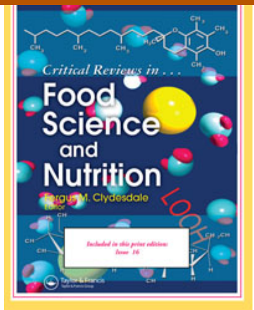

Critical Reviews in Food Science and Nutrition

ISSN: 1040-8398 (Print) 1549-7852 (Online) Journal homepage: https://www.tandfonline.com/loi/bfsn20

Comparative effects of different dietary approaches on blood pressure in hypertensive and pre-hypertensive patients: A systematic review and network meta-analysis

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To cite this article: Lukas Schwingshacklhttps://orcid.org/0000-0003-3407-7594, Anna Chaimani, Carolina Schwedhelm, Estefania Toledo, Marina Pünsch, Georg Hoffmann & Heiner Boeing (2019) Comparative effects of different dietary approaches on blood pressure in hypertensive and pre-hypertensive patients: A systematic review and network meta-analysis, Critical Reviews in Food Science and Nutrition, 59:16, 2674-2687, DOI: 10.1080/10408398.2018.1463967

To link to this article: https://doi.org/10.1080/10408398.2018.1463967

CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
2019, VOL. 59, NO. 16, 2674–2687
https://doi.org/10.1080/10408398.2018.1463967

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REVIEW

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Comparative effects of different dietary approaches on blood pressure in hypertensive and pre-hypertensive patients: A systematic review and network meta-analysis

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ABSTRACT

Background: Pairwise meta-analyses have shown beneficial effects of individual dietary approaches on blood pressure but their comparative effects have not been established. Objective: Therefore we performed a systematic review of different dietary intervention trials and estimated the aggregate blood pressure effects through network meta-analysis including hypertensive and pre-hypertensive patients. Design: PubMed, Cochrane CENTRAL, and Google Scholar were searched until June 2017. The inclusion criteria were defined as follows: i) Randomized trial with a dietary approach; ii) hypertensive and pre-hypertensive adult patients; and iii) minimum intervention period of 12 weeks. In order to determine the pooled effect of each intervention relative to each of the other intervention for both diastolic and systolic blood pressure (SBP and DBP), random effects network meta-analysis was performed. Results: A total of 67 trials comparing 13 dietary approaches (DASH, low-fat, moderate-carbohydrate, high-protein, low-carbohydrate, Mediterranean, Palaeolithic, vegetarian, low-GI/GL, low-sodium, Nordic, Tibetan, and control) enrolling 17,230 participants were included. In the network meta-analysis, the DASH, Mediterranean, low-carbohydrate, Palaeolithic, high-protein, low-glycaemic index, low-sodium, and low-fat dietary approaches were significantly more effective in reducing SBP (−8.73 to −2.32 mmHg) and DBP (−4.85 to −1.27 mmHg) compared to a control diet. According to the SUCRAs, the DASH diet was ranked the most effective dietary approach in reducing SBP (90%) and DBP (91%), followed by the Palaeolithic, and the low-carbohydrate diet (ranked 3rd for SBP) or the Mediterranean diet (ranked 3rd for DBP). For most comparisons, the credibility of evidence was rated very low to moderate, with the exception for the DASH vs. the low-fat dietary approach for which the quality of evidence was rated high. Conclusion: The present network meta-analysis suggests that the DASH dietary approach might be the most effective dietary measure to reduce blood pressure among hypertensive and pre-hypertensive patients based on high quality evidence.

KEYWORDS
Dietary approaches; hypertension; network meta-analysis; blood pressure; evidence synthesis

1. Background

According to the World Health Organization, approximately 1 billion adults worldwide suffer from hypertension, and the prevalence is increasing (NCD-Risk-Factor-Collaboration 2017; World-Health-Organization 2012). Hypertension is the most important modifiable risk factor for premature cardiovascular disease worldwide. Nearly 50% of all ischemic heart diseases and stroke events are attributable to hypertension (Lawes, Vander Hoorn, and Rodgers 2008).

Dietary modifications play an important role in the prevention and management of hypertension. Evidence from a recent dose-response meta-analysis of prospective cohort studies indicates that optimal consumption of certain food groups (whole grains, fruit, nuts, legumes, dairy products, red and processed meat and sugar sweetened beverages) is associated with as strong reduction in hypertension risk (Schwingshackl et al. 2017b). According to the most recent guidelines by the American Heart Association, hypertensive and pre-hypertensive patients should follow dietary modifications (alcohol moderation, sodium reduction, and emphasis on increased consumption of fresh fruits, vegetables, and low-fat dairy products) (Eckel et al. 2014; Smith et al. 2011). However, considering various guidelines, dietary recommendations for the prevention and management of hypertension are still not comprehensive (Eckel et al. 2014; Mancia et al. 2013b; Smith et al. 2011).

Pairwise meta-analyses comparing Dietary approaches to stop hypertension (DASH) (Saneei et al. 2014), combined

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Financial support: No funding to declare.
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dietary approaches (Ndanuko et al. 2016), or lower sodium intake with usual care/control diets, indicate modest reductions in blood pressure (Aburto et al. 2013). Due to the high prevalence of hypertension, and the preventive effects of dietary factors, one of the most important questions that remain to be answered is which dietary approach offers the greatest benefits. For answering this question, a promising approach is network meta-analysis (Leucht et al. 2016; Mavridis et al. 2015; Salanti 2012). The methodology of network meta-analysis is an extension of the standard pairwise meta-analysis that enables a simultaneous comparison of multiple interventions forming a connected network while preserving the internal randomization of individual trials. This systematic review and network meta-analysis aims to establish a clinically meaningful hierarchy of different dietary approaches on blood pressure in hypertensive patients in a systematic review through the synthesis of available evidence from randomized trails.

2. Methods and design

The study protocol was registered in PROSPERO International Prospective Register of Systematic Reviews (https://www.crd.york.ac.uk/prospero/, identifier CRD42016049243) and published a priori (Schwingshackl et al. 2017a). The present systematic review adheres to the PRISMA guidelines and the corresponding extension for network meta-analyses (Chaimani et al. 2017; Hutton et al. 2015).

2.1. Search strategy

Literature searches were performed in PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), and Google Scholar until June 2017, by applying no language restriction using a predefined search strategy **(Supplemental Appendix 1)**.

Moreover, the reference lists from the identified articles were screened to search for additional relevant studies.

