BMJ Open

Non pharmacological interventions for prevention of hypertension in Low and Middle Income Countries: Protocol for a systematic review and meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-020724
Article Type:	Protocol
Date Submitted by the Author:	21-Nov-2017
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Keywords:	Intervention, Prevention, Hypertension < CARDIOLOGY, Non pharmacological, Systematic review, LMIC

Title: Non pharmacological interventions for prevention of hypertension in Low and Middle Income Countries: Protocol for a systematic review and meta-analysis

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Word Count: 2030

ABSTRACT:

Introduction: In current days, hypertension has become one of the major public health problems in both developed and developing world and is responsible for death due to heart diseases and stroke. Increasing trend in prevalence of hypertension in low and middle income countries and it's catastrophic consequences have made the phenomena important to continue to investigate interventions for prevention. There are different dietary and life style related approaches for prevention of hypertension. Aim of this review is to explore the available non pharmacological approaches for prevention of hypertension in low and middle income countries.

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

Ethics and dissemination: This systematic review protocol is registered with International Prospective Register of Systematic Reviews (PROSPERO) CRD42017055423. Approval from institutional review board has been taken for this review. Findings will be summarized in a single manuscript.

This review is an attempt to explore the available non pharmacological approaches for prevention of hypertension in low and middle income countries. Findings from the review will highlight effective measures for prevention of hypertension and will guide the policy makers to identify appropriate approach.

Key Words: Intervention, Prevention, Hypertension, Non pharmacological, Systematic review, LMIC

INTRODUCTION

In current days, hypertension has become one of the major public health problems in both developed and developing world. According to the World Health Organization (WHO), global prevalence of hypertension (defined as systolic and/or diastolic blood pressure equal to or above 140/90 mmHg[1]) in adults aged 18 years and over was around 22% in 2014[2]. High blood pressure has been estimated to be increased to 29% by the year 2025[3]. Hypertension is the leading cause of death due to heart disease (45%) and stroke (51%)[4]. Recent trend of epidemiological transition is reflected with increased prevalence of hypertension in developing countries whereas a decreasing tendency in the developed world[5]. In 2010, the prevelance of adult hypertensive population was 31.1%, among which high-income countries were less prevalent (28.5%) than in low- and middle-income countries31.5%. Between the last decades (from 2000 to 2010), the age-standardized prevalence of hypertension increased by 7.7% in low- and middle-income countries and decreased by 2.6% in high-income countries[6]. In 2015, more than half of the global disability adjusted life years (DALYs) were related to systolic blood pressure in countries like China, India, Russia, Indonesia, and the United States[7]. A recent systematic review describes that the pooled estimate of the overall prevalence of hypertension in Low and Middle income countries was 32.3%[8]. Overall prevalence for hypertension in India was 29.8% according to a systematic review though there was significant difference in hypertension prevalence between rural and urban areas[9]. Similar results have been found in Bangladeshi population based survey which shows overall age-standardized prevalence of pre-hypertension and hypertension were 27.1% and 24.4% respectively[10]. In Pakistan, the overall prevalence of hypertension was 26% among the low income community with an increased proportion among the males[11]. Highly increasing prevalence of hypertension leads to the high morbidity and mortality which has made the phenomena an important public health issue and therefore, it is important to continue to investigate interventions that can prevent hypertension. There are different dietary and life style related approaches for prevention of hypertension[12]. Specific interventions with certain supplementations like increased calcium intake has been proved as effective which reduces both systolic and diastolic blood pressure in normotensive people, suggesting a role in the prevention of hypertension[13]. Other than general exercise, yoga[14] and tai chai[15] also successfully prevent and control hypertension which is evident.

Even some medications have been tested as a preventive medication among prehypertensive persons as means of prevention in randomized controlled trials [16].

Prevention of hypertension can minimize the fatal morbid conditions and consequences of cardiovascular events. Despite of different approaches, an effective preventive strategy or intervention can help the public health experts and policy makers to plan properly for addressing the increasing burden.

OBJECTIVE:

This review is an attempt to explore the available non pharmacological approaches including lifestyle modification, exercise, dietary supplementation and restriction etc for prevention of hypertension in low and middle income countries which will find the effective measures for prevention of hypertension as well.

METHODS:

PROTOCOL

This is a protocol for systematic review and meta analysis which has been developed addressing the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) guidelines for reporting systematic reviews evaluating health care interventions[17 18]. A PRISMA-P checklist for this protocol is attached (Additional file 1).

