides, amount of evidence was observed for effects on stroke with smoking, overweight, physical activities, depression, long sleep duration and environmental management.[16–20] However, none of these studies focused on any existing evidence between modifiable factors and stroke risk systematically. Besides, though a number of systematic reviews and meta-analyses were performed, the methodological quality of them and quality of evidence remain to be assessed by validated tools. More importantly, since the general public increasingly focus on prevention through daily self-management, a systematic umbrella review could provide scientific, instructive and meaningful guidance for them to some extent.[21] Thus, this umbrella review of meta-analyses was conducted to gain a systematic, comprehensive overview of the existing evidence of cohort studies on modifiable factors and incidence of stroke and to assess its strength and validity.

METHODS

Umbrella reviews are systematic reviews that consider many related factors for the management of the same disease or condition. This is probably more useful for health assessments that aim to inform guidelines and clinical practice where all the management options need to be considered and weighed.[22] The umbrella review followed the guidelines for Preferred Reporting Items for Systematic Reviews and Meta-Analyses, and the protocol was registered in PROSPERO (registration no. CRD42021249921). In addition to the factors stated in the protocol, to make the review more comprehensive, instructive and meaningful, factors of physical, emotional health and environmental management were included in the present review. Revised information has been updated in PROSPERO on 12 March 2022.

Patient and public involvement

Meta-analyses of prospective and retrospective cohort studies were included in this review. Thus, in prospective cohort study, participants were general population whose age were ≥18 years old, while in retrospective cohort study, participants who suffered stroke were included. Exposure levels of modifiable factors were compared. Stroke was considered as an outcome which had been ascertained by the method of record linkage with the national and regional stroke registers.

Literature search and study selection

The systematic literature search was conducted in PubMed, Web of Science, Embase, Wanfang and China National Knowledge Infrastructure databases until March 2021 for meta-analyses of cohort studies investigating the association between modifiable factors and stroke risk. We included studies published from database inception through January 2021. Literature search was conducted by two authors (XW and ML). Disagreements were resolved by consensus. In the review, categories of modifiable factors including dietary factors, factors of physical health management and emotional health management were defined a priori. Detailed factors were further confirmed according to categories in the process. The search strategy including detailed factors is shown in online supplemental table S1. Subsequently, we performed a manual search of reference lists from the retrieved articles. We also screened the reference lists of relevant reviews and meta-analyses. No language restriction was performed.

Study selection

The criteria for eligibility were: (1) systematic reviews and meta-analyses of cohort studies on the associations between modifiable factors and stroke risk in humans with multivariable adjusted summary risk estimates and corresponding 95% CIs and (2) studies focusing on the subtypes of stroke. We excluded individual studies from eligible systematic reviews or meta-analyses according to the following criteria: (1) studies in which modifiable factor was not the exposure of interest and stroke incidence was not the outcome of interest; (2) publications reporting on exposure of plasma levels or biomarkers rather than dietary intake; (3) animal studies. If a systematic review or meta-analysis performed a subgroup analysis stratified by the study design (case-control and cohort studies), then the results for cohort studies were included. If more than one published meta-analysis on the same association was identified, we chose only one meta-analysis for each exposure to avoid the inclusion of duplicate studies. In that case, we included the most comprehensive and accurate one with greater sample size. If an article presented separate meta-analyses of more than one eligible modifiable factor, each was assessed individually.

Data extraction

Data were extracted independently by two authors (XW and ML). For each published meta-analysis, we extracted the following data: name of the first author, publication year, exposure, number of included studies, case number, study population, most adjusted risk estimates (relative risk, OR, HR or incident risk ratio) and corresponding 95% CIs.

For each primary study included in the published meta-analysis, the first author's name, year of publication, exposure (including dose of exposure), number of total cases, number of participants and HRs that adjusted for the most confounders, 95% CIs as well as adjustment factors included in the model were extracted.

Assessment of methodological quality

Assess the methodological quality of systematic reviews 2 (AMSTAR 2), which has good inter-rater agreement, content validity and test–retest reliability, was used to evaluate the methodological quality of each included published meta-analysis.[23] This tool has a total of 16 domains and generates an overall rating based on the weaknesses of those domains which is rated as high, moderate, low and critically low.

Statistical analysis

All calculations were conducted with Stata V.15.1. Adjusted summary HRs and corresponding 95% CIs of the included meta-analyses were recalculated by using the random effects model by DerSimonian and Laird.[24] I^2 and τ^2 were used to evaluate heterogeneity among studies. We estimated the 95% prediction interval (PI), the range in which we expect the effect of the association will lie for 95% of future studies. The presence of small-study effects was assumed by Egger regression asymmetry test. Small-study effect was claimed when Egger p value was <0.1. We used the excess significance test to investigate whether the observed number of studies (O) with nominally significant results ('positive' studies, p<0.05) was larger than the expected number of significant results (E).[25] In each meta-analysis, E is calculated from the sum of the statistical power estimates for each component study. We calculated the power of each study by using a non-central t distribution. The excess significance test was considered positive for p values <0.10. Moreover, we corrected for subgroup analyses using a Bonferroni correction that divides the p value by the number of tests (p<0.05/2). When the published meta-analysis presented HRs from the same cohort separately by subgroups, we first combined the HRs per cohort using fixed effect methods, before conducting the overall meta-analysis. If the primary study was not available, we extracted the adjusted summary HRs from the published meta-analysis.

Reviewing the existing evidence

Statistically significant (p<0.05) associations between modifiable factors and stroke risk were rated into five levels (strong, highly suggestive, suggestive, weak and no) using specific criteria.[26] Detailed criteria are shown in online supplemental table S2.

Sensitivity analyses

For each meta-analysis initially graded as showing convincing, highly suggestive or suggestive evidence, adjusted confounding factors of primary studies were re-examined. A sensitivity analysis was performed by including adjusted estimates of the most consistent potential confounders to assess the robustness of the main analysis. Besides, sensitivity analyses including the omission of small-sized studies (<25th percentile) from those meta-analyses with evidence of small-study effects and low-quality studies were also performed.

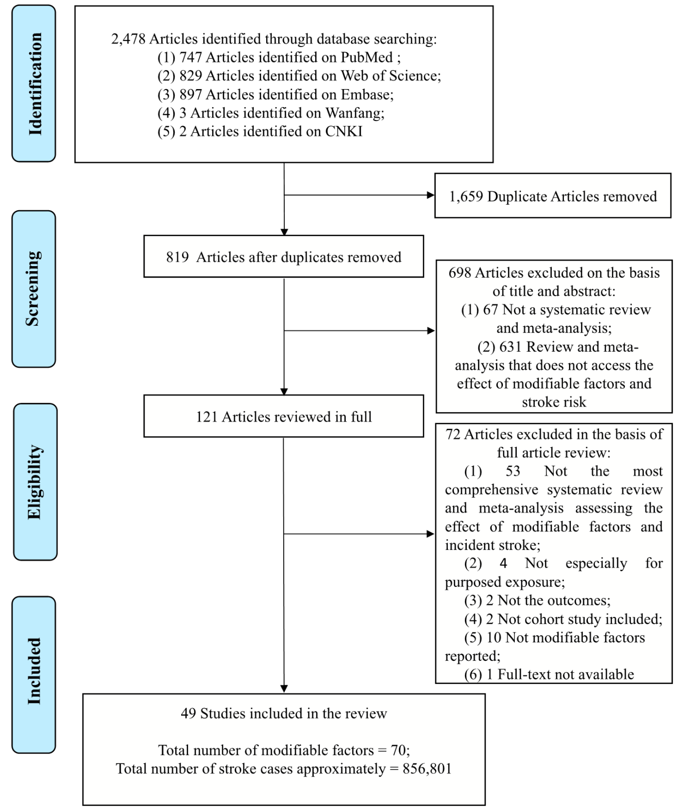

Figure 1 Flow diagram of the study search and selection process. CNKI, China National Knowledge Infrastructure.

RESULTS

A total of 2478 records were identified through database searching; 1659 duplicate records were removed; 698 records were excluded on the basis of title and abstract and 121 records were reviewed in full. After excluding records which were not the most comprehensive systematic review and meta-analysis (n=53), not especially for purposed exposure (n=4), not the purposed outcomes (n=2), not modifiable factors reported (n=10) and whose full text was not available (n=1), 49 articles, including 70 modifiable factors and approximately 856 801 stroke cases, were included and re-analysed in the present review[7 8 10 12 13 16–20 27–65] (figure 1, online supplemental table S3 and S4). The detailed characteristics of included studies are shown in online supplemental table S5.

Modifiable factors and stroke

The associations between modifiable factors and risk of total stroke are shown in figures 2–5, and online supplemental table S6. Further subgroup analyses of ischaemic and haemorrhagic stroke are shown in online supplemental table S7 and S8.

Food factors, beverages and dietary behaviours

For total stroke, high intake levels of fruit and vegetable, olive oil, milk, high fat diary, nuts, cheese, white meat, chocolate, fish, tea (three cups/day), high levels of coffee, high adherence of Mediterranean and DASH diet were inversely and high intake levels of salt, high fat milk, total meat, red meat, processed meat and high-to-heavy

Exposure	Main Comparison		No. of PS	SHR (95% CI)	*P* value	AMSTAR 2
Food factors						
Fruit and vegetable [27]	High vs low	Intake	8	0.74 (0.69, 0.79)	< 0.0001	Critically low
Olive oil [29]	Dose-response	25 g/d	2	0.75 (0.59, 0.96)	0.02	Critically low
Milk [33]	Dose-response	200 g/d	14	0.90 (0.83, 0.98)	0.02	Critically low
Nuts [34]	Dose-response	12 g/d	11	0.89 (0.80, 0.98)	0.02	Critically low
Cheese [35]	High vs low	Intake	6	0.93 (0.88, 0.99)	0.02	Critically low
High fat diary [33]	Dose-response	200 g/d	5	0.97 (0.94, 1.00)	0.04	Critically low
White meat [36]	High vs low	Intake	2	0.87 (0.78, 0.96)	8.00×10^{-3}	Critically low
Chocolate [37]	High vs low	Intake	7	0.80 (0.73, 0.88)	< 0.0001	Critically low
Fish [10]	High vs low	Intake	31	0.91 (0.86, 0.97)	2.00×10^{-3}	Critically low
Salt [28]	High vs low	Intake	10	1.25 (1.09, 1.44)	2.00×10^{-3}	Critically low
High fat milk [33]	Dose-response	200 g/d	4	1.11 (1.02, 1.20)	0.02	Critically low
Total meat [36]	High vs low	Intake	4	1.18 (1.09, 1.28)	< 0.0001	Critically low
Red meat [36]	High vs low	Intake	5	1.11 (1.03, 1.20)	6.00×10^{-3}	Critically low
Processed meat [36]	High vs low	Intake	5	1.16 (1.07, 1.26)	< 0.0001	Critically low
Legumes [30]	High vs low	Intake	5	0.95 (0.84, 1.07)	0.38	Critically low
Whole grain [31]	High vs low	Intake	6	0.90 (0.74, 1.10)	0.30	Critically low
Refined grain [32]	High vs low	Intake	7	1.01 (0.93, 1.11)	0.78	Critically low
Low fat milk [33]	Dose-response	200 g/d	4	0.94 (0.83, 1.08)	0.40	Critically low
Yogurt [33]	Dose-response	100 g/d	3	1.07 (0.98, 1.16)	0.15	Critically low
Fermented dairy [33]	Dose-response	200 g/d	5	0.92 (0.85, 1.01)	0.07	Critically low
Low fat dairy [33]	Dose-response	200 g/d	6	0.97 (0.92, 1.02)	0.22	Critically low
Soy [12]	High vs low	Intake	3	0.94 (0.82, 1.08)	0.37	Critically low
Cream [35]	High vs low	Intake	3	0.91 (0.78, 1.07)	0.26	Critically low
Butter [35]	High vs low	Intake	3	0.97 (0.88, 1.08)	0.59	Critically low
Poultry [38]	High vs low	Intake	5	0.97 (0.85, 1.12)	0.71	Critically low
Lean fish [10]	High vs low	Intake	5	0.84 (0.69, 1.02)	0.08	Critically low
Fatty fish [10]	High vs low	Intake	6	0.89 (0.76, 1.05)	0.17	Critically low
Shellish [10]	High vs low	Intake	5	0.97 (0.82, 1.15)	0.76	Critically low
Egg [39]	High vs low	Intake	16	0.96 (0.87, 1.06)	0.44	Critically low
Beverages						
Tea [13]	Dose-response	3 cups/d	14	0.80 (0.70, 0.91)	1.00×10^{-3}	Critically low
Coffee [41]	High vs low	Intake	21	0.86 (0.79, 0.94)	1.00×10^{-3}	Critically low
Alcohol [40]	High vs low	High-to-heavy Intake	29	1.32 (1.03, 1.70)	0.03	Critically low
Alcohol [40]	High vs low	Light-to-moderate Intake	29	0.98 (0.87, 1.10)	0.72	Critically low
Dietary behaviours						
Mediterranean diet [8]	High vs low	Adherence	4	0.80 (0.67, 0.95)	9.00×10^{-3}	Critically low
DASH [7]	High vs low	Adherence	12	0.87 (0.81, 0.93)	< 0.0001	Critically low

