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The effect of dietary sodium modification on blood pressure in studies of participants with systolic blood pressure less than 140mmHg: A systematic review

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Executive summary

Background: Modifying dietary sodium intake is a cornerstone of diet advice for lowering blood pressure under the assumption that it is protective against cardiovascular disease. Previous meta-analyses of normotensive participants have not excluded all studies that recruited participants with systolic blood pressure (SBP) >140mmHg, which greatly hinders generalization to the wider normotensive population.

Objectives: The objective of this review was to identify the effectiveness of reducing or increasing sodium intake on blood pressure in normotensive participants with systolic blood pressure ≤140mmHg.

Inclusion criteria

Types of participants: This review considered studies on adult participants (≥ 18 years) with SBP ≤140mmHg. Studies in pregnant women or patients prescribed antihypertensive or vasoactive medications were excluded.

Types of interventions: Interventions that quantitatively evaluated dietary sodium intake for equal to or greater than 4 weeks duration were considered. Only studies that included two study arms comprising of different levels of sodium intake were included.

Types of outcomes: Studies that reported systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse wave velocity (PWV), pulse wave analysis, or flow mediated dilatation were considered.

Types of studies: Experimental study designs including randomized controlled trials and non-randomized controlled trials were considered.

Search strategy: An initial search strategy was conducted on databases MEDLINE and CINAHL before an extensive search of all relevant published and grey literature databases, and clinical trial registries were searched.

Methodological quality: Potential papers were assessed for methodological validity using the standardised critical appraisal instrument from the Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI).

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Data collection and synthesis: Quantitative data was extracted from papers using the standardised data extraction tool from JBI-MAStARI and pooled in statistical meta-analysis. Effect sizes were expressed as weighted mean differences and 95% confidence intervals. Meta-analysis was conducted using a random-effect model, and heterogeneity assessed statistically using the standard Chi square test and the I^2 index. Sub-group analyses were undertaken on studies achieving ≥40mmol versus <40mmol in urinary sodium excretion, studies ≤12 weeks and studies with a mean BMI ≥30 versus less than 30.

Results:
Five trials were included with a total of 1214 participants. The overall reduction in SBP was -0.71mmHg (95% CI: -2.62, 1.20, p=0.47); and DBP -0.57mmHg (95% CI: -1.26, 0.12, p=0.10). There was no significant change in PWV following reduction of dietary sodium over a four to six week period. Sub-group analysis did not find a significant effect of urinary sodium excretion, study duration ≤12 weeks or BMI on outcomes, however trend towards a greater reduction in blood pressure was observed in those with a higher BMI (MD -2.41, 95%CI -5.72, +0.91, p=0.16).

Conclusions: Blood pressure in normotensive participants was not significantly affected by sodium modification, and was controlled to within 1% of baseline values overall and with extended study duration. Reducing dietary sodium in normotensive participants may still be of importance for cardiovascular risk management, however good quality interventional research is limited.

Implications for Practice: Healthy normotensive populations effectively respond to changes in sodium intake by regulating blood pressure. Sodium reduction may still be cardio-protective but given the lack of data from intervention studies on the safety and efficacy of very low levels of sodium intake (<1500mg/day) in those with normal blood pressure, superfluous sodium restriction should be avoided.

Implications for Research: To better understand true normotensive blood pressure response, and the impact of sodium on cardiovascular risk, further intervention studies in subjects with SBP ≤130-140mmHg are required. Studies should be at least 1-year in duration and follow up participant's cardiovascular risk and outcomes long term.

Keywords: Normotensive, normotension, blood pressure, pulse wave analysis, salt, sodium

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Summary of findings:

Low sodium compared to High sodium in Normotensive subjects

Patient or population: Normotensive subjects
Setting: Community settings (i.e. free living populations) and controlled conditions (e.g. metabolic ward, hospital, study centre)
Intervention: Low sodium
Comparison: High sodium

