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BMJ Open

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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Keywords:	Intervention, Prevention, Hypertension < CARDIOLOGY, Non pharmacological, Systematic review, LMIC

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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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2
3 **32 ABSTRACT:**
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6
7 **34 Introduction:** In current days, hypertension has become one of the major public health problems
8
9 **35** in both developed and developing world and is responsible for death due to heart diseases and
10
11 **36** stroke. Increasing trend in prevalence of hypertension in low and middle income countries and
12
13 **37** it's catastrophic consequences have made the phenomena important to continue to investigate
14
15 **38** interventions for prevention. There are different dietary and life style related approaches for
16
17 **39** prevention of hypertension. Aim of this review is to explore the available non pharmacological
18
19 **40** approaches for prevention of hypertension in low and middle income countries.

20
21 **41 Methods and analysis:** Eight electronic databases will be searched for the period between 1990
22
23 **42** and 2016 to identify relevant studies and screened by two reviewers independently. Articles will
24
25 **43** be included for full text extraction applying definitive inclusion and exclusion criteria.
26
27 **44** Appropriate critical appraisal tools including Cochrane Handbook for Systematic Reviews of
28
29 **45** Interventions. Risk of bias will be judged. Disagreement between the independent reviewers will
30
31 **46** be resolved by a third reviewer. Narrative synthesis of the findings will be provided along with
32
33 **47** summaries of intervention effect. A meta analysis will be conducted using a random effect model
34
35 **48** where applicable. Heterogeneity between the studies will be assessed and sensitivity analysis
36
37 **49** will be conducted based on study quality.

38
39 **50 Ethics and dissemination:** This systematic review protocol is registered with International
40
41 **51** Prospective Register of Systematic Reviews (PROSPERO) CRD42017055423. Approval from
42
43 **52** institutional review board has been taken for this review. Findings will be summarized in a single
44
45 **53** manuscript.

46
47 **54** This review is an attempt to explore the available non pharmacological approaches for
48
49 **55** prevention of hypertension in low and middle income countries. Findings from the review will
50
51 **56** highlight effective measures for prevention of hypertension and will guide the policy makers to
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53 **57** identify appropriate approach.
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Key Words: Intervention, Prevention, Hypertension, Non pharmacological, Systematic review, LMIC

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94 INTRODUCTION

95
96 In current days, hypertension has become one of the major public health problems in both
97 developed and developing world. According to the World Health Organization (WHO), global
98 prevalence of hypertension (defined as systolic and/or diastolic blood pressure equal to or above
99 140/90 mmHg[1]) in adults aged 18 years and over was around 22% in 2014[2]. High blood
100 pressure has been estimated to be increased to 29% by the year 2025[3]. Hypertension is the
101 leading cause of death due to heart disease (45%) and stroke (51%)[4]. Recent trend of
102 epidemiological transition is reflected with increased prevalence of hypertension in developing
103 countries whereas a decreasing tendency in the developed world[5]. In 2010, the prevalence of
104 adult hypertensive population was 31.1%, among which high-income countries were less
105 prevalent (28.5%) than in low- and middle-income countries 31.5%. Between the last decades
106 (from 2000 to 2010), the age-standardized prevalence of hypertension increased by 7.7% in low-
107 and middle-income countries and decreased by 2.6% in high-income countries[6]. In 2015, more
108 than half of the global disability adjusted life years (DALYs) were related to systolic blood
109 pressure in countries like China, India, Russia, Indonesia, and the United States[7]. A recent
110 systematic review describes that the pooled estimate of the overall prevalence of hypertension in
111 Low and Middle income countries was 32.3%[8]. Overall prevalence for hypertension in India
112 was 29.8% according to a systematic review though there was significant difference in
113 hypertension prevalence between rural and urban areas[9]. Similar results have been found in
114 Bangladeshi population based survey which shows overall age-standardized prevalence of pre-
115 hypertension and hypertension were 27.1% and 24.4% respectively[10]. In Pakistan, the overall
116 prevalence of hypertension was 26% among the low income community with an increased
117 proportion among the males[11]. Highly increasing prevalence of hypertension leads to the high
118 morbidity and mortality which has made the phenomena an important public health issue and
119 therefore, it is important to continue to investigate interventions that can prevent hypertension.
120 There are different dietary and life style related approaches for prevention of hypertension[12].
121 Specific interventions with certain supplementations like increased calcium intake has been
122 proved as effective which reduces both systolic and diastolic blood pressure in normotensive
123 people, suggesting a role in the prevention of hypertension[13]. Other than general exercise,
124 yoga[14] and tai chai[15] also successfully prevent and control hypertension which is evident.