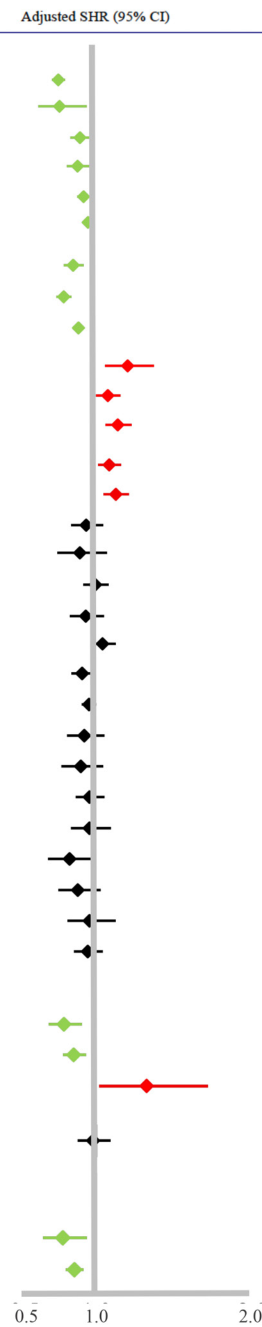

Figure 2 Adjusted summary HRs (SHR) with 95% confidence intervals and quality of evidence for association between food factors, beverages, dietary patterns and incidence of stroke. AMSTAR = assess the methodological quality of systematic reviews; DASH = dietary approaches to stop hypertension; PS = primary studies.

levels of alcohol were positively associated with stroke (all p<0.05). After excluding null values of 95% PI, only inverse association of chocolate was observed (95% PI 0.75 to 0.92). For ischaemic stroke, associations for high levels of fruit and vegetable, cheese, chocolate, tea (three cups/day), light-to-moderate levels of alcohol and high adherence of DASH diet showed p<0.025 by the random-effects model, suggesting decreased risk. Associations for high levels of total meat, processed meat and high-to-heavy levels of alcohol showed p<0.025 by the random-effects model, suggesting increased risk. After excluding null values of 95% PI, processed meat was positively associated with ischaemic stroke (95% PI 1.01 to 1.35). For haemorrhagic stroke, high intake levels of fruit and vegetable, chocolate and fish were inversely associated with and high-to-heavy levels of alcohol were positively associated with haemorrhagic stroke (all p<0.025). After excluding null values of 95% PI, only inverse association of fish was observed (95% PI 0.79 to 0.99). Most studies (total stroke, 71.88%; ischaemic stroke, 66.67%;

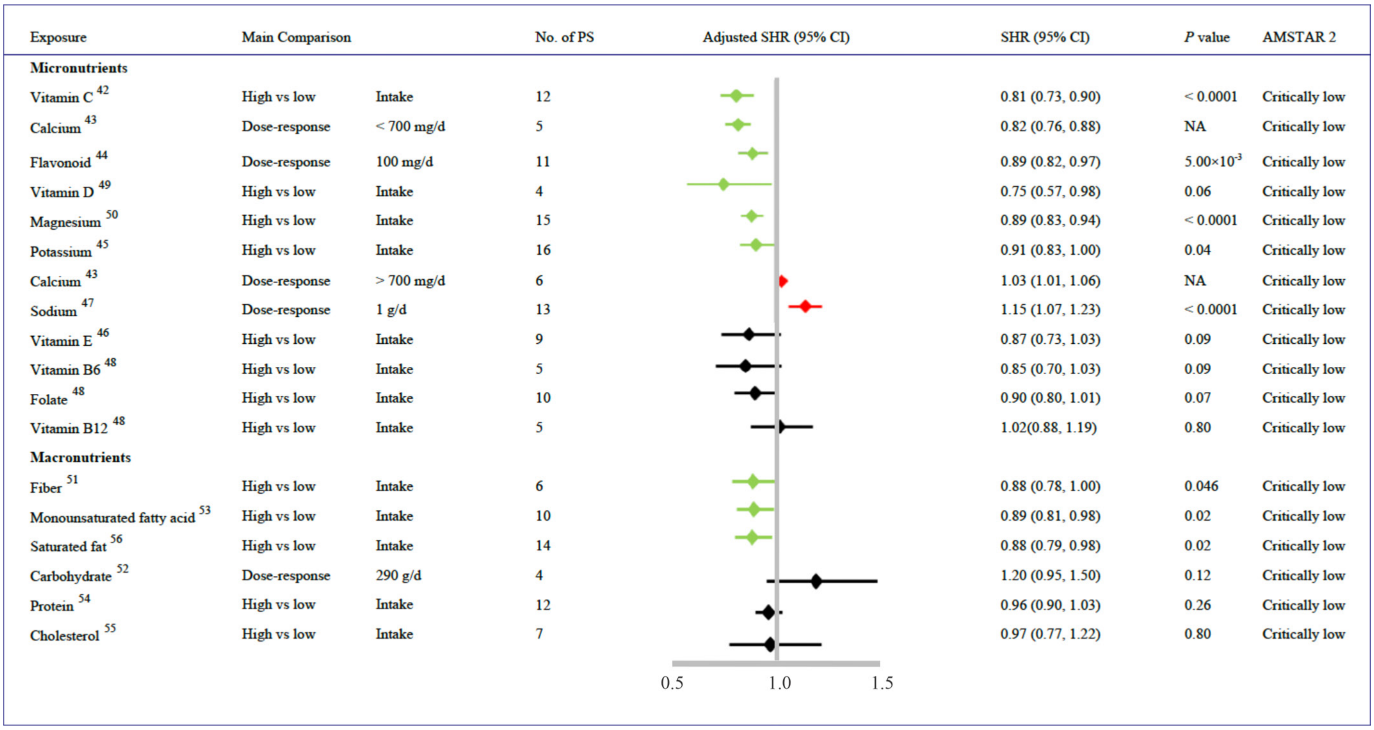

Figure 3 Adjusted summary HRs (SHR) with 95% confidence intervals and quality of evidence for association between micronutrients, macronutrients and incidence of stroke. AMSTAR = assess the methodological quality of systematic reviews; NA = not available; PS = primary studies.

haemorrhagic stroke, 70.83%) showed low heterogeneity ($I^2 \leq 50\%$).

Macronutrients and micronutrients

For total stroke, associations for high levels of vitamin C and D, calcium (<700 mg/day), flavonoid, potassium, magnesium fibre, monounsaturated fatty acid and saturated fat showed p<0.05 by the random-effects model, suggesting decreased risk. Associations for high level of sodium and calcium (>700 mg/day) showed p<0.05 by the random-effects model, suggesting increased risk. After excluding null values of 95% PI, associations of vitamin C, flavonoid and magnesium were observed (95% PI were 0.71 to 0.93, 0.81 to 0.98 and 0.82 to 0.95, respectively). For ischaemic stroke, high levels

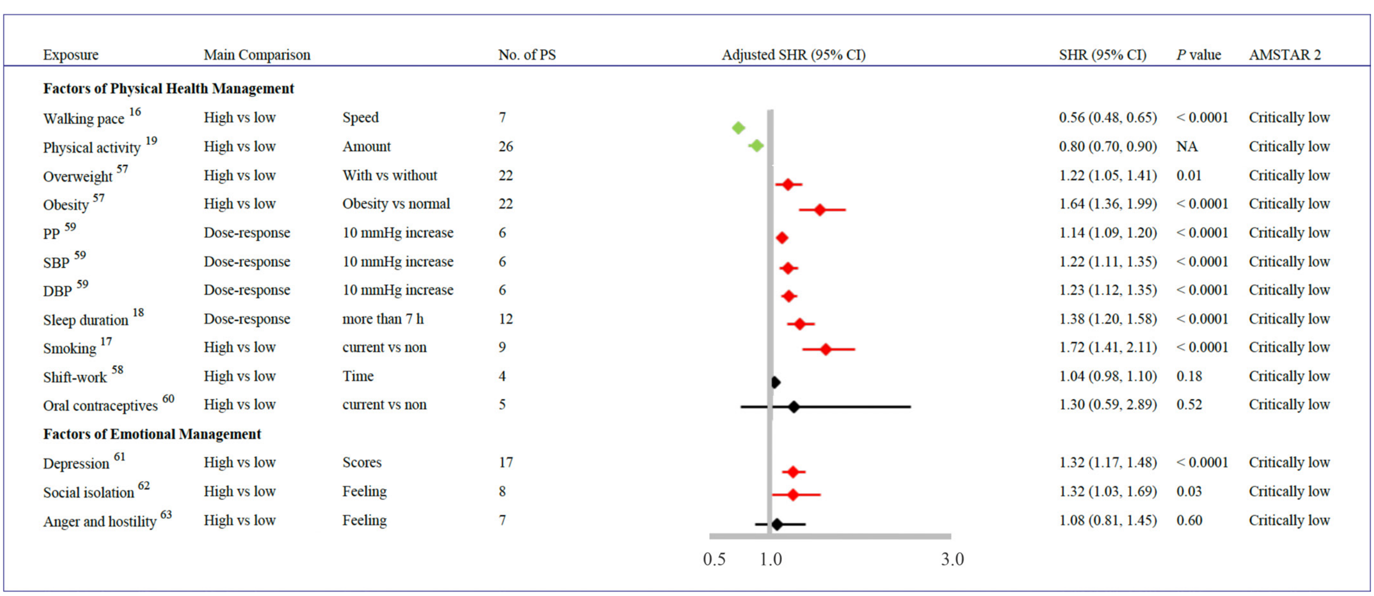

Figure 4 Adjusted summary HRs (SHR) with 95% confidence intervals and quality of evidence for association between factors of physical health and emotional management and incidence of stroke AMSTAR = assess the methodological quality of systematic reviews; DBP = diastolic blood pressure; NA = not available; PP = pulse pressure; PS = primary studies; SBP = systolic blood pressure.

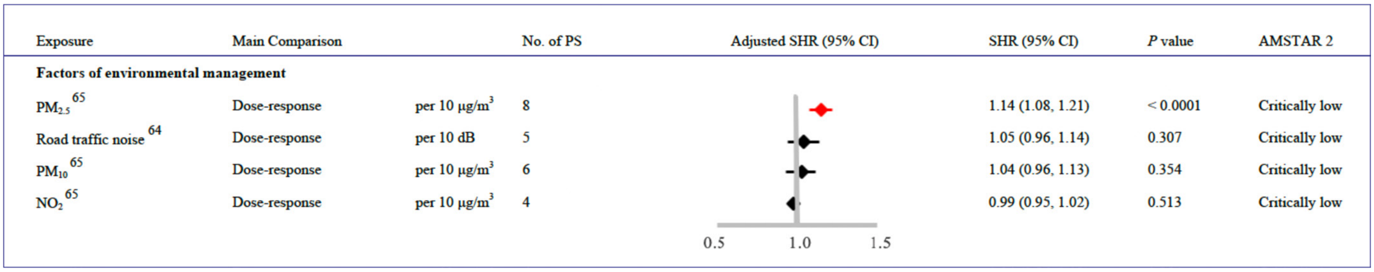

Figure 5 Adjusted summary HRs (SHR) with 95% confidence intervals and quality of evidence for association between factors of environmental management and incidence of stroke. AMSTAR = assess the methodological quality of systematic reviews; PM = particulate matter; PS = primary studies.

of vitamin C and D, potassium, folate, magnesium and saturated fat were inversely associated with the risk (all p<0.025). After excluding null values of 95% PI, association of potassium was observed (95% PI 0.80 to 0.97). For haemorrhagic stroke, saturated fat was inversely associated with the risk ($p=4\times10^{-3}$), while high-to-heavy alcohol and high level of carbohydrate were positively associated with stroke (all p<0.025). After excluding null values of 95% PI, no association was observed. Most studies (total stroke, 66.67%; ischaemic stroke, 68.75%; haemorrhagic stroke, 81.25%) showed low heterogeneity (I^2 ≤50%).