ELIGIBILITY CRITERIA

Studies will be selected according to the criteria outlined below.

PARTICIPANTS

Included studies will be on normotensive (Systolic BP 120-139 mm hg and diastolic BP 80-89 mm hg)[19] adults of low and middle income countries (LMIC's) as defined by the World Bank[20].

INTERVENTIONS

Studies assessing the effect of nonpharmacological interventions for the prevention of hypertension among normotensive adult population will be considered for inclusion. Interventions will be including life style 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 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 type of setting such as hospital based or community setting.

STUDY DESIGNS

We will include randomized controlled trials (RCTs) (including cluster RCTs) to assess the beneficial effect of the interventions. Non-randomized studies including controlled before-and-after studies, prospective comparative cohort studies, case-control studies and cross-sectional studies will be excluded.

INFORMATION SOURCES

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, intervention and outcome. 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 bibliographic databases in combination with database-specific filters for controlled trials, where these are available. Key search terms for population, intervention, comparison and outcome are as follow:

Table 1: Key terms used for developing 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"	"Randomized Controlled Trials" (RCT)

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 re-run just before the final analyses and further studies retrieved for inclusion. Comprehensive search strategy prepared for pubmed is provided in Table 2.

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 program [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-ji [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	Randomized controlled trial [tiab] OR controlled clinical trial [tiab] OR randomized [tiab] OR placebo [tiab] OR randomization [tiab] OR randomization [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]
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 Additional file 2.

STUDY RECORDS

DATA MANAGEMENT

Reference management software EndNote will be used to organize 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 title and abstract of retrieved articles will be conducted by two reviewers independently to identify the included studies. The screening of retrieved outcome of comprehensive search strategy 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. We will report multiple publications from the same study. Summary of included and excluded studies will be demonstrated using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow-diagram[21].

DATA EXTRACTION

Quality assessment of included studies will be conducted and data will be extracted using a standardized form. We will extract information including study population, study setting, baseline demographics characteristics of study participants, study methodology, details regarding the intervention and control groups, enrollment and attrition rates, outcomes measurement, and information for assessing of the risk of bias. Data extraction will be conducted by two reviewers independently. Any dispute will be resolved through discussion with a third reviewer.

RISK OF BIAS ASSESSMENT

Two reviewers will assess the risk of bias independently following guidelines from Cochrane assessment of risk of bias for randomized controlled trials[22]. According to the guideline, specific six domains including selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias are considered. Reviewers will provide their judgments to make comments on whether studies are at high risk of bias. For assessing selection bias, allocation concealment and random sequence generation will be considered. Performance and detection bias will be assessed through assessment of blinding at the level of participants, implementers and outcome assessors. Loose to follow up will be considered to assess attrition bias. Selective reporting and selective presentation of outcome will also be considered. There will be search for any other potential bias. Any disagreements between the review authors while assessing the risk

of bias will be resolved by discussion and if necessary, a third reviewer will opine to resolve the issue.

ASSESSMENT OF THE BODY OF EVIDENCE—THE GRADE APPROACH

We will use the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach for assessment of quality of evidence[23] 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 as high risk of bias, indirect and imprecise evidence will lead to downgrade the evidence by one or two level.

STRATEGY FOR DATA SYNTHESIS

A narrative synthesis of the findings from the included studies will be provided focusing the characteristics of target population, type of intervention and outcome. A summary of intervention effects for individual studies will be provided by calculating risk ratios or odds ratio or standardized mean differences for dichotomous and continuous outcomes respectively. Studies with the same interventions, comparators and outcome measure, will be pooled using a random-effects meta-analysis and 95% confidence intervals and two sided P values will be calculated for each outcome. Standard deviations will be adjusted for the design effect where the effects of clustering have not been taken into account,. Both the Chi-squared test and the I-squared statistic will be considered for measuring the heterogeneity of effect measures. I-squared value greater than 50% will be indicative of substantial heterogeneity. We will conduct sensitivity analyses based on study quality where applicable. We will also assess the included articles for potential publication bias.

STRENGTH

- Strong methodology
- Includes Randomized Controlled Trials only
- Assessment of risk of bias (ROB) following Cochrane guideline for assessing risk of bias

LIMITATIONS

- Includes articles written in English only

PUBLICATION PLAN

This systematic review protocol is registered with International Prospective Register of Systematic Reviews (PROSPERO) CRD42017055423. Findings will be summarized in a single manuscript.