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3 125 Even some medications have been tested as a preventive medication among prehypertensive
4 126 persons as means of prevention in randomized controlled trials [16].

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6 127 Prevention of hypertension can minimize the fatal morbid conditions and consequences of
7
8 128 cardiovascular events. Despite of different approaches, an effective preventive strategy or
9
10 129 intervention can help the public health experts and policy makers to plan properly for addressing
11
12 130 the increasing burden.

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14 131

15 132 **OBJECTIVE:**

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19 134 This review is an attempt to explore the available non pharmacological approaches including
20
21 135 lifestyle modification, exercise, dietary supplementation and restriction etc for prevention of
22
23 136 hypertension in low and middle income countries which will find the effective measures for
24
25 137 prevention of hypertension as well.

26 138

27 139 **METHODS:**

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29 140

30 31 141 **PROTOCOL**

32
33 142 This is a protocol for systematic review and meta analysis which has been developed addressing
34
35 143 the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-
36
37 144 P) guidelines for reporting systematic reviews evaluating health care interventions[17 18]. A
38
39 145 PRISMA-P checklist for this protocol is attached (Additional file 1).

40 146

41 147 **ELIGIBILITY CRITERIA**

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43 148 Studies will be selected according to the criteria outlined below.

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45 149

46 150 **PARTICIPANTS**

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48 151 Included studies will be on normotensive (Systolic BP 120-139 mm hg and diastolic BP 80-89
49
50 152 mm hg)[19] adults of low and middle income countries (LMIC's) as defined by the World
51
52 153 Bank[20].

53 154

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55 155

156 INTERVENTIONS

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158 Studies assessing the effect of nonpharmacological interventions for the prevention of
159 hypertension among normotensive adult population will be considered for inclusion.
160 Interventions will be including life style modification, dietary restriction, non pharmacological
161 diet supplementation, exercise and any combination of the above mentioned interventions.

163 COMPARATORS

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

166 OUTCOMES

167 Primary outcomes

168 Hypertension, Systolic and diastolic blood pressure

169 Secondary outcomes

170 Any adverse event; Cardiovascular events; Myocardial infarction; Stroke; Kidney stone
171 formation; Iron deficiency anaemia; mortality; Sudden death

173 SETTING

174 There will be no restrictions by type of setting such as hospital based or community setting.

176 STUDY DESIGNS

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

182 INFORMATION SOURCES

183 Following electronic bibliographic databases will be searched systematically using a
184 comprehensive search strategy. The databases are: MEDLINE through pubmed, Embase, The
185 Cochrane Library (Cochrane Central Register of Controlled Trials (CENTRAL), Web of
186 Science, Scopus, Clinical Trials. gov, EBSCO and WICTRP (International Clinical Trials

187 Registry Platform). The search strategy will include terms relating to or describing the
 188 population, intervention and outcome. The terms will be combined with the Cochrane
 189 MEDLINE filter for controlled trials of interventions.

191 SEARCH STRATEGY

192 A comprehensive search strategy will be developed for MEDLINE. The search terms will be
 193 adapted for other bibliographic databases in combination with database-specific filters for
 194 controlled trials, where these are available. Key search terms for population, intervention,
 195 comparison and outcome are as follow:

197 **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)

199
 200 Only English language literature will be searched. Studies published between January 1990 and
 201 the date the searches are run will be sought. The searches will be re-run just before the final
 202 analyses and further studies retrieved for inclusion. Comprehensive search strategy prepared for
 203 pubmed is provided in Table 2.