Factors of physical, emotional health and environmental management

For total stroke, physical activity and high speed of walking pace were inversely associated with the risk, while overweight, obesity, 10 mm Hg increase of pulse, diastolic and systolic blood pressure (PP, DBP and SBP), >7 hours sleep duration, anti-inflammatory drugs, smoking, depression, social isolation and particulate matter 2.5 ($PM_{2.5}$) were positively associated with the risk (all p<0.05). After excluding null values of 95% PI, associations of 10 mm Hg increase of PP, high speed of walking pace and 10 µg/m^3 increase of $PM_{2.5}$ were observed (95% PI were 1.02 to 1.28, 0.46 to 0.69 and 1.01 to 1.30, respectively). For ischaemic stroke, speed of walking pace was inversely and >7 hours sleep duration and smoking were positively associated with the risk (all p<0.025). After excluding null values of 95% PI, association of smoking was observed (95% PI 1.26 to 1.93). For haemorrhagic stroke, high speed of walking pace was inversely and smoking was positively associated with the risk ($p=8\times10^{-3}$ and 0.01, respectively). After excluding null values of 95% PI, no association was observed; 27.78% studies of total stroke, 50.00% studies of ischaemic stroke and 75.00% studies of haemorrhagic stroke showed low heterogeneity (I^2 ≤50%).

Small-study effects

According to online supplemental table S6, S7 and S8, publication bias existed in some meta-analyses (all p<0.10). Consequently, a trim-and-fill method was conducted to evaluate the sensitivity. The results remained after this method, except Valtorta's study which could be explained by reporting bias.[62]

Excess significance

For total stroke, the excess significant finding was calculated in 25 comparisons, in which 10 comparisons showed evidence of excess significant finding. For ischaemic stroke, the excess significant finding was calculated in 21 comparisons, in which 11 comparisons showed evidence of excess significant finding. For total stroke, the excess significant finding was calculated in 20 comparisons, in which 2 comparisons showed evidence of excess significant finding (online supplemental table S6, S7 and S8).

Methodological quality of studies

As shown in online supplemental table S9, the methodological quality of three meta-analyses was low,[10 49 56] while others were critically low.[7 8 12 13 16–20 27–48 50–55 57–65] The main methodological problems found according to AMSTAR 2 were as follows: meta-analyses did not contain an explicit statement that the review methods were established prior and did not report any significant deviations from the protocol, did not provide a list of excluded studies and justify the exclusions, did not report the sources of funding for each original study and assess the impact of risk of bias in individual studies on the results of the meta-analysis or other evidence synthesis.

Sensitivity analyses

In the results, evidence of walking pace was strong. High suggestive evidence mainly included total meat, processed meat, chocolate, sodium, obesity, PP, SBP, DBP, sleep duration and smoking. Suggestive evidence mainly included DASH diet, vitamin C, magnesium, depression and $PM_{2.5}$. After excluding primary studies that did not adjust for important potential confounders, evidence of DASH diet, magnesium and depression turned to weak (table 1 and online supplemental table S10). Detailed information about countries and regions of the evidence is provided in online supplemental table S11, which suggested the review was a global review.

DISCUSSION

Main findings

In the present umbrella review, a broad overview of the existing evidence was provided and the methodological quality of the meta-analyses and quality of evidence for all these associations were evaluated. The present review

Table 1 Summary of sensitivity analyses

Study	Main comparison	Exposure	Quality of evidence				
				Sensitivity analyses			
			Primary analysis	Including studies adjusted for potential confounding variables	Omission of small-sized studies	Omission of low-quality studies	QES
Food factors							
Kim *et al*[36]	High versus low	Total meat	Highly suggestive	Highly suggestive	NA	Highly suggestive*	Highly suggestive
		Processed meat	Highly suggestive	Highly suggestive	NA	Highly suggestive*	Highly suggestive
Kim *et al*[36] (IS)	High versus low	Processed meat	Suggestive	Suggestive	NA	Suggestive*	Suggestive
Yuan *et al*[37]	High versus low	Chocolate	Highly suggestive	Highly suggestive	Highly suggestive	Highly suggestive*	Highly suggestive
Dietary behaviours							
Feng *et al*[7]	High versus low	DASH	Suggestive	Weak	NA	Suggestive*	Weak
Micronutrients							
Chen *et al*[42]	High versus low	Vitamin C	Suggestive	Suggestive	NA	Suggestive†	Suggestive
Jayedi *et al*[47]	Dose-response	Sodium	Highly suggestive	Highly suggestive	NA	Highly suggestive*	Highly suggestive
Zhao *et al*[50]	High versus low	Magnesium	Suggestive	Weak	Suggestive	Suggestive*	Weak
Factors of physical health management							
Strazzullo *et al*[57]	High versus low	Obesity	Highly suggestive	Highly suggestive [c]	NA	Highly suggestive‡	Highly suggestive
Liu *et al*[59]	Dose-response	PP	Highly suggestive	Highly suggestive	NA	Highly suggestive*	Highly suggestive
		SBP	Highly suggestive	Highly suggestive	NA	Highly suggestive*	Highly suggestive
		DBP	Highly suggestive	Highly suggestive	NA	Highly suggestive*	Highly suggestive
He *et al*[18]	Dose-response	Sleep duration	Highly suggestive	Highly suggestive	NA	Highly suggestive	Highly suggestive
He *et al*[18] (IS)	Dose-response	Sleep duration	Highly suggestive	Highly suggestive	NA	Highly suggestive*	Highly suggestive
Pan *et al*[17]	High versus low	Smoking	Highly suggestive	Highly suggestive	Highly suggestive	Highly suggestive†	Highly suggestive
Pan *et al*[17] (IS)	High versus low	Smoking	Suggestive	Strong	NA	Suggestive†	Suggestive
Quan *et al*[16]	High versus low	Walking pace	Strong	Strong	NA	Strong*	Strong
Factors of emotional health management							
Dong *et al*[61]	High versus low	Depression	Suggestive	Weak	NA	Suggestive†	Weak
Factors of environmental management							
Niu *et al*[65]	Dose-response	$PM_{2.5}$	Suggestive	Suggestive	NA	Suggestive*	Suggestive

NA because sensitivity analysis was not performed because of no evidence of small-study effects.
*Meta-analysis reported all good-quality studies.
†No information on quality assessment of primary studies.
‡Data extracted from published meta-analysis, no re-analysis possible.
IS, ischaemic stroke; NA, not applicable; PM, particulate matter; QES, quality of evidence after sensitivity analyses.

suggested fruit and vegetable, olive oil, milk, nuts, cheese, meat, chocolate, poultry, fish, tea, alcohol, coffee, Mediterranean and DASH diet, vitamins, calcium, flavonoid, potassium, sodium, magnesium, fibre, monounsaturated fatty acid, saturated fat, depression, social isolation, overweight, obesity, physical activity, PP, DBP and SBP, sleep duration, anti-inflammatory drugs, smoking, walking pace and $PM_{2.5}$ may play different roles in pathological mechanism of stroke. Among these factors, after sensitivity analyses, evidence of total meat, processed meat, chocolate, vitamin C, sodium, obesity, PP, DBP and SBP, sleep duration, smoking, walking pace and $PM_{2.5}$ suggested strength of 'suggestive evidence' and above.

Foods having the correct balance of macronutrients and micronutrients are the key elements of a healthy diet.[66] In the present review, the protective effects of fruit and vegetable and their main nutritional ingredients including vitamin C, flavonoid, potassium and fibre were observed on stroke. Previous studies demonstrated high intake of fruit and vegetable could reduce blood pressure.[67] As raised blood pressure was a risk factor, we speculate the contributions of Mediterranean diet and food factors above to stroke risk may be explained by this.[68] In the same way, high salt, processed meat manufactured with the preservative sodium nitrate and sodium intake which are the main risk factor of hypertension and consequently exerts negative effects on the cardiovascular systems were associated with increased stroke risk in the result. The harmful effect of processed meat remained on ischaemic stroke as a suggestive evidence. Besides, highly suggestive evidence of chocolate showed as an abundant source of flavanols, chocolate has benefits for stroke. Previous meta-analysis suggested that flavanol-rich chocolate and cocoa products caused a significant reduction in both SBP and DBP, which are risk factors of stroke.[69] Therefore, chocolate may account for the reduced risks of stroke in our review. Based on the evidence above, it could be speculated dietary factors and behaviours which could control blood pressure may also play protective roles in stroke. In addition to the food factors above, associations of other food factors (olive oil, milk, nuts, cheese, red meat and fish), beverages (tea, alcohol and coffee), nutrients (calcium, vitamin D, magnesium and monounsaturated fatty acid), dietary behaviours including Mediterranean and DASH were also observed in the present review. Since the grade of evidence was weak, further studies are warranted to confirm these findings.

Physical and emotional health and environmental management in preventing diseases have attracted more and more attention in recent years. In the present review, highly suggestive evidence of obesity revealed it was positively associated with stroke, while more physical activity and strong evidence of high speed of walking pace were inversely associated with the risk, suggesting the importance of exercising consistently and maintaining a healthy weight. Besides, in the present review, PP in conjunction with SBP and DBP may be used to identify patients at high risk of stroke for improving stroke prevention, which is also a highly suggestive evidence. Specifically, association between sleep durations and stroke risk was studied and the result showed long sleepers (>7 hours) had a higher predicted risk of stroke, which is a highly suggestive evidence. Although the mechanisms are not fully understood, it may be explained by increase in some inflammatory biomarkers and association with carotid artery atherosclerosis and atrial fibrillation.[70 71] In addition, smoking has proven to be associated with mounts of cardiovascular diseases, even sudden cardiac death.[72] The highly suggestive evidence of smoking on stroke risk reminds us it is definitely essential to stay away from smoking, which is the most critical and effective measure. As an environmental factor accompanied by people's concern commonly, the role of $PM_{2.5}$ in stroke was explored widely. The result showed $PM_{2.5}$ (per 10 $\mu g/m^3$ increment) increased the risk of stroke. Although the accurate mechanisms remain unclear, it could be explained by the dysfunction of the autonomic system which is the major pathway that could result in air pollution-related adverse cardiovascular outcomes, such as stroke.[73] Besides, depression, social isolation and taking anti-inflammatory drugs also increased stroke risk according to the present result. Since the evidence of them was weak, further studies underlying the associations are needed.

Strengths and limitations

Our review systematically summarised broad evidence of modifiable factors in the prevention of stroke and its subtypes. Moreover, our umbrella review assessed the overlapping and excess significant finding among included meta-analyses, which provide evidence on the quality of previous reviews. However, our review also has several limitations that must be considered when interpreting the results. First, the qualities of included meta-analyses were low as they did not meet the standards of AMSTAR 2, such as they did not establish a protocol a priori and the report did not justify any significant deviations from the protocol, which can lead to potential bias in the results of meta-analyses. Future studies need to pay more attention to these standards. Second, the selection of included and excluded meta-analyses only considered the categories of modifiable factors including dietary factors, factors of physical health management and emotional health management. The detailed factors were confirmed according to the categories in the process, which may lead to flaws in the results. Third, only evidence derived from systematic reviews and meta-analyses of cohort studies was included in our umbrella review. Evidence from original studies in other databases was beyond our scope of discussion. This condition might result in conclusion bias of association between modifiable factors and stroke. Lastly, although subgroup analyses were conducted by subtypes of stroke, subgroup analysis by sex or geographical locations or sensitivity analysis (eg, exclusion of studies at high risk of bias) were not explored. Further studies underlying this are needed in the future.

CONCLUSION

In summary, evidence indicates that modifiable factors have an important role in the primary prevention of stroke. Diet with rich macronutrients and micronutrients, healthy dietary patterns as well as favourable physical, emotional health and environmental management significantly decrease the risk of stroke. These lifestyle modifications should be promoted in both individual and population levels to prevent and decrease the burden of stroke in the future. Although many modifiable factors were evaluated in the review, the quality of evidence was high for a small number of associations. To achieve high quality of evidence for and be able to give strong recommendation, further studies are needed regarding the following aspects: studies investigating the association between dietary factors and stroke should improve dietary measurement methods and assess changes in dietary behaviour over time; potential confounders of stroke are needed to adjust in the multivariate analysis completely and more research should focus on the physical, emotional and environmental health management the evidence of which is not enough.

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Table S1. Search term in PubMed, Web of Science, Embase, Wanfang, and China National Knowledge Infrastructure databases.

