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Non-pharmacological interventions for the prevention of hypertension in low-income and middle-income countries: protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction In recent times, hypertension has become one of the major public health concerns in both the developed and the developing world and is responsible for death due to heart diseases and stroke. The increasing trend of the prevalence of hypertension in low-income and middle-income countries (LMICs) and it's catastrophic consequences have made the phenomenon important to continue to investigate interventions for its prevention and control. Different dietary and lifestyle-related approaches have been recommended for the prevention of hypertension. The aim of this proposed review is to explore the available non-pharmacological interventions tried for the prevention of hypertension in LMICs.

Methods and analysis Eight electronic databases will be searched covering the period between 1990 and 2016 to identify relevant studies and will be screened by two independent reviewers. The searched articles will be included for full-text extraction applying definitive inclusion and exclusion criteria. Appropriate critical appraisal tools including the Cochrane Handbook for Systematic Reviews of Interventions will be used to assess the risk of bias. Disagreement between the two reviewers will be resolved by a third reviewer. Narrative synthesis of the findings will be provided along with summaries of the intervention effect. A meta-analysis will be undertaken using the random-effects model where applicable. Heterogeneity between the studies will be assessed, and sensitivity analysis will be conducted based on study quality.

Ethics and dissemination Approval from the institutional review board has been taken for this review. Findings will be summarised in a single manuscript. This review is an attempt to explore the available non-pharmacological approaches for the prevention of hypertension in LMICs. Findings from the review will highlight effective non-pharmacological measures for the prevention of hypertension to guide policy for future strategies.

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Strengths and limitations of this study

- This systematic review protocol strongly follows the methods of the Cochrane systematic review.
- Only randomised controlled trials (RCTs) are included in this systematic review.
- This systematic review protocol describes the assessment of risk of bias (ROB) following the Cochrane guidelines for assessing ROB and critical appraisal of included articles using the Critical Appraisals Skills Programme checklist for RCTs.
- This systematic review only includes articles written in English and thus there is a possibility of missing information from articles written in other languages.

INTRODUCTION

In recent times, hypertension has become one of the major public health concerns in both the developed and the developing world. Global prevalence of hypertension (defined as systolic and/or diastolic blood pressure equal to or above 140/90 mm Hg[1]) among adults aged 18 years and over was around 22% in 2014[2] which is projected to increase to 29% by the year 2025.[3] Hypertension is the cause of death due to heart disease (45%) and stroke (51%) in majority of the cases.[4] Recent epidemiological transition is reflected with increased prevalence of hypertension in low-income and middle-ncome countries (LMICs) and a decreasing trend in the developed world.[5] In 2010, the global prevalence of adult hypertension was 31.1%, with a prevalence of 28.5% in high-income countries and 31.5% in LMICs. Between 2000 and 2010, the age-standardised prevalence of hypertension increased by 7.7% in LMICs and decreased by 2.6% in high-income countries.[6] In 2015, more than half of the global disability adjusted life years were related to systolic blood pressure in countries like China, India, Russia, Indonesia and USA.[7] A recent systematic review describes that the

pooled estimate of the overall prevalence of hypertension in LMICs was 32.3%.[8] One systematic review depicts that overall prevalence of hypertension in India was 29.8% with a significant difference between rural and urban areas.[9] Similar results have been reported from population-based studies in Bangladesh where age-standardised prevalence of prehypertension and hypertension were 27.1% and 24.4%, respectively.[10] In Pakistan, the overall prevalence of hypertension was 26% in the low-income community with an increased proportion among men.[11] Increasing prevalence of hypertension leads to higher rates of morbidity and mortality directly or indirectly, which has made the phenomenon an important public health issue, particularly in LMICs. Hence, it is important and justified to continue investigating interventions proven effective to prevent hypertension. There are certain dietary and lifestyle-related approaches for the prevention of hypertension.[12] Specific interventions such as supplementations with increased calcium intake have proved effective in reducing both systolic and diastolic blood pressures in normotensive people, suggesting a role in the prevention of hypertension.[13] Other than general exercise, *yoga*[14] and *tai chai*[15] could also successfully prevent hypertension. Some medications have also been tested through randomised controlled trials (RCTs) in the prehypertensive population to prevent the high prevalence of hypertension.[16]