TIMELINE

Review start date: 1st March 2017

Review finishing date: 28 February 2018

Reporting date: 28 February 2018

ABBREVIATIONS

BSMMU: Bangabandhu sheikh mujib medical university

DALYs: Disability adjusted life years

GRADE: Grades of Recommendation, Assessment, Developmentand Evaluation

LMICs: Low and middle income countries

MESH: Medical subject headings

PRISMA-P: Preferred reporting items for systematic reviews and meta-analysis protocols

PROSPERO: International prospective register of systematic reviews

RCT: Randomized controlled trial WHO: World health organization

DECLARATIONS

FUNDING

This review has been conducted by the Systematic Review Centre (SRC) of Department of Public Health and Informatics at Bangabandhu Sheikh Mujib Medical University (BSMMU), Bangladesh which has been established with the support of SHARE (Strengthening Health Applying Research Evidence) project of icddr,b funded by the European Union. icddr,b acknowledges with gratitude the commitment of European Union (EU) to its research efforts.

icddr,b is also grateful to the Governments of Bangladesh, Canada, Sweden and the UK for providing core/unrestricted support.

AVAILABILITY OF DATA AND MATERIALS

The datasets generated and/or analyzed during the current review shall be available from the corresponding author on reasonable request.

AUTHORS' CONTRIBUTIONS

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

COMPETING INTERESTS

The authors declare that they have no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Approval for conducting this systematic review has been taken from the Institutional Review Board (IRB) of Bangabandhu Sheikh Mujib Medical University (BSMMU). No additional formal ethical assessment and no informed consent are required.

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 PROSPERO register will remain updated with the protocol and amendments.

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	12
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	13
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	12
Sponsor	5b	Provide name for the review funder and/or sponsor	12
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	12
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5-6
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6-7
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6-7
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	7-9

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9-10
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	5-6, 9-10
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	10
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	6-7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	10
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	11
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	11
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	11
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	11
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10-11
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	11

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Additional file 2: Search strategy for low and middle income countries (LMICs)

1	"developing country"[tw] OR "developing countries"[tw] OR "developing nation"[tw] OR "developing nations"[tw] OR "developing population"[tw] OR "developing populations"[tw] OR "developing world"[tw] OR "less developed country"[tw] OR "less developed countries"[tw] OR "less developed nation"[tw] OR "less developed nations"[tw] OR "less developed population"[tw] OR "less developed populations"[tw] OR "less developed world"[tw] OR "lesser developed country"[tw] OR "lesser developed countries"[tw] OR "lesser developed nation"[tw] OR "lesser developed nations"[tw] OR "lesser developed population"[tw] OR "lesser developed populations"[tw] OR "lesser developed world"[tw] OR "under developed country"[tw] OR "under developed countries"[tw] OR "under developed nation"[tw] OR "under developed nations"[tw] OR "under developed population"[tw] OR "under developed populations"[tw] OR "under developed world"[tw] OR "underdeveloped country"[tw] OR "underdeveloped countries"[tw] OR "underdeveloped nation"[tw] OR "underdeveloped nations"[tw] OR "underdeveloped population"[tw] OR "underdeveloped populations"[tw] OR "underdeveloped world"[tw] OR "middle income country"[tw] OR "middle income countries"[tw] OR "middle income nation"[tw] OR "middle income nations"[tw] OR "middle income population"[tw] OR "middle income populations"[tw] OR "low income country"[tw] OR "low income countries"[tw] OR "low income nation"[tw] OR "low income nations"[tw] OR "low income population"[tw] OR "low income populations"[tw] OR "lower income country"[tw] OR "lower income countries"[tw] OR "lower income nation"[tw] OR "lower income nations"[tw] OR "lower income population"[tw] OR "lower income populations"[tw] OR "underserved country"[tw] OR "underserved countries"[tw] OR "underserved nation"[tw] OR "underserved nations"[tw] OR "underserved population"[tw] OR "underserved populations"[tw] OR "underserved world"[tw] OR "under served country"[tw] OR "under served countries"[tw] OR "under served nation"[tw] OR "under served nations"[tw] OR "under served population"[tw] OR "under served populations"[tw] OR "under served world"[tw] OR "deprived country"[tw] OR "deprived countries"[tw] OR "deprived nation"[tw] OR "deprived nations"[tw] OR "deprived population"[tw] OR "deprived populations"[tw] OR "deprived world"[tw] OR "poor country"[tw] OR "poor countries"[tw] OR "poor nation"[tw] OR "poor nations"[tw] OR "poor population"[tw] OR "poor populations"[tw] OR "poor world"[tw] OR "poorer country"[tw]

