

BMJ Open Dietary sodium, potassium intake, sodium-to-potassium ratio and risk of hypertension: a protocol for systematic review and dose-response meta-analysis of cohort studies

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ABSTRACT

Introduction Hypertension (HTN) is the leading cause of disease and death on a global scale. Diet's sodium and potassium levels may synergistically affect blood pressure. Currently, the sodium-to-potassium (Na/K) ratio is becoming a more reliable indicator. There has not been a systematic investigation of the dose-response relationship between dietary sodium, potassium, the Na/K ratio and the incidence of HTN based on the same study criteria. This study will conduct a thorough dose-response meta-analysis of cohort studies to estimate the effects of dietary sodium, potassium, and the Na/K ratio on the incidence of HTN to provide the most accurate reference for sodium and potassium intake.

Methods and analysis We will identify all relevant prospective and retrospective cohort studies by searching PubMed, Embase and Web of Science (from inception until December 2022). Exposures are 24 hours urinary excretions, and the outcome is the incidence of HTN. Two researchers will perform the literature selection and data extraction separately. The Newcastle-Ottawa Scale will be used to evaluate the quality of the included studies. We will use both linear and non-linear regression models to investigate the dose-response relationship among different levels (≥ 3) of sodium, potassium, Na/K ratio intake and the incidence of HTN (OR/RR/HR). Subgroup and sensitivity analyses will be applied to assess the potential heterogeneity sources and examine the stability of the results. We will also evaluate heterogeneity across studies and publication bias. Stata V.15.0 and RevMan V.5.0 will be used for statistical analyses.

Ethics and dissemination According to the Institutional Review Board/Independent Ethics Committee of the Guang'anmen Hospital of the China Academy of Chinese Medical Science, this systematic meta-analysis protocol does not require ethical approval or informed consent. This meta-analysis will be published in a scientific journal with peer reviews.

PROSPERO registration number CRD42022331203.

INTRODUCTION

Hypertension (HTN) is the leading cause of disease and death worldwide, accounting for approximately 10.4 million deaths annually.¹

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ According to our knowledge, this is the first dose-response meta-analysis of sodium, potassium and the Na/K ratio concerning the incidence of hypertension based on the same study criteria.
- ⇒ This protocol is reported referring to the recommendations of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols.
- ⇒ This meta-analysis will combine data from various studies to create the most comprehensive cohort study dataset.
- ⇒ The insufficient number of included studies, small sample size, inadequate categories (<3) of exposures, study heterogeneity and the instruments used to measure exposures may limit the results of the proposed meta-analysis.
- ⇒ Salt-sensitive individuals are at an increased risk of hypertension under high sodium intake, but few studies have classified them, which may account for the potential bias in this study.

Between 1990 and 2019, the number of 30–79-year-olds with HTN doubled,^{2 3} which is expected to reach 1.56 billion by 2025.⁴ HTN is closely linked to higher all-cause mortality and significantly predicts cardiovascular diseases (CVDs), cerebrovascular and renal diseases. Controlling blood pressure has become an essential clinical management strategy for preventing damage to target organs and reducing CVD events.^{5 6}

Despite the increasing prevalence of HTN, awareness, therapies and management of associated risks remain inadequate, particularly in low-income and middle-income nations. In addition to well-known risks for HTN, such as obesity, alcohol consumption, smoking and physical inactivity, a diet's high sodium and low potassium intake are also considered significant risk factors.⁷ The WHO suggested that an individual's sodium intake should not

exceed 2 g per day,⁸ while the global average daily sodium intake in 2010 was estimated to be as much as 3.95 g, nearly double the recommended maximum. More than 1 in 10 CVD deaths each year were due to sodium intake above the reference level.⁹ Moreover, a high sodium intake was frequently accompanied by a suboptimal potassium intake.¹⁰ In epidemiological studies, people with low-potassium diets tended to have higher blood pressure, and potassium intake demonstrated a negative correlation with HTN and blood pressure.¹¹

