ABSTRACT

Introduction: The objective of this systematic review is to investigate the effectiveness, efficacy and safety of multiple concomitant lifestyle modification therapies for patients with hypertension or prehypertension.

Methods and analysis: Electronic searches will be performed in the Cochrane Library, OVID, EMBASE, etc., along with manual searches in the reference lists of relevant papers found during electronic search. We will identify eligible randomised controlled trials utilising multiple lifestyle modifications to lower blood pressure. The control could be drug therapy, single lifestyle change or no intervention. Changes in systolic blood pressure and diastolic blood pressure constitute primary end points, and secondary end points include the number of patients meeting the office target blood pressure, the number of patients reporting microvascular or macrovascular complications, etc. We will extract descriptive, methodological and efficacy data from identified randomised controlled trials (RCTs). We will calculate the relative risk for proportion of patients with a normal blood pressure in the experimental group. Dichotomous data will be analysed using risk difference and continuous data using weighted mean difference, both with 95% CI. We will use the $\chi^2$ test and the $I^2$ statistic to assess heterogeneity. We will use the fixed effects model to compute the efficacy unless there is evidence of heterogeneity. If heterogeneity of effect size persists with respect to blood pressure change, further metaregression will be performed within groups. We will examine the potential for publication bias by using a funnel plot.

Dissemination: We will synthesise results from RCTs which provide more precise and accurate information on the effect of multiple lifestyle changes on blood pressure. The results of this review will increase the understanding of multiple lifestyle modifications for patients with hypertension or prehypertension.

Trail registration number: Our protocol is registered on PROSPERO (CRD42013006476), http://www.crd.your.ac.uk/PROSPERO.

Strengths and limitations of this study

- To the best of our knowledge, this is the first systematic review to investigate the effectiveness, efficacy and safety of multiple lifestyle changes for patients with hypertension.
- The results of this systematic review can provide clinicians with useful clinical information to guide their patient care and increase the understanding of lifestyle modifications, as well as motivate patients with hypertension to adopt and maintain multiple lifestyle changes.
- The limitation of this systematic review is that it may be difficult to retrieve all the multiple lifestyle modifications for patients with hypertension. We will cooperate with the experienced medical librarian to design an appropriate search strategy, in order to ensure a broad search.

BACKGROUND

Essential hypertension continues to be an important public health challenge worldwide.\(^1\) Hypertension (7%) is the leading cause of death followed by stroke (16.6%) and heart failure (7.3%).\(^2\) It is an independent risk factor affecting the development of cardiovascular disease (myocardial infarction, heart failure and stroke), chronic kidney disease and peripheral vascular disease.\(^3\) Hypertension affects 29.3% of the adult population in the USA.\(^4\) It affects almost 18.8% of the Chinese population according to the fourth National Nutrition and Health Survey in 2002.\(^5\) The Joint National Committee (JNC)-7 created a new category of hypertension, ‘prehypertension’,\(^6\) which is defined as systolic blood pressure (SBP) of 120–139 mm Hg or diastolic blood pressure (DBP) of 80–89 mm Hg. Patients in this category are at increased risk for progression to hypertension. Numerous studies emerged
later to investigate the risk of prehypertension for various types of adverse outcomes, including stroke, coronary heart disease and cardiovascular disease (CVD), and all-cause mortality.6–9 From 2005 to 2006, approximately three of eight adults in the USA had blood pressure in the prehypertensive range of 120–139/80–89 mm Hg and roughly one in eight adults had blood pressure in the range of 130–139/85–89 mm Hg.10 Furthermore, the number of patients with hypertension and prehypertension patients is still increasing. Although hypertension and prehypertension affects a large portion of the population, recognition and adequate treatment are less than ideal.11 Despite the availability of multiple effective antihypertensive drugs, hypertension control rates remain poor. Hypertension expenditures represent a significant amount of healthcare resource use.12 The total annual medical expenditures attributed to hypertension including comorbidities are estimated to range from US$108 to US$110 billion.13 As we all known, some antihypertensive drugs may cause side effects such as dizziness, headache, fatigue, chest discomfort, cough and sexual dysfunction, prompting some patients to discontinue therapy. Therefore, there is an urgent need to develop and implement non-pharmacological methods (such as salt reduction, weight loss and exercise) to improve prevention and treatment of this major cause of death. As a modifiable risk factor, treatment of prehypertension and hypertension through lifestyle changes is a vital approach.14 Lifestyle interventions have a profound impact on the national economic impact of hypertension.12 The JNC-815 and 2013 ESH/ESC16 guidelines and the results of trials17–20 on lifestyle modification for hypertension recommended that lifestyle modification is capable of lowering the blood pressure. However, little is known about the efficacy of programmes that intervene on multiple lifestyle factors to maximise the blood pressure lowering effect. Evidence regarding the magnitude of multiple lifestyle modification-related reductions in blood pressure is inconsistent. Also, the benefits of multiple lifestyle changes have not been carefully examined. We raised the following questions: (1) Is a multiple concomitant lifestyle modification therapy effective for patients with hypertension or prehypertension? (2) If so, what is the magnitude of multiple lifestyle modification-related reductions on blood pressure? We will pool results from randomised control trials to provide more precise and accurate information on the effect of multiple lifestyle changes on blood pressure.

