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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.

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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.

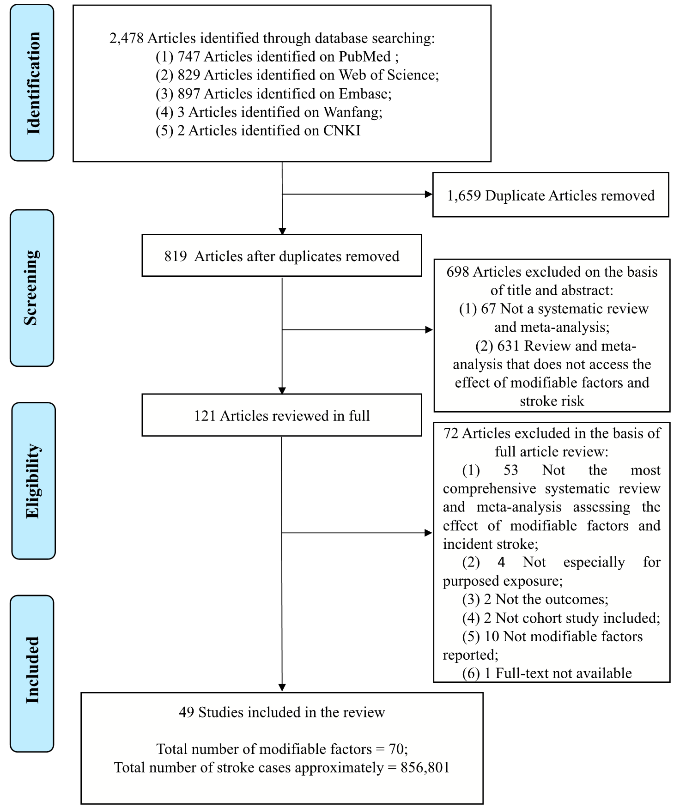


Figure 1 Flow diagram of the study search and selection process. CNKI, China National Knowledge Infrastructure.

RESULTS

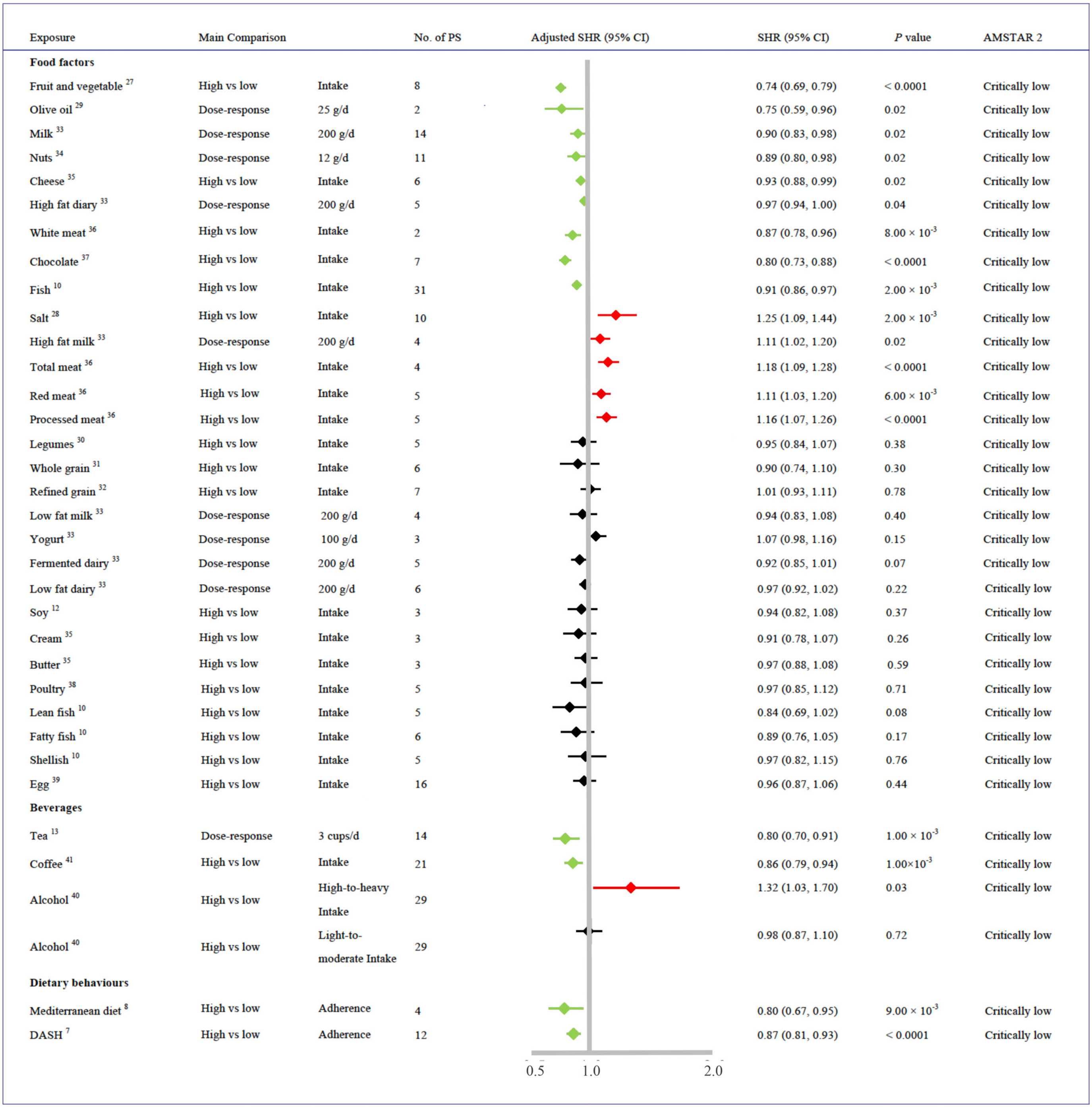
A total of 2478 records were identified through database searching; 1659 duplicate records were removed; 698 records were excluded on the basis of title and abstract and 121 records were reviewed in full. After excluding records which were not the most comprehensive systematic review and meta-analysis (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%;