	OR "poorer countries"[tw] OR "poorer nation"[tw] OR "poorer nations"[tw] OR "poorer population"[tw] OR "poorer populations"[tw] OR "poorer world"[tw] OR "developing economy"[tw] OR "developing economies"[tw] OR "less developed economy"[tw] OR "less developed economies"[tw] OR "lesser developed economy"[tw] OR "lesser developed economies"[tw] OR "under developed economy"[tw] OR "under developed economies"[tw] OR "underdeveloped economy"[tw] OR "underdeveloped economies"[tw] OR "middle income economy"[tw] OR "middle income economies"[tw] OR "low income economy"[tw] OR "low income economies"[tw] OR "lower income economy"[tw] OR "lower income economies"[tw] OR "low gdp"[tw] OR "low gnp"[tw] OR "low gross domestic"[tw] OR "low gross national"[tw] OR "lower gdp"[tw] OR "lower gnp"[tw] OR "lower gross domestic"[tw] OR "lower gross national"[tw] OR lmic[tw] OR lmics[tw] OR "third world"[tw] OR "lami country"[tw] OR "lami countries"[tw] OR "transitional country"[tw] OR "transitional countries"[tw]
2	Africa[tw] OR Asia[tw] OR Caribbean[tw] OR West Indies[tw] OR South America[tw] OR Latin America[tw] OR Central America[tw] OR Afghanistan[tw] OR Angola[tw] OR OR Armenia[tw] OR Armenian[tw] OR Bangladesh[tw] OR Benin[tw] OR Byelarus[tw] OR Byelorussian[tw] OR Belorussian[tw] OR Belorussia[tw] OR Bhutan[tw] OR Bolivia[tw] OR Hercegovina[tw] OR Brasil[tw] OR Burkina Faso[tw] OR Burkina Fasso[tw] OR Upper Volta[tw] OR Burundi[tw] OR Urundi[tw] OR Cambodia[tw] OR Khmer Republic[tw] OR Kampuchea[tw] OR Cameroon[tw] OR Cameroons[tw] OR Cameron[tw] OR Camerons[tw] OR Cape Verde[tw] OR Central African Republic[tw] OR Chad[tw] OR Comoros[tw] OR Comoro Islands[tw] OR Comores[tw] OR Mayotte[tw] OR Congo[tw] OR Zaire[tw] OR Cote d'Ivoire[tw] OR Ivory Coast[tw] OR Czechoslovakia[tw] OR Slovakia[tw] OR Djibouti[tw] OR French Somaliland[tw] OR East Timor[tw] OR East Timur[tw] OR Timor Leste[tw] OR Egypt[tw] OR El Salvador[tw] OR Eritrea[tw] OR Ethiopia[tw] OR Gambia[tw] OR Gaza[tw] OR Georgia Republic[tw] OR Georgian Republic[tw] OR Ghana[tw] OR Gold Coast[tw] OR Guatemala[tw] OR Guinea[tw] OR Guiana[tw] OR Haiti[tw] OR Honduras[tw] OR India[tw] OR Indonesia[tw] OR Isle of Man[tw] OR Jordan[tw] OR Kazakh[tw] OR Kenya[tw] OR Kiribati[tw] OR Kosovo[tw] OR Kyrgyzstan[tw] OR Kirghizia[tw] OR Kyrgyz Republic[tw] OR Kirghiz[tw] OR Kirgizstan[tw] OR "Lao PDR"[tw] OR Laos[tw] OR Lesotho[tw] OR

