

# BMJ Open Impact of different dietary approaches on blood pressure in hypertensive and prehypertensive patients: protocol for a systematic review and network meta-analysis

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## ABSTRACT

**Introduction** Lifestyle modification is one of the cornerstones in the management of hypertension. According to the most recent guidelines by the American Heart Association, all patients with hypertension should adopt the following dietary advices: increased consumption of fresh fruits, vegetables, low-fat dairy products and sodium reduction. The aim of the present study is to assess the efficacy of different dietary approaches on systolic and diastolic blood pressure in patients with hypertension and high normal blood pressure in a systematic review including a pairwise and network meta-analysis of randomised trials.

**Methods and analysis** We conducted searches in Cochrane Central Register of Controlled Trials in the Cochrane Library, PubMed and Google Scholar until November 2016. Citations, abstracts and relevant papers were screened for eligibility by two reviewers independently. Randomised trials were included if they met the following criteria: (1) hypertension (as mean values  $\geq 140$  mm Hg systolic blood pressure and/or  $\geq 90$  mm Hg diastolic blood pressure) or high normal blood pressure (mean systolic blood pressure  $\geq 130$  mm Hg and/or mean diastolic blood pressure  $\geq 85$  mm Hg), (2) age  $\geq 18$  years, (3) intervention diets (different type of dietary approaches, eg, dietary approach to stop hypertension diet; Mediterranean diet, vegetarian diet, palaeolithic diet, low sodium diet) either hypocaloric, isocaloric or ad libitum diets, (4) intervention period  $\geq 12$  weeks. For each outcome measure of interest, random effects pairwise and network meta-analyses were performed in order to determine the pooled relative effect of each intervention relative to every other intervention in terms of the postintervention values (or change scores). Subgroup analyses were planned for hypertensive status, study length, sample size, age and sex.

**Ethics and dissemination** As this study is based solely on the published literature, no ethics approval was required. We published our network meta-analysis in a peer-reviewed scientific journal.

**Systematic review registration** PROSPERO: CRD42016049243

## Strengths and limitations of this study

- The protocol addresses the important question of which dietary approach offers the most benefits in the management of elevated blood pressure.
- The present network meta-analysis has a clearly established aim, stringent inclusion criteria, state-of-the-art methods for data collection and quantitative and qualitative synthesis.
- Limitations include variations in trial design and regimen, adherence to dietary protocols, lack of blinding across the included intervention trials and ecological fallacy.

## BACKGROUND

Due to its frequent occurrence and high impact on the development of cardiovascular and kidney disease, hypertension is one of the most challenging problems adversely affecting public health worldwide.<sup>1</sup> The prevalence of hypertension accounts for nearly 40% of people older than 25 years worldwide, and the number of patients has increased from 600 million to a billion in 2008.<sup>2</sup>

Lifestyle modification is one of the cornerstones of the management of hypertension. According to the most recent guidelines by the American Heart Association and the European Society of Cardiology and Hypertension, all patients with hypertension should follow dietary modifications: increased consumption of fresh fruits, vegetables, low-fat dairy products and sodium reduction.<sup>3,4</sup>

Accumulating evidence indicates that dietary factors have a predominant role in the management of elevated blood pressure.<sup>5</sup> In individuals without hypertension, dietary changes reduce blood pressure and prevent hypertension, thereby lowering the risk of blood pressure-related complications.

Epidemiological studies suggest that even slight reductions in blood pressure will reduce the risk of cardiovascular disease.<sup>6,7</sup>

Whereas it is already well established that aerobic exercise is more effective in reducing blood pressure in hypertensive patients compared with resistance training,<sup>8</sup> the question regarding the most effective dietary approach in the treatment of hypertension and high normal pressure has not been evaluated.

To our knowledge, no up-to-date systematic review and network meta-analysis has been conducted to compare different dietary modifications in the management of hypertension and high normal blood pressure. Some pairwise meta-analyses have been published comparing dietary approach to stop hypertension (DASH),<sup>9</sup> combined dietary approaches<sup>10</sup> and lower sodium intake versus usual care/control diet.<sup>11</sup> One of the most important questions that remain to be answered is which dietary approach offers the most benefits in the management of elevated blood pressure?

Therefore, our aim is to compare the efficacy of different dietary approaches on blood pressure in patients with hypertension and high normal blood pressure in a systematic review including a pairwise and network meta-analysis of randomised trials.

## METHODS AND DESIGN

The systematic review and network meta-analysis was registered in International Prospective Register of Systematic Reviews (PROSPERO) (CRD42016049243), and reported in adherence to guidelines for network meta-analysis protocols<sup>12–15</sup> (see online supplementary file).

### Eligibility criteria

Studies were included in the meta-analysis if they met all of the criteria mentioned below.