Prevention of hypertension can minimise the fatal morbid conditions and consequences of cardiovascular events. Changes in lifestyle variables, along with other non-pharmacological interventions may play an important role in halting the increasing trend of the prevalence of hypertension in LMICs where there is a scarcity of programmes for the prevention and control of high blood pressure.[17] Prevention of the onset of hypertension with such interventions is evident and will contribute to reducing the premature mortality and disability related to hypertension in this region.Besides the different therapeutic approaches, an effective preventive strategy can help policy makers to formulate specific context-specific strategies for the prevention and control of the increasing burden of hypertension in LMICs.

OBJECTIVE

This review is an attempt to explore the available non-pharmacological approaches including lifestyle modification, exercise, dietary supplementation and restriction for the prevention of hypertension in LMICs to inform policy for effective measures for the prevention of hypertension.

METHODS

Protocol

This is a protocol for systematic review and meta analysis and has been developed addressing the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) guidelines for reporting systematic reviews evaluating healthcare interventions.[18 19] A PRISMA-P checklist for this protocol is attached (online supplementary file 1).

Eligibility criteria

Studies will be selected according to the criteria outlined below.

Participants

Included studies will be on normotensive (systolic blood pressure 120–139 mm Hg and diastolic blood pressure 80–89 mm Hg)[20] adults in LMICs as defined by the World Bank.[21]

Interventions

Studies assessing the effect of non-pharmacological interventions in the prevention of hypertension in the normotensive adult population will be considered for inclusion. Interventions will include lifestyle modification, dietary restriction, non-pharmacological diet supplementation, exercise and any combination of the above-mentioned interventions.

Comparators

A comparison will be made with non-pharmacological interventions versus no intervention.

Outcomes

Primary outcomes

Hypertension, systolic blood pressure and diastolic blood pressure.

Secondary outcomes

Any adverse event, cardiovascular events, myocardial infarction, stroke, kidney stone formation, iron deficiency anaemia, mortality, sudden death.

Setting

There will be no restrictions by study setting such as hospital or community. Any non-pharmacological intervention for hypertension in any setting will be included in the review.

Study designs

We will include RCTs (including cluster RCTs) to assess the beneficial effect of interventions. Non-randomised studies including pretest-post-test controlled studies, prospective comparative cohort studies, case-control studies and cross-sectional studies will be excluded.

Exclusion criteria

Studies conducted outside LMICs will be excluded. Hypertensive people with intervention, population below 18 years of age, pregnant women and people with other diseases will be excluded. We will exclude studies with pharmacological interventions and combinations of pharmacological interventions with non-pharmacological intervention. Systematic reviews, reviews, ongoing trials, trial protocols and studies other than RCTs will be excluded. Letters, editorials and conference papers will

Table 1 Key terms used for developing a comprehensive search strategy

Population (P)	Intervention (I)	Outcome (O)	Filter
LMICs 'Developing country'	Exercise 'Physical activity' 'Weight loss' 'Sodium restriction' 'Dietary potassium' 'Calcium supplementation' 'Fish oil supplementation' Lifestyle	Hypertension 'Blood pressure'	'Randomised controlled trials' (RCTs)

LMICs, low-income middle-income countries.

be excluded. Articles written in languages other than English will be excluded as well.

Information sources

The following electronic bibliographic databases will be searched systematically using a comprehensive search strategy. The databases are: MEDLINE through Pubmed, Embase, The Cochrane Library (Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, Scopus, Clinical Trials. gov, EBSCO and WICTRP (International Clinical Trials Registry Platform). The search strategy will include terms relating to or describing the population, interventions and outcomes. The terms will be combined with the Cochrane MEDLINE filter for controlled trials of interventions.