	Basutoland[tw] OR Liberia[tw]
3	Madagascar[tw] OR Malagasy Republic[tw] OR Malaya[tw] OR Malay[tw] OR Sabah[tw] OR Sarawak[tw] OR Malawi[tw] OR Nyasaland[tw] OR Mali[tw] OR Mauritania[tw] OR OR Agalega Islands[tw] OR Micronesia[tw] OR Middle East[tw] OR Moldova[tw] OR Moldovia[tw] OR Moldovian[tw] OR Mongolia[tw] OR Morocco[tw] OR Ifni[tw] OR Mozambique[tw] OR Myanmar[tw] OR Myanma[tw] OR Burma[tw] OR Nepal[tw] OR Nicaragua[tw] OR Niger[tw] OR Nigeria[tw] OR Muscat[tw] OR Pakistan[tw] OR Palestine[tw] OR Philippines[tw] OR Philipines[tw] OR Phillipines[tw] OR Phillippines[tw] OR Rumania[tw] OR Roumania[tw] OR Russia[twOR Rwanda[tw] OR Ruanda[tw] OR Saint Kitts[tw] OR St Kitts[tw] OR Nevis[tw] OR Saint Vincent[tw] OR St Vincent[tw] OR Grenadines[tw] OR Navigator Island[tw] OR Navigator Islands[tw] OR Sao Tome[tw] OR Senegal[tw] OR Sierra Leone[tw] OR Sri Lanka[tw] OR Ceylon[tw] OR Solomon Islands[tw] OR Somalia[tw] OR Sudan[tw] OR Surinam[tw] OR Swaziland[tw] OR Syria[tw] OR Tajikistan[tw] OR Tadzhikistan[tw] OR Tadjikistan[tw] OR Tadzhik[tw] OR Tanzania[tw] OR Togo[tw] OR Togolese Republic[tw] OR Tunisia[tw] OR Turkmen[tw] OR Uganda[tw] OR Ukraine[tw] OR USSR[tw] OR Soviet Union[tw] OR Union of Soviet Socialist Republics[tw] OR Uzbekistan[tw] OR Uzbek OR Vanuatu[tw] OR New Hebrides[tw] OR Vietnam[tw] OR Viet Nam[tw] OR West Bank[tw] OR Yemen[tw] OR Yugoslavia[tw] OR Zambia[tw] OR Zimbabwe[tw] OR Rhodesia[tw]
4	Developing Countries[Mesh:noexp] OR Africa[Mesh:noexp] OR Africa, Northern[Mesh:noexp] OR Africa South of the Sahara[Mesh:noexp] OR Africa, Central[Mesh:noexp] OR Africa, Eastern[Mesh:noexp] OR Africa, Southern[Mesh:noexp] OR Africa, Western[Mesh:noexp] OR Asia[Mesh:noexp] OR Asia, Central[Mesh:noexp] OR Asia, Southeastern[Mesh:noexp] OR Asia, Western[Mesh:noexp] OR Caribbean Region[Mesh:noexp] OR West Indies[Mesh:noexp] OR South America[Mesh:noexp] OR Latin America[Mesh:noexp] OR Central America[Mesh:noexp] OR Afghanistan[Mesh:noexp] OR Angola[Mesh:noexp] OR Armenia[Mesh:noexp] OR Bangladesh[Mesh:noexp] OR Benin[Mesh:noexp] OR Byelarus[Mesh:noexp] OR