The combined effect of excessive sodium consumption and poor potassium intake on the genesis of HTN is greater than the sum of their individual effects.^{12–13} It has been demonstrated that potassium supplementation has a more significant hypotensive effect at higher sodium intake levels.¹⁴ Toshiyuki *et al* identified that the Na/K ratio measurements from urine were more accurate and correlated better with urine sodium and potassium measurements for 24 hours urine estimation. Accordingly, the Na/K ratio is considered a reliable estimation of sodium and potassium intake in normotensive individuals.¹⁵ Research and expert opinion have also shown that the Na/K ratio is a more accurate indicator of HTN and CVD than sodium and potassium levels alone.¹⁶

Studies have identified a stronger correlation between the Na/K ratio than sodium or potassium intake alone and the incidence of HTN.¹⁷ A cross-sectional study found that potassium intake had no effect on HTN risk in the whole population, whereas the Na/K ratio increased the HTN risk by 10% and 20% in men and women, respectively,¹⁸ which may be due to the interaction between sodium–potassium excretion balance. It remains controversial whether dietary sodium intake, potassium intake, the Na/K ratio and HTN are related. An investigation in The China Health and Nutrition Survey cohort showed strong independent dose–response relationships between dietary sodium, potassium, Na/K ratio and the incidence of HTN.¹⁹ In contrast, Mirmiran *et al* reported no significant correlation between dietary sodium, potassium, Na/K ratio and the HTN risk in a cohort study in Iran over a 6.3-year follow-up period.¹² Given the limited availability of high-quality cohort studies, there are fewer meta-analyses on the preventive effects of low sodium, high potassium intake and low Na/K ratio on HTN. Only Filippini *et al* conducted a systematic review and dose–response meta-analysis on the relationship between dietary sodium and the incidence of HTN, confirming a linear correlation between sodium intake and the risk of HTN.²⁰ The relationship between dietary Na/K ratio and incident HTN remains a critical research gap. No systematic dose–response meta-analyses of dietary sodium, potassium intake and more representative and reliable Na/K ratio with the incidence of HTN has not been conducted under the same study criteria.

Therefore, we will perform a comprehensive dose–response meta-analysis on all prospective and retrospective cohort studies with the aim of quantitatively assessing whether there are potential linear and non-linear

dose–response relationships between dietary sodium, potassium intake and sodium-to-potassium ratio and the incidence of HTN. In order to offer the optimum reference for dietary sodium, potassium intake, and Na/K ratio to prevent HTN.

The rationale of the sodium and potassium effect on blood pressure

The sodium-induced elevations in blood pressure involve an imbalance of sodium in the Renin–Angiotensin–Aldosterone System (RAAS), sympathetic activation and an aberrant vascular resistance response. A high salt intake results in sodium accumulation, which increases blood volume, blood flow and cardiac output. The vascular bed raises systemic blood flow resistance through autoregulation, causing the kidneys to eliminate more salt and water, maintaining water–sodium homeostasis and limiting sodium changes.²¹ Approximately 50%–60% of the global population is considered to be salt-sensitive present. High sodium intake, sodium retention and volume overload may significantly diminish RAAS activity in this population, causing decreased responses at the relevant receptors and elevated blood pressure.^{22–23} Enhanced sympathetic activity may cause an increase in catecholamine levels, which may lead to intracellular calcium buildup, vascular smooth muscle contraction and aberrant sodium absorption.²⁴ In addition, salt-sensitive individuals cannot effectively dilate blood vessels due to poor NO production in the endothelium, decreasing response to salt loading, and increasing total peripheral resistance.^{25–26} In contrast, high potassium consumption can improve renal vascular resistance by reducing oxidative stress in endothelial cells of the vascular walls and smooth muscle proliferation. Additionally, a high potassium diet may decrease sodium reabsorption through the sodium-chloride cotransporter in the distal convoluted tubule,²⁷ increasing the glomerular filtration rate and modifying the arterial pressure to sodium excretion.²⁸ These are known pathological pathways of sodium and potassium on HTN.

Objectives

This study aimed to examine the potential dose–response relationship between dietary sodium, potassium intake, Na/K ratio and HTN risk in the adult population by a comprehensive systematic review and dose–response meta-analysis. This meta-analysis protocol was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) Statement, 2015²⁹ and registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (registration number: CRD42022331203). Changes to the study will be reflected in the PROSPERO.