2.2. Eligibility criteria

As previously described the following inclusion criteria were established (Schwingshackl et al. 2017a):

i) Randomized comparison/controlled design (parallel or cross-over) between different dietary approaches (Schwingshackl et al. 2018):
   a. DASH diet: high intake of fruits & vegetables, low-fat dairy products, and whole grains, and low in sodium (Appel et al. 1997);
   b. Mediterranean dietary pattern: high consumption of fruit, vegetables, olive oil, legumes, cereals, fish, and moderate intake of red wine during meals (Schwingshackl and Hoffmann 2014a, 2014c, 2015a, 2016; Schwingshackl et al. 2015b);
   c. Low carbohydrate (LC) diet: <25% carbohydrates of total energy intake; high intake of animal and/ or plant protein; often high intake of fat (Schwingshackl and Hoffmann 2013a);
   d. Palaeolithic Diet: lean meat, fish, fruit, leafy and cruciferous vegetables, root vegetables, eggs and nuts, while excluding dairy products, cereal grains, beans, refined fats, sugar, candy, soft drinks, beer and extra addition of salt (Jonsson et al. 2009);
   e. Moderate-carbohydrate diet: 25–45% carbohydrates of total energy intake; 10–20% protein intake (Schwingshackl and Hoffmann 2013a);
   f. High protein (HP) diet: >20% protein intake of total energy intake; high intake of animal and/ or plant protein; <35% fat (Schwingshackl and Hoffmann 2013b);
   g. Nordic Diet: whole-grain products, abundant use of berries, fruit and vegetables, rapeseed oil, three fish meals per week, low-fat dairy products and avoidance of sugar-sweetened products (Uusitupa et al. 2013);
   h. Tibetan Diet: high-protein and vitamin-rich food, preferably cooked and warm food (von Haehling et al. 2013);
   i. Low fat (LF) diet: <30% fat of total energy intake; high intake of cereals & grains; 10–15% protein intake (Schwingshackl and Hoffmann 2013a,2014b);
   j. Low glycaemic index/load (LGI/LGL) diet (Schwingshackl, Hobl, and Hoffmann 2015a; Schwingshackl and Hoffmann 2013c);
   k. Vegetarian/Vegan diet: no meat and fish/ no animal products (Haider et al. 2017)
   l. Low-sodium diet (Whelton et al. 1998);
   m. Control diet: usual diet.

ii) Minimum intervention period of 12 weeks;
iii) Participants with a mean age ≥18 years;
iv) Hypertension or pre-hypertension (high normal blood pressure: 130–139 mmHg for systolic and/or 85–89 for diastolic blood pressure) defined according to the European Society of Hypertension and the European Society of Cardiology (Mancia et al. 2013a);
v) The outcomes include systolic (SBP) and diastolic blood pressure (DBP) (mmHg).

The following studies were excluded:

i) Randomized trials including pregnant women, children, and adolescents;
ii) Intervention studies solely based on dietary supplements or single foods;
iii) Intervention studies using dietary supplements as placebo;
iv) Studies with an exercise/medication (Schwingshackl et al. 2013; Schwingshackl et al. 2014) co-intervention that was not applied in all the intervention/control groups;
v) Interventions based on very low energy diets (i.e. <600 kcal/day);

2.3. Data extraction

After determination of the study selection, two reviewers extracted the following characteristics: name of first author, year of publication, country, sample size, study design, mean baseline Body Mass Index (BMI), mean baseline SBP and DBP, mean baseline age, % female, study duration, description of the different dietary arms, type of diet (energy restricted, ad libitum, iso-caloric), drop outs, % hypertension, % presence of comorbidities (obesity, hyperlipidaemia, type 2 diabetes, metabolic syndrome, coronary heart disease), % antihypertensive medication, and % lipid lowering medication. Outcome data include: post-intervention values with corresponding standard deviations for SBP and DBP.

2.4. Risk of bias assessment

One author assessed the risk of bias of the included trials, by applying the Cochrane risk of bias tool (Higgins et al. 2011). The following items were assessed: random sequence generation and allocation concealment, blinding of participants and personnel, incomplete outcome data, and selective reporting.

Studies were classified as being at low risk of bias (if at least three out of a maximum of five items were rated as low risk; and maximum one item rated with a high risk of bias), high risk of bias (if at least two out of a maximum of five items were rated as high risk), and moderate/unclear risk (all other studies).

2.5. Dealing with missing data

We contacted authors to receive missing outcome data (1 author sent additional data). If the post-intervention values with the corresponding standard deviations were not available, the change scores with the corresponding standard deviations were used, according to the guidelines of the Cochrane Handbook (Higgins and Green 2011).

2.6 Data synthesis

2.6.1 Description of the available data

Direct comparisons between different dietary approaches were illustrated by using a network diagram (Chaimani et al. 2013). Moreover, the contribution matrix was used to identify the direct comparisons with greater influence in the network relative effects (Chaimani et al. 2013; Krahn, Binder, and Konig 2013).

2.6.2 Assessment of transitivity

To evaluate the assumption of transitivity we compared the distribution of the potential effect modifiers (age, study length, Body Mass Index (BMI)) across the available direct comparisons.

2.6.3 Statistical analysis

In order to quantify the pooled relative effect of each dietary approach against every other dietary approach in terms of the post-intervention values (or changes from baseline values) of the different dietary measures we performed a random effects network meta-analysis for SBP and DBP. We performed network meta-analysis to synthesize all the available evidence. Compared to the standard pairwise meta-analysis model, network meta-analysis methods are extensions that enable a simultaneous comparison of multiple interventions forming a connected network while preserving the internal randomization of individual trials.

Random effects network meta-analysis for SBP and DBP were performed to estimate all possible pairwise relative effects and obtain a relative ranking of the different dietary approaches. The summary mean differences with their 95% CI were presented in a League table. We estimated the relative ranking of the different dietary approaches for SBP and DBP (Salanti, Ades, and Ioannidis 2011) with using the distribution of the ranking probabilities and the surface under the cumulative ranking curves (SUCRA). For SBP and DBP, we assumed a common network-specific heterogeneity parameter and estimated the predictive intervals to assess how much this heterogeneity affects the relative effects with respect to the additional uncertainty anticipated in future studies (Riley, Higgins, and Deeks 2011). Statistical analyses were performed by using Stata 14.0 (StataCorp. 2015) (*network* package (White 2015)) and produced presentation tools with the *network graphs* package (Chaimani and Salanti 2015).