205 **Table 2: Search strategy: PubMed format**

1	LMIC's*
2	Exercise [MeSH Terms] OR “Physical Exercise” [tw] OR “Physical activity” [tw]

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- 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]
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- 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]
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- 7 Salt Restrict*[tiab] OR low Sodium*[tiab] OR low salt*[tiab] OR Potassium, Diet* [tw]
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- 8 Magnesium [tw] OR Calcium [tw]
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- 9 “Salt intake” [tw] OR Sodium Chloride, Dietary [MeSH Term] OR “Dietary salt” [tw] OR “Dietary Salt intake” [tw] OR “Dietary Salt restriction” [tw]
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- 10 Garlic [MeSH Terms] OR Garlic [tw]
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- 11 Smoking Cessation [MeSH Term] OR “Smoking Cessation” [tw] OR Tobacco Use Cessation*[tw]
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- 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])
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- 13 Alcohol Drink*[tw] OR Alcohol consum*[tw] OR Drinking Alcohol*[tw] OR Alcoholi*[tw] OR non pharmacol*[tw]
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- 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]
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- 17 **OR/ 2-16**
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- 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] OR "Hypertension/drug therapy"[Majr] OR "Hypertension/epidemiology"[Majr] OR "Hypertension/etiology"[Majr] OR "Hypertension/genetics"[Majr] OR "Hypertension/metabolism"[Majr] OR "Hypertension/mortality"[Majr]
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- 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**
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- 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]
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- 22 **#1 AND #17 AND #20 AND #21**
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- 23 animals [mh] NOT humans [mh]
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- 24 **#22 NOT #23**
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- 25 Restrict #24 to year=1990 and up to date
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- 26 Restrict #25 to English language
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- 27 Restrict #26 to Age 18+ years
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207 Search terms and search strategy for LMICs are provided in Additional file 2.

208

209 STUDY RECORDS

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211 DATA MANAGEMENT

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

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

219

220 **SELECTION PROCESS**

221 Screening of title and abstract of retrieved articles will be conducted by two reviewers
222 independently to identify the included studies. The screening of retrieved outcome of
223 comprehensive search strategy will be done using the EPPI reviewer software. After inclusion
224 for full text review, eligible studies will be assessed independently for final inclusion. Any
225 disagreement between reviewers over the decision of inclusion will be resolved through
226 discussion with a third reviewer. Reasons for exclusion will be recorded. We will report multiple
227 publications from the same study. Summary of included and excluded studies will be
228 demonstrated using the Preferred Reporting Items for Systematic Reviews and Meta-analyses
229 (PRISMA) flow-diagram[21].

230

231 **DATA EXTRACTION**

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

238

239 **RISK OF BIAS ASSESSMENT**

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

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

252

253 **ASSESSMENT OF THE BODY OF EVIDENCE—THE GRADE APPROACH**

254 We will use the Grades of Recommendation, Assessment, Development and Evaluation
255 (GRADE) approach for assessment of quality of evidence[23] which focuses on five domains
256 including study limitations, imprecision, indirectness, effect consistency and publication bias.
257 Considering these domains, the quality of the body of evidence will be assessed for specific
258 outcomes. Assessing as high risk of bias, indirect and imprecise evidence will lead to downgrade
259 the evidence by one or two level.