#### Types of studies

Randomised trial design comparison between different dietary approaches (eg, DASH; Mediterranean diet; vegetarian diet; palaeolithic diet; low sodium diet; low fat diet; low carbohydrate diet; high protein diet; low glycaemic index/load diet) with a minimum intervention period of 3 months according to recent Cochrane Reviews on diet and cardiovascular risk.<sup>16,17</sup> If randomised trials were more than one different length of outcomes (eg, 12 weeks and 12 months), we included the long-term data.

#### Types of participants

We considered only adults with a mean age  $\geq 18$  years. Hypertension was defined according to the European Society of Cardiology and European Society of Cardiology and Hypertension as mean values  $\geq 140$  mm Hg systolic blood pressure and/or  $\geq 90$  mm Hg diastolic blood pressure. Moreover, all patients taking antihypertensive medication were included.<sup>18</sup>

High normal blood pressure (mean systolic blood pressure  $\geq 130$  mm Hg and/or mean diastolic blood pressure

$\geq 85$  mm Hg) was also defined according to the European Society of Cardiology and Hypertension and the recently published Systolic Blood Pressure Intervention Trial (SPRINT) trial.<sup>18,19</sup> Including patients with high normal blood pressure is of major relevance, since it is part of the metabolic syndrome diagnosis criteria.<sup>20</sup>

### Types of interventions

Accumulating evidence indicates that dietary factors play an important role in the treatment of elevated blood pressure. Likewise, dietary modifications decrease blood pressure<sup>21</sup> and reduce the risk of hypertension in people without established high blood pressure.<sup>22</sup> Even if modest, a reduction in blood pressure can have an important impact on the health of entire populations.<sup>5</sup> We included all intervention trials that met the above inclusion criteria and included at least one of the following intervention diets and a control group (indirect evidence) or at least two intervention diets (direct evidence).

Eligible types of dietary approaches were as follows:

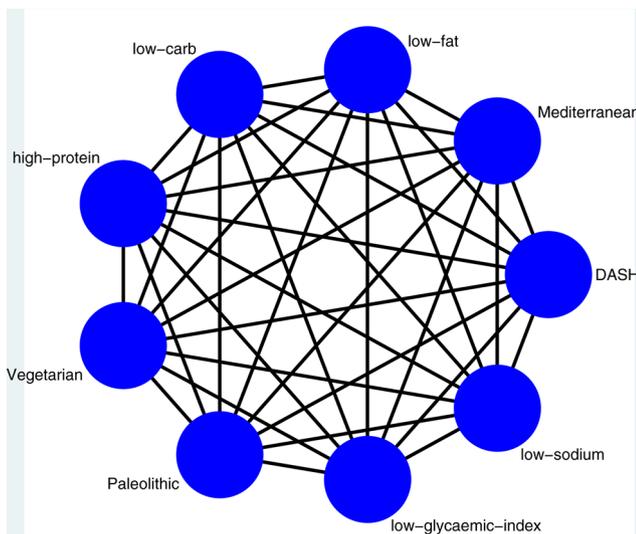
- ▶ DASH: high intake of fruits & vegetables, low-fat dairy, whole grains<sup>21</sup>
- ▶ Mediterranean dietary pattern: olive oil, vegetables, fruits, legumes, cereals, fish and a moderate intake of red wine during meals<sup>23–27</sup>
- ▶ Low carbohydrate diet (<30% of the total energy intake from carbohydrates, high intake of animal or/and plant protein)<sup>28</sup>
- ▶ High protein diet<sup>29</sup> ( $\geq 25\%$  of total energy intake from protein)
- ▶ Low fat diet (<30% of total energy intake from fat, high in grains and cereals)<sup>28,30</sup>
- ▶ Vegetarian diet (no meat or fish)<sup>31</sup>
- ▶ Palaeolithic diet (lean meat, fish, eggs, vegetables, fruits, berries, and nuts; dairy products, cereals, added salt, and refined fats and sugar were excluded)<sup>32</sup>
- ▶ Low sodium diet<sup>33</sup>
- ▶ Low glycaemic index/load diet<sup>34</sup>

Either energy-restricted diets, isocaloric or ad libitum diets were considered.

The following types of randomised controlled trials were excluded:

- ▶ Intervention studies solely based on dietary supplements (eg, vitamin C, vitamin E, calcium, potassium, garlic, soy protein) or single foods (eg, nuts);
- ▶ Placebo used in any form of dietary supplements (eg, potassium);
- ▶ Studies with an exercise/medication<sup>35,36</sup> cointervention that was not applied in all of the intervention/control groups;
- ▶ Interventions based on very low energy diets (ie, <600 kcal/day)

Figure 1 shows the network of possible pairwise comparisons between the eligible dietary interventions. We identified a study that combined low sodium and a low fat diet (and did not fulfil the criteria of a DASH diet),



**Figure 1** Network of all possible pairwise comparisons between the eligible dietary interventions. DASH, dietary approach to stop hypertension.

we handled this study as evaluating a different dietary regimen (low fat + low sodium) in the network meta-analysis. If food-based interventions also fulfilled the criteria of a nutrient-based dietary regimen, we performed sensitivity analysis for food-based versus nutrient-based dietary regimen taking into account possible overlaps.