(meta-analysis OR review OR systematic review OR systematic overview)
AND
(stroke OR cerebral infarction OR ischemic stroke OR cerebral hemorrhage OR hemorrhagic stroke)
AND
((association OR associated OR relationship OR related OR risk) OR (diet OR dietetic OR diets OR dietary) OR (nutrition OR nutrient) OR (food OR food group OR food cluster) OR beverage) OR (cereal OR grain OR corn OR wholegrain OR soy OR soya OR whole wheat OR potatoes OR granary OR tuber OR pulses OR legumes OR lentils OR beans OR rice OR quinoa OR fruit and vegetable OR milk OR dairy OR dairy products OR yogurt OR cheese OR cream OR egg OR meat OR pork OR lamb OR chicken OR poultry OR beef OR turkey OR duck OR fish OR seafood OR shellfish OR salt OR oil OR butter OR margarine OR nut OR desert OR sweets OR candy OR chocolate) OR (alcohol OR caffeine OR coffee OR tea OR juice OR beer OR lemonade OR drinks OR drinking OR wine OR liquor OR sugar sweetened beverage) OR (dietary pattern OR mediterranean OR vegetarian OR dietary approaches to stop hypertension) OR (macronutrient OR fat OR fatty acid OR carbohydrate OR fiber OR fiber OR cholesterol OR starch OR fructose OR protein) OR (micronutrient OR vitamin OR mineral OR calcium OR flavonoid OR iron OR iodine OR zinc OR selenium OR copper OR manganese OR chromium OR cobalt OR pantothenic acid OR folic acid OR potassium OR sodium OR folate OR magnesium) OR (physical OR exercise OR walking OR weight OR obesity OR blood pressure OR pulse pressure OR sleep OR smoking OR drug OR work OR rest) OR (emotion OR mental OR depression OR despondent OR social isolation OR anger OR hostility) OR (traffic OR pollution))

Table S2. Criteria for quality of evidence classification in observed studies.

Category	Criteria
Strong evidence	No. of cases > 1,000
	$P < 1\times10^{-6}$
	$I^2 < 50\%$
	95% prediction interval excluding the null
	No small-study effects
	No excess significance bias
Highly suggestive evidence	No. of cases > 1,000
	$P < 1\times10^{-6}$
	Largest study with a statistically significant effect
Suggestive evidence	No. of cases > 1,000
	$P < 1\times10^{-6}$
Weak evidence	$P < 0.05$
No significant evidence	$P > 0.05$

Table S3. List of excluded studies

Eligibility in the basis of full article review	n [ref]
Not the largest and most comprehensive systematic review and meta-analysis assessing the effect	53 [1-53]
Not especially for purposed exposure	4 [54-57]
Not the outcomes	2 [58 59]
Not cohort study included	2 [60 61]
Not modifiable factors reported	10 [62-70]
Full-text not avaliable	1 [71]

Table S4. List of excluded studies according to each exposure.

Exposure	Searched (n [ref])	Excluded (n [ref] reasons)
Food factors		
Fruit and vegetable	2 [1 72]	1 [1] (not the largest and most comprehensive)
Salt	2 [54 55]	1 [54] (not the largest and most comprehensive)
Olive oil	1 [73]	NA
Legumes	2 [2 74]	1 [2] (not the largest and most comprehensive)
Whole grain	1 [75]	NA
Refined grain	1 [76]	NA
Milk	4 [3-5 77]	3 [3-5] (not the largest and most comprehensive)
Low fat milk	4 [3-5 77]	3 [3-5] (not the largest and most comprehensive)
High fat milk	4 [3-5 77]	3 [3-5] (not the largest and most comprehensive)
Yogurt	4 [3-5 77]	3 [3-5] (not the largest and most comprehensive)
Fermented dairy	4 [3-5 77]	3 [3-5] (not the largest and most comprehensive)
Low fat dairy	4 [3-5 77]	3 [3-5] (not the largest and most comprehensive)
High fat dairy	4 [3-5 77]	3 [3-5] (not the largest and most comprehensive)
Soy	1 [78]	NA
Nuts	2 [2 79]	1 [2] (not the largest and most comprehensive)
Cheese	2 [3 4]	1 [4] (not the largest and most comprehensive)
Cream	2 [3 4]	1 [4] (not the largest and most comprehensive)
Butter	2 [3 4]	1 [4] (not the largest and most comprehensive)
Total meat	2 [6 57]	1 [6] (not the largest and most comprehensive)
Red meat	2 [6 57]	1 [6] (not the largest and most comprehensive)
Processed meat	2 [6 57]	1 [6] (not the largest and most comprehensive)
White meat	2 [6 57]	1 [6] (not the largest and most comprehensive)
Chocolate	3 [7 8 80]	2 [7 8] (not the largest and most comprehensive)
Poultry	2 [57 81]	1 [57] (not especially for poultry)
Fish	8 [9-14 57 82]	7 [9-14 57] (not the largest and most comprehensive)
Lean fish	8 [9-14 57 82]	7 [9-14 57] (not the largest and most comprehensive)
Fatty fish	8 [9-14 57 82]	7 [9-14 57] (not the largest and most comprehensive)
Shellish	8 [9-14 57 82]	7 [9-14 57] (not the largest and most comprehensive)
Egg	5 [10 11 15 16 83]	4 [10 11 15 16] (not the largest and most comprehensive)
Beverages		
Tea	2 [17 84]	1 [17](not the largest and most comprehensive)
Alcohol	10 [18-26 85]	9 [18-26] (not the largest and most comprehensive)
Coffee	4 [10 27-29]	3 [27-29] (not the largest and most comprehensive)
Dietary behaviours		
Mediterranean diet	1 [86]	NA
DASH	1 [87]	NA
Micronutrients		

Vitamin C	1 [88]	NA
Calcium	3 [30 31 89]	2 [30 31] (not the largest and most comprehensive)
Flavonoid	1 [90]	NA
Potassium	7 [32-36 56 91]	5 [32-36] (not the largest and most comprehensive) 1 [56] (not especially for potassium)
Vitamin E	3 [60 92]	2 [60] (not cohort)
Sodium	3 [54-56]	2 [54 55](not especially for sodium)
Vitamin B6	2 [58 93]	1 [58] (not the outcome)
Folate	2 [58 93]	1[58] (not the outcome)
Vitamin B12	2 [58 93]	1 [58] (not the outcome)
Vitamin D	1 [94]	NA
Magnesium	6 [32 33 37-39 95]	5 [32 33 37-39](not the largest and most comprehensive)
Macronutrients		
Fiber	1[96]	NA
Carbohydrate	1 [97]	NA
Monounsaturated fatty acid	1 [98]	NA
Protein	1 [99]	NA
Cholesterol	1 [100]	
Saturated fat	3 [40 41 101]	2 [40 41](not the largest and most comprehensive)
Factors of physical health management		
Overweight	2 [23 102]	1 [23](not the largest and most comprehensive)
Obesity	2 [23 102]	1 [23](not the largest and most comprehensive)
Shift-work	1 [103]	NA
Physical activity	5 [42-45 104]	4 [42-45] (not the largest and most comprehensive)
		1 [59] (not the outcome) ;
PP	2 [53 59 105]	1 [53](not the largest and most comprehensive)
SBP	2 [59 105]	1 [59] (not the outcome)
DBP	2 [105]	1 [59] (not the outcome)
Sleep duration	3 [46 47 106]	2 [46 47](not the largest and most comprehensive)
Oral contraceptives	1 [107]	NA
Anti-inflammatory drugs	1 [108]	NA
Smoking	4 [23 48 49 109]	3 [23 48 49](not the largest and most comprehensive)
walking pace	1 [110]	NA
Factors of emotional health management		
Depression	1 [111]	NA
Social isolation	1 [112]	NA
Anger and hostility	1 [113]	NA

Factors of environmental health management		
Road traffic noise	1 [114]	NA
$PM_{2.5}$	4 [50-52 115]	3 [50-52] (not the largest and most comprehensive)
PM_{10}	4 [50-52 115]	3 [50-52] (not the largest and most comprehensive)
NO_2	4 [50-52 115]	3 [50-52] (not the largest and most comprehensive)

Abbreviations: NA, not available; DASH, dietary approaches to stop hypertension; PP, pulse pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table S5. Main characteristics of included systematic reviews or meta-analyses that evaluate modifiable factors and stroke risk.

First Author, Year	Main Comparison		Exposure	No. of primary cohort studies	Follow-up duration (years)	No. of participants / No. of cases	AMSTAR 2
Food factors							
He, 2006 [72]	High vs low	Intake	Fruit and vegetable	8	3.09-20.00	257,551 / 4,917	Critically low
Strazzullo, 2009 [55]	High vs low	Intake	Salt	10	3.50-19.00	154,282 / 5,346	Critically low
Mart´ınez-Gonza´lez, 2014 [73]	Dose-response	25 g/d	Olive oil	2	4.80-10.40	31,226 / 543	Critically low
Shi, 2014 [74]	High vs low	Intake	Legumes	5	12.50-26.00	173,229 / 4,030	Critically low
Fang, 2015 [75]	High vs low	Intake	Whole grain	6	5.50-24.00	247,487 / 1,635	Critically low
Wu, 2015 [76]	High vs low	Intake	Refined grain	7	5.50-15.20	410,821 / 8,284	Critically low
		200 g/d	Milk	14	10.00-25.00	603, 919 / 24,887	
		200 g/d	Low fat milk	4	10.00-13.60	159,547 / 5,942	
		200 g/d	High fat milk	4	10.00-13.60	159,547 / 5,942	
de Goede, 2016 [77]	Dose-response	100 g/d	Yogurt	3	13.60-17.30	116,555 / 3,894	Critically low
		200 g/d	Fermented dairy	5	10.00-17.30	160,048 / 7,032	
		200 g/d	Low fat dairy	6	10.00-24.30	263,425 /10,044	
		200 g/d	High fat dairy	5	10.20-24.30	262,643 / 8,990	
Lou, 2016 [78]	High vs low	Intake	Soy	3	6.30-14.70	119,884 / 2,032	Critically low
Shao, 2016 [79]	Dose-response	12 grams/day	Nuts	11	4.30-22.70	671,301 / 7,665	Critically low
		Intake	Cheese	6	10.00-17.30	224,101 / 10,483	
Gholami, 2017 [3]	High vs low	Intake	Cream	3	10.20-13.60	127,962 / 8,546	Critically low
		Intake	Butter	3	10.00-13.69	111,280 / 5,299	
		Intake	Total meat	4	7.50-18.00	213,722 / 8,848	

Kim, 2017 [57]	High vs low	Intake	Red meat	5	5.50-26.00	254,742 / 9,522	Critically low
		Intake	Processed meat	5	10.10-26.00	254,742 / 9,522	
		Intake	White meat	2	5.50-26.00	138,761 / 4,759	
Yuan, 2017 [80]	High vs low	Intake	Chocolate	7	4.70-16.00	231,038 / 8,197	Critically low
Mohammadi, 2018 [81]	High vs low	Intake	Poultry	5	5.50-26.00	354,728 / 7,705	Critically low
Zhao, 2019 [82]	High vs low	Intake	Fish	31	4.00-30.00	1,145,154 / 32,738	Low
			Lean fish	5	4.30-18.00	101,594 / 2,966	
			Fatty fish	6	4.30-18.00	125,906 / 3,387	
			Shellfish	5	4.30-12.00	200,046 / 2,152	
Tang, 2020 [116]	High vs low	Intake	Egg	16	8.80-32.00	1,387,653 / 5,8451	Critically low
Beverages							
Shen, 2012 [84]	Dose-response	3 cups/d	Tea	14	4.00-24.00	513,804 / 10,192	Critically low
Larsson, 2016 [117]	High vs low	Light-to-moderate High-to-heavy	Alcohol	29	3.80-29.10	1102642 / 222,825	Critically low
Shao, 2021 [29]	High vs low	Intake	Coffee	21	3.50-28.00	2,483,086 / 26,241	Critically low
Dietary behaviors							
Psaltopoulou, 2013 [86]	High vs low	Adherence	Mediterranean diet	4	7.89-20.00	152843/ 2560	Critically low
Feng, 2018 [87]	High vs low	Adherence	DASH	12	7.90-24.00	548,632 / 15,270	Critically low
Micronutrients							
Chen, 2013 [88]	High vs low	Intake	Vitamin C	12	6.10-30.00	217,454 / 3,762	Critically low
Larsson, 2013 [89]	Dose-response	< 700 mg/d	Calcium	5	9.60-22.0	153,280 / 2,634	Critically low
		> 700 mg/d		6	98.00-13.60	250,551 / 6,461	
Tang, 2016 [90]	Dose-response	100 mg/d	Flavonoid	11	6.10-28.00	356,627 / 5,154	Critically low
Vinceti, 2016 [91]	High vs low	Intake	Potassium	16	3.70-25.80	639,440 / 19,522	Critically low