260

261 **STRATEGY FOR DATA SYNTHESIS**

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

274

275 **STRENGTH**

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

279

280 **LIMITATIONS**

- 1
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3 281 • Includes articles written in English only
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5 282

6
7 283 **PUBLICATION PLAN**

8 284 This systematic review protocol is registered with International Prospective Register of
9 Systematic Reviews (PROSPERO) CRD42017055423. Findings will be summarized in a single
10 285 manuscript.
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15 288 **TIMELINE**

16
17 289 Review start date: 1st March 2017
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19 290 Review finishing date: 28 February 2018
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21 291 Reporting date: 28 February 2018
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24 293 **ABBREVIATIONS**

25 294 BSMMU: Bangabandhu sheikh mujib medical university
26
27 295 DALYs: Disability adjusted life years
28
29 296 GRADE: Grades of Recommendation, Assessment, Development and Evaluation
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31 297 LMICs: Low and middle income countries
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33 298 MESH: Medical subject headings
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35 299 PRISMA-P: Preferred reporting items for systematic reviews and meta-analysis protocols
36 300 PROSPERO: International prospective register of systematic reviews
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38 301 RCT: Randomized controlled trial WHO: World health organization
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41 303 **DECLARATIONS**

42 304

43
44
45 305 **FUNDING**

46 306 This review has been conducted by the Systematic Review Centre (SRC) of Department of
47 Public Health and Informatics at Bangabandhu Sheikh Mujib Medical University (BSMMU),
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3 311 icddr,b is also grateful to the Governments of Bangladesh, Canada, Sweden and the UK for
4 312 providing core/unrestricted support.
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8 314 **AVAILABILITY OF DATA AND MATERIALS**

9
10 315 The datasets generated and/or analyzed during the current review shall be available from the
11 316 corresponding author on reasonable request.
12
13
14 317

15 318 **AUTHORS' CONTRIBUTIONS**

16
17 319 IA, SI, SH, SR and MH conceptualized the review in consultation with the co-reviewers. SR
18 320 wrote the first draft of this protocol with substantial inputs from all authors. SR and MH will
19 321 contribute to the literature search. Screening, collection and analysis of data for all the included
20 322 interventions will be conducted by SR and MH with close consultation from SH, SS, SI, AR,
21 323 MK, FH and IA. All authors will provide input, review and finalize the paper before
22 324 dissemination. The corresponding author is the guarantor of this review. All authors read and
23 325 approved the final manuscript.
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27
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29 326

30 327 **COMPETING INTERESTS**

31 328 The authors declare that they have no competing interests.
32
33
34 329

35 330 **ETHICS APPROVAL AND CONSENT TO PARTICIPATE**

36 331 Approval for conducting this systematic review has been taken from the Institutional Review
37 332 Board (IRB) of Bangabandhu Sheikh Mujib Medical University (BSMMU). No additional
38 333 formal ethical assessment and no informed consent are required.
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44 335 45 336 **AMENDMENTS**

46 337 Any updates or amendments to this protocol will be described in a table including the date of
47 338 each amendment, description of the change and rationale for the change. The PROSPERO
48 339 register will remain updated with the protocol and amendments.
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For peer review only

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

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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	<p>"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]</p>
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BMJ Open

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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Manuscripts

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

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3 **32 ABSTRACT:**
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7 **34 Introduction:** In recent times, hypertension has become one of the major public health problems
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9 **35** in both developed and developing world and is responsible for death due to heart diseases and
10 **36** stroke. Increasing trend in prevalence of hypertension in low and middle income countries
11 **37** (LMICs) and it's catastrophic consequences have made the phenomena important to continue to
12 **38** investigate interventions for prevention and control. Different dietary and life style related
13 **39** approaches have been recommended for prevention of hypertension. Aim of this proposed
14 **40** review is to explore the available non pharmacological interventions tried for prevention of
15 **41** hypertension in LMICs.

16 **42 Methods and analysis:** Eight electronic databases will be searched covering period between
17 **43** 1990 and 2016 to identify relevant studies and screened by two independent reviewers. Searched
18 **44** articles will be included for full text extraction applying definitive inclusion and exclusion
19 **45** criteria. Appropriate critical appraisal tools including Cochrane Handbook for Systematic
20 **46** Reviews of Interventions will be used to assess the risk of bias. Disagreement between two
21 **47** reviewers will be resolved by a third reviewer. Narrative synthesis of the findings will be
22 **48** provided along with summaries of intervention effect. A meta-analysis will be undertaken using
23 **49** the random-effect model where applicable. Heterogeneity between the studies will be assessed,
24 **50** and sensitivity analysis will be conducted based on study quality.