2.6.4 Assessment of inconsistency

To evaluate the presence of statistical inconsistency, the loop-specific approach (Bucher et al. 1997) (detection of loops of evidence that might present important inconsistency), and the side-splitting approach (Dias et al. 2010) (detect comparisons for which direct estimates disagree with indirect evidence from the entire network) were applied. Global methods jointly investigate the presence of inconsistency from all possible sources in the entire network simultaneously. For this purpose, we used the design-by-treatment interaction model (Higgins et al. 2012; Jackson et al. 2014).

2.6.5 Subgroup and sensitivity analyses

Subgroup analyses according to hypertension status, study length (≥12 months vs. <12 months), and sample size (≥100 vs. <100) were performed for SBP and DBP. We also conducted a sensitivity analysis by analysing only studies considered being at low risk of bias. Additionally, we ran meta-regressions by participant and study characteristics for SBP and DBP: age, study length, and mean differences in weight change (by comparing study arms within each trial).

2.6.6 Small study effects and publication bias

The presence of small-study effects for each SBP and DBP was evaluated by drawing comparison-adjusted funnel plot that accounts for the fact that different studies compare different sets of interventions (Chaimani et al. 2013). Funnel plots included all comparisons of dietary approaches compared to a low-fat or control diet.

2.7 Credibility of the evidence

To assess the credibility of evidence from the network meta-analysis, we used the GRADE system extended for network meta-analysis following the approach suggested by Salanti et al. **(Supplemental Appendix 2)** (Salanti et al. 2014).

3. Results

Of a total of 2,949 records identified in the literature search, 115 full text articles were assessed in detail (**Supplemental Figure 1**). Of these, 48 were excluded, for the exclusion criteria summarized in **Supplemental Table 1**, **Supplemental References**.

Overall 67 trials met the eligibility criteria and were included in the meta-analysis (Table 1). 17,230 pre-hypertensive or hypertensive patients were enrolled, and the trials were published between 1981 and 2016. Eighteen trials were conducted in North America, 29 trials in Europe, 4 trials in Asia, and 15 trials in Australia and New Zealand, and one study in South America. Study length ranged between 3 and 48 months; the patients' mean age was between 23.6 and 71 years, and their BMI between 23.6 and 45.4 kg/m2. The general and specific study characteristics are summarized in **Supplemental Table 2–3**.

Twenty-three trials were judged to be low risk of bias, five trials to be high risk of bias, and 39 trials were classified as moderate/unclear risk of bias studies. With regard to the specific items of the risk of bias assessment tool by the Cochrane Collaboration, 46% of the included studies indicate a low risk of bias for random-sequence generation, 21% for allocation concealment, 0% for blinding, 60% for incomplete data outcome, and 96% for selective reporting (**Supplemental Figure 2**).

The definition of the different intervention diets was heterogeneous for the intensity and type of dietary approach (i.e. group meeting, dietary counselling) and for the prescribed diets (ad-libitum, iso-caloric, hypocaloric). Across the included low-fat dietary approaches the overall amount of fat intake varied between ~10–15% of total energy intake. We thus had to harmonize the single trials and formed classes of dietary approaches (Schwingshackl et al. 2017a).

Figure 1 shows the network diagram of direct comparison for SBP with the number of studies reflected by the size of the edges, and the number of patients reflected by the size of the nodes. The comparisons with the largest amount of trials include: HP vs. LF (Brinkworth et al. 2004a; Brinkworth et al. 2004b; Campbell and Meckling 2012; Dalle Grave et al. 2013; Dansinger et al. 2005; Delbridge et al. 2009; Kim et al. 2014; Krebs et al. 2012; Luger et al. 2013; Tang et al. 2013; Watson et al. 2016; Wycherley et al. 2010) (n = 12), low-sodium vs. control (Alli et al. 1992; Chalmers et al. 1986; Costa et al. 1981; Dodson et al. 1989; Erwteman et al. 1984; Jula and Karanko 1994; Makela et al. 2008; Silman et al. 1983; Whelton 1997; Whelton et al. 1998) (n = 10), LF vs. control (Anderssen et al. 1995; Andrews et al. 2011; Ard et al. 2016; Coppell et al. 2010; Gordon, Scott, and Levine 1997; Heilbronn, Noakes, and Clifton 1999; Rock et al. 2014; Uusitupa et al. 1993; Watkins et al. 2003) (n = 9), and LC vs. LF dietary approaches (Daly et al. 2006; Guldbrand et al. 2012; Iqbal et al. 2010; Liu et al. 2013; Stern et al. 2004; Tay et al. 2008; Tay et al. 2015; Veum et al. 2017) (n = 8). Table 2 shows the percentage of statistical contribution coming from direct and indirect comparisons for each dietary approach compared to each other. It was shown that most of the contribution to the study effects came from indirect comparisons. Direct comparisons dominated the comparisons of DASH, Vegetarian, Mediterranean, HP, moderate-carbohydrate, LC, LGI/LGG, Palaeolithic, Tibetan, and a control diet with a LF diet for both outcomes. In general, there are some important differences in the examined effect modifiers across comparisons for BMI and study duration. For some comparisons, though, we did not have enough studies and we could not test transitivity appropriately (**Supplemental Figure 3–5**).

Table 3 summarizes the pooled estimates of SBP and DBP for the comparison of every dietary approach using both direct and indirect evidence. The DASH, Mediterranean, LC, Palaeolithic, HP, LGI/LGL, low-sodium, and LF dietary approaches were more effective in reducing SBP and DBP compared to a control diet. The DASH diet was more effective in reducing SBP compared to a LF (mean difference (MD): −5.05 mmHg, 95% −7.08, −3.03), Mediterranean (MD: −3.31 mmHg, 95% −6.20, −0.42), HP (MD: −4.78 mmHg, 95% −7.72, −1.85), moderate-carbohydrate (MD: −5.57 mmHg, 95% −8.75, −2.39), LGI/LGL (MD: −4.92 mmHg, 95% −8.55, −1.30), Nordic (MD: −4.74 mmHg, 95% −9.11, −0.37), and low-sodium dietary approaches (MD: −4.42 mmHg, 95% −7.12, −1.72), and more effective in reducing DBP compared to a LF diet (MD: −3.10 mmHg, 95% −4.52, −1.68), moderate-carbohydrate (MD: −3.05 mmHg, 95% −5.37, −0.74), Nordic