Search strategy

A comprehensive search strategy will be developed for MEDLINE. The search terms will be adapted for other bibliographical databases in combination with database-specific filters for controlled trials, where these are available. Table 1 demonstrates the key search terms for population, intervention, comparison and outcome.

Only English language literature will be searched. Studies published between January 1990 and the date the searches are run will be sought. The searches will be rerun just before the final analyses and further studies retrieved for inclusion. A comprehensive search strategy prepared for Pubmed is provided in table 2.

Study records

Data management

Reference management software EndNote will be used to organise articles retrieved from the comprehensive literature search. Search results from different electronic databases will be combined and uploaded in a single EndNote library. Duplicate articles will be checked and removed.

Remaining literature search results will be uploaded to EPPI reviewer, a software with facilities of citation screening and supports collaboration between reviewers. Citation abstracts and full-text articles will be uploaded to the EPPI reviewer software.

Selection process

Screening of the title and abstract of retrieved articles will be conducted by two reviewers independently to identify studies eligible for inclusion. The screening will be done using the EPPI reviewer software. After inclusion for full-text review, eligible studies will be assessed independently for final inclusion. Any disagreement between reviewers over the decision of inclusion will be resolved through discussion with a third reviewer. Reasons for exclusion will be recorded. Multiple publications from the same study will be reported. Summaries of included and excluded studies will be demonstrated using the PRISMA flow diagram.[22]

Data extraction

Rigorous quality assessment will be undertaken applying the Critical Appraisals Skills Programme checklist for RCTs. Data on study population, study setting, baseline characteristics of study participants, study methodology, intervention details for prevention of hypertension, enrolment and attrition rates, outcomes measurement, and information for assessing the risk of bias (ROB) will be extracted independently by two reviewers using a standardised form.

ROB assessment

Two reviewers will assess the ROB independently following guidelines from the Cochrane assessment of ROB for RCTs.[23] According to the guidelines, six specific domains of bias are considered including selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias. Reviewers will provide their judgements as per the guidelines and make comments on whether studies are at high ROB. For assessing selection bias, 'allocation concealment' and 'random sequence generation' will be considered. Performance and detection bias will be explored through assessment of blinding at the level of the participants, implementers and outcome assessors, while those lost to follow-up will be considered to assess attrition bias. Selective reporting and presentation of outcomes will also be considered. There will be search for any other potential bias. Any disagreements between the reviewers while assessing the ROB will be resolved by discussion, and if necessary, a third reviewer will opine to make a consensus.

Assessment of the body of evidence—the GRADE approach

We will use the 'Grades of Recommendation, Assessment, Development and Evaluation (GRADE)' approach for