25 **51 Ethics and dissemination:** This systematic review protocol is registered with International
26 **52** Prospective Register of Systematic Reviews (PROSPERO) CRD42017055423. Approval from
27 **53** institutional review board has been taken for this review. Findings will be summarized in a single
28 **54** manuscript.

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63 STRENGTH AND LIMITATIONS

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

71
72 **Key Words:** Intervention, Prevention, Hypertension, Non pharmacological, Systematic review,
73 LMICs

94 INTRODUCTION

95
96 In recent times, hypertension has become one of the major public health problems in both
97 developed and developing world. Global prevalence of hypertension (defined as systolic and/or
98 diastolic blood pressure equal to or above 140/90 mmHg [1]) among adults aged 18 years and
99 over was around 22% in 2014 [2] which is projected to be increased to 29% by the year 2025 [3].
100 Hypertension is the cause of death due to heart disease (45%) and stroke (51%) in majority of
101 cases [4]. Recent epidemiological transition is reflected with increased prevalence of
102 hypertension in LMICs and a decreasing trend in the developed world [5]. In 2010, the global
103 prevalence of adult hypertensive was 31.1%, with a prevalence of 28.5% in high-income
104 countries and 31.5% LMICs. Between 2000 and 2010, the age-standardized prevalence of
105 hypertension increased by 7.7% in LMICs and decreased by 2.6% in high income countries[6].
106 In 2015, more than half of the global disability adjusted life years (DALYs) were related to
107 systolic blood pressure in countries like China, India, Russia, Indonesia, and the United States
108 [7]. A recent systematic review describes that the pooled estimate of the overall prevalence of
109 hypertension in LMICs was 32.3% [8]. One systematic review depicts that overall prevalence for
110 hypertension in India was 29.8% with significant difference between rural and urban areas [9].
111 Similar results have been reported from population based studies in Bangladesh where age-
112 standardized prevalence of pre-hypertension and hypertension were 27.1% and 24.4%
113 respectively [10]. In Pakistan, the overall prevalence of hypertension was 26% among the low
114 income community with an increased proportion among the males [11]. Increasing prevalence of
115 hypertension leads to higher rates of morbidity and mortality directly or indirectly, which has
116 made the phenomena an important public health issue in particularly in LMICs. Hence, it is
117 important and justified to continue investigating interventions proven effective to prevent
118 hypertension. There are certain dietary and life style related approaches for prevention of
119 hypertension [12]. Specific interventions such as supplementations with increased calcium intake
120 has been proved effective to reduce both systolic and diastolic blood pressure in normotensive
121 people, suggesting a role in the prevention of hypertension [13]. Other than general exercise,
122 *yoga* [14] and *tai chai* [15] could also successfully prevent hypertension. Some medications have
123 also been tested through randomized controlled trials among pre-hypertensive population to
124 prevent high prevalence of hypertension [16].

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3 125 Prevention of hypertension can minimize the fatal morbid conditions and consequences of
4 126 cardiovascular events. Changes in life style variables, along with other non-pharmacological
5 127 interventions may play an important role to halt increasing trend in the prevalence of
6 128 hypertension in LMICs where there is a scarcity of programs for prevention and control of high
7 129 blood pressure [17]. Prevention of onset of hypertension with such intervention is evident and
8 130 will contribute to reduce the premature mortality and disability related to hypertension in this
9 131 region. Despite different therapeutic approaches, an effective preventive strategy can help policy
10 132 makers to formulate specific context-specific strategies for prevention and control of the
11 133 increasing burden of hypertension in LMICs.
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20 135 **OBJECTIVE:**