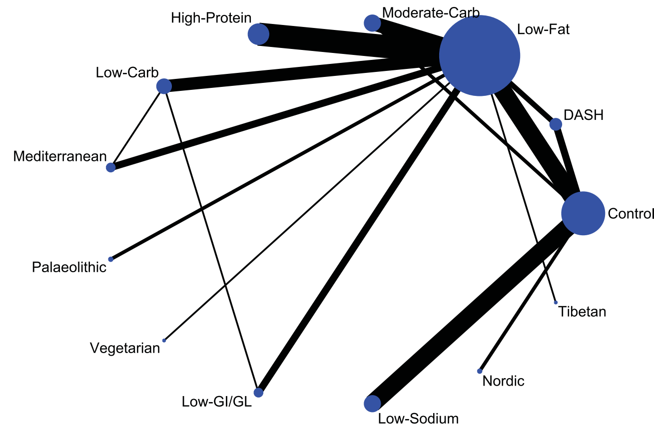

Figure 1. Network diagram for diastolic blood pressure: The size of the nodes is proportional to the total number of participants allocated to each dietary approach and the thickness of the lines proportional to the number of studies evaluating each direct comparison.

Table 1. References of the 67 trials included in the present network meta-analysis.

Alli et al. 1992; Anderssen et al. 1995; Andrews et al. 2011; Appel et al. 2003; Ard et al. 2016; Azadbakht et al. 2005; Blumenthal et al. 2010; Brehm et al. 2009; Brinkworth et al. 2004a; Brinkworth et al. 2004b; Campbell and Meckling 2012; Chalmers et al. 1986; Clifton et al. 2004; Coppell et al. 2010; Costa et al. 1981; Dalle Grave et al. 2013; Daly et al. 2006; Dansinger et al. 2005; Delbridge et al. 2009; Deluis et al. 2010; Dodson et al. 1989; Edwards et al. 2011; Erwteman et al. 1984; Esposito et al. 2009; Esposito et al. 2004; Frisch et al. 2009; Gordon, Scott, and Levine 1997; Guldbrand et al. 2012; Heilbronn, Noakes, and Clifton 1999; Iqbal et al. 2010; Itsiopoulos et al. 2011; Jonsson et al. 2009; Jula and Karanko 1994; Kim et al. 2014; Kirpizidis, Stavrati, and Geleris 2005; Klemsdal et al. 2010; Krebs et al. 2012; Lean et al. 1997; Lima et al. 2013; Liu et al. 2013; Luger et al. 2013; Ma et al. 2008; Makela et al. 2008; Mellberg et al. 2014; Nicholson et al. 1999; Nowson et al. 2005; Philippou et al. 2009; Poulsen et al. 2015; Rock et al. 2014; Shai et al. 2008; Silman et al. 1983; Stern et al. 2004; Tang et al. 2013; Tay et al. 2008; Tay et al. 2015; Toledo et al. 2013; Uusitupa et al. 2013; Uusitupa et al. 1993; Veum et al. 2017; von Haehling et al. 2013; Walker et al. 1995; Watkins et al. 2003; Watson et al. 2016; Westman et al. 2008; Whelton 1997; Whelton et al. 1998; Wycherley et al. 2010

Table 2. Percentage contribution of each direct estimate derived from direct (blue) and indirect (red) comparisons (the colour corresponds to the percentage of contribution). The values above the diet classes correspond to the percentage contribution of direct and indirect comparisons between the row and columns for DBP (eg, the percentage contribution of direct comparisons for DBP between Mediterranean and Low-Carb diet is 35%, and 65% for the indirect comparisons). The values below the diet classes correspond to the percentage contribution of direct and indirect comparisons between the column and the rows for SBP (eg, the percentage contribution of direct comparisons for SBP between Mediterranean and Low-Carb diet is 34%, and 66% for the indirect comparisons. DASH, Dietary Approaches to Stop Hypertension; DBP, diastolic blood pressure; SBP, systolic blood pressure.

DBP																									
DASH		0%	100%	0%	100%	0%	100%	0%	100%	0%	100%	0%	100%	0%	100%	0%	100%	0%	100%	0%	100%	59%	41%	60%	40%
0%	100%	Mediterranean		35%	65%	0%	100%	0%	100%	0%	100%	0%	100%	0%	100%	0%	100%	0%	100%	0%	100%	87%	13%	0%	100%
0%	100%	34%	66%	Low-Carb		0%	100%	0%	100%	0%	100%	0%	100%	16%	84%	0%	100%	0%	100%	0%	100%	72%	28%	0%	100%
0%	100%	0%	100%	0%	100%	Palaeolithic		0%	100%	0%	100%	0%	100%	0%	100%	0%	100%	0%	100%	0%	100%	100%	0%	0%	100%
0%	100%	0%	100%	0%	100%	0%	100%	High-Protein		0%	100%	0%	100%	0%	100%	0%	100%	0%	100%	0%	100%	100%	0%	0%	100%
0%	100%	0%	100%	0%	100%	0%	100%	0%	100%	Vegetarian		0%	100%	0%	100%	0%	100%	0%	100%	0%	100%	100%	0%	0%	100%
0%	100%	0%	100%	0%	100%	0%	100%	0%	100%	0%	100%	Moderate-Carb		0%	100%	0%	100%	0%	100%	0%	100%	79%	21%	27%	73%
0%	100%	0%	100%	16%	84%	0%	100%	0%	100%	0%	100%	0%	100%	Low GI/GL		0%	100%	0%	100%	0%	100%	90%	10%	0%	100%
0%	100%	0%	100%	0%	100%	0%	100%	0%	100%	0%	100%	0%	100%	0%	100%	Nordic		0%	100%	0%	100%	0%	100%	100%	0%
0%	100%	0%	100%	0%	100%	0%	100%	0%	100%	0%	100%	0%	100%	0%	100%	0%	100%	Tibetan		0%	100%	100%	0%	0%	100%
0%	100%	0%	100%	0%	100%	0%	100%	0%	100%	0%	100%	0%	100%	0%	100%	0%	100%	0%	100%	Low-Sodium		0%	100%	100%	0%
62%	38%	87%	13%	73%	27%	100%	0%	100%	0%	100%	0%	81%	19%	90%	10%	0%	100%	100%	0%	0%	100%	Low-Fat		74%	26%
57%	43%	0%	100%	0%	100%	0%	100%	0%	100%	0%	100%	27%	73%	0%	100%	100%	0%	0%	100%	100%	0%	73%	27%	Control	
SBP																									

Table 3. League table: The values above the diet classes correspond to the difference in mean (95% CI) in DBP (mmHg) between the row and columns (e.g, the mean difference in average DBP between DASH and Low-Fat diets diet is −3.10 mmHg). The value below the diet classes correspond to the difference in mean in SBP (mmHg) between the column and the row (e.g, the mean difference in average SBP between DASH and Low-Fat diet is −5.05 mmHg). DASH, Dietary Approaches to Stop Hypertension; DBP, diastolic blood pressure; SBP, systolic blood pressure.