METHODS AND ANALYSIS

Search strategy

We will carefully search PubMed, Embase and Web of Science for cohort studies examining the association

between sodium, potassium, Na/K ratio and HTN incidence from inception to December 2022. Using Boolean operators and asterisks (*) as truncations, we identified publications containing MesH, keywords and other entry terms by searching the PubMed and Embase databases. As Web of Science is a unique citation indexing database, we selected to conduct advanced searches on topic fields encompassing title, abstract, author keywords and Keyword Plus. Citation indexing of search sources covered Science Citation Index Expanded (SCI-EXPANDED), Social Sciences Citation Index (SSCI), Current Contents (CCR-EXPANDED) and Index Medicus (IC). There are no linguistic constraints. The search strategy was developed with the assistance of a university library specialist. Details of the retrieval strategy are given in [table 1](#). In addition, the references of included articles and previous meta-analysis articles regarding sodium, potassium intake or Na/K ratio to HTN risk will be manually retrospectively identified to identify potentially eligible studies of a supplement.

Type of participants

Adults (18 or older) without HTN at the beginning of the study will be eligible, regardless of their gender, nationality, race or educational background.

Patient and public involvement

Patients and/or the public will not be directly involved in the research's conception, execution, reporting or dissemination. This study utilised only previously existing data from the above sources and scholarly literature.

Type of studies

Prospective or retrospective cohort studies assessing the relationship between dietary sodium, potassium intake, Na/K ratio and the incidence of HTN. We will exclude case-control studies, cross-sectional studies or abstract-only publications. There will be no language limits on qualified studies. Suppose data from multiple published studies on the relationship between dietary sodium, potassium intake, the Na/K ratio and HTN risk were collected from the same cohort. In that case, we will select publications with complete information (eg, reporting more exposure doses or adjusting for more associated factors).

Exposures and comparisons

According to experts, 24-hour urine collection is the gold standard for assessing sodium and potassium intake.^{30 31} Therefore, we measured dietary sodium intake, potassium and Na/K ratio using 24-hour urinary excretions. Compare the exposure doses for at least three quantified categories. Experimental studies with pharmacological intervention (antihypertensive or related drugs) will be excluded.

Type of outcomes

The incidence of HTN during the follow-up period is the outcome measure for this study. Risk estimates reported for study outcomes will be extracted, including adjusted

relative risks (RRs), ORs or HRs with 95% CIs for HTN. Alternatively, adequate information, such as case counts and participants/person-years, is reported to calculate these values in each sodium, potassium and Na/K ratio exposure category. Studies reporting dietary sodium, potassium intake or Na/K ratio per unit increments were also included. Data with incomplete or inaccessible extraction or literature only reporting crude ORs/RRs/HRs without any adjustment will be excluded.

Study selection process

All search results will be transferred into EndNote X9, and duplicate information will be eliminated. In the first stage, two reviewers will independently examine the title and abstract of the research based on eligibility criteria, excluding unrelated literature. After evaluating the title and abstract, two researchers will review the full text of the literature. The excluded studies will be documented, together with the reasons for their exclusion. In case of any dispute in the selection process, resolve it after discussing it with a third reviewer. When pertinent data are lacking, we will attempt to contact the authors to obtain the essential information; if this is unsuccessful, the reviewer will finally decide whether to exclude the material. The PRISMA flowchart ([figure 1](#)) will detail the selection criteria and exclusion reasons.

Quality of evidence

We will evaluate the quality of the cohort studies using the Newcastle-Ottawa Scale (NOS),³² which highlights eight features of each study across three dimensions. Among these elements are the selection of study participants, the comparability of study groups and the assessment of study outcomes. Each question will be awarded a maximum of 1 point with selection and outcome. Depending on the comparability of the study groups, a study may receive a maximum of 2 points. Each study can earn a maximum of 9 points for the three topics.³³ The higher the score, the better the methodological quality. A research score of 0–3 indicates low quality, whereas a score of 4–6 reflects acceptable quality and a score of 7–9 means high quality.³⁴ Two authors will independently evaluate the methodological quality of the included papers. Any disagreement over the scores allocated to a particular research will be settled by consensus after consultation with a third investigator. We will include all research, regardless of the risk of bias and methodological quality. Potential risks for inclusion studies will be evaluated using sensitivity analyses excluding each individually.