	Bhutan[Mesh:noexp] OR Bolivia[Mesh:noexp] OR Burkina Faso[Mesh:noexp] OR Burundi[Mesh:noexp] OR Cambodia[Mesh:noexp] OR Cameroon[Mesh:noexp] OR Cape Verde[Mesh:noexp] OR Central African Republic[Mesh:noexp] OR Chad[Mesh:noexp] OR Comoros[Mesh:noexp] OR Congo[Mesh:noexp] OR Cote d'Ivoire[Mesh:noexp] Czechoslovakia[Mesh:noexp] OR Slovakia[Mesh:noexp] OR Djibouti[Mesh:noexp] OR "Democratic Republic of the Congo"[Mesh:noexp] OR East Timor[Mesh:noexp] OR Egypt[Mesh:noexp] OR El Salvador[Mesh:noexp] OR Eritrea[Mesh:noexp] OR Ethiopia[Mesh:noexp] OR Gambia[Mesh:noexp] OR "Georgia (Republic)"[Mesh:noexp] OR Ghana[Mesh:noexp] OR Guatemala[Mesh:noexp] OR Guinea[Mesh:noexp] OR Guinea-Bissau[Mesh:noexp] OR Haiti[Mesh:noexp] OR Honduras[Mesh:noexp] OR India[Mesh:noexp] OR Indonesia[Mesh:noexp] OR Jordan[Mesh:noexp] OR Kenya[Mesh:noexp] OR Kosovo[Mesh:noexp] OR Kyrgyzstan[Mesh:noexp] OR Laos[Mesh:noexp] OR Lesotho[Mesh:noexp] OR Liberia[Mesh:noexp] OR Madagascar[Mesh:noexp] OR Malawi[Mesh:noexp] OR Mali[Mesh:noexp] OR Mauritania[Mesh:noexp] OR Micronesia[Mesh:noexp] OR Middle East[Mesh:noexp] OR Moldova[Mesh:noexp] OR Mongolia[Mesh:noexp] OR Morocco[Mesh:noexp] OR Mozambique[Mesh:noexp] OR Myanmar[Mesh:noexp] OR Nepal[Mesh:noexp] OR Nicaragua[Mesh:noexp] OR Niger[Mesh:noexp] OR Nigeria[Mesh:noexp] OR Pakistan[Mesh:noexp] OR Papua New Guinea[Mesh:noexp] OR Philippines[Mesh:noexp] OR Russia[Mesh:noexp] OR "Russia (Pre-1917)"[Mesh:noexp] OR Rwanda[Mesh:noexp] OR "Saint Kitts and Nevis"[Mesh:noexp] OR Senegal[Mesh:noexp] OR Sierra Leone[Mesh:noexp] OR Sri Lanka[Mesh:noexp] OR Somalia[Mesh:noexp] OR Sudan[Mesh:noexp] OR Swaziland[Mesh:noexp] OR Syria[Mesh:noexp] OR Tajikistan[Mesh:noexp] OR Tanzania[Mesh:noexp] OR Togo[Mesh:noexp] OR Tunisia[Mesh:noexp] OR Uganda[Mesh:noexp] OR Ukraine[Mesh:noexp OR USSR[Mesh:noexp] OR Uzbekistan[Mesh:noexp] OR Vanuatu[Mesh:noexp] OR Vietnam[Mesh:noexp] OR Yemen[Mesh:noexp] OR Yugoslavia[Mesh:noexp] OR Zambia[Mesh:noexp] OR Zimbabwe[Mesh:noexp]
5	OR/1-4

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-020724.R1
Article Type:	Protocol
Date Submitted by the Author:	22-Feb-2018
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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Public health
Keywords:	Intervention, Prevention, Hypertension < CARDIOLOGY, Non pharmacological, Systematic review, LMICs

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

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Word Count: 2030

ABSTRACT:

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

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

Ethics and dissemination: This systematic review protocol is registered with International Prospective Register of Systematic Reviews (PROSPERO) CRD42017055423. Approval from institutional review board has been taken for this review. Findings will be summarized in a single manuscript.

This review is an attempt to explore the available non-pharmacological approaches for prevention of hypertension in LMICs. Findings from the review will highlight effective non pharmacological measures for prevention of hypertension to guide policy for future strategies.

STRENGTH AND LIMITATIONS

- This systematic review protocol follows strong methods of Cochrane systematic review.
- Only Randomized Controlled Trials (RCTs) are included in this systematic review.
- This systematic review protocol describes the assessment of risk of bias (ROB) following Cochrane guideline for assessing risk of bias and critical appraisal of included articles using the Critical Appraisal Skills Program (CASP) checklist for RCTs.
- This systematic review includes articles written only in English and thus there is possibility of missing information from articles written in other languages.

Key Words: Intervention, Prevention, Hypertension, Non pharmacological, Systematic review, LMICs

INTRODUCTION

In recent times, hypertension has become one of the major public health problems in both developed and developing world. Global prevalence of hypertension (defined as systolic and/or diastolic blood pressure equal to or above 140/90 mmHg [1]) among adults aged 18 years and over was around 22% in 2014 [2] which is projected to be increased to 29% by the year 2025 [3]. Hypertension is the cause of death due to heart disease (45%) and stroke (51%) in majority of cases [4]. Recent epidemiological transition is reflected with increased prevalence of hypertension in LMICs and a decreasing trend in the developed world [5]. In 2010, the global prevalence of adult hypertensive was 31.1%, with a prevalence of 28.5% in high-income countries and 31.5% LMICs. Between 2000 and 2010, the age-standardized 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 (DALYs) were related to systolic blood pressure in countries like China, India, Russia, Indonesia, and the United States [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 for hypertension in India was 29.8% with significant difference between rural and urban areas [9]. Similar results have been reported from population based studies in Bangladesh where age-standardized prevalence of pre-hypertension and hypertension were 27.1% and 24.4% respectively [10]. In Pakistan, the overall prevalence of hypertension was 26% among the low income community with an increased proportion among the males [11]. Increasing prevalence of hypertension leads to higher rates of morbidity and mortality directly or indirectly, which has made the phenomena an important public health issue in particularly in LMICs. Hence, it is important and justified to continue investigating interventions proven effective to prevent hypertension. There are certain dietary and life style related approaches for prevention of hypertension [12]. Specific interventions such as supplementations with increased calcium intake has been proved effective to reduce both systolic and diastolic blood pressure 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 randomized controlled trials among pre-hypertensive population to prevent high prevalence of hypertension [16].