Table 2 Search strategy: pubMed format

1	LMIC's*
2	Exercise (MeSH Terms) OR 'Physical Exercise' (tw) OR 'Physical activity' (tw)
3	('Weight Loss/classification'(Mesh) OR 'Weight Loss/complications'(Mesh) OR 'Weight Loss/diagnosis'(Mesh) OR 'Weight Loss/diet therapy'(Mesh) OR 'Weight Loss/drug effects'(Mesh) OR 'Weight Loss/drug therapy'(Mesh) OR 'Weight Loss/epidemiology'(Mesh) OR 'Weight Loss/etiology'(Mesh) OR 'Weight Loss/genetics'(Mesh) OR 'Weight Loss/metabolism'(Mesh) OR 'Weight Loss/mortality'(Mesh) OR 'Weight Loss/prevention and control'(Mesh) OR 'Weight Loss/rehabilitation'(Mesh) OR 'Weight Loss/statistics and numerical data'(Mesh))
4	Exercise therapy (mesh) OR Exercise test (mesh OR Exercise Movement Techniques (mesh)
5	'weight loss' (tw) OR weight reduction programme (MeSH Terms) OR 'weight reduction' (tw) OR losing weight (tw)
6	'Sodium restriction' (tw) OR Dietary potassium (MeSH Terms) OR 'Dietary potassium' (tw) OR 'Calcium supplementation' OR 'Fish oil supplementation' (tw)
7	Salt Restrict*(tiab) OR low Sodium*(tiab) OR low salt*(tiab) OR Potassium, Diet* (tw)
8	Magnesium (tw) OR Calcium (tw)
9	'Salt intake' (tw) OR Sodium Chloride, Dietary (MeSH Term) OR 'Dietary salt' (tw) OR 'Dietary Salt intake' (tw) OR 'Dietary Salt restriction' (tw)
10	Garlic (MeSH Terms) OR Garlic (tw)
11	Smoking Cessation (MeSH Term) OR 'Smoking Cessation' (tw) OR Tobacco Use Cessation*(tw)
12	decreased (tw) AND ('alcohol drinking'(MeSH Terms) OR ('alcohol'(tw) AND 'drinking'(tw)) OR 'alcohol drinking'(tw) OR ('alcohol'(tw) AND 'intake'(tw)) OR 'alcohol intake'(tw))
13	Alcohol Drink*(tw) OR Alcohol consum*(tw) OR Drinking Alcohol*(tw) OR Alcoholi*(tw) OR non pharmacol*(tw)
14	life style*(tw) OR lifestyl*(tw) OR diet therapy (mesh) OR fat Restrict*(tiab) OR low fat*(tiab) OR Carbohydrate Restrict*(tiab)) OR low carb*(tiab) OR Caloric Restrict*(tw) OR Food, Formulated (tw) OR Formulated Food*(tw) OR diet (tw) OR dietary (tw)
15	Disease Management*(tw) OR kinesiotherap*(tw) OR Physical Endurance (mesh) OR Anaerobic*(tiab) OR aerobic*(tiab) OR Resistance Training*(tiab) OR Motor activit*(tw) OR Physical Activit*(tiab) OR Locomotor Activit*(tiab)
16	Social support*(tw) OR Social Network*(tiab) OR relaxation therap* (tw) OR tai-chi (tw) OR yoga (tw)
17	OR/2–16
18	'Hypertension/classification'(Majr) OR 'Hypertension/complications'(Majr)) OR 'Hypertension/diet therapy'((Majr) OR 'Hypertension/drug effects'(Majr) OR 'Blood Pressure/classification'(Mesh) OR 'Blood Pressure/complications'((Mesh) OR 'Blood Pressure/diagnosis'(Mesh) OR 'Blood Pressure/drug effects'(Mesh)) OR 'Blood Pressure/etiology'(Mesh) OR 'Blood Pressure/genetics'(Mesh) OR 'Blood Pressure/metabolism'(Mesh) OR 'Blood Pressure/methods'(Mesh) OR 'Blood Pressure/statistics and numerical data'(Mesh) OR 'Blood Pressure/therapy'(Mesh) 'Hypertension/drug therapy'(Majr) OR 'Hypertension/epidemiology'(Majr) OR 'Hypertension/etiology'(Majr) OR 'Hypertension/genetics'(Majr) OR 'Hypertension/metabolism'(Majr) OR 'Hypertension/mortality'(Majr)
19	'Hypertension/prevention and control'(Majr) OR 'Hypertension/rehabilitation'(Majr) OR 'Hypertension/therapy'(Majr) OR 'Blood Pressure/classification'(Mesh) OR 'Blood Pressure/complications'(Mesh) OR 'Blood Pressure/diagnosis'(Mesh) OR 'Blood Pressure/drug effects'(Mesh) OR 'high blood pressure' (tw) OR 'Blood pressure' (tw) OR bloodpressure (tw) OR ('Systole/drug effects'(Majr) OR 'Systole/etiology'(Majr) OR 'Systole/genetics'(Majr)) OR 'Blood Pressure/etiology'(Mesh) OR 'Blood Pressure/genetics'(Mesh) OR 'Blood Pressure/metabolism'(Mesh) OR 'Blood Pressure/methods'(Mesh) OR 'Blood Pressure/statistics and numerical data'(Mesh) OR 'Blood Pressure/therapy'(Mesh) OR 'high blood pressure' (tw) OR 'Blood pressure' (tw) OR bloodpressure (tw) OR ('Systole/drug effects'(Majr) OR 'Systole/etiology'(Majr) OR 'Systole/genetics'(Majr)) OR ('Diastole/drug effects'(Mesh) OR 'Diastole/etiology'(Mesh) OR 'Diastole/genetics'(Mesh)) OR ((arterial OR diastolic OR systolic) AND pressure) OR Hypertension (tw) OR 'Blood Pressure' (tw)
20	OR/18–19
21	Randomised controlled trial (tiab) OR controlled clinical trial (tiab) OR randomised (tiab) OR placebo (tiab) OR randomisation (tiab) OR randomisation (tiab) OR drug therapy (tiab) OR randomly (tiab) OR trial (tiab) OR groups (tiab)
22	#1 AND #17 AND #20 AND #21
23	animals (mh) NOT humans (mh)