### Outcome measures

Although cardiovascular diseases are determined by variables that cannot be influenced, such as age or heritability,<sup>37 38</sup> there are several predictors for cardiovascular disease that can be affected by lifestyle improvements. As mentioned above, blood pressure is the most important of these modifiable risk factors. Epidemiological studies show that a reduction of approximately 3 mm Hg in systolic blood pressure has been estimated to reduce risks of coronary heart disease by 5%–9%, stroke by 8%–14% and all-cause mortality by 4%.<sup>39</sup> Lowering diastolic blood pressure by 5 mm Hg reduces the risk of stroke by 32%, and ischaemic heart disease by an estimated 20%.<sup>40</sup>

Several other systematic reviews and pairwise meta-analyses have included systolic and diastolic blood pressure as outcomes.<sup>9 10</sup> In order to achieve a better comparability between the data compiled by different studies, the patients should ideally hold a sitting position for 3–5 min prior to blood pressure measurement.<sup>18</sup>

### Search strategy

The search was performed by LS and CS, and differences were resolved by discussion with a third reviewer (HB). We conducted searches in PubMed, Cochrane Library and Google Scholar. We searched for articles of original research by using the following search terms:

#1 diet (MeSH Terms)

#2 low carbohydrate OR high carbohydrate OR low fat OR high fat OR low protein OR high protein OR

vegetarian OR vegan OR Mediterranean OR DASH OR dietary approaches to stop hypertension OR low glycaemic index OR low glycaemic load OR Palaeolithic OR low-calorie OR Atkins OR low sodium

#3 blood pressure OR hypertension OR diastolic OR systolic

#4 random\* NOT animals

#5 (#1 AND #2 AND #3 AND #4)

Moreover, the reference lists from the retrieved articles, systematic reviews and meta-analyses were checked to search for further relevant studies (umbrella review of systematic reviews and meta-analyses). There were no restrictions on language or publication year. Studies published in languages other than English were translated by international scientists in our institute.

### Study selection process

Titles and abstracts of all the retrieved bibliographic records were screened by two authors (LS, CS).

Potentially eligible full-text reports passing the title and abstract screening level were examined by two authors based on the a priori established inclusion and exclusion criteria.<sup>41 42</sup> Discussions and consensus between the two reviewers were used to resolve disagreements by adjudication of another author. The study selection process and reasons for exclusions were outlined in a flow diagram. We included the records containing the most comprehensive information (eg, longest follow-up duration and/or largest number of study participants), if a trial was published in duplicate.

### Data extraction

The following data were extracted from each study: name of first author, publication year, country of origin, study design (randomised trial or cross-over trial), study length, number of arms, participants' sex and age (effect modifier), sample size, diagnostic criteria for hypertension, mean baseline systolic and diastolic blood pressure, mean baseline body mass index, method of blood pressure ascertainment, body weight (effect modifier), medication intake (predominately antihypertensive drugs), dietary protocols, dietary assessment method, any physical activity details, participant health status (diabetes mellitus type 2, coronary artery disease, alcohol intake, smoking), specification of the control group (if available) and where dropouts and funding source were reported.

### Risk of bias assessment

Two authors assessed the methodological quality of the included trials using the risk of bias assessment tool from the Cochrane Collaboration.<sup>43</sup> Selection bias, performance bias, attrition bias and reporting bias were assessed.

Studies were classified as being at high risk of bias if achieving fewer than four out of a maximum yield of five items at low risk of bias using the risk of bias assessment tool from the Cochrane Collaboration. Studies were classified as being at low risk of bias in general only if at least

three out of five of the domains established a low risk of bias.

### Dealing with missing data

We aimed to obtain relevant missing data from authors of the included randomised trials by mail. If the postintervention values with the corresponding SD were not available, the changed scores with the corresponding SD were imputed, according to the guidelines of the Cochrane Handbook.<sup>44</sup>

## EVALUATION OF SYNTHESIS ASSUMPTIONS

### Data synthesis

#### Description of the available data

We derived each pairwise comparison from descriptive statistics on available data and selected variables for study and population characteristics such as age, study length and outcome-relevant baseline risk factors. A network diagram was used for each outcome to present the direct comparisons between different dietary interventions and control groups.<sup>45</sup> In these diagrams, nodes (circles) represented dietary interventions and their sizes were proportional to the sample size of each respective intervention; edges (lines) indicated direct comparisons and their thicknesses were proportional to the number of studies available. We also identified those direct comparisons having a greater influence on the network's relative effects by analysing the contribution matrix.<sup>45 46</sup>