METHOD AND DESIGN
Criteria for considering studies for this review
Type of studies
The review will include randomised controlled trials published in the English language only. Completed or ongoing trials will be included in this review, as well as trials using only the parallel design.

Participant characteristics
Participants to be included are adult participants (≥18 years of age) presenting with prehypertension (SBP: 120–139 mm Hg; DBP 80–89 mm Hg) or essential hypertension (SBP ≥140 mm Hg; DBP ≥90 mm Hg), according to the JNC guideline.5 Restrictions will not be placed on the gender or ethnic background of participants.

Intervention characteristics
Studies utilising multiple lifestyle modifications (a combination of at least two of the following methods: weight loss,21 DASH diet,22–25 dietary sodium reduction,26 physical activity,27 moderation of alcohol consumption) will be reviewed. We include multiple lifestyle modifications consisting of at least dietary pattern changes (including sodium reduction) and physical activity. We also allow cointerventions if they are applied in all arms (including antihypertensive drugs, self-monitoring). The lifestyle modification should last for at least 4 weeks, and the follow-up phase should be at least 4 weeks. And how did the patients implement the lifestyle changing must be specified in the original article. However, studies using nurse, physician or pharmacologist counselling (face-to-face, group counselling, etc), and computer or telephone monitoring will be excluded.

Control arm characteristics
Studies utilising any type of non-pharmacological treatment, single lifestyle change, waiting list, no intervention or any type of antihypertensive drugs as a control arm will be included.

We will include the following controls:
1. Multiple lifestyle modifications+antihypertensive drugs versus antihypertensive drugs;
2. Multiple lifestyle modifications versus waiting list control or no intervention;
3. Multiple lifestyle modifications versus sham control (irrelevant lifestyle modification for hypertension);
4. Multiple lifestyle modifications versus single lifestyle modification.

Outcome measures
The primary outcomes of this systematic review are the changes of SBP and DBP between baseline and after treatment. The secondary outcomes including (1) the number of patients meeting the office target blood pressure; (2) the number of patients reporting microvascular complications (retinopathy, neuropathy, nephropathy); (3) the number of patients with macrovascular complications (cardiovascular disease, stroke/transient ischaemic attack, myocardial infarction, peripheral vascular disease); (4) All cause mortality, cardiovascular mortality, cerebrovascular mortality.

The whole process of this systematic review is presented in figure 1.
**Database and search**

We will identify relevant randomised controlled trials, only in the English language, by a systematic search of EMBASE, MEDLINE, AMED, the Cochrane library, CINAHL, ISI Web of Knowledge and the Cochrane Central Registry of Controlled Trials. An experienced medical librarian designed terms (see Table 1) to retrieve trials enrolling participants with prehypertension or hypertension managed with multiple lifestyle modifications. Reviewers will scan all the retrieved trials and other relevant articles. We will review the reference list of previously published articles for possible candidates. We also searched for ongoing trials from mainstream registries, such as the metaRegister of Controlled Trials, ClinicalTrials.gov trials registry, the Australian New Zealand Clinical Trials Registry, etc.

**Studies selection**

Two experienced reviewers (JL and JC) will independently screen the titles and abstracts of identified citations for potential eligible trials and exclude the duplicates. Then they will apply eligibility criteria to the full text of potentially eligible trials. If the reviewers (HZ and JL) cannot clearly screen the trials according to the titles and abstracts, the other two reviewers (JC and CL) will screen the full copies of these studies. Conflicts will be resolved by team discussion. If disagreements persist, a third reviewer (F-RL) will be consulted.

**Data extraction**

Data concerning patient characteristics (age, gender, BMI, etc), study characteristics (interventions, control arms, length of intervention, length of follow-up and so on), type of blood pressure monitoring (office, home, ambulatory), co-intervention and outcome (SBP, DBP, cardiovascular events, etc) were extracted independently by two reviewers (HZ and JL) using a standardised extraction form. If data are missing from published reports, we will contact the authors of the included trials for further information. Disagreements will be resolved by team discussion. FRL will review the data to ensure no input data errors.

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**Table 1** Search strategy used in the OVID MEDLINE database

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<tr>
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Figure 1 The flow chart of the systematic review.


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Risk of bias assessment

Two reviewers will assess the risk of bias independently using the Cochrane risk of bias tool. The following items will be assessed (http://www.cochrane-handbook.org): random sequence generation (selection bias); allocation concealment (selection bias); blinding (performance bias and detection bias); incomplete outcome data (attrition bias); selective outcome reporting (reporting bias). The risk of bias is categorised as a low/unclear/high risk of bias. Trials which meet none of the criteria will be judged as having a high risk of bias, whereas trials which meet none of the criteria will be judged as having a high risk of bias and trials with insufficient information to judge will be classified as an unclear risk of bias. Disagreement between the reviewers over the risk of bias in specific studies will be resolved by discussion and consensus, with the involvement of a third review author (FRL) where necessary.