Outcomes	Anticipated absolute effects* (95% CI)		№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with High sodium	Risk with Low sodium			
Change in systolic blood pressure (SBP) assessed with: mmHg follow up: range 4 weeks to 36 months	The mean change in systolic blood pressure ranged from **-2.8 to 3.0**	The mean change in systolic blood pressure in the intervention group was 0.71 lower (2.62 lower to 1.2 higher)	1399 (5 RCTs)	⨁⨁⨁⨁ HIGH	Moderate heterogeneity was observed. Strict inclusion criteria reduced the risk of bias but limited the number of studies available for pooling.
Change in diastolic blood pressure (DBP) assessed with: mmHg follow up: range 4 weeks to 36 months	The mean change in diastolic blood pressure ranged from **-2.4 to +2.4**	The mean change in diastolic blood pressure in the intervention group was 0.57 lower (1.26 lower to 0.12 higher)	1399 (5 RCTs)	⨁⨁⨁⨁ HIGH	Low heterogeneity was observed.
Changes in pulse wave velocity (PWV) assessed with: m/s follow up: range 4 weeks to 6 weeks	The mean changes in pulse wave velocity ranged from **-1.4 to +0.13** m/s	The mean changes in pulse wave velocity in the intervention group was 0.82 m/s higher (0.7 lower to 2.33 higher)	100 (2 RCTs)	⨁⨁⨁◯ MODERATE [1][2][3]	Low heterogeneity was observed. Few published trials and the small sample size may have limited the ability of this meta-analysis to detect a significant change

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1. Publication bias not detected with searching of clinical trial registries and grey literature
2. Small sample size
3. Pooling of data from non-obese and obese subjects

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Introduction

Background

Hypertension is a significant risk factor for cardiovascular disease (CVD) and has been identified as the leading single risk factor in the global burden of disease[1, 2] Hypertension guidelines frequently recommend salt reduction as an important simple strategy to reduce high blood pressure.[2-4] This recommendation is often extended to normotensive individuals as well, particularly those at risk of becoming hypertensive.[5] However, it has not been conclusively shown that dietary sodium reduction in normotensive adults is effective in lowering blood pressure.

The pressure–natriuresis relationship that was first described by Guyton[6] proposes a link between dietary sodium intake and renal sodium handling. Specifically, the hypothesis states that in a normal individual, consumption of a dietary sodium load will elicit a transient rise in blood pressure that stimulates the kidney to excrete sodium. The kidney will excrete excess sodium leading to restoration of normal blood pressure. This hypothesis explains how blood pressure is maintained over the longer term even though most individuals report day-to-day variation in sodium intake.[6, 7] Following this hypothesis, intervention studies in normotensive subjects may be expected to observe a small amount of variation in blood pressure with changes to dietary sodium intake, but this variation should be small enough to be considered clinically irrelevant. Intervention studies examining the effect of dietary sodium have reported a range of different responses; from significant changes[8, 9] to moderate effects on blood pressure, to no effect at all.[10-12] Normotensive studies that report blood pressure changes over the longer term have previously documented changes in systolic blood pressure (SBP) ranging from -1mmHg[12] to increases of 8.2mmHg.[8] This variation may be largely explained by the inclusion of participants with SBP >140mmHg in earlier normotensive studies, or the exclusion of subjects with SBP <120mmHg.

We searched Cochrane and JBI libraries, Prospero and Medline and identified three previous systematic reviews of blood pressure response to dietary sodium restriction.[13-15] Unfortunately we also identified a major limitation common to all three reviews[14] and those with an element of selection bias, from pooled results. Whilst some may argue that normotensive response to sodium is irrelevant, it is actually critically important for interpretation of evidence in clinical practice that a baseline response to dietary sodium is established. A stronger and more robust analysis of response would also assist in the development of future clinical trials and public health recommendations, such as WHO guidance and dietary guidelines[2, 16].

If the blood pressure reduction in truly normotensive subjects is indeed clinically irrelevant, as Guytons hypothesis suggests it should be, future recommendations for sodium reduction in normotensive populations with no other blood pressure risk factors would need to establish other cardiovascular benefits, such as effects on other markers of arterial function or a direct reduction in cardiovascular risk. Whilst literature does not currently provide sufficient quality evidence to directly link sodium intake with mortality in normotensive subjects[5], it will be important for future reviews to consider this if large scale intervention studies are ever conducted. A number of randomised controlled trials have however investigated the effects of dietary sodium intake on arterial function, and found that these effects may be at least partly independent of blood pressure.[17-22] As these effects may be key in extending our understanding of sodium intake and disease risk, they form part of the bigger picture for dietary sodium intake and chronic disease risk. It is therefore important to consider data on arterial function such as pulse wave analysis, pulse wave velocity and flow mediated dilation in current and future meta-analyses of sodium restriction.