DBP (mmHg)												
DASH	−1.56 (−3.55,0.44)	−1.74 (−3.92,0.43)	0.48 (−3.72,4.68)	−1.91 (−3.92,0.10)	−5.90 (−19.60,7.80)	−3.05 (−5.37,−0.74)	−1.60 (−4.05,0.85)	−3.22 (−6.14,−0.31)	−3.20 (−6.32,−0.08)	−1.91 (−3.70,−0.12)	−3.10 (−4.52,−1.68)	−4.37 (−5.78,−2.97)
−3.31 (−6.20, −0.42)	Mediterranean	−0.18 (−2.11,1.75)	2.04 (−2.16,6.24)	−0.35 (−2.35,1.65)	−4.34 (−18.04,9.36)	−1.50 (−3.85,0.86)	−0.04 (−2.47,2.39)	−1.66 (−4.80,1.47)	−1.64 (−4.75,1.47)	−0.35 (−2.47,1.76)	−1.54 (−2.95,−0.13)	−2.81 (−4.63,−1.00)
−2.86 (−5.96,0.25)	0.45 (−2.35,3.26)	Low-Carb	2.22 (−2.07,6.51)	−0.17 (−2.35,2.01)	−4.16 (−17.89,9.57)	−1.31 (−3.82,1.19)	0.14 (−2.34,2.63)	−1.48 (−4.73,1.77)	−1.46 (−4.69,1.77)	−0.17 (−2.45,2.11)	−1.36 (−3.01,0.30)	−2.63 (−4.64,−0.62)
1.35 (−6.31,9.01)	4.66 (−3.02,12.34)	4.21 (−3.55,11.97)	Palaeolithic	−2.39 (−6.59,1.82)	−6.38 (−20.57,7.81)	−3.53 (−7.92,0.85)	−2.08 (−6.51,2.35)	−3.70 (−8.55,1.14)	−3.68 (−8.51,1.16)	−2.39 (−6.66,1.88)	−3.58 (−7.53,0.38)	−4.85 (−8.97,−0.73)
−4.78 (−7.72,−1.85)	−1.47 (−4.44,1.50)	−1.92 (−5.11,1.26)	−6.13 (−13.83,1.56)	High-Protein	−3.99 (−17.69,9.71)	−1.15 (−3.51,1.22)	0.31 (−2.14,2.76)	−1.31 (−4.45,1.82)	−1.29 (−4.41,1.83)	−0.00 (−2.14,2.14)	−1.19 (−2.61,0.23)	−2.46 (−4.28,−0.64)
−0.65 (−17.15,15.84)	2.66 (−13.85,19.16)	2.20 (−14.34,18.75)	−2.00 (−19.97,15.96)	4.13 (−12.38,20.64)	Vegetarian	2.84 (−10.92,16.60)	4.30 (−9.47,18.07)	2.68 −11.24,16.59)	2.70 (−11.21,16.61)	3.99 (−9.74,17.71)	2.80 (−10.83,16.43)	1.53 (−12.15,15.20)
−5.57 (−8.75,−2.39)	−2.26 (−5.54,1.03)	−2.71 (−6.19,0.76)	−6.92 (−14.74,0.90)	−0.79 (−4.11,2.53)	−4.91 (−21.48,11.66)	Moderate-Carb	1.46 (−1.29,4.20)	−0.17 (−3.48,3.14)	−0.14 (−3.50,3.21)	1.14 (−1.24,3.52)	−0.04 (−1.93,1.84)	−1.32 (−3.42,0.78)
−4.92 (−8.55,−1.30)	−1.61 (−5.25,2.03)	−2.07 (−5.74,1.61)	−6.27 (−14.26,1.71)	−0.14 (−3.83,3.55)	−4.27 (−20.92,12.38)	0.65 (−3.29,4.59)	Low GI/GL	−1.62 (−5.06,1.81)	−1.60 (−5.02,1.82)	−0.31 (−2.88,2.25)	−1.50 (−3.49,0.49)	−2.77 (−5.06,−0.48)
−4.74 (−9.11,−0.37)	−1.43 (−6.11,3.26)	−1.88 (−6.70,2.94)	−6.09 (−14.59,2.41)	0.04 (−4.66,4.75)	−4.08 (−20.99,12.82)	0.83 (−3.98,5.65)	0.19 (−4.98,5.35)	Nordic	0.02 (−3.91,3.96)	1.31 (−1.49,4.11)	0.12 −2.67,2.92)	−1.15 (−3.70,1.41)
−3.95 (−8.48,0.57)	−0.64 (−5.19,3.91)	−1.10 (−5.79,3.59)	−5.30 (−13.73,3.12)	0.83 (−3.75,5.40)	−3.30 (−20.17,13.57)	1.61 (−3.17,6.40)	0.97 (−4.07,6.01)	0.78 (−5.05,6.61)	Tibetan	1.29 (−1.92,4.49)	0.10 (−2.68,2.88)	−1.17 (−4.17,1.83)
−4.42 (−7.12,−1.72)	−1.11 (−4.26,2.03)	−1.57 (−4.92,1.79)	−5.77 (−13.55,2.00)	0.36 (−2.86,3.58)	−3.77 (−20.32,12.78)	1.15 (−2.24,4.53)	0.50 (−3.38,4.38)	0.31 (−3.93,4.56)	−0.47 (−5.19,4.25)	Low-Sodium	−1.19 (−2.79,0.41)	−2.46 (−3.59,−1.32)
−5.05 (−7.08,−3.03)	−1.74 (−3.82,0.34)	−2.20 (−4.56,0.17)	−6.40 (−13.80,0.99)	−0.27 (−2.40,1.86)	−4.40 (−20.77,11.97)	0.51 (−2.03,3.06)	−0.13 (−3.14,2.88)	−0.32 (−4.51,3.88)	−1.10 (−5.15,2.95)	−0.63 (−3.06,1.80)	Low-Fat	−1.27 (−2.41,−0.14)
−7.38 (−9.43,−5.33)	−4.07 (−6.72,−1.41)	−4.52 (−7.41,−1.64)	−8.73 (−16.31,−1.15)	−2.60 (−5.29,0.10)	−6.72 (−23.18,9.73)	−1.81 (−4.69,1.07)	−2.46 (−5.89,0.97)	−2.64 (−6.50,1.22)	−3.42 (−7.80,0.95)	−2.96 (−4.74,−1.17)	−2.32 (−3.98,−0.67)	Control
SBP (mmHg)												