Cheng, 2018 (1) [92]	High vs low	Intake	Vitamin E	9	6.10-15.00	220,371 / 3,284	Critically low
Jayedi, 2019 [118]	Dose-response	1 gr/d	Sodium	13	4.70-28.00	252,985 / 9,503	Critically low
Chen, 2020 [93]	High vs low	Intake	Vitamin B6	5	10.00-16.20	264,253 / 7,334	Critically low
		Intake	Folate	10	4.20-19.00	255,458 / 8,477	
		Intake	Vitamin B12	5	4.20-14.00	130,965 / 5,458	
Shi, 2020 [94]	High vs low	Intake	Vitamin D	4	10.00-34.00	67,238 / 2,616	Low
Zhao, 2020 [95]	High vs low	Intake	Magnesium	15	NR	692,998 / 20138	Critically low
Macronutrients							
Chen, 2013 [96]	High vs low	Intake	Fiber	6	6.00-8.00	314,864 / 8,920	Critically low
Cai, 2015 [97]	Dose-response	290 g/d	Carbohydrate	4	5.00-18.00	170,348 / 1,851	Critically low
Cheng, 2016 [98]	High vs low	Intake	Monounsaturated fatty acid	10	7.60-20.00	307,087 / 5,827	Critically low
Zhang, 2016 [119]	High vs low	Intake	Protein	12	5.00-26.00	528,982 / 1,1340	Critically low
Cheng, 2018 (2) [100]	High vs low	Intake	Cholesterol	7	6.10-15.00	269,777 / 4,604	Critically low
Kang, 2020 [101]	High vs low	Intake	Saturated fat	14	7.40-20.00	598,435 / 12,084	Low
Factors of physical health management							
Strazzullo, 2010 [102]	High vs low	With vs without	Overweight	22	7.00-28.00	2,159,827 / 2,7357	Critically low
			Obesity	22	7.00-28.00	1,800,924 / 22,279	
Li 2016 [103]	High vs low	Time	Shift-work	4	NR	488,699 / 4,231	Critically low
Kyu 2016 [104]	High vs low	Amount	Physical activity	26	5.80-16.40	1,573,231 / NR	Critically low
Liu, 2016 [105]	Dose-response	10 mmHg increase	PP	6	6.50-12.00	122,265 / 3,147	Critically low
			SBP	6	6.50-12.01	122,265 / 3,147	
			DBP	6	6.50-12.02	122,265 / 3,147	
He, 2017 [105]	Dose-response	More than 7 h	Sleep duration	12	7.80-14.70	528,653 / 12,193	Critically low
Xu, 2018 [107]	High vs low	Current vs non	Oral contraceptives	5	3.00-11.00	NR / 1,951	Critically low

Islam, 2018 [108]	High vs low	With vs without	Anti-inflammatory drugs	5	2.00-13.00	1,578,679 / NR	Critically low
Pan, 2019 [109]	High vs low	Current vs non	Smoking	9	8.00-18.00	393,598 / 3,412	Critically low
Quan, 2019 [110]	High vs low	Speed	Walking pace	7	5.20-11.90	135,645 / 2,229	Critically low
Factors of emotional health management							
Dong, 2012 [111]	High vs low	Scores	Depression	17	3.00-29.00	206,641 / 6,086	Critically low
Valtorta, 2016 [112]	High vs low	Feeling	Social isolation	8	4.00-18.60	105,514 / 2,577	Critically low
Chen, 2019 [113]	High vs low	Feeling	Anger and hostility	7	2.00-8.50	52,277 / NR	Critically low
Factors of environmental management							
Dzhambov, 2016 [114]	Dose-response	10 dB	Road traffic noise	5	7.90-13.00	243,145 / 6,672	Critically low
Niu, 2021 [115]	Dose-response	10 μg/m^3	$PM_{2.5}$	8	1.00-21.00	558,698 / 26,200	
			PM_{10}	6	4.00-21.00	1,097,987 / 23,122	Critically low
			NO_2	4	4.00-25.00	1,112,832 / 18,336	

Abbreviations: AMSTAR, assess the methodological quality of systematic reviews; NR, not reported; DASH, dietary approaches to stop hypertension; PP, pulse pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table S6. Modifiable factors and total stroke risk.

First Author, Year	Exposure	SHR (95% CI)	*P* value	I^2 (%)	τ^2	95% PI	Egger's *P* value	O	E	*P*	ESF
Food factors											
He, 2006 [72, a]	Fruit and vegetable	0.74 (0.69, 0.79)	< 0.0001	NA	NA	NA	NA	NA	NA	NA	NA
Strazzullo, 2009 [55]	Salt	1.25 (1.09, 1.44)	2.00×10^{-3}	56.70	0.02	(0.85, 1.85)	0.10	3	5.97	0.12	No
Mart´ınez-Gonza´lez, 2014 [73]	Olive oil	0.75 (0.59, 0.96)	0.02	34.50	0.02	NA	NA	2	NA	NA	NA
Shi, 2014 [74]	Legumes	0.95 (0.84, 1.07)	0.38	39.40	7.40×10^{-3}	(0.67, 1.33)	0.25	0	NA	NA	NA
Fang, 2015 [75]	Whole grain	0.90 (0.74, 1.10)	0.30	31.60	0.02	(0.56, 1.45)	0.72	1	0.92	0.93	No
Wu, 2015 [76]	Refined grain	1.01 (0.93, 1.11)	0.78	0.00	< 0.00001	(0.90, 1.14)	0.59	0	4.65	1.38×10^{-3}	Yes
	Milk	0.90 (0.83, 0.98)	0.02	80.00	0.01	(0.69, 1.19)	0.21	3	NA	NA	NA
	Low fat milk	0.94 (0.83, 1.08)	0.40	69.00	0.01	(0.54, 1.66)	0.61	1	NA	NA	NA
	High fat milk	1.11 (1.02, 1.20)	0.02	0.00	< 0.00001	(0.92, 1.32)	0.77	1	NA	NA	NA
de Goede, 2016 [77]	Yogurt	1.07 (0.98, 1.16)	0.15	0.00	< 0.00001	(0.61, 1.86)	0.31	0	NA	NA	NA
	Fermented dairy	0.92 (0.85, 1.01)	0.07	72.40	6.40×10^{-3}	(0.69, 1.24)	5.00×10^{-3}	2	NA	NA	NA
	Low fat dairy	0.97 (0.92, 1.02)	0.47	59.30	7.00×10^{-4}	(0.91, 1.08)	0.08	2	NA	NA	NA
	High fat dairy	0.97 (0.94, 1.00)	0.04	0.00	< 0.00001	(0.92, 1.02)	0.97	1	NA	NA	NA
Lou, 2016 [78]	Soy	0.94 (0.82, 1.08)	0.37	0.00	< 0.00001	(0.38, 2.29)	0.93	0	0.15	0.32	No
Shao, 2016 [79]	Nuts	0.89 (0.80, 0.98)	0.02	8.20	2.30×10^{-3}	(0.76, 1.04)	0.57	1	NA	NA	NA
	Cheese	0.93 (0.88, 0.99)	0.02	0.00	< 0.00001	(0.86, 1.01)	0.99	0	1.44	0.23	No
Gholami, 2017 [3]	Cream	0.91 (0.78, 1.07)	0.26	82.60	0.02	(0.14, 5.90)	0.35	1	0.15	1.28×10^{-8}	Yes
	Butter	0.97 (0.88, 1.08)	0.59	13.80	1.20×10^{-3}	(0.45, 2.12)	0.15	0	NA	NA	NA
	Total meat	1.18 (1.09, 1.28)	< 0.0001	0.00	< 0.00001	(0.99, 1.41)	0.50	2	NA	NA	NA

	Red meat	1.11 (1.03, 1.20)	6.00×10^{-3}	0.90	1.00×10^{-4}	(0.98, 1.26)	0.75	2	NA	NA	NA
Kim, 2017 [57]	Processed meat	1.16 (1.07, 1.26)	< 0.0001	15.90	1.40×10^{-3}	(0.97, 1.39)	0.40	3	NA	NA	NA
	White meat	0.87 (0.78, 0.96)	8.00×10^{-3}	0.00	< 0.00001	NA	NA	1	NA	NA	NA
Yuan, 2017 [80]	Chocolate	0.83 (0.77, 0.89)	< 0.0001	0.00	< 0.00001	(0.75, 0.92)	2.00×10^{-3}	5	2.62	0.15	No
Mohammadi, 2018 [81]	Poultry	0.97 (0.85, 1.12)	0.71	50.40	0.01	(0.64, 1.47)	0.25	1	NA	NA	NA
	Fish	0.91 (0.86, 0.97)	2.00×10^{-3}	47.60	0.01	(0.73, 1.13)	0.18	7	12.30	0.19	No
Zhao, 2019 [82]	Lean fish	0.84 (0.69, 1.02)	0.08	0.00	< 0.00001	(0.61, 1.15)	0.42	1	0.25	3.10×10^{-3}	Yes
	Fatty fish	0.89 (0.76, 1.05)	0.17	29.50	0.01	(0.61, 1.30)	1.00	1	1.17	0.87	No
	Shellfish	0.97 (0.82, 1.15)	0.76	20.90	7.90×10^{-3}	(0.66, 1.45)	0.39	1	1.16	0.87	No
Tang, 2020 [116]	Egg	0.96 (0.87, 1.06)	0.44	74.10	0.02	(0.69, 1.34)	0.81	5	7.03	0.46	No
Beverages											
Shen, 2012 [84]	Tea	0.80 (0.70, 0.91)	1.00×10^{-3}	59.00	0.03	(0.52, 1.21)	0.49	6	NA	NA	NA
Larsson, 2016 [117, a]	Light-to-moderate Alcohol	0.98 (0.87, 1.10)	NA	NA	NA	NA	NA	NA	NA	NA	NA
	High-to-heavy Alcohol	1.32 (1.03, 1.70)	NA	NA	NA	NA	NA	NA	NA	NA	NA
Shao, 2021 [29]	Coffee	0.86 (0.79, 0.94)	1.00×10^{-3}	39.80	0.01	(0.66, 1.13)	0.06	7	2.24	0.02	Yes
Dietary behaviours											
Psaltopoulou, 2013 [86]	Mediterranean diet	0.80 (0.67, 0.95)	9.00×10^{-3}	25.30	8.20×10^{-3}	(0.46, 1.37)	0.76	1	1.00	1.00	No
Feng, 2018 [87]	DASH	0.87 (0.81, 0.93)	< 0.0001	48.90	5.30×10^{-3}	(0.72, 1.04)	0.16	7	NA	NA	NA
Micronutrients											
Chen, 2013 [88]	Vitamin C	0.81 (0.73, 0.90)	< 0.0001	3.10	1.00×10^{-3}	(0.71, 0.93)	0.62	3	0.75	2.04×10^{-3}	Yes
Larsson, 2013 [89, a]	Calcium (< 700 mg/d)	0.82 (0.76, 0.88)	NA	0.00	NA	NA	NA	3	NA	NA	NA
	Calcium (> 700 mg/d)	1.03 (1.01, 1.06)	NA	0.00	NA	NA	NA	2	NA	NA	NA
Tang, 2016 [90]	Flavonoid	0.89 (0.82, 0.97)	5.00×10^{-3}	0.00	< 0.00001	(0.81, 0.98)	0.24	1	NA	NA	NA
Vinceti, 2016 [91]	Potassium	0.91 (0.83, 1.00)	0.04	64.80	0.02	(0.66, 1.24)	0.67	6	2.18	0.04	Yes