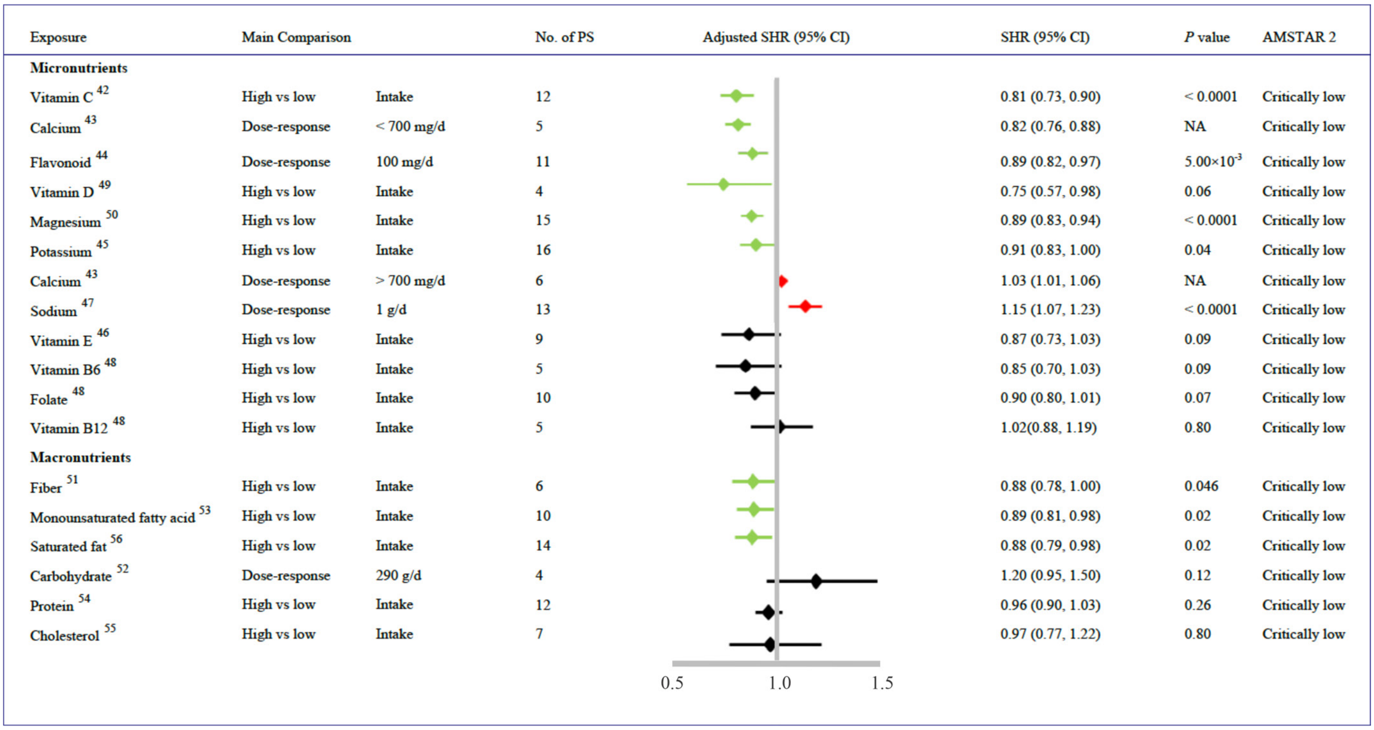


Figure 3 Adjusted summary HRs (SHR) with 95% confidence intervals and quality of evidence for association between micronutrients, macronutrients and incidence of stroke. AMSTAR = assess the methodological quality of systematic reviews; NA = not available; PS = primary studies.