(MD: −3.22 mmHg, 95% −6.14, −0.31), Tibetan (MD: −3.20 mmHg, 95% −6.32, −0.08) and low-sodium diet (MD: −1.91 mmHg, 95% −3.70, −0.12). The Mediterranean dietary approach was more effective in reducing DBP compared to a LF diet (MD: −1.54 mmHg, 95% −2.95, −0.13). According to the SUCRAs, the DASH diet was ranked the most effective dietary approach in reducing SBP (90%) and DBP (91%), followed by the Palaeolithic, and the low-carbohydrate diet (ranked 3rd for SBP) or the Mediterranean diet (ranked 3rd for DBP) **(Supplemental Table 4–5)**.

The rankograms showed uncertainty in ranking (similar distribution of rank probabilities across many possible ranks indicates uncertain ranking for that dietary approach) for the HP, LC, LGI/LGL, moderate-carbohydrate, Mediterranean, low-sodium, Nordic, and Tibetan dietary approach compared to the other dietary approaches **(Supplemental Figure 6–7)**.

The side-splitting approach suggested no significant inconsistency for SBP and DBP **(Supplemental Table 6–7)**. The loop-specific approach identified two-loops (control – LF – moderate-carbohydrate; and LF – LC – Mediterranean) for SBP presenting statistical inconsistency, and one-loop for DBP (LF – LC – LGI/GL) **(Supplemental Figure 8–9)**. The design-by-treatment model did not suggest the presence of statistical inconsistency for SBP ($p = 0.65$), and DBP ($p = 0.83$). The important inconsistency in the loop specific approach might be explained by several differences across LF dietary approaches (hypocaloric if compared to a control diet; often iso-caloric if compared to other dietary approaches), differences in total fat to carbohydrate intake ratio, and fatty acids composition among moderate carbohydrate approaches, and LC dietary approaches (larger weight loss compared to other interventions).

3.1 Subgroup and sensitivity analysis

In sensitivity analysis including only studies with a low risk of bias, the results of the primary analysis for the best ranked dietary approach, i.e. the DASH diet could be confirmed (Table 4). No significant effects for all other dietary approaches were observed in the low risk of bias sensitivity analysis.

The a priori planned subgroup analysis for age was not possible to conduct since only 8 trials included participants >60 years of age. In the subgroup analyses comparing longer-term (≥12 months) vs. shorter-term trials (<12 months), most of the results of the primary analysis were not confirmed among longer-term studies. Moreover, it seems that trials with a smaller sample size (<100) yielded more significant results compared to studies with a larger sample size (≥100) **(Supplemental Table 8–15)**.

Due to the low number of studies presenting results for hypertensive patients ($n = 12$), it was not possible to conduct sensitivity analysis.

In univariate meta-regression analysis we could show that mean reduction in SBP and DBP was larger in short-term trial, and among trials including younger participants. Moreover, we could show that larger differences in body weight change between study arms within trials were associated with a stronger impact on SBP and DBP, compared to smaller differences **(Supplemental Figure 10–15)**, thereby showing that weight loss is a major contributing factor for blood pressure control.

Small study effects

The comparison-adjusted funnel plots for SBP and DBP appeared asymmetric suggesting that small studies tend to favour the dietary approaches when compared to control dietary approaches, and slightly asymmetric for low fat diets **(Supplemental Figure 16–19)**.

3.2 Credibility of the evidence

For most comparisons in the network meta-analysis, the credibility of evidence was rated very low to moderate with the exception for the DASH vs. LF dietary approach the quality of evidence was rated high **(Supplemental Figure 20, Supplemental Appendix 2)**.

4. Discussion

In this meta-analysis of 67 trials including 17230 hypertensive and pre-hypertensive patients we compared the effects of 13 different dietary approaches (DASH, Control, Low-Fat, Moderate-carbohydrate, High-protein, Low-carbohydrate, Mediterranean, Palaeolithic, Vegetarian, Low-GI/GL, Low-sodium, Nordic, and Tibetan) using network meta-analysis. According to the SUCRAs, the DASH diet was ranked the most effective dietary approach in reducing SBP (90%) and DBP (91%), followed by the Palaeolithic, and the low-carbohydrate diet (ranked 3rd for SBP) or the Mediterranean diet (ranked 3rd for DBP). The DASH, Mediterranean, low-carbohydrate, Palaeolithic, high-protein, low-glycaemic index, low-sodium, and low-fat dietary approach were significantly more effective in reducing SBP (−8.73 to −2.32 mmHg) and DBP (−4.85 to −1.27 mmHg) compared to a control diet. For most comparisons, the credibility of evidence was rated very low to moderate, with the exception for the DASH vs. the low-fat dietary approach the quality of evidence was rated high.

Compared to a LF or a control diet, the DASH dietary approach reduced SBP by approximately 5–7 mmHg, and DBP by 3–4 mm Hg. With respect to other therapeutic options, a recent meta-analysis investigating the effect of different exercise modalities resulted in some less pronounced effect of aerobic exercise on blood pressure (Cornelissen and Smart 2013). Moreover, the blood-pressure lowering effect of the DASH dietary pattern in our meta-analysis was comparable to drug monotherapy (Elmer et al. 2006).