Cheng, 2018 (1) [92]	Vitamin E	0.87 (0.73, 1.03)	0.09	35.70	0.02	(0.58, 1.29)	0.88	2	NA	NA	NA
Jayedi, 2019 [118]	Sodium	1.15 (1.07, 1.23)	< 0.0001	51.90	7.50×10^{-3}	(0.93, 1.41)	0.12	2	NA	NA	NA
Chen, 2020 [93]	Vitamin B6	0.85 (0.70, 1.03)	0.09	68.80	0.03	(0.46, 1.55)	0.95	1	3.66	0.02	Yes
	Folate	0.90 (0.80, 1.01)	0.07	37.60	0.01	(0.68, 1.19)	0.17	4	0.50	2.04×10^{-12}	Yes
	Vitamin B12	1.02 (0.88,1.19)	0.80	26.60	8.50×10^{-3}	(0.69, 1.50)	0.96	0	2.26	0.09	Yes
Shi, 2020 [94]	Vitamin D	0.75 (0.57, 0.98)	0.04	49.00	0.03	(0.26, 2.03)	0.88	3	1.53	0.18	No
Zhao, 2020 [95]	Magnesium	0.89 (0.83, 0.94)	< 0.0001	1.20	2.00×10^{-4}	(0.82, 0.95)	5.00×10^{-3}	2	NA	NA	NA
Macronutrients											
Chen, 2013 [96]	Fiber	0.88 (0.78, 1.00)	0.05	40.00	9.00×10^{-3}	(0.64, 1.21)	0.50	1	NA	NA	NA
Cai, 2015 [97]	Carbohydrate	1.20 (0.95, 1.50)	0.12	50.00	0.03	(0.51, 2.81)	0.60	1	NA	NA	NA
Cheng, 2016 [98]	Monounsaturated fatty acid	0.89 (0.80, 0.98)	0.02	33.00	7.30×10^{-3}	(0.71, 1.12)	0.90	2	1.15	0.43	No
Zhang, 2016 [119]	Protein	0.96 (0.90, 1.03)	0.26	70.30	5.00×10^{-3}	(0.81, 1.15)	0.16	4	NA	NA	NA
Cheng, 2018 (2) [100]	Cholesterol	0.97 (0.77, 1.22)	0.80	56.00	0.04	(0.52, 1.80)	0.10	2	0.95	0.24	No
Kang, 2020 [101]	Saturated fat	0.88 (0.79, 0.98)	0.02	45.90	0.01	(0.67, 1.16)	0.46	5	NA	NA	NA
Factors of physical health management											
Strazzullo, 2010 [102, a]	Overweight	1.22 (1.05, 1.41)	0.01	89.00	NA	NA	NA	NA	NA	NA	NA
	Obesity	1.64 (1.36, 1.99)	< 0.0001	88.00	NA	NA	NA	NA	NA	NA	NA
Li 2016 [103]	Shift-work	1.04 (0.98, 1.10)	0.18	3.70	5.00×10^{-4}	(0.89, 1.22)	0.24	0	NA	NA	NA
Kyu 2016 [104, a]	Physical activity	0.80 (0.70, 0.90)	NA	NA	NA	NA	NA	NA	NA	NA	NA
Liu, 2016 [105]	PP	1.14 (1.09, 1.20)	< 0.0001	35.40	1.10×10^{-3}	(1.02, 1.28)	0.47	5	NA	NA	NA
	SBP	1.22 (1.11, 1.35)	< 0.0001	85.30	0.01	(0.88, 1.69)	0.33	5	NA	NA	NA
	DBP	1.23 (1.12, 1.35)	< 0.0001	71.00	8.10×10^{-3}	(0.93, 1.63)	0.60	5	NA	NA	NA
He, 2017 [105]	Sleep duration	1.38 (1.20, 1.58)	< 0.0001	67.30	0.04	(0.88, 2.15)	0.47	9	NA	NA	NA
Xu, 2018 [107]	Oral contraceptives	1.30 (0.59, 2.89)	0.52	85.60	0.70	(0.07, 25.26)	0.60	3	NA	NA	NA

Islam, 2018 [108]	Anti-inflammatory drugs	1.59 (1.13, 2.25)	8.00×10^{-3}	89.70	0.12	(0.46, 5.47)	0.84	3	NA	NA	NA
Pan, 2019 [109]	Smoking	1.71 (1.37, 2.13)	< 0.0001	72.80	0.06	(0.89, 3.28)	0.07	6	NA	NA	NA
Quan, 2019 [110]	Walking pace	0.56 (0.48, 0.65)	< 0.0001	0.00	< 0.00001	(0.46, 0.69)	1.00	4	3.07	0.57	No
Factors of emotional health management											
Dong, 2012 [111]	Depression	1.32 (1.17, 1.48)	< 0.0001	55.20	0.01	(0.92, 1.88)	0.17	9	NA	NA	NA
Valtorta, 2016 [112]	Social isolation	1.32 (1.03, 1.69)	0.03	58.00	0.06	(0.66, 2.64)	0.04	4	0.72	2.47×10^{-6}	Yes
Chen, 2019 [113]	Anger and hostility	1.08 (0.81, 1.45)	0.60	53.00	0.08	(0.48, 2.42)	0.07	2	1.83	0.91	No
Factors of environmental management											
Dzhambov, 2016 [114]	Road traffic noise	1.05 (0.96, 1.14)	0.31	83.60	6.50×10^{-3}	(0.78, 1.40)	0.22	3	NA	NA	NA
Niu, 2021 [115]	$PM_{2.5}$	1.14 (1.08, 1.21)	< 0.0001	40.20	2.10×10^{-3}	(0.78, 1.40)	0.32	5	NA	NA	NA
	PM_{10}	1.04 (0.96, 1.13)	0.35	60.40	4.60×10^{-3}	(1.01, 1.30)	0.09	2	NA	NA	NA
	NO_2	0.99 (0.95, 1.02)	0.51	0.00	0.00	(0.85, 1.28)	0.75	0	NA	NA	NA

Abbreviations: SHR, summary hazard ratio; O, observed number of significant; E, expected value of significant finding; CI, confidence interval; ESF, Excess significant finding; NA, Not Applicable; DASH, dietary approaches to stop hypertension; PP, pulse pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure.

[a] Summary hazard ratio extracted from published meta-analysis, no re-analysis possible.

Table S7. Modifiable factors and ischemic stroke risk.

First Author, Year	Main Comparison	SHR (95% CI)	*P* value [b]	I^2	τ^2	95% PI	Egger's *P* value	O	E	*P*	ESF
Food factors											
He, 2006 [72, a]	Fruit and vegetable	0.72 (0.66, 0.79)	NA	NA	NA	NA	NA	NA	NA	NA	NA
Strazzullo, 2009 [55]	Salt	1.42 (0.74, 2.75)	0.29	91.40	0.21	NA	NA	1	1.87	0.01	Yes
Shi, 2014 [74]	Legumes	0.91 (0.73, 1.13)	0.39	71.30	0.04	(0.35, 2.32)	0.17	1	NA	NA	NA
Fang, 2015 [75]	Whole grain	0.83 (0.62, 1.09)	0.18	38.20	0.02	(0.06, 11.92)	0.89	1	0.86	0.85	No
Wu, 2015 [76]	Refined grain	1.04 (0.91, 1.19)	0.56	0.00	0.00	(0.78, 1.39)	0.70	0	0.19	0.31	No
de Goede, 2016 [77]	Milk	0.92 (0.85, 1.00)	0.05	56.30	4.60×10^{-3}	(0.72, 1.19)	0.55	1	NA	NA	NA
	Yogurt	0.99 (0.71, 1.40)	0.97	32.80	0.03	NA	NA	0	NA	NA	NA
	Low fat dairy	0.93 (0.83, 1.05)	0.24	69.20	4.90×10^{-3}	NA	NA	1	NA	NA	NA
	High fat dairy	0.96 (0.91, 1.01)	0.15	0.00	0.00	NA	NA	0	NA	NA	NA
Shao, 2016 [79]	Nuts	0.97 (0.73, 1.28)	0.81	67.50	0.06	(0.30, 3.16)	0.08	2	NA	NA	NA
Gholami, 2017 [3]	Cheese	0.90 (0.82, 0.98)	0.01	0.00	0.00	NA	NA	0	0.45	0.29	No
	Cream	0.92 (0.71, 1.18)	0.50	92.00	0.03	NA	NA	1	0.24	1.30×10^{-3}	Yes
Kim, 2017 [57]	Total meat	1.17 (1.07, 1.28)	1.00×10^{-3}	0.00	0.00	(0.96, 1.43)	0.47	2	NA	NA	NA
	Red meat	1.14 (0.98, 1.31)	0.08	49.60	0.01	(0.74, 1.74)	0.98	2	NA	NA	NA
	Processed meat	1.17 (1.07, 1.28)	< 0.0001	0.00	0.00	(1.01, 1.35)	0.22	2	NA	NA	NA
	White meat	0.90 (0.78, 1.03)	0.11	0.00	0.00	NA	NA	0	NA	NA	NA
Yuan, 2017 [80]	Chocolate	0.87 (0.78, 0.96)	7.00×10^{-3}	0.00	0.00	(0.44,1,70)	0.28	0	0.83	0.25	No
Mohammadi, 2018 [81]	Poultry	0.91 (0.79, 1.04)	0.17	0.00	0.00	NA	NA	0	NA	NA	NA
Zhao, 2019 [82]	Fish	0.95 (0.87, 1.05)	0.31	42.50	0.01	(0.74, 1.23)	0.32	2	0.72	0.07	Yes
	Lean fish	0.73 (0.54, 1.00)	0.05	0.00	0.00	NA	NA	1	0.15	4.22×10^{-9}	Yes

	Fatty fish	0.87 (0.66, 1.13)	0.29	0.00	0.00	NA	NA	0	1.99	2.30×10^{-115}	Yes
Tang, 2020 [116]	Egg	0.93 (0.84, 1.04)	0.19	52.70	5.90×10^{-3}	(0.72, 1.21)	0.47	1	1.86	0.53	No
Beverages											
Shen, 2012 [84]	Tea	0.76 (0.63, 0.92)	5.00×10^{-3}	9.80	4.60×10^{-3}	NA	NA	1	NA	NA	NA
Larsson, 2016 [117, a]	Light-to-moderate	0.91 (0.88, 0.94)	NA	9.10	NA	NA	NA	NA	NA	NA	NA
	High-to-heavy Alcohol	1.09 (1.03, 1.16)	NA	.00	NA	NA	NA	NA	NA	NA	NA
Shao, 2021 [29]	Coffee	0.89 (0.70, 1.12)	0.32	73.80	0.04	(0.33, 2.41)	0.05	3	0.99	0.02	Yes
Dietary behaviors											
Psaltopoulou, 2013 [86]	Mediterranean diet	0.79 (0.52, 1.20)	0.27	73.00	0.10	(0.01, 96.96)	0.76	1	0.22	3.17×10^{-4}	Yes
Feng, 2018 [87]	DASH	0.88 (0.80, 0.98)	0.02	44.20	6.20×10^{-3}	(0.68, 1.15)	0.20	2	0.61	0.02	Yes
Micronutrients											
Chen, 2013 [88]	Vitamin C	0.78 (0.64, 0.95)	0.01	32.70	0.02	(0.46, 1.31)	1.78	2	3.12	0.68	No
Tang, 2016 [90]	Flavonoid	0.93 (0.80, 1.07)	0.30	0.00	0.00	(0.37, 2,35)	0.38	0	NA	NA	NA
Vinceti, 2016 [91]	Potassium	0.88 (0.82, 0.95)	1.00×10^{-3}	0.00	0.00	(0.80, 0.97)	0.82	2	0.93	0.22	No
Cheng, 2018 (1) [92]	Vitamin E	0.90 (0.73, 1.11)	0.31	14.40	6.30×10^{-3}	(0.16, 4.88)	0.89	0	NA	NA	NA
Jayedi, 2019 [118]	Sodium	1.42 (0.93, 2.16)	0.11	84.20	0.15	(0.21, 9.34)	0.29	2	NA	NA	NA
	Vitamin B6	1.08 (0.72, 1.64)	0.71	75.60	0.07	NA	NA	0	1.23	0.08	Yes
Chen, 2020 [93]	Folate	0.83 (0.73, 0.95)	5.00×10^{-3}	12.70	3.20×10^{-3}	(0.51, 1.69)	0.43	2	0.26	2.63×10^{-11}	Yes
	Vitamin B12	0.94 (0.74, 1.19)	0.60	42.50	0.02	(0.09, 9.75)	0.78	0	0.87	0.24	No
Shi, 2020 [94]	Vitamin D	0.73 (0.60, 0.89)	2.00×10^{-3}	.00	0.00	NA	NA	1	0.15	4.55×10^{-9}	Yes
Zhao, 2020 [95]	Magnesium	0.89 (0.82, 0.96)	4.00×10^{-3}	13.80	2.50×10^{-3}	(0.77, 1.03)	0.67	1	0.60	0.49	No
Macronutrients											
Chen, 2013 [96]	Fiber	0.84 (0.71, 1.00)	0.05	53.70	0.02	(0.43, 1.64)	0.22	1	NA	NA	NA
Cai, 2015 [97]	Carbohydrate	1.06 (0.76, 1.46)	0.74	45.80	0.04	(0.04, 27.54)	0.09	0	NA	NA	NA

Cheng, 2016 [98]	Monounsaturated fatty	0.92 (0.83, 1.01)	0.08	9.50	2.30×10^{-3}	(0.77, 1.09)	0.64	1	NA	NA	NA
Zhang, 2016[119]	Protein	0.95 (0.81, 1.10)	0.47	75.30	0.03	(0.59, 1.50)	0.27	2	NA	NA	NA
Cheng, 2018 (2) [100]	Cholesterol	0.98 (0.72, 1.32)	0.87	71.40	0.07	(0.36, 2.61)	0.16	2	NA	NA	NA
Kang, 2020 [101]	Saturated fat	0.89 (0.82, 0.97)	0.01	17.70	3.50×10^{-3}	(0.75, 1.06)	0.76	3	NA	NA	NA
Factors of physical health management											
Li 2016 [103]	Shift-work	1.18 (0.81, 1.74)	0.39	66.40	0.06	NA	NA	0	NA	NA	NA
He, 2017 [105]	Sleep duration	1.60 (1.32, 1.93)	< 0.0001	54.10	0.02	(0.77, 3.32)	0.59	3	NA	NA	NA
Xu, 2018 [107]	Oral contraceptives	2.25 (0.44, 11.6)	0.33	77.60	1.12	NA	NA	1	NA	NA	NA
Pan, 2019 [109]	Smoking	1.56 (1.34 ,1.81)	< 0.0001	.00	0.00	(1.26, 1.93)	0.46	4	NA	NA	NA
Quan, 2019 [110]	Walking pace	0.63 (0.47, 0.85)	3.00×10^{-3}	48.60	0.05	(0.20, 1.96)	1.00	2	2.23	0.84	No
Factors of emotional health management											
Dong, 2012 [111]	Depression	1.44 (1.04, 2.01)	0.03	41.40	0.04	(0.05, 39.12)	0.26	2	NA	NA	NA

Abbreviations: SHR, summary hazard ratio; O, observed number of significant; E, expected value of significant finding; CI, confidence interval; ESF, Excess significant finding; NA, Not Applicable; DASH, dietary approaches to stop hypertension; PP, pulse pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure.