Continued

Table 2 Continued

24	#22 NOT #23
25	Restrict #24 to year=1990 and up to date
26	Restrict #25 to English language
27	Restrict #26 to Age 18+years

*Search terms and search strategy for LMICs are provided in online supplementary file 2.
LMICs, low-income middle-income countries.

assessing the quality of evidence[24] which focuses on five domains including study limitations, imprecision, indirectness, effect consistency and publication bias. Considering these domains, the quality of the body of evidence will be assessed for specific outcomes. Assessing high ROB, and indirect and imprecise evidence, will downgrade the evidence by one or two levels.

Strategy for data synthesis

A narrative synthesis of the findings from the included studies will be provided focusing on the characteristics of the target population,the type of intervention and outcome. A summary of effect size for individual studies will be presented by estimating risk ratios and ORs for dichotomous outcomes (developing hypertension) or standardised mean differences for continuous outcomes (systolic blood pressure and diastolic blood pressure), respectively. Studies with the same interventions for the prevention of hypertension, comparators and outcome measures, will be pooled using the random-effect model meta-analysis methods with 95% CIs and two-tailed p values will be calculated for each outcome. SD will be adjusted for the design effect where the effects of clustering have not been taken into account. Both the χ^2 test and the I^2 statistic will be considered for measuring the heterogeneity of effect measures. An I^2 value greater than 50% will be indicative of substantial heterogeneity. We will conduct sensitivity analyses based on study quality, where applicable. Potential publication bias will also be assessed for individual studies through generating a funnel plot using review manager software (RevMan).

Patient and public involvement

This is a protocol for a systematic review and no patients are directly involved in the process. The review question and outcome measures are developed for the overall betterment of the people who are at risk of developing hypertension.

Amendments

Any updates or amendments to this protocol will be described in a table including the date of each amendment, description of the change and rationale for the change. The International Prospective Register of Systematic Reviews will be updated with the protocol and amendments.

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Contributors KMSUR, IA, SSI, SH and MH conceptualised the review in consultation with the co-reviewers. KMSUR wrote the first draft of this protocol with substantial inputs from all authors. KMSUR and MH will contribute to the literature search. Screening, collection and analysis of data for all the included interventions will be conducted by KMSUR and MH with close consultation from SH, SS, SSI, AR, MK, FH and IA. All authors will provide input, and review and finalise the paper before dissemination. The corresponding author is the guarantor of this review. All authors read and approved the final manuscript.

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Competing interests None declared.

Patient consent Not required.

Ethics approval Approval for conducting this systematic review has been taken from the Institutional Review Board (IRB) of Bangabandhu Sheikh Mujib Medical University (BSMMU).

Provenance and peer review Not commissioned; externally peer reviewed.

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