Data extraction

Data will be collected using a standard electronic form by Microsoft Office Excel 2007 (online supplemental appendix 1). Two investigators will independently extract the data elements based on each included study. Disagreements will be resolved through group discussion. We extracted the information listed below:

Table 1 Search strategy for PubMed, Embase and Web of Science databases

Database	Search items
PubMed	
No.	
#1	'Hypertension' (MeSH) OR 'Hypertension' (Title/Abstract) OR 'High Blood Pressure*' (Title/Abstract)
#2	'sodium, dietary' (MeSH) OR 'sodium chloride' (MeSH) OR 'sodium' (MeSH) OR 'sodium dietary' (Title/Abstract) OR 'sodium chloride' (Title/Abstract) OR 'sodium' (Title/Abstract) OR 'NaCl' (Title/Abstract) OR 'salt' (Title/Abstract) OR 'dietary sodium' (Title/Abstract)
#3	'potassium, dietary' (MeSH) OR 'potassium' (MeSH) OR 'potassium dietary' (Title/Abstract) OR 'potassium' (Title/Abstract) OR 'dietary potassium' (Title/Abstract)
#4	'sodium to potassium ratio' (Title/Abstract)
#5	#2 OR #3 OR #4
#6	'Incidence' (MeSH) OR 'Risk' (MeSH) OR 'Incidence*' (Title/Abstract) OR 'Risk*' (Title/Abstract) OR 'proportion*, incidence' (Title/Abstract) OR 'Incidence Proportion*' (Title/Abstract) OR 'Relative Risk*' (Title/Abstract)
#7	'Cohort Studies' (MeSH) OR 'follow-up studies' (MeSH) OR 'Cohort Study*' (Title/Abstract) OR 'follow-up study*' (Title/Abstract) OR 'incidence study' (Title/Abstract) OR 'prospective' (Title/Abstract) OR 'longitudinal' (Title/Abstract) OR 'Cohort' (Title/Abstract)
#8	'Animals' (MeSH) NOT 'Humans' (MeSH)
#9	'comment' (Publication Type) OR 'editorial' (Publication Type) OR 'letter' (Publication Type) OR 'review' (Publication Type)
#10	#1 AND #5 AND #6 AND #7 NOT #8 NOT #9
Web of Science	
#1	TOPIC: (Hypertension) OR TOPIC: (High Blood Pressure) OR TOPIC: (High Blood Pressures) Timespan: All years. Databases: WOSCC, KJD, MEDLINE, RSCI, SCIELO, BIOSIS. Search language=Auto
#2	TOPIC: (sodium, dietary) OR TOPIC: (sodium chloride) OR TOPIC: (sodium) OR TOPIC: (NaCl) OR TOPIC: (salt) OR TOPIC: (sodium intake) OR TOPIC: (dietary sodium) OR TOPIC: (potassium, dietary) OR TOPIC: (potassium) OR TOPIC: (dietary potassium) OR TOPIC: (potassium intake) OR TOPIC: (sodium to potassium ratio) Timespan: All years. Databases: WOSCC, KJD, MEDLINE, RSCI, SCIELO, BIOSIS. Search language=Auto
#3	TOPIC: (incidence) OR TOPIC: (incidence proportion) OR TOPIC: (risk) OR TOPIC: (relative risk) Timespan: All years. Databases: WOSCC, KJD, MEDLINE, RSCI, SCIELO, BIOSIS. Search language=Auto
#4	TOPIC: (cohort studies) OR TOPIC: (follow-up studies) OR TOPIC: (prospective) OR TOPIC: (longitudinal) OR TOPIC: (cohort) OR TOPIC: (incidence study) Timespan: All years. Databases: WOSCC, KJD, MEDLINE, RSCI, SCIELO, BIOSIS. Search language=Auto
#5	#1 AND #2 AND #3 AND #4 AND Document Types: (Article)
Embase	
#1	'hypertension'/exp
#2	'high blood pressure':ab,ti OR 'blood pressure, high':ab,ti OR 'hypertension':ab,ti
#3	#1 OR #2
#4	'sodium chloride'/exp OR 'sodium intake'/exp OR 'sodium'/exp OR 'potassium intake'/exp OR 'potassium'/exp
#5	'salt':ab,ti OR 'sodium':ab,ti OR 'natrium intake':ab,ti OR 'dietary sodium':ab,ti OR 'sodium intake':ab,ti OR 'sodium chloride':ab,ti OR 'potassium intake':ab,ti OR 'potassium':ab,ti OR 'dietary potassium':ab,ti OR 'sodium to potassium ratio':ab,ti
#6	#4 OR #5
#7	'incidence'/exp OR 'risk'/exp
#8	'cohort studies':ab,ti OR 'longitudinal':ab,ti OR 'cohort':ab,ti OR 'prospective':ab,ti OR 'incidence study':ab,ti OR 'follow-up studies':ab,ti
#9	'human'/exp
#10	article:it
#11	#3 AND #6 AND #7 AND #8 AND #9 AND #10