[a] Summary hazard ratio extracted from published meta-analysis, no re-analysis possible.

[b] $P < 0.025$ was significant after Bonferroni correction.

Table S8. Modifiable factors and hemorrhagic stroke risk.

First Author, Year	Main Comparison	SHR (95% CI)	*P* value [b]	I^2	τ^2	95% PI	Egger's *P* value	O	E	*P* value	ESF
Food factors											
He, 2006 [72, a]	Fruit and vegetable	0.73 (0.61, 0.87)	NA	NA	NA	NA	NA	N	NA	NA	NA
Strazzullo, 2009 [55]	Salt	1.15 (0.93, 1.42)	0.20	0.00	0.00	NA	NA	0	0.44	0.29	No
Shi, 2014 [74]	Legumes	1.16 (0.93, 1.44)	0.20	0.00	0.00	(0.27, 4.87)	0.09	0	NA	NA	NA
Fang, 2015 [75]	Whole grain	1.24 (0.73, 2.10)	0.42	0.00	0.00	NA	NA	0	0.18	0.31	No
Wu, 2015 [76]	Refined grain	0.97 (0.82, 1.17)	0.78	0.00	0.00	NA	NA	0	0.14	0.31	No
de Goede, 2016 [77]	Milk	0.95 (0.73, 1.24)	0.69	0.86	0.06	(0.28, 3.21)	0.12	2	NA	NA	NA
	Low fat dairy	0.99 (0.88, 1.12)	0.89	0.00	0.00	NA	NA	0	NA	NA	NA
	High fat diary	1.05 (0.93, 1.19)	0.44	0.00	0.00	NA	NA	0	NA	NA	NA
Shao, 2016 [79]	Nuts	1.16 (0.53, 2.51)	0.71	80.00	0.26	NA	NA	0	NA	NA	NA
Gholami, 2017 [3]	Cheese	0.95 (0.78, 1.15)	0.57	0.00	0.00	NA	NA	0	0.25	0.31	No
	Cream	0.89 (0.73, 1.09)	0.25	0.00	0.00	NA	NA	0	0.15	0.31	No
Kim, 2017 [57]	Total meat	1.18 (0.83, 1.68)	0.36	59.60	0.07	(0.29, 4.80)	0.88	1	NA	NA	NA
	Red meat	1.01 (0.81, 1.27)	0.90	4.60	2.60×10^{-3}	(0.59, 1.74)	0.79	0	NA	NA	NA
	Processed meat	1.19 (0.96, 1.48)	0.12	2.90	1.50×10^{-3}	(0.72, 1.98)	0.70	0	NA	NA	NA
	White meat	0.70 (0.51, 0.97)	0.03	0.00	0.00	NA	NA	0	NA	NA	NA
Yuan, 2017 [80]	Chocolate	0.83 (0.71, 0.97)	0.02	0.00	0.00	(0.31, 2.24)	0.42	0	1.08	0.20	No
Mohammadi, 2018 [81]	Poultry	0.86 (0.62, 1.22)	0.40	34.70	0.02	NA	NA	0	NA	NA	NA
Zhao, 2019 [82]	Fish	0.88 (0.80, 0.97)	0.01	1.00	3.00×10^{-4}	(0.79, 0.99)	0.99	2	2.90	0.67	No
Tang, 2020 [116]	Egg	1.03 (0.72, 1.46)	0.89	89.60	0.11	(0.31, 3.41)	0.59	2	3.80	0.09	Yes
Beverages											

Shen, 2012 [84]	Tea	0.77 (0.40, 1.49)	0.44	62.60	0.15	NA	NA	0	NA	NA	NA
Larsson, 2016 [117, a]	Light-to-moderate Alcohol	1.04 (0.86, 1.27)	NA	72.10	NA	NA	NA	N	NA	NA	NA
	High-to-heavy Alcohol	1.49 (1.26, 1.76)	NA	0.00	NA	NA	NA	N	NA	NA	NA
Shao, 2021 [29]	Coffee	1.13 (0.59, 2.16)	0.72	73.00	0.22	NA	0.61	1	0.16	5.02×10^{-8}	Yes
Dietary behaviors											
Psaltopoulou, 2013 [86]	Mediterranean diet	0.84 (0.61, 1.14)	0.26	0.00	0.00	NA	NA	0	0.50	0.28	No
Feng, 2018 [87]	DASH	0.85 (0.73, 0.99)	0.04	0.00	0.00	(0.60, 1.20)	0.17	0	0.66	0.29	No
Micronutrients											
Chen, 2013 [88]	Vitamin C	0.94 (0.52, 1.69)	0.84	55.20	0.15	(0.00, 474.69)	0.46	0	0.83	0.25	No
Tang, 2016 [90]	Flavonoid	0.89 (0.59, 1.32)	0.55	53.30	0.07	(0.01, 58.29)	0.34	0	NA	NA	NA
Vinceti, 2016 [91]	Potassium	0.92 (0.80, 1.07)	0.29	0.00	0.00	(0.75, 1.14)	0.36	0	1.07	0.27	No
Cheng, 2018 (1) [92]	Vitamin E	0.89 (0.50, 1.58)	0.70	47.80	0.09	NA	NA	0	NA	NA	NA
Jayedi, 2019 [118]	Sodium	1.20 (0.99, 1.46)	0.07	0.00	0.00	(0.78, 1.85)	0.10	0	NA	NA	NA
Chen, 2020 [93]	Vitamin B6	0.91 (0.71, 1.16)	0.45	0.00	0.00	NA	NA	0	0.29	0.31	No
	Folate	0.91 (0.68, 1.23)	0.55	9.20	0.01	(0.40, 2.07)	0.49	0	0.31	0.31	No
	Vitamin B12	1.08 (0.87, 1.36)	0.48	0.00	0.00	(0.25, 4.62)	0.56	0	0.19	0.31	No
Shi, 2020 [94]	Vitamin D	0.69 (0.36, 1.29)	0.24	80.00	0.17	NA	NA	1	1.53	0.40	No
Zhao, 2020 [95]	Magnesium	0.93 (0.82, 1.06)	0.28	0.00	0.00	(0.79, 1.09)	0.62	0	1.64	0.23	No
Macronutrients											
Chen, 2013 [96]	Fiber	0.86 (0.70, 1.06)	0.15	0.00	0.00	(0.22, 3.35)	0.82	0	NA	NA	NA
Cai, 2015 [97]	Carbohydrate	1.58 (1.15, 2.18)	5.00×10^{-3}	0.00	0.00	(0.20, 12.57)	0.76	2	NA	NA	NA
Cheng, 2016 [98]	Monounsaturated fatty acid	0.68 (0.48, 0.96)	0.03	0.00	0.00	(0.32, 1.43)	0.76	0	NA	NA	NA
Zhang, 2016 [119]	Protein	1.03 (0.96, 1.11)	0.37	2.70	7.00×10^{-4}	(0.92, 1.16)	0.09	0	NA	NA	NA
Cheng, 2018 (2) [100]	Cholesterol	0.96 (0.70, 1.31)	0.78	0.00	0.00	(0.48, 1.92)	0.93	0	0.20	0.31	No

Kang, 2020 [101]	Saturated fat	0.58 (0.40, 0.84)	4.00×10^{-3}	49.20	0.07	(0.14, 2.34)	0.94	2	NA	NA	NA
Factors of emotional health management											
He, 2017 [105]	Sleep duration	1.19 (0.97, 1.48)	0.10	0.00	0.00	(0.75, 1.90)	0.79	0	NA	NA	NA
Xu, 2018 [107]	Oral contraceptives	1.10 (0.42, 2.88)	0.84	85.40	0.99	(0.03, 37.62)	NA	2	NA	NA	NA
Pan, 2019 [109]	Smoking	1.32 (1.06, 1.64)	0.01	35.70	0.03	(0.80, 2.18)	0.21	1	NA	NA	NA
Quan, 2019 [110]	Walking pace	0.47 (0.27, 0.82)	8.00×10^{-3}	14.10	0.03	NA	NA	1	0.55	0.37	No

Abbreviations: SHR, summary hazard ratio; O, observed number of significant; E, expected value of significant finding; CI, confidence interval; ESF, Excess significant finding; NA, Not Applicable; DASH, dietary approaches to stop hypertension; PP, pulse pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure.

[a] Summary hazard ratio extracted from published meta-analysis, no re-analysis possible.

[b] $P < 0.025$ was significant after Bonferroni correction.

Table S9. Detailed evaluation of the methodological quality with AMSTAR 2.

First Author, Year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	All
He, 2006 [72]	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Strazzullo, 2009 [55]	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	No	Critically low
Strazzullo, 2010 [102]	Yes	No	Yes	Partial Yes	No	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	Critically low
Shen, 2012 [84]	Yes	No	Yes	No	No	Yes	No	Yes	Yes	No	Yes	No	No	Yes	Yes	No	Critically low
Dong, 2012 [111]	Yes	No	Yes	No	No	Yes	No	Yes	Partial Yes	No	Yes	No	Yes	Yes	Yes	Yes	Critically low
Larsson, 2013 [89]	Yes	No	Yes	Yes	No	Yes	No	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes	Critically low
Chen, 2013 (1) [88]	Yes	No	Yes	Partial Yes	No	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	No	Critically low
Chen, 2013 (2) [96]	Yes	No	Yes	No	No	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Psaltopoulou, 2013 [86]	Yes	No	Yes	No	No	Yes	No	Yes	Yes	No	Yes	No	No	Yes	Yes	No	Critically low
Mart´ınez-Gonza´lez, 2014 [73]	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Critically low
Shi, 2014 [74]	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Critically low
Cai, 2015 [97]	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Critically low
Fang, 2015 [75]	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Critically low
Wu, 2015 [76]	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Critically low
de Goede, 2016 [77]	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Critically low
Larsson, 2016 [117]	Yes	No	Yes	No	Yes	Yes	No	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Critically low
Cheng, 2016 [98]	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	No	Critically low
Lou, 2016 [78]	Yes	No	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Critically low
Shao, 2016 [79]	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	No	Critically low
Tang, 2016 [90]	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Critically low
Vinceti, 2016 [91]	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Critically low

Zhang, 2016 [119]	Yes	No	Yes	Yes	No	No	No	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Critically low
Liu, 2016 [105]	Yes	No	Yes	Partial Yes	No	Yes	No	Partial	Yes	No	Yes	No	No	Yes	No	Yes	Critically low
Valtorta, 2016 [112]	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Kyu, 2016[104]	Yes	No	Yes	Partial Yes	No	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Critically low
Li 2016 [103]	Yes	No	Yes	Yes	No	No	No	Partial	Yes	No	Yes	No	No	Yes	No	Yes	Critically low
Dzhambov, 2016 [114]	Yes	No	Yes	Yes	Yes	No	No	Partial	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Critically low
Gholami, 2017 [3]	Yes	No	Yes	No	No	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Critically low
Kim, 2017 [57]	Yes	No	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Critically low
Yuan, 2017 [80]	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Critically low
Mohammadi, 2018 [81]	Yes	No	Yes	Partial Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Critically low
He, 2017 [105]	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Cheng, 2018 (1) [92]	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Critically low
Cheng, 2018 (2) [100]	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Critically low
Feng, 2018 [87]	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Critically low
Xu, 2018 [107]	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	Critically low
Islam, 2018 [108]	Yes	No	Yes	Yes	Yes	Yes	No	Partial	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Critically low
Jayedi, 2019 [118]	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes	No	Yes	Yes	Critically low
Zhao, 2019 [82]	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Low
Pan, 2019 [109]	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Critically low
Chen, 2019 [113]	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Partial Yes	No	Yes	No	Yes	No	No	Yes	Critically low
Quan, 2019 [110]	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Critically low
Chen, 2020 [93]	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Critically low
Kang, 2020 [101]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Low
Shi, 2020 [94]	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Low

Tang, 2020 [90]	Yes	No	Yes	Yes	No	No	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Critically low
Zhao, 2020 [95]	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Critically low
Shao, 2021 [29]	Yes	No	Yes	Partial Yes	No	No	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Critically low
Niu, 2021 [115]	Yes	No	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Critically low

AMSTAR, assess the methodological quality of systematic reviews; Q, Question; Q1: Did the research questions and inclusion criteria for the review include the components of PICO?, Q2: Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?, Q3: Did the review authors explain their selection of the study designs for inclusion in the review?, Q4: Did the review authors use a comprehensive literature search strategy?, Q5: Did the review authors perform study selection in duplicate?, Q6: Did the review authors perform data extraction in duplicate?, Q7: Did the review authors provide a list of excluded studies and justify the exclusions?, Q8: Did the review authors describe the included studies in adequate detail?, Q9: Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?, Q10: Did the review authors report on the sources of funding for the studies included in the review?, Q11: If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?, Q12: If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?, Q13: Did the review authors account for RoB in primary studies when interpreting/discussing the results of the review?, Q14: Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?, Q15: If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?, Q16: Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

Table S10. Sensitivity analyses for associations with strong, high suggestive or suggestive evidence.