The importance of blood pressure reduction, as shown for several dietary approaches is strengthen by a large meta-analysis of epidemiological studies which have shown that a decrease of approximately 10 mmHg reduction in SBP was inversely associated with risk of cardiovascular disease events by 20%, coronary heart disease by 17%, stroke by 27%, heart failure by 28% and all-cause mortality by 13% (Ettehad et al. 2016), whereas a 5 mmHg decrease in DBP reduces the risk of ischemic heart disease by 20%, and the risk of stroke by 32% (Law, Wald, and Morris 2003). Another meta-analysis stressed the fact that even a small decline in SBP of about 2 mm Hg will be accompanied by a 10% lower risk of death due to stroke or 7% due to ischemic heart disease (Lewington et al. 2002). Albeit

Table 4. League table (Low risk of bias sensitivity analysis): The values above the diet classes correspond to the difference in mean (95% CI) in DBP (mmHg) between the row and columns (eg, the mean difference in average DBP between DASH and Low-Fat diets is −3.18 mmHg). The value below the diet classes correspond to the difference in mean in SBP (mmHg) between the column and the row (eg, the mean difference in average SBP between DASH and Low-Fat diets is −5.83 mmHg);DASH, Dietary Approaches to Stop Hypertension; DBP, diastolic blood pressure; SBP, systolic blood pressure.

DBP (mmHg)										
DASH	−1.91 (−4.00, 0.18)	−2.59 (−5.05, −0.13)	0.82 (−5.55, 7.19)	−1.83 (−4.55, 0.88)	−4.01 (−7.76, −0.27)	−2.80 (−5.98, 0.38)	−1.09 (−4.90, 2.72)	−3.42 (−5.83, −1.02)	−3.18 (−4.89, −1.47)	−3.79 (−5.72, −1.86)
−4.15 (−7.46, −0.85)	Mediterranean	−0.68 (−2.62, 1.26)	2.73 (−3.55, 9.00)	0.07 (−2.41, 2.56)	−2.10 (−5.79, 1.58)	−0.89 (−3.84, 2.06)	0.82 (−3.06, 4.69)	−1.52 (−4.02, 0.99)	−1.27 (−2.59, 0.05)	−1.88 (−3.93, 0.16)
−4.24 (−8.09, −0.39)	−0.08 (−3.18, 3.01)	Low-Carb	3.41 (−2.99, 9.81)	0.76 (−2.04, 3.55)	−1.42 (−5.32, 2.47)	−0.21 (−3.24, 2.83)	1.50 (−2.58, 5.57)	−0.83 (−3.64, 1.97)	−0.59 (−2.42, 1.24)	−1.20 (−3.61, 1.21)
3.17 (−11.04, 17.38)	7.32 (−6.81, 21.46)	7.41 (−6.86, 21.67)	Palaeolithic	−2.65 (−9.15, 3.84)	−4.83 (−11.86, 2.20)	−3.62 (−10.30, 3.07)	−1.91 (−9.05, 5.22)	−4.24 (−10.74, 2.25)	−4.00 (−10.13, 2.13)	−4.61 (−10.94, 1.72)
−7.12 (−11.76, −2.47)	−2.96 (−7.36, 1.43)	−2.88 (−7.69, 1.93)	−10.29 (−24.78, 4.20)	High-Protein	−2.18 (−6.23, 1.87)	−0.96 (−4.39, 2.46)	0.74 (−3.48, 4.97)	−1.59 (−4.61, 1.43)	−1.35 (−3.49, 0.80)	−1.96 (−4.61, 0.70)
−6.96 (−12.50, −1.42)	−2.81 (−8.32, 2.71)	−2.73 (−8.58, 3.13)	−10.13 (−25.00, 4.74)	0.16 (−6.23, 6.54)	Moderate-Carb	1.21 (−3.13, 5.56)	2.92 (−1.87, 7.71)	0.59 (−3.18, 4.36)	0.83 (−2.61, 4.27)	0.22 (−3.27, 3.71)
−2.96 (−8.16, 2.24)	1.19 (−3.72, 6.10)	1.27 (−3.69, 6.24)	−6.13 (−20.81, 8.54)	4.15 (−1.76, 10.06)	4.00 0 (−2.79, 10.79)	Low GI/GL	1.71 (−2.80, 6.22)	−0.63 (−4.03, 2.78)	−0.38 (−3.04, 2.27)	−0.99 (−4.08, 2.09)
−3.18 (−9.51, 3.15)	0.97 (−5.47, 7.41)	1.05 (−5.67, 7.78)	−6.35 (−21.59, 8.89)	3.94 (−3.26, 11.13)	3.78 (−3.72, 11.28)	−0.22 (−7.78, 7.34)	Nordic	−2.33 (−5.92, 1.25)	−2.09 (−5.73, 1.55)	−2.70 (−5.99, 0.59)
−6.15 (−10.01, −2.29)	−2.00 (−6.04, 2.04)	−1.92 (−6.41, 2.57)	−9.32 (−23.71, 5.06)	0.96 (−4.20, 6.13)	0.81 (−4.77, 6.39)	−3.19 (−8.84, 2.46)	−2.97 (−9.04, 3.09)	Low sodium	0.24 (−1.88, 2.37)	−0.37 (−1.80, 1.07)
−5.83 (−8.44, −3.22)	−1.68 (−3.81, 0.46)	−1.59 (−4.49, 1.30)	−9.00 (−22.97, 4.97)	1.29 (−2.56, 5.14)	1.13 (−3.97, 6.23)	−2.87 (−7.35, 1.61)	−2.65 (−8.73, 3.44)	0.32 (−3.12, 3.77)	Low-Fat	−0.61 (−2.18, 0.96)
−6.88 (−9.89, −3.87)	−2.73 (−5.97, 0.51)	−2.65 (−6.43, 1.14)	−10.05 (−24.24, 4.13)	0.24 (−4.33, 4.80)	0.08 (−4.95, 5.11)	−3.92 (−9.03, 1.20)	−3.70 (−9.26, 1.86)	−0.73 (−3.14, 1.68)	−1.05 (−3.51, 1.41)	Control
SBP (mmHg)										

the overall net effect was modest for several dietary approaches, it is important to note that the control/low-fat groups also experienced some benefit and the results were incremental reductions experienced by those groups adopting dietary interventions.

Although this is the first network meta-analysis to assess the comparative effects of different dietary approaches, several previous pairwise meta-analyses have been published, either including only one dietary approach or mixing normotensive and hypertensive patients. A recent standard pairwise meta-analysis of 24 randomized trials including 23858 normotensive and hypertensive participants showed that the DASH, the Mediterranean, a low-sodium and a low-calorie diet were all effective in reducing blood pressure, whereas the Mediterranean diet did not significantly decrease SBP compared to control diets (Gay et al. 2016). Similar to our findings, previous meta-analyses reported a strong reduction in SBP and DBP by the DASH diet (Ndanuko et al. 2016; Saneei et al. 2014; Siervo et al. 2015).