#### Standard pairwise meta-analyses and network meta-analyses

To determine the pooled relative effect of each intervention (in terms of the postintervention values or the changes from baseline scores), we presented random effects pairwise and network meta-analyses. We used data on intention-to-treat analyses when available. We compared all the interventions with available direct evidence in separate pairwise meta-analyses. Heterogeneity between trial results was measured using the  $I^2$  statistic; substantial heterogeneity was considered where  $I^2$  was  $>50\%$ . Study-specific effect sizes along with 95% CIs were shown in forest plots. All available evidences were then synthesised using network meta-analysis. As extensions of the standard pairwise meta-analysis model, methods of network meta-analysis allowed for a simultaneous comparison of multiple interventions while preserving the internal randomisation of individual trials. Using a random effects network meta-analysis for each outcome, we estimated all possible pairwise relative effects and presented clinically meaningful relative ranking of the different dietary interventions. In the case of multiarm trials, we accounted for the correlation of effect sizes. Summary mean differences were presented in a league table. For each outcome, we used the distribution of the ranking probabilities and the surface under the cumulative ranking curves to estimate the relative ranking of the different diets.<sup>47</sup> Furthermore, by assuming a common network-specific heterogeneity parameter and estimating predictive intervals, we were able to assess the impact of

this heterogeneity on the relative effects with respect to additional uncertainty anticipated in future studies.<sup>48</sup> All analyses hereby described were fitted in a frequentist framework using Stata<sup>49</sup> (*network* package<sup>50</sup>) and our results were presented with the *network graphs* package.<sup>51</sup>

#### Assumption of transitivity

Transitivity is the fundamental assumption of indirect comparisons and network meta-analysis. Not fulfilling this assumption compromises the validity of findings from a network of studies. Changes in body weight and mean baseline age were considered as potential effect modifiers.

#### Assessment of inconsistency

Statistical inconsistency, meaning the presence of disagreement between the different sources of evidence, can be evaluated with help of local and global approaches.<sup>52</sup> In our study, we used both methods. The loop-specific approach<sup>53</sup> was used to identify loops of evidence that might present important inconsistency, and the node-splitting approach<sup>54</sup> was used to identify comparisons for which direct estimates disagreed with indirect evidence from the entire network. Globally, a design-by-treatment interaction model and  $I^2$  statistic methods were used to identify inconsistencies jointly from all possible sources in the network.<sup>55 56</sup>

#### Subgroup and sensitivity analyses

In case of possible important heterogeneity or inconsistency, we explored the possible sources using subgroup and meta-regression analyses. Subgroup analyses were planned for hypertensive status, comorbidities, study length (short-term vs long-term), sample size, age and sex. Sensitivity analyses were planned for diastolic and systolic blood pressure by analysing only studies considered being at low risk of bias.

#### Small study effects and publication bias

We assessed the presence of small-study effects by using comparison-adjusted funnel plots.<sup>45</sup> Contour-enhanced funnel plots<sup>57</sup> were used to examine whether funnel plot asymmetry was likely to be explained by publication bias.

In case the publication bias was detected, we attempted to fit a selection model that represented the relationship between relative effects and probability of a study for being published and we obtained relative effects 'adjusted' for the impact of publication bias.<sup>58</sup>

## QUALITY OF THE EVIDENCE

The NutriGrade tool has been especially developed for nutrition research to address specific requirements for the evaluation of meta-evidence.<sup>59</sup> We first used this tool to evaluate and judge the meta-evidence for the pairwise comparisons. We then used our judgement about the direct comparisons and the individual contribution to the estimates within the network as described by Salanti *et al*.<sup>52</sup>

to draw inferences about the quality of evidence of the network meta-analysis.

## DISCUSSION

According to the Global Burden of Disease Group in 2012, unhealthy diet is the leading risk factor for premature death and disability.<sup>60</sup> Given the high prevalence and incidence of hypertension and the potential impact of diet, the conduct of the present systematic review with network meta-analysis is of high clinical and practical relevance. This network meta-analysis was one of the first to compare the direct and indirect effects of different dietary approaches in the management of hypertension and prehypertension. The results of the present network meta-analysis will influence evidence-based decision-making in treatment prescription, since it will be fundamental for reliable recommendations in the management of hypertension and prehypertension.

**Contributors** LS, AC, HB and GH contributed to the conception and design of the systematic review and meta-analysis. LS, AC and HB were involved in the acquisition and analysis of the data. LS, AC, CS and HB interpreted the results. LS, AC, GH, CS and HB drafted this protocol. All authors provided critical revisions of the protocol and approved submission of the final manuscript.

**Competing interests** None declared.

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

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