A revised systematic review and meta-analysis of normotensive response to sodium modification is required.[23] This systematic review will consider the evidence for longer term dietary sodium restriction in participants with SBP <140mmHg on arterial function.

Objectives

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The objectives are to identify the effect of reducing or increasing sodium intake on blood pressure in normotensive adults with SBP ≤140mmHg, and the effect of sodium reduction or supplementation on arterial function in participants with baseline SBP ≤140mmHg.

Inclusion criteria

Types of participants

This review considered studies on adult participants with SBP ≤140mmHg conducted in community settings (i.e. free living populations) and controlled conditions (e.g. metabolic ward, hospital, study centre). Studies in pregnant women or participants prescribed antihypertensive or vasoactive medications were excluded.

Types of interventions

Interventions that evaluated dietary sodium intake for ≥4 week's duration were considered. Only studies that included two study arms comprising of different levels of sodium intake, and that modified sodium intake via dietary modification, salt reduction and/or salt supplementation were included.

Types of outcomes

Studies that reported SBP, diastolic blood pressure (DBP), pulse wave velocity, pulse wave analysis, or flow mediated dilatation (FMD) by Doppler ultrasound were considered.

Types of studies

Experimental study designs including randomized controlled trials and non-randomized controlled trials were considered. Studies with an element of selection bias (e.g. normotensive studies that excluded subjects with systolic blood pressure <120mmHg) were excluded.

Search strategy

The search strategy (Appendix I) endeavoured to find both published and unpublished studies. A three-step search strategy was utilised in this review. An initial limited search of MEDLINE and CINAHL was undertaken followed by analysis of the text words contained in the title and abstract, and of the index terms used to describe article. A second search using all identified keywords and index terms was then undertaken across all included databases. Thirdly, the reference lists of all identified reports and articles were searched for additional studies. Studies published in any language were considered for inclusion in this review, with non-English publications translated to English. Titles and/or abstracts published in non-English language were translated before decision to include or exclude. Studies published between 1980 and the present day were considered for inclusion in this review. Prior to 1980, the definition of normotension exceeded 160mmHg systole. In addition, such studies were not well controlled or reported as per the CONSORT statement.[24]

The databases searched included; MEDLINE, CINAHL, PROQUEST, Scopus, EMBASE, Cochrane Library, and Wiley InterScience. Additionally clinical trial registrars Australia and New Zealand Clinical Trials Registry, ClinicalTrials.gov, ISRCTN, WHOICTRP were searched using the search terms listed below. These registries were rechecked prior to manuscript submission to ensure no other recently published studies matched the inclusion criteria of this review. The search for unpublished studies included: Proquest Dissertations and Theses Database, Dissertations and Theses International, Mednar, OpenSIGLE, EAGLE. Initial keywords used were: sodium, salt, blood pressure, normotens*, systolic, diastolic, pulse wave, controlled, endothelial function, diabet*.

Method of the review

Critical appraisal

Potential papers selected for retrieval were assessed for methodological validity prior to inclusion using the standardised critical appraisal instrument from the Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI; Appendix II). The papers retrieved were assessed by two reviewers (SK, JK) prior to inclusion in the review using standardised critical appraisal instruments from the Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI) (Appendix II). The JBI_MAStARI tool captured study design limitations and

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the critical appraisal process also identified elements of selection bias (e.g. studies excluding true normotensive participants <120mmHg) and variation within interventions such as the dose, method and duration of dietary sodium modification that were evaluated. Where a a study scored poorly on the JBI-MASTARI tool or a high level of selection bias (eg. exclusion of participants with SBP<120mmHg) or significant confounding was identified, studies were excluded from the review. Any disagreements that arose between the reviewers were resolved through discussion, or through a third reviewer (KD or AT). Where a reviewer had been involved in research work that had resulted in the publication of an included study, the respective study was assigned to an alternative reviewer for quality analysis.