The DASH dietary pattern is based on several food groups like whole grains, fruits, vegetables, dairy products (mainly low-fat), and nuts and lower intakes of red and processed meat as well as and sweets (Schwingshackl and Hoffmann 2015b). Optimal consumption of risk-decreasing foods (whole grains, fruits, nuts, legumes and dairy products) resulted in a 41% reduction of hypertension compared to non-consumption of these foods (Schwingshackl et al. 2017b). One potential explanation for the superiority of the DASH diet compared to the Mediterranean diet is the recommendation to increase dairy products and at the same time to lower sodium intake (Sacks et al. 2001) in the former regime, whereas the latter discourages higher intakes of dairy products and does not consider sodium in the diet (Trichopoulou et al. 2003). The original DASH diet was tested independent of sodium intake (Appel et al. 1997). However, 6 out of the included 7 trials investigating the DASH approach in the present NMA tested the effects of the refined DASH diet implementing sodium restriction, whereas one trial did not provide the corresponding information (Edwards et al. 2011).

Anti-hypertensive effects of DASH dietary components are biologically plausible, given the high intake of constituents like phytochemicals and nutrients such as magnesium, potassium, calcium, lactotripeptides, selenium, zinc, antioxidants, vitamins, unsaturated fatty acid, and fibre which have been shown to lower blood pressure (Alonso et al. 2006; Appel et al. 2006; Fekete, Givens, and Lovegrove 2015; Han et al. 2017; Houston 2011; Schwingshackl, Strasser, and Hoffmann 2011; Whelton et al. 2005).

Whereas the evidence for an antihypertensive effect of the DASH diet is highly consistent, inconsistent results were reported for the Mediterranean Diet. One recent meta-analysis of six trials including more than 7,000 participants found insufficient evidence to suggest that the Mediterranean Diet decreased blood pressure (Nissensohn et al. 2016). In contrast, another recent meta-analysis showed that the Mediterranean dietary approach was effective in reducing SBP and DBP (Ndanuko et al. 2016).

Across all dietary approaches, only the low-sodium diet was rated with a high quality of meta-evidence. The blood pressure lowering effect observed in the present meta-analysis is consistent with several pairwise meta-analyses of randomized trials (Aburto et al. 2013). In line with our and previous findings the European Society of Hypertension and Cardiology rated the recommendation for the prevention and management of hypertension of a maximum daily salt intake of 5–6 gram with the highest level of evidence (Mancia et al. 2013b).

Previous meta-analyses reported conflicting results regarding the blood pressure lowering effects of LC and HP diets (Bueno et al. 2013; Mansoor et al. 2016; Santesso et al. 2012; Schwingshackl and Hoffmann 2013b; Wycherley et al. 2012). Although in the present network meta-analysis the LC and the HP diets were more effective in reducing blood pressure compared to control diets, the effects compared to LF diets were not statistically significant.

The results based on the Palaeolithic, Vegetarian, Nordic, and Tibetan dietary approach should be interpreted with caution, since only a very low number of trials (≤ 2) were available. Nevertheless, our findings for the Palaeolithic diet are in line with a previous pairwise meta-analysis showing a reduction in SBP (Manheimer et al. 2015). Blood pressure reductions of the Vegetarian diet and the Nordic diet as reported by previous meta-analyses could not be confirmed (Ndanuko et al. 2016; Yokoyama et al. 2014) in pre-hypertensive and hypertensive individuals. Similar to our findings, a recent meta-analysis comparing LGI/LGL vs. high-GI diets showed evidence of a blood pressure reducing effect of low GI/GL diets (Evans et al. 2017).

Beside diet and physical activity, but very likely mediated via these measures, weight loss is the third big lifestyle pillar in the prevention and management of hypertension (Mancia et al. 2013a). In a comprehensive dose-response meta-analysis, each kilogram of weight loss showed a reduction of approximately 1 mmHg of diastolic and systolic blood pressure, respectively (Neter et al. 2003). In line with these observations, the meta-regression analysis showed that larger differences in body weight changes between arms within trials were associated with a stronger impact on SBP and DBP, compared to smaller differences.

4.1. Strengths & limitations

The present systematic review has several strengths including the application of network meta-analyses methodology, which simultaneously combined direct and indirect evidence, the stringent inclusion and exclusion criteria, the high number of included dietary approaches, participants and trials, the comprehensive literature search, the assessment of the risk of bias, subgroup and sensitivity analyses, the a priori published systematic review protocol, the quality of meta-evidence assessment, and the overall low observed heterogeneity.

Several limitations should be considered when interpreting the results. First, all analyses were based on the original intended randomized design, not by adherence to the actual dietary approach and/or macronutrient composition and caloric intake consumed. This means that although participants were randomized to various dietary approaches, details on their actual adherence to the dietary program were not accounted for in the analyses. Second, 44 of 67 trials were rated as unclear or high risk of bias mostly due to lack of allocation concealment and blinding. The risk of bias sensitivity analysis was based on

23 trials, and only the primary results for the DASH dietary pattern could be confirmed. Third, was the substantial clinical heterogeneity for the included populations in terms of age, sex, study methods, study duration, sample size, and differences in food intake included across the various dietary pattern. Blood pressure reduction was lower in long-term studies, suggesting that participant's adherence decline over time. Moreover, larger size studies (sample size: $\geq$100) had a lower effect on blood pressure reduction compared to studies with a smaller sample size ($<$100). Fourth, due to the low number of studies including hypertensive patients, we were not able to run a sensitivity network meta-analysis. Finally, several nodes were not well connected, due to the low number of trials and this should be taken into account when interpreting the results of the present network meta-analysis.

5. Conclusion

Our network meta-analysis suggest that the DASH dietary approach might be the most effective dietary approach to improve blood pressure in pre-hypertensive and hypertensive patients based on high quality evidence. The findings of the present network meta-analysis have important clinical and public health implications, suggesting that dietary modifications characterized by high consumption of fruit and vegetables, whole grains, legumes, nuts and seeds, and dairy products and low consumption of red and processed meat, sugar sweetened beverages and sodium are an effective method for controlling blood pressure within pre-hypertensive and hypertensive populations.

Competing interests

Authors declare to have no competing of interest.

Acknowledgments

We thank Thomas Wolever, PhD for sending us additional data for the corresponding meta-analysis.

Authors' contributions

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

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