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24 137 This review is an attempt to explore the available non pharmacological approaches including
25 138 lifestyle modification, exercise, dietary supplementation and restriction etc for prevention of
26 139 hypertension in LMICs to inform policy for effective measures for prevention of hypertension.
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31 141 **METHODS:**

32 142 33 143 **PROTOCOL**

34 144 This is a protocol for systematic review and meta analysis which has been developed addressing
35 145 the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-
36 146 P) guidelines for reporting systematic reviews evaluating health care interventions[18 19]. A
37 147 PRISMA-P checklist for this protocol is attached (Additional file 1).
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44 149 **ELIGIBILITY CRITERIA**

45 150 Studies will be selected according to the criteria outlined below.
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50 152 **PARTICIPANTS**

51 153 Included studies will be on normotensive (Systolic BP 120-139 mm Hg and diastolic BP 80-89
52 154 mm Hg)[20] adults of LMIC's as defined by the World Bank[21].
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3 156
4 157 **INTERVENTIONS**
5 158

7 159 Studies assessing the effect of non pharmacological interventions for the prevention of
8
9 160 hypertension among normotensive adult population will be considered for inclusion.
10
11 161 Interventions will include life style modification, dietary restriction, non pharmacological diet
12 162 supplementation, exercise and any combination of the above mentioned interventions.
13

14 163
15
16 164 **COMPARATORS**

17 165 A comparison will be made with non pharmacological interventions versus no intervention.
18
19 166

20
21 167 **OUTCOMES**

22
23 168 Primary outcomes

24 169 Hypertension, Systolic and diastolic blood pressure

25
26 170 Secondary outcomes

27
28 171 Any adverse event; Cardiovascular events; Myocardial infarction; Stroke; Kidney stone
29 172 formation; Iron deficiency anaemia; mortality; Sudden death

30
31 173
32
33 174 **SETTING**

34
35 175 There will be no restrictions by study-setting such as, hospital or community. Any non
36 176 pharmacological intervention for hypertension in any settings will be included in the review.
37

38 177
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40 178 **STUDY DESIGNS**

41 179 We will include randomized controlled trials (RCTs) (including cluster RCTs) to assess the
42 180 beneficial effect of interventions. Non-randomized studies including pretest-posttest controlled
43 181 studies, prospective comparative cohort studies, case-control studies and cross-sectional studies
44 182 will be excluded.
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50 184 **EXCLUSION CRITERIA**

51
52 185 Studies conducted outside LMICs will be excluded. Intervention provided on hypertensive
53 186 people, population below 18 years of age, pregnant women and people with other diseases will
54 187 be excluded. We will exclude pharmacological intervention and combination of pharmacological
55
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188 intervention with non pharmacological intervention. Systematic reviews, reviews, ongoing trials,
 189 trial protocols, and studies other than RCTs will be excluded. Letter, editorials and conference
 190 papers will be excluded. Articles written in language other than English will be excluded as well.

191

192 INFORMATION SOURCES

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

200

201 SEARCH STRATEGY

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

206

207 **Table 1: Key terms used for developing comprehensive search strategy**

208

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)

209
210 Only English language literature will be searched. Studies published between January 1990 and
211 the date the searches are run will be sought. The searches will be re-run just before the final
212 analyses and further studies retrieved for inclusion. Comprehensive search strategy prepared for
213 Pubmed is provided in Table 2.

214

215 **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
 19 "Hypertension/diet therapy"[Majr] OR "Hypertension/drug effects"[Majr] OR "Blood
 20 Pressure/classification"[Mesh] OR "Blood Pressure/complications"[Mesh] OR "Blood
 21 Pressure/diagnosis"[Mesh] OR "Blood Pressure/drug effects"[Mesh] OR "Blood
 22 Pressure/etiology"[Mesh] OR "Blood Pressure/genetics"[Mesh] OR "Blood
 23 Pressure/metabolism"[Mesh] OR "Blood Pressure/methods"[Mesh] OR "Blood
 24 Pressure/statistics and numerical data"[Mesh] OR "Blood Pressure/therapy"[Mesh]
 25 "Hypertension/drug therapy"[Majr] OR "Hypertension/epidemiology"[Majr] OR
 26 "Hypertension/etiology"[Majr] OR "Hypertension/genetics"[Majr] OR
 27 "Hypertension/metabolism"[Majr] OR "Hypertension/mortality"[Majr]