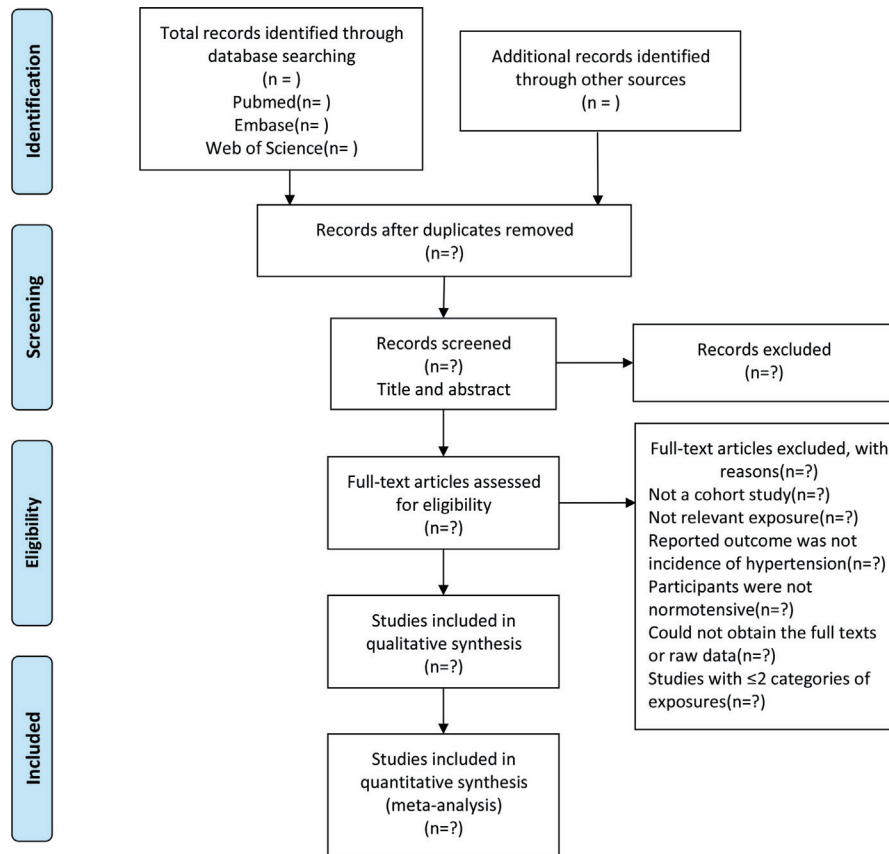


Figure 1 Searching process flowchart for eligible trials selection.⁵²

1. Study identification: first author's name, publication year, cohort and journal.
2. Study characteristics: study country, study period, total population, number of HTN occurrences and no occurrence during follow-up, number of patients in each exposure category, number of HTN occurrence cases in each corresponding category, and follow-up duration.
3. Population characteristics: age, male proportion, race, body mass index (BMI), uric acid, alcohol consumption, family history of HTN proportion, smoking proportion, diabetes proportion, renal dysfunction proportion, hyperlipidaemia proportion, coronary disease proportion.
4. Assessment of exposure: 24 hours urine collection method (eg, disposable or repetitive 24 urine collection, model of measuring instrument and the other measurement method detail), and training of the surveyors and number of measurements.
5. Blood pressure measurement methods: mercury sphygmomanometer or electronic sphygmomanometer, sphygmomanometer model, cuff size, subject position, clinic or home measurement, measurement times and interval time, rest time before the subject take the measurement, whether the measurement personnel has been training, and calculate mode for blood pressure.
6. HTN criteria: diagnostic criteria for HTN.
7. Adjusted factors: all adjustments for potential confounders will be recorded. Such as age, gender, BMI, smoking, alcohol usage and family history and others. Any adjustment for the variables will be considered in the meta-analysis.
8. Dose: various doses of dietary sodium, potassium intake and Na/K ratio reported in the study will be recorded.
9. Effect size (95% CI): fully multivariate-adjusted RR/OR/HR values and their 95% CIs will be extracted from each dietary sodium, potassium intake, and Na/K ratio dose category.
10. NOS score.

Data synthesis and dose-response meta-analysis

Based on the adjusted RR/OR/HRs and 95% CIs derived from each study, the association between sodium, potassium, the Na/K ratio and HTN risk will be investigated. Data from Kaplan-Meier survival curves or log-rank tests will be used to calculate HR when necessary. We calculated the standard errors according to the extracted RR/OR/HR CIs. Then, the values of each study and the corresponding standard errors were converted into their natural logarithms to stabilise the variance and normalise the distribution.³⁵ The HRs or ORs were considered equivalent to RRs.³⁶ If the reference category is not the lowest, we will apply Hamling *et al's* method to recalculate the RR values with the lowest category as the reference