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

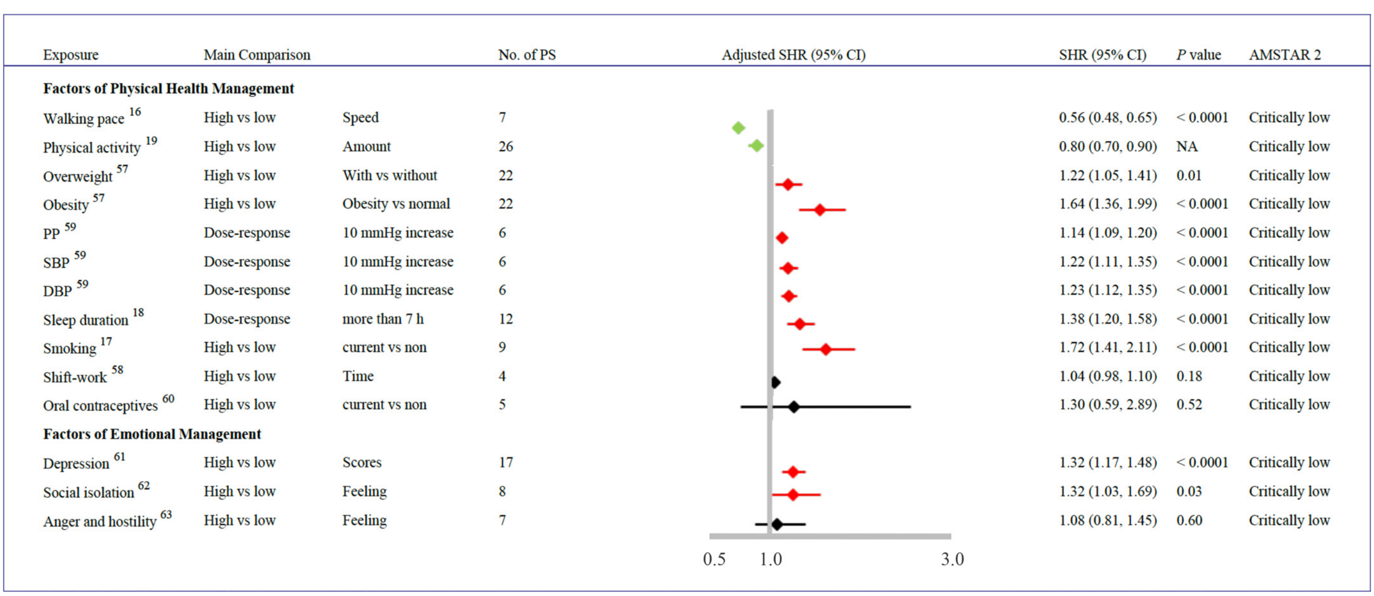


Figure 4 Adjusted summary HRs (SHR) with 95% confidence intervals and quality of evidence for association between factors of physical health and emotional management and incidence of stroke AMSTAR = assess the methodological quality of systematic reviews; DBP = diastolic blood pressure; NA = not available;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

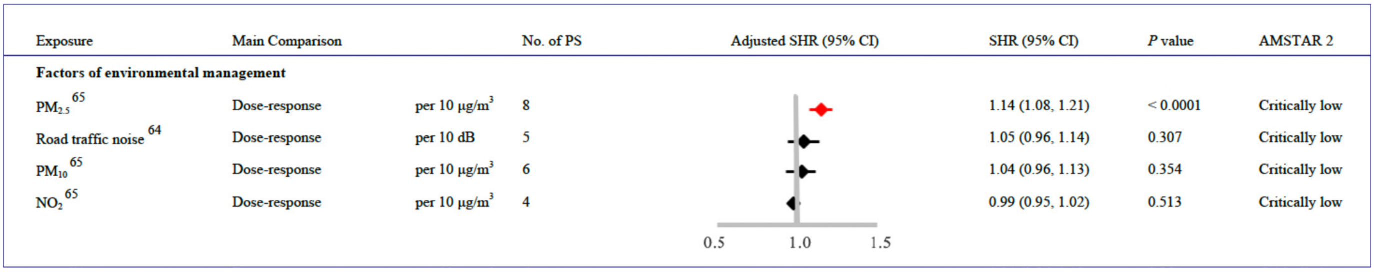


Figure 5 Adjusted summary HRs (SHR) with 95% confidence intervals and quality of evidence for association between factors of environmental management and incidence of stroke. AMSTAR = assess the methodological quality of systematic reviews; PM = particulate matter; PS = primary studies.

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 ($I^2 \leq 50\%$).

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 ($I^2 \leq 50\%$).

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				QES
			Primary analysis	Sensitivity analyses: Including studies adjusted for potential confounding variables	Sensitivity analyses: Omission of small-sized studies	Sensitivity analyses: Omission of low-quality studies	
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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