 19 "Hypertension/prevention and control"[Majr] OR "Hypertension/rehabilitation"[Majr] OR
 20 "Hypertension/therapy"[Majr] OR "Blood Pressure/classification"[Mesh] OR "Blood
 21 Pressure/complications"[Mesh] OR "Blood Pressure/diagnosis"[Mesh] OR "Blood
 22 Pressure/drug effects"[Mesh] OR "high blood pressure" [tw] OR "Blood pressure" [tw] OR
 23 bloodpressure [tw] OR ("Systole/drug effects"[Majr] OR "Systole/etiology"[Majr] OR
 24 "Systole/genetics"[Majr]) OR "Blood Pressure/etiology"[Mesh] OR "Blood
 25 Pressure/genetics"[Mesh] OR "Blood Pressure/metabolism"[Mesh] OR "Blood
 26 Pressure/methods"[Mesh] OR "Blood Pressure/statistics and numerical data"[Mesh] OR
 27 "Blood Pressure/therapy"[Mesh] OR "high blood pressure" [tw] OR "Blood pressure" [tw]
 28 OR bloodpressure [tw] OR ("Systole/drug effects"[Majr] OR "Systole/etiology"[Majr] OR
 29 "Systole/genetics"[Majr]) OR ("Diastole/drug effects"[Mesh] OR "Diastole/etiology"[Mesh]
 30 OR "Diastole/genetics"[Mesh]) OR ((arterial OR diastolic OR systolic) AND pressure) OR
 31 Hypertension [tw] OR "Blood Pressure" [tw]

 20 **OR/18-19**

 21 Randomized controlled trial [tiab] OR controlled clinical trial [tiab] OR randomized [tiab] OR
 22 placebo [tiab] OR randomization [tiab] OR randomization [tiab] OR drug therapy [tiab] OR
 23 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

216

217 Search terms and search strategy for LMICs are provided in Additional file 2.

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222 STUDY RECORDS

223

224 DATA MANAGEMENT

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

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

232

233 SELECTION PROCESS

234 Screening of title and abstract of retrieved articles will be conducted by two reviewers
235 independently to identify studies eligible for inclusion. The screening will be done using the
236 EPPI reviewer software. After inclusion for full text review, eligible studies will be assessed
237 independently for final inclusion. Any disagreement between reviewers over the decision of
238 inclusion will be resolved through discussion with a third reviewer. Reasons for exclusion will
239 be recorded. Multiple publications from same study will be reported. Summaries of included and
240 excluded studies will be demonstrated using the Preferred Reporting Items for Systematic
241 Reviews and Meta-analyses (PRISMA) flow-diagram[22].

242

243 DATA EXTRACTION

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

249

250 RISK OF BIAS ASSESSMENT

251 Two reviewers will assess the risk of bias independently following guidelines from Cochrane
252 assessment of risk of bias for randomized controlled trials [23]. According to the guideline, six

1
2
3 253 specific domains of bias are considered including selection bias, performance bias, detection
4 254 bias, attrition bias, reporting bias and other bias. Reviewers will provide their judgments as per
5 255 guideline and make comments on whether studies are at high risk of bias. For assessing selection
6 256 bias, ‘allocation concealment’ and ‘random sequence generation’ will be considered.
7
8 257 Performance and detection bias will be explored through assessment of blinding at the level of
9 258 participants, implementers and outcome assessors, while lost to follow up will be considered to
10 259 assess attrition bias. Selective reporting and presentation of outcome will also be considered.
11 260 There will be search for any other potential bias. Any disagreements between the reviewers
12 261 while assessing the risk of bias will be resolved by discussion and if necessary, a third reviewer
13 262 will opine to make a consensus.
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264 **ASSESSMENT OF THE BODY OF EVIDENCE—THE GRADE APPROACH**