category.³⁷ We will determine the linear dose–response relationship utilising the generalised least squares trend estimation proposed by Orsini and Bellocco.³⁸ With the help of restricted cubic splines with knots at the top, middle and bottom (10%, 50%, and 90%) of the distribution,³⁶ possible non-linear relationships between sodium, potassium, Na/K ratio and HTN risk will be examined in normotensive individuals. Using a random-effects model developed by DerSimonian and Laird, We will pool the results for each study.³⁹ The above is known as the two-stage approach. Afterward, we will analyse the difference in model fit between the linear and non-linear models with a likelihood ratio test.⁴⁰ The dose–response analysis will only include studies that investigate exposure with three or more categories, acquire the distributions of cases, controls, or person-years and effect estimates with the variance estimates in each category. Each study's mean of the lower and upper levels will be used to estimate the average sodium level, potassium level and Na/K ratio. An open upper level for the highest category will have a mean level estimated to be 1.2× that of the lower levels.⁴¹

For studies that only offer salt levels, we will convert them to their sodium equivalents (eg, 1 g salt=1 g NaCl, 1 g NaCl contains 0.393 g sodium). Na/K ratio doses reported in mg/mg units will be converted to mmol/mmol using a scale factor of 1.69 (eg, 1 mmol sodium=23 mg, 1 mmol potassium=39 mg, so 1 mmol/mmol Na/K ratio=0.59 mg/mg, 1 mg/mg Na/K ratio=1.69 mmol/mmol). If the number of cases is missing for a given category, the total number of cases and the reported effect size will be used to infer this data. In the absence of exposure person-years or participant numbers for each category, groups will be deemed equal. Suppose a study separately provides risk estimates for subgroups (eg, male and female). In that case, we will summarise the data using a fixed-effect model and include the pooled estimate in the meta-analysis. Using the `ftocci` command created by Orsini, convert data that only give floating CIs or floating standard errors to conventional CIs.³⁶ For studies reporting effect sizes for specific unit increases in exposure, the logarithm of the RR for each study was multiplied by the SD of 24-hour urinary sodium, potassium, and Na/K ratio excretion to calculate the RR for each SD increase in exposure level.⁴² If a study's results are inadequate for meta-analysis, the preliminary study characteristics and findings will be given in narrative format.