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

METHODS:

PROTOCOL

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

ELIGIBILITY CRITERIA

Studies will be selected according to the criteria outlined below.

PARTICIPANTS

Included studies will be on normotensive (Systolic BP 120-139 mm Hg and diastolic BP 80-89 mm Hg)[20] adults of LMIC's as defined by the World Bank[21].

INTERVENTIONS

Studies assessing the effect of non pharmacological interventions for the prevention of hypertension among normotensive adult population will be considered for inclusion. Interventions will include life style 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 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 settings will be included in the review.

STUDY DESIGNS

We will include randomized controlled trials (RCTs) (including cluster RCTs) to assess the beneficial effect of interventions. Non-randomized studies including pretest-posttest 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. Intervention provided on hypertensive people, population below 18 years of age, pregnant women and people with other diseases will be excluded. We will exclude pharmacological intervention and combination of pharmacological

intervention with non pharmacological intervention. Systematic reviews, reviews, ongoing trials, trial protocols, and studies other than RCTs will be excluded. Letter, editorials and conference papers will be excluded. Articles written in language other than English will be excluded as well.

INFORMATION SOURCES

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, intervention and outcome. 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 bibliographic 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.

Table 1: Key terms used for developing 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"	"Randomized controlled trials" (RCT)

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 re-run just before the final analyses and further studies retrieved for inclusion. Comprehensive search strategy prepared for Pubmed is provided in Table 2.

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 program [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-ji [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	Randomized controlled trial [tiab] OR controlled clinical trial [tiab] OR randomized [tiab] OR placebo [tiab] OR randomization [tiab] OR randomization [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]
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 Additional file 2.

STUDY RECORDS

DATA MANAGEMENT

Reference management software EndNote will be used to organize 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 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 same study will be reported. Summaries of included and excluded studies will be demonstrated using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow-diagram[22].

DATA EXTRACTION

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

RISK OF BIAS ASSESSMENT

Two reviewers will assess the risk of bias independently following guidelines from Cochrane assessment of risk of bias for randomized controlled trials [23]. According to the guideline, 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 judgments as per guideline and make comments on whether studies are at high risk of bias. 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 participants, implementers and outcome assessors, while lost to follow up will be considered to assess attrition bias. Selective reporting and presentation of outcome will also be considered. There will be search for any other potential bias. Any disagreements between the reviewers while assessing the risk of bias 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 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 as high risk of bias, indirect and imprecise evidence will lead to downgrade the evidence by one or two level.

STRATEGY FOR DATA SYNTHESIS

A narrative synthesis of the findings from the included studies will be provided focusing the characteristics of target population, type of intervention and outcome. A summary of effect-size for individual studies will be presented by estimating risk ratios and odds ratio for dichotomous outcomes (developing hypertension) or standardized mean differences for continuous outcomes (systolic and diastolic blood pressure) respectively. Studies with the same interventions for prevention of hypertension, comparators and outcome measure, will be pooled using the random effect model meta-analysis methods with 95% confidence intervals and two-tailed *p* values will be calculated for each outcome. Standard deviations will be adjusted for the design effect where the effects of clustering have not been taken into account. Both the Chi-squared test and the I-squared statistic will be considered for measuring the heterogeneity of effect measures. I-squared 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 systematic review and no patients are directly involved in the process. The review question and outcome measures are developed for the overall betterment of people who are at risk of developing hypertension.

PUBLICATION PLAN

This systematic review protocol is registered with International Prospective Register of Systematic Reviews (PROSPERO) CRD42017055423. Findings will be summarized in a single manuscript.