Exposure	First Author, Year	No. of primary cohort study	Main Comparison	SHR (95% CI)	*P* value	I^2 (%)	τ^2	95% PI	Egger's *P* value	O	E	*P*	ESF
				Credibility assessment									
Exclusion of primary studies with number of study participants lower than 25th percentile (applicable to those meta-analyses with evidence of small-study effects in primary) [a]													
Chocolate	Yuan, 2017 [80]	1	High vs low	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Magnesium	Zhao, 2020 [95]	0	High vs low	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Smoking	Pan, 2019 [109]	0	High vs low	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Primary studies adjusted for confounding variables													
Total meat	Kim,2017 [57]	4	High vs low	1.18 (1.09, 1.28)	< 0.0001	0.00	< 0.00001	(0.99, 1.41)	0.50	2	NA	NA	NA
Processed meat		5	High vs low	1.16 (1.07, 1.26)	< 0.0001	16.00	1.40×10^{-3}	(0.97, 1.39)	0.40	3	NA	NA	NA
Processed meat (IS)	Kim, 2017 [57]	5	High vs low	1.17 (1.07, 1.28)	< 0.0001	0.00	0.00	(1.01, 1.35)	0.22	2	NA	NA	NA
Chocolate	Yuan, 2017 [80]	7	High vs low	0.83 (0.77, 0.89)	< 0.0001	0.00	< 0.00001	(0.75, 0.92)	2.00×10^{-3}	5	2.62	0.15	No
DASH	Feng, 2018 [87]	6	High vs low	0.87 (0.79, 0.96)	5.00×10^{-3}	65.00	8.70×10^{-3}	(0.65, 1.17)	0.30	4	NA	NA	NA
Vitamin C	Chen, 2013 [88]	6	High vs low	0.81 (0.72, 0.91)	< 0.0001	0.00	0.00	(0.69,0.95)	0.78	1	NA	NA	NA
Sodium	Jayedi, 2019 [118]	10	Dose-response	1.19 (1.09, 1.31)	< 0.0001	54.00	0.01	(0.92, 1.54)	0.18	5	NA	NA	NA
Magnesium	Zhao, 2020 [95]	12	High vs low	0.90 (0.85, 0.96)	2.00×10^{-3}	0.00	0.00	(0.84, 0.97)	0.07	1	NA	NA	NA
Obesity [b]	Strazzullo, 2010 [102]	22	With vs without	1.64 (1.36, 1.99)	< 0.0001	88.00	NA	NA	NA	NA	NA	NA	NA
PP	Liu, 2016 [105]	6	Dose-response	1.14 (1.09, 1.20)	< 0.0001	35.00	1.10×10^{-3}	(1.02, 1.28)	0.47	5	NA	NA	NA
SBP		6		1.22 (1.11, 1.35)	< 0.0001	85.00	0.01	(0.88, 1.69)	0.33	5	NA	NA	NA
DBP		6		1.23 (1.12, 1.35)	< 0.0001	71.00	8.10×10^{-3}	(0.93, 1.63)	0.60	5	NA	NA	NA
Sleep duration	He, 2017 [105]	11	Dose-response	1.37 (1.19, 1.57)	< 0.0001	70.00	0.04	(0.86, 2.17)	0.57	8	NA	NA	NA
Sleep duration (IS)	He, 2017 [105]	4	Dose-response	1.60 (1.32, 1.93)	< 0.0001	54.1	0.02	(0.77, 3.32)	0.59	3	NA	NA	NA

Smoking	Pan, 2019 [109]	6	High vs low	1.35 (1.22, 1.49)	< 0.0001	0.00	0.00	(1.17, 1.55)	0.57	3	4.86	0.08	Yes
Smoking (IS)	Pan, 2019 [109]	4	High vs low	1.49 (1.28, 1.74)	< 0.0001	0.00	0.00	(1.06, 2.09)	0.18	3	1.74	0.27	No
Depression	Dong, 2012 [111]	7	High vs low	1.47 (1.18, 1.84)	1.00×10^{-3}	64.50	0.05	(0.76, 2.83)	0.08	5	NA	NA	NA
$PM_{2.5}$	Niu, 2021 [115]	6	Dose-response	1.15 (1.10, 1.21)	< 0.0001	32.60	1.10×10^{-3}	(1.03, 1.29)	0.07	5	NA	NA	NA
Primary studies with high quality													
Total meat [c]	Kim,2017 [57]	4	High vs low	1.18 (1.09, 1.28)	< 0.0001	0.00	< 0.00001	(0.99, 1.41)	0.50	2	NA	NA	NA
Processed meat [c]		5	High vs low	1.16 (1.07, 1.26)	< 0.0001	15.90	1.40×10^{-3}	(0.97, 1.39)	0.40	3	NA	NA	NA
Processed meat (IS) [c]	Kim,2017 [57]	5	High vs low	1.17 (1.07, 1.28)	< 0.0001	0.00	0.00	(1.01, 1.35)	0.22	2	NA	NA	NA
Chocolate [c]	Yuan, 2017 [80]	7	High vs low	0.83 (0.77, 0.89)	< 0.0001	0.00	< 0.00001	(0.75, 0.92)	2.00×10^{-3}	5	2.62	0.15	No
DASH [c]	Feng, 2018 [87]	12	High vs low	0.87 (0.81, 0.93)	< 00001	48.90	5.30×10^{-3}	(0.72, 1.04)	0.16	7	NA	NA	NA
Vitamin C [d]	Feng, 2018 [20]	12	High vs low	0.81 (0.73, 0.90)	< 0.0001	3.10	1.00×10^{-3}	(0.71, 0.93)	0.62	3	0.75	2.04×10^{-3}	Yes
Sodium [c]	Jayedi, 2019 [118]	13	Dose-response	1.15 (1.07, 1.23)	< 0.0001	51.90	7.50×10^{-3}	(0.93, 1.41)	0.12	2	NA	NA	NA
Magnesium [c]	Zhao, 2020 [95]	15	High vs low	0.89 (0.83, 0.94)	< 0.0001	1.20	2.00×10^{-4}	(0.82, 0.95)	5.00×10^{-3}	2	NA	NA	NA
Obesity [b]	Strazzullo, 2010 [102]	22	With vs without	1.64 (1.36, 1.99)	< 0.0001	88.00	NA	NA	NA	NA	NA	NA	NA
PP [c]		6		1.14 (1.09, 1.20)	< 0.0001	35.40	1.10×10^{-3}	(1.02, 1.28)	0.47	5	NA	NA	NA
SBP [c]	Liu, 2016 [105]	6	Dose-response	1.22 (1.11, 1.35)	< 0.0001	85.30	0.01	(0.88, 1.69)	0.33	5	NA	NA	NA
DBP [c]		6		1.23 (1.12, 1.35)	< 0.0001	71.00	8.10×10^{-3}	(0.93, 1.63)	0.60	5	NA	NA	NA
Sleep duration	He, 2017 [105]	10	Dose-response	1.37 (1.18, 1.59)	< 0.0001	72.30	0.04	(0.83, 2.24)	0.69	8	NA	NA	NA
Sleep duration (IS) [c]	He, 2017 [105]	4	Dose-response	1.60 (1.32, 1.93)	< 0.0001	54.10	0.02	(0.77, 3.32)	0.59	3	NA	NA	NA
Smoking [d]	Pan, 2019 [109]	9	High vs low	1.71 (1.37, 2.13)	< 0.0001	72.80	0.06	(0.89, 3.28)	0.07	6	NA	NA	NA
Smoking (IS) [d]	Pan, 2019 [109]	6	High vs low	1.56 (1.34 ,1.81)	< 0.0001	0.00	0.00	(1.26, 1.93)	0.46	4	NA	NA	NA
Walking pace [c]	Quan, 2019 [110]	7	High vs low	0.56 (0.48, 0.65)	< 0.0001	0.00	< 0.00001	(0.46, 0.69)	1.00	4	3.07	0.57	No
Depression [d]	Dong, 2012 [111]	17	High vs low	1.32 (1.17, 1.48)	< 0.0001	55.20	0.01	(0.92, 1.88)	0.17	9	NA	NA	NA
$PM_{2.5}$ [c]	Niu, 2021 [115]	8	Dose-response	1.14 (1.08, 1.21)	< 0.0001	40.20	2.10×10^{-3}	(1.01, 1.30)	0.32	5	NA	NA	NA

Abbreviations: SHR, summary hazard ratio; O, observed number of significant; E, expected value of significant finding; CI, confidence interval; ESF, Excess significant finding; IS, ischemic stroke; NA, Not Applicable; DASH, dietary approaches to stop hypertension; PP, pulse pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure.

[a] Not performed due to limited number of primary studies.

[b] Data extracted from published meta-analysis, no re-analysis possible.

[c] Meta-analysis reported all good-quality studies.

[d] No information on quality assessment of primary studies.

Table S11. Regional distribution of strong, highly suggestive and suggestive evidence.

First Author, Year	Main Comparison	Exposure	Primary analysis	QES	Countries or regions
Food factors					
Kim,2017 [57]	High vs low	Total meat	highly suggestive	highly suggestive	Sweden; USA
		Processed meat	highly suggestive	highly suggestive	Spain; Sweden; USA
Kim,2017 [57] (IS)	High vs low	Processed meat	suggestive	suggestive	Spain; Sweden; USA
Yuan, 2017 [80]	High vs low	Chocolate	highly suggestive	highly suggestive	Germany; Japan; Sweden; UK; USA
Dietary behaviours					
Feng, 2018 [87]	High vs low	DASH	suggestive	weak	Multinational [a]
Micronutrients					
Chen, 2013 [88]	High vs low	Vitamin C	suggestive	suggestive	Multinational
Jayedi, 2019 [118]	Dose-response	Sodium	highly suggestive	highly suggestive	Multinational
Zhao, 2020 [95]	High vs low	Magnesium	suggestive	weak	Multinational
Factors of physical health Management					
Strazzullo, 2010 [102]	High vs low	Obesity	highly suggestive	highly suggestive	China; Finland; Sweden; USA
Liu, 2016 [105]	Dose-response	PP	highly suggestive	highly suggestive	China; Denmark; Japan; USA
		SBP	highly suggestive	highly suggestive	China; Denmark; Japan; USA
		DBP	highly suggestive	highly suggestive	China; Denmark; Japan; USA
He, 2017 [106]	Dose-response	sleep duration	highly suggestive	highly suggestive	Multinational
He, 2017 [106] (IS)	Dose-response	sleep duration	highly suggestive	highly suggestive	China; Japan
Pan, 2019 [109]	High vs low	smoking	highly suggestive	highly suggestive	China; Japan; Norway; Sweden; USA
Pan, 2019 [109] (IS)	High vs low	smoking	suggestive	suggestive	China; Japan; Sweden; USA
Quan, 2019 [110]	High vs low	Walking pace	strong	strong	UK; USA
Factors of emotional health Management					

Dong, 2012 [111]	High vs low	Depression	suggestive	weak	Finland; Japan; Netherlands; Sweden; USA
Factors of environmental management					
Niu, 2021 [115]	Dose-response	$PM_{2.5}$	suggestive	suggestive	Multinational

Abbreviations: QES, quality of evidence after sensitivity analyses.

[a] More than five countries.

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