265 We will use the ‘Grades of Recommendation, Assessment, Development and Evaluation
266 (GRADE)’ approach for assessing the quality of evidence [24] which focuses on five domains
267 including study limitations, imprecision, indirectness, effect consistency and publication bias.
268 Considering these domains, the quality of the body of evidence will be assessed for specific
269 outcomes. Assessing as high risk of bias, indirect and imprecise evidence will lead to downgrade
270 the evidence by one or two level.
271

271

272 **STRATEGY FOR DATA SYNTHESIS**

273 A narrative synthesis of the findings from the included studies will be provided focusing the
274 characteristics of target population, type of intervention and outcome. A summary of effect-size
275 for individual studies will be presented by estimating risk ratios and odds ratio for dichotomous
276 outcomes (developing hypertension) or standardized mean differences for continuous outcomes
277 (systolic and diastolic blood pressure) respectively. Studies with the same interventions for
278 prevention of hypertension, comparators and outcome measure, will be pooled using the random
279 effect model meta-analysis methods with 95% confidence intervals and two-tailed *p* values will
280 be calculated for each outcome. Standard deviations will be adjusted for the design effect where
281 the effects of clustering have not been taken into account. Both the Chi-squared test and the I-
282 squared statistic will be considered for measuring the heterogeneity of effect measures. I-squared
283 value greater than 50% will be indicative of substantial heterogeneity. We will conduct

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3 284 sensitivity analyses based on study quality where applicable. Potential publication bias will also
4
5 285 be assessed for individual studies through generating a funnel plot using review manager
6
7 286 software (RevMan).
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10 288 **PATIENT AND PUBLIC INVOLVEMENT**

11 289 This is a protocol for systematic review and no patients are directly involved in the process. The
12
13 290 review question and outcome measures are developed for the overall betterment of people who
14
15 291 are at risk of developing hypertension.
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17 292

18 293 **PUBLICATION PLAN**

19 294 This systematic review protocol is registered with International Prospective Register of
20
21 295 Systematic Reviews (PROSPERO) CRD42017055423. Findings will be summarized in a single
22
23 296 manuscript.
24
25 297

26 298 **TIMELINE**

27 299 Review start date: 1st March 2017
28
29 300 Review finishing date: 28 February 2018
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31 301 Reporting date: 28 February 2018
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33 302

34 303 **ABBREVIATIONS**

35
36 304 BSMMU: Bangabandhu Sheikh Mujib Medical University
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38 305 DALYs: Disability adjusted life years
39
40 306 GRADE: Grades of Recommendation, Assessment, Development and Evaluation
41
42 307 LMICs: Low and middle income countries
43
44 308 MESH: Medical subject headings
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46 309 PRISMA-P: Preferred reporting items for systematic reviews and meta-analysis protocols
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48 310 PROSPERO: International Prospective Register of Systematic Reviews
49
50 311 RCT: Randomized Controlled Trial
51
52 312 WHO: World Health Organization
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315 **DECLARATIONS**

316

317 **FUNDING**

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

326

327 **AVAILABILITY OF DATA AND MATERIALS**

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

330

331 **AUTHORS' CONTRIBUTIONS**

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

339

340 **COMPETING INTERESTS**

341 The authors declare that they have no competing interests.

342

343 **ETHICS AND DISSEMINATION**

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

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

348

349

350 **AMENDMENTS**

351 Any updates or amendments to this protocol will be described in a table including the date of
352 each amendment, description of the change and rationale for the change. The PROSPERO
353 register will remain updated with the protocol and amendments.

354

355

356 Reference

357

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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	<p>"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]</p>
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	<p>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]</p>
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3	<p>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 Moldova[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[tw] OR 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 Tadzhiakistan[tw] OR Tadjikistan[tw] OR Tadzhi[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]</p>
4	<p>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</p>

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5	OR/1-4