We will perform pooling analyses based on the type of study (reviewed or prospective). *Statistical significance* is defined as $p < 0.05$ (two-sided). RevMan software (V.5.0, Cochrane Collaboration, Oxford, UK) and Stata software (V.15.0, StataCorp., College Station, Texas, USA) will be used for all statistical analyses.

Subgroup and sensitivity analyses

Taking into account the option of employing different covariates in the study, we will conduct a subgroup analysis to investigate the effect of each study characteristic

on the preliminary results. Depending on the availability of data, we may also perform subgroup analyses by age, gender, race (yellow, white or black), region (Asia, Mediterranean, Americas or multinational), follow-up years (<10 years or ≥ 10 years) and study quality. Covariates (smoking, alcohol consumption, BMI and chronic disease at baseline) will also be considered. Sensitivity analyses will be conducted by removing each included study to determine the impact on remaining aggregate estimates and heterogeneity statistics.

Assessment of publication bias

Conducting visual examinations of funnel plots and applying Begg's and Egger's tests to determine publication bias.⁴³

Assessment of heterogeneity

The heterogeneity among studies will be evaluated using the Cochrane Q test and inconsistency index (I^2 statistic). I^2 values of <25%, 25%–50% and >50% indicated low, moderate, and high heterogeneity, respectively (significance level $p < 0.05$).⁴⁴

GRADE framework for the strength of evidence

According to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE)⁴⁵ framework all included studies will assess the quality of evidence and the strength of recommendations.

ETHICS AND DISSEMINATION

This systematic review and meta-analysis involve no medical behaviour activities and no contact with patients. According to the Institutional Review Board/Independent Ethics Committee of the Guang'anmen Hospital of the China Academy of Chinese Medical Science, this systematic meta-analysis protocol does not require ethical approval or informed consent. This meta-analysis will be published in a scientific journal with peer reviews.

DISCUSSION

Despite substantial breakthroughs in pharmaceutical treatment, HTN continues to be a leading cause of premature morbidity and mortality worldwide.⁴⁶ Current guidelines promote dietary modification to prevent and manage HTN.^{47 48} Dietary patterns that reduce dietary sodium and increase intake of fruits and vegetables, that is, potassium, have been tested in early studies to reduce blood pressure and prevent CVD,⁴⁹ such as the Dietary Approaches to Stop Hypertension diet, with positive results.⁵⁰ More and more studies have been conducted on the relationship between dietary sodium, potassium intake, Na/K ratio and the risk of HTN, but the results are still controversial. The Na/K ratio as an observational indicator is gradually showing greater representativeness. We will combine all the data from current cohort studies to investigate the possible linear and non-linear dose–response meta-analysis between dietary sodium,

potassium intake, Na/K ratio and the risk of HTN. To offer the optimum reference for dietary sodium, potassium intake and Na/K ratio to prevent HTN. Our review and analysis of the existing literature will help fill the gaps in the evidence-based relationship between dietary Na/K ratio and risk of HTN, as well as further investigate the role of sodium–potassium interactions in the incidence of HTN to inform future research and clinical practice. On the other hand, this meta-analysis may have several limitations. First, this review may be prone to substantial heterogeneity due to the low number of qualifying studies and small sample sizes. Some exposures might not be classified into sufficiently different categories (≥ 3), resulting in insufficient data for dose–response analyses. Second, there may be significant heterogeneity since the methodologies employed to assess 24-hour urinary excretion may differ from study to study. Third, salt-sensitive individuals demonstrate aberrant individual reactions and a higher risk of HTN under high-sodium diet conditions,⁵¹ but few eligible studies have characterised them, which could introduce bias into this study.

Contributors YY and SW contributed to the study's conception and design and the protocol's revision. YY and QW drafted the manuscript of the protocol. QL and JL will independently search and select the eligible studies. YY and LL will retrieve the data from the studies qualified for inclusion. QL and QW will assess methodological quality and the risk of bias. YY will conduct the meta-analysis. SW is the guarantor of the study. All authors contributed substantially to the drafting of the paper and its revisions. All the authors approved the protocol publication.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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