Strategy for data synthesis

Weight mean differences will be calculated for the overall mean change from baseline of SBP and DBP (using office, casual or ambulatory blood pressure measurements) for experimental and control groups. When the proportion of responders (participants who report a BP lower than 140/90 mm Hg after treatment) is the proportion of responders (participants who report a BP lower than 140/90 mm Hg after treatment) is reported, we will calculate the relative risk using the control group as a reference.

We will assess heterogeneity using the Higgins I² statistics; an I²>50% will be considered as heterogeneity existing among studies. In that case, we will first use metaregression to find out the source of heterogeneity (age, gender, interventions, outcome measurements, etc) and then use subgroup analysis. If the problem remains, we will use the random effect model and explain the results with caution. A fixed effect model will be used when there is no evidence of heterogeneity.

We will examine the potential for publication bias by using a funnel plot. If the data are not appropriate to perform a meta-analysis, we will just do a narrative synthesis.

Analyses will be performed with R project 3.02 (http://www.r-project.org). If the required data are not reported, we will request data from the corresponding author. However, if the missing data are out of reach, we will exclude such studies and synthesise the data from the rest of the included studies.

Analysis of subgroups or subset

To investigate the potential heterogeneity across studies, we will conduct subgroup analysis based on the different combinations of lifestyles, classification of blood pressure (prehypertension, mild hypertension, moderate hypertension, severe hypertension) and quality of evidence. Random effects metaregression models will be used to quantify the difference between subgroups and to test for statistical significant interactions among subgroups.

Sensitivity analysis

We will conduct sensitivity analysis to assess the effects of individual studies on the combined estimates and determine whether certain studies dominate the pooled event (particularly if these studies were at a high risk of bias). If certain studies have borderline eligibility status for any reason, analysis will be conducted with and without such studies.

DISCUSSION

Many existing systematic reviews focus on the effect of a single lifestyle modification on blood pressure. Although the single lifestyle modification has been shown to lower elevated blood pressure, it is currently not known whether their combined use produces an additive antihypertensive effect. Of the various lifestyle interventions, physical activity and dietary intervention have been shown to diminish the blood pressure and reduce CVD events, which have emerged as the two most effective and physiologically desirable approaches. That is why we defined that the multiple lifestyle changes should at least include physical activity and dietary intervention.

This is first systematic review that attempts to investigate the effectiveness of multiple lifestyle changes simultaneously. The aim of this systematic review is to synthesise the available evidence of effectiveness of multiple lifestyle interventions in the treatment of prehypertension and hypertension. The systematic review also intends to help clinicians to make decisions on the clinical applicability of multiple lifestyle modifications; at the same time, the results of this review will increase the understanding of multiple lifestyle changes for patients with prehypertension and hypertension; encourage and motivate patients with prehypertension or hypertension to adopt and maintain multiple lifestyle changes in their daily home life so as to improve hypertension outcomes.

However, we will select the trials which implemented the multiple lifestyle interventions for at least 4 weeks. The multiple lifestyle interventions have to be sustained for a time to achieve the effect of lowering the blood pressure. Trials employing lifestyle modification therapies usually intervene for more than 4 weeks.

The reason why we excluded trials utilising counseling or monitoring was that both of them had been reported to achieve antihypertensive effects. No matter counselling or monitoring, lots of manpower, material resources and financial resources have to be invested. Moreover, we excluded such trials so as to investigate the genuine effects of multiple lifestyle modifications.

This systematic review will provide a general view and evidence of the effects of multiple lifestyle changes on blood pressure. The results of this systematic review will also provide clinicians with useful information to guide their patient care. The finding of the systematic review will be disseminated through publication in a peer-
reviewed journal; reporting of the systematic review will follow recommendations described in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and the Cochrane Handbook for Intervention Reviews, and will be formatted according to the specific journal publication guideline.

**Author affiliations**
1. Chengdu University of Traditional Chinese Medicine, Chengdu, Sichuan, People’s Republic of China
2. Third Affiliated Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu, Sichuan, People’s Republic of China
3. Fujian University of Traditional Chinese Medicine, Fuzhou, Fujian, People’s Republic of China
4. Chengdu Medical College, Chengdu, Sichuan, People’s Republic of China
5. First Affiliated Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu, Sichuan, People’s Republic of China

**Acknowledgements** The author would like to thank Wen-xiang Zeng for his assistance in the development of the search strategies for this protocol.

**Contributors** HZ and JL conceptualised the study and prepared the draft of the research proposal. H-BD, XL, JC, X-PT, Y-JJ, F-RL, S-LZ, YK, CL and Z-HL assisted with the manuscript preparation. All authors have read and approved the final manuscript.

**Funding** This trial was supported financially by the National Basic Research Program of China’973 Program’ (No. 2012CB518501).

**Patient consent** Obtained.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data sharing statement** The additional unpublished data are still being extracted by JL and HZ and will be published later.

**Competing interests** None.

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**REFERENCES**