TIMELINE

Review start date: 1st March 2017

Review finishing date: 28 February 2018

Reporting date: 28 February 2018

ABBREVIATIONS

BSMMU: Bangabandhu Sheikh Mujib Medical University

DALYs: Disability adjusted life years

GRADE: Grades of Recommendation, Assessment, Development and Evaluation

LMICs: Low and middle income countries

MESH: Medical subject headings

PRISMA-P: Preferred reporting items for systematic reviews and meta-analysis protocols

PROSPERO: International Prospective Register of Systematic Reviews

RCT: Randomized Controlled Trial

WHO: World Health Organization

DECLARATIONS

FUNDING

There is no external funding for this systematic review. This review has been conducted by the Systematic Review Centre (SRC) of Department of Public Health and Informatics at Bangabandhu Sheikh Mujib Medical University (BSMMU), Bangladesh which has been established with the support of SHARE (Strengthening Health Applying Research Evidence) project of icddr,b funded by the European Union (Grant Contract No DCI-SANTE/2014/342-479). icddr,b acknowledges with gratitude the commitment of European Union (EU) to its research efforts. icddr,b is also grateful to the Governments of Bangladesh, Canada, Sweden and the UK for providing core/unrestricted support.

AVAILABILITY OF DATA AND MATERIALS

The datasets generated and/or analyzed during the current review shall be available from the corresponding author on reasonable request.

AUTHORS' CONTRIBUTIONS

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

COMPETING INTERESTS

The authors declare that they have no competing interests.

ETHICS AND DISSEMINATION

Approval for conducting this systematic review has been taken from the Institutional Review Board (IRB) of Bangabandhu Sheikh Mujib Medical University (BSMMU). No additional

formal ethical assessment and no informed consent are required. Findings of the systematic review will be published in international peer reviewed journal for dissemination.

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 PROSPERO register will remain updated with the protocol and amendments.

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	12
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	13
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	12
Sponsor	5b	Provide name for the review funder and/or sponsor	12
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	12
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5-6
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6-7
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6-7
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	7-9

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9-10
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	5-6, 9-10
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	10
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	6-7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	10
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	11
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	11
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	11
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	11
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10-11
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	11

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Additional file 2: Search strategy for low and middle income countries (LMICs)

1	"developing country"[tw] OR "developing countries"[tw] OR "developing nation"[tw] OR "developing nations"[tw] OR "developing population"[tw] OR "developing populations"[tw] OR "developing world"[tw] OR "less developed country"[tw] OR "less developed countries"[tw] OR "less developed nation"[tw] OR "less developed nations"[tw] OR "less developed population"[tw] OR "less developed populations"[tw] OR "less developed world"[tw] OR "lesser developed country"[tw] OR "lesser developed countries"[tw] OR "lesser developed nation"[tw] OR "lesser developed nations"[tw] OR "lesser developed population"[tw] OR "lesser developed populations"[tw] OR "lesser developed world"[tw] OR "under developed country"[tw] OR "under developed countries"[tw] OR "under developed nation"[tw] OR "under developed nations"[tw] OR "under developed population"[tw] OR "under developed populations"[tw] OR "under developed world"[tw] OR "underdeveloped country"[tw] OR "underdeveloped countries"[tw] OR "underdeveloped nation"[tw] OR "underdeveloped nations"[tw] OR "underdeveloped population"[tw] OR "underdeveloped populations"[tw] OR "underdeveloped world"[tw] OR "middle income country"[tw] OR "middle income countries"[tw] OR "middle income nation"[tw] OR "middle income nations"[tw] OR "middle income population"[tw] OR "middle income populations"[tw] OR "low income country"[tw] OR "low income countries"[tw] OR "low income nation"[tw] OR "low income nations"[tw] OR "low income population"[tw] OR "low income populations"[tw] OR "lower income country"[tw] OR "lower income countries"[tw] OR "lower income nation"[tw] OR "lower income nations"[tw] OR "lower income population"[tw] OR "lower income populations"[tw] OR "underserved country"[tw] OR "underserved countries"[tw] OR "underserved nation"[tw] OR "underserved nations"[tw] OR "underserved population"[tw] OR "underserved populations"[tw] OR "underserved world"[tw] OR "under served country"[tw] OR "under served countries"[tw] OR "under served nation"[tw] OR "under served nations"[tw] OR "under served population"[tw] OR "under served populations"[tw] OR "under served world"[tw] OR "deprived country"[tw] OR "deprived countries"[tw] OR "deprived nation"[tw] OR "deprived nations"[tw] OR "deprived population"[tw] OR "deprived populations"[tw] OR "deprived world"[tw] OR "poor country"[tw] OR "poor countries"[tw] OR "poor nation"[tw] OR "poor nations"[tw] OR "poor population"[tw] OR "poor populations"[tw] OR "poor world"[tw] OR "poorer country"[tw]

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