Data collection

Quantitative data were extracted from papers included in the review using the standardised data extraction tool from JBI-MAStARI (see Appendix III). The data were extracted independently by two reviewers (JK, SK), and included specific details about the interventions, populations, study methods and outcomes of significance to the review question and specific objectives. Any difference in data extraction was resolved through discussion, or by a third reviewer (AT). A process reviewer checked adherence to study protocol (SH). For studies with missing data, an attempt was made to contact corresponding authors in order to make a decision about the studies eligibility and/or to include in our analysis.

Data synthesis

For each trial retrieved, outcome variables for overall treatment effect were calculated. For crossover trials, the calculated treatment effect was the difference between end of reduced sodium period and the end of control period from baseline. For parallel trials, the treatment effect was the difference between the intervention (i.e. reduced dietary sodium) and control groups change from baseline to the end of follow-up for each of the measured outcomes. A correlation coefficient (r) of 0.5 was used to impute the missing SD of change.[19] The SD of net change for cross-over trials was also imputed using r = 0.5. Quantitative data was, where possible, pooled in statistical meta-analysis using RevMan (version 5.3.3). All results were subject to double data entry. Due to the variation observed in the characteristic of trials included, the DerSimonian and Laird random-effect model was used in conducting the meta-analysis. Heterogeneity assessed statistically using the standard Chi square and the I^2 index. An I^2 value of 25% was considered to represent low heterogeneity, and 75% high heterogeneity.[25] Values were considered statistically different from zero using a Z-test analysis where $p < 0.05$ was observed. Where statistical pooling was not possible the findings were presented in narrative form including tables and figures to aid in data presentation where appropriate. A one-by-one sensitivity analysis was performed by assessing the effect of individual studies on the overall results of meta-analysis. To assess the robustness of chosen correlation coefficient, sensitivity analysis of alternative coefficients (r = 0.2 and 0.8) was also conducted. Sub-group analyses were planned to examine studies recruiting participants with SBP ≤130mmHg, studies achieving a 40mmol or greater reduction in urinary sodium excretion, studies conducted in participants of different ethnicities, and studies conducted in those with and without a diagnosis of diabetes. We only identified one study each in participants with SBP ⩽130mmHg, participants of African American ethnicity, and in participants with diabetes, therefore sub-group analysis was not conducted.

Results

Number of studies found and retrieved

The search strategy identified 1724 studies, from which 1491 were excluded on the basis of title and abstract review. Upon detailed review, 221 articles were excluded primarily for reasons outlined in the PRISMA flow chart (see Figure 1). The most common reasons for exclusion were inclusion of participants with baseline systolic blood pressure above >140mmHg, use of antihypertensive medications, or study duration less than four weeks (see appendix IV for excluded studies). A total of 12 studies were initially retrieved but following eligibility assessment a further seven were excluded for being outside the inclusion criteria for this review. Two of these studies[26, 27] were excluded following contact with authors that confirmed both studies had five percent of participants with SBP greater than 140mmHg at baseline. Two studies[28, 29] did not have values for SBP inclusion at baseline and were excluded when the authors were unable to provide appropriate statistical data, and one study used a 25% potassium chloride salt substitute and reported a four-fold greater increase in potassium excretion in the intervention group compared with the control group.[30] Two further studies[31, 32] were excluded, as

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they only recruited pre-hypertensive participants and excluded participants with SBP <120mmHg. These studies were not considered of appropriate design to inform the main objective of this review – to establish the effect of modifying dietary sodium intake in normotensive participants, due to the significant population of normotensive subjects that were excluded. The exclusion of subjects with SBP<120mmHg was considered to introduce a significant element of selection bias that was likely to impact the outcome of these studies. Further identification of potential studies was carried out by analysing all included studies' reference lists, and one additional study was retrieved. Following quality analysis one further study[33] was excluded (Table 1) to give a total of five studies. One non-English study was identified as meeting the inclusion criteria,[33] this study was available in English format and was excluded on quality assessment. One study reported the SD of change from baseline[7] however mean (SD) of outcome measures were not reported and a correlation coefficient could not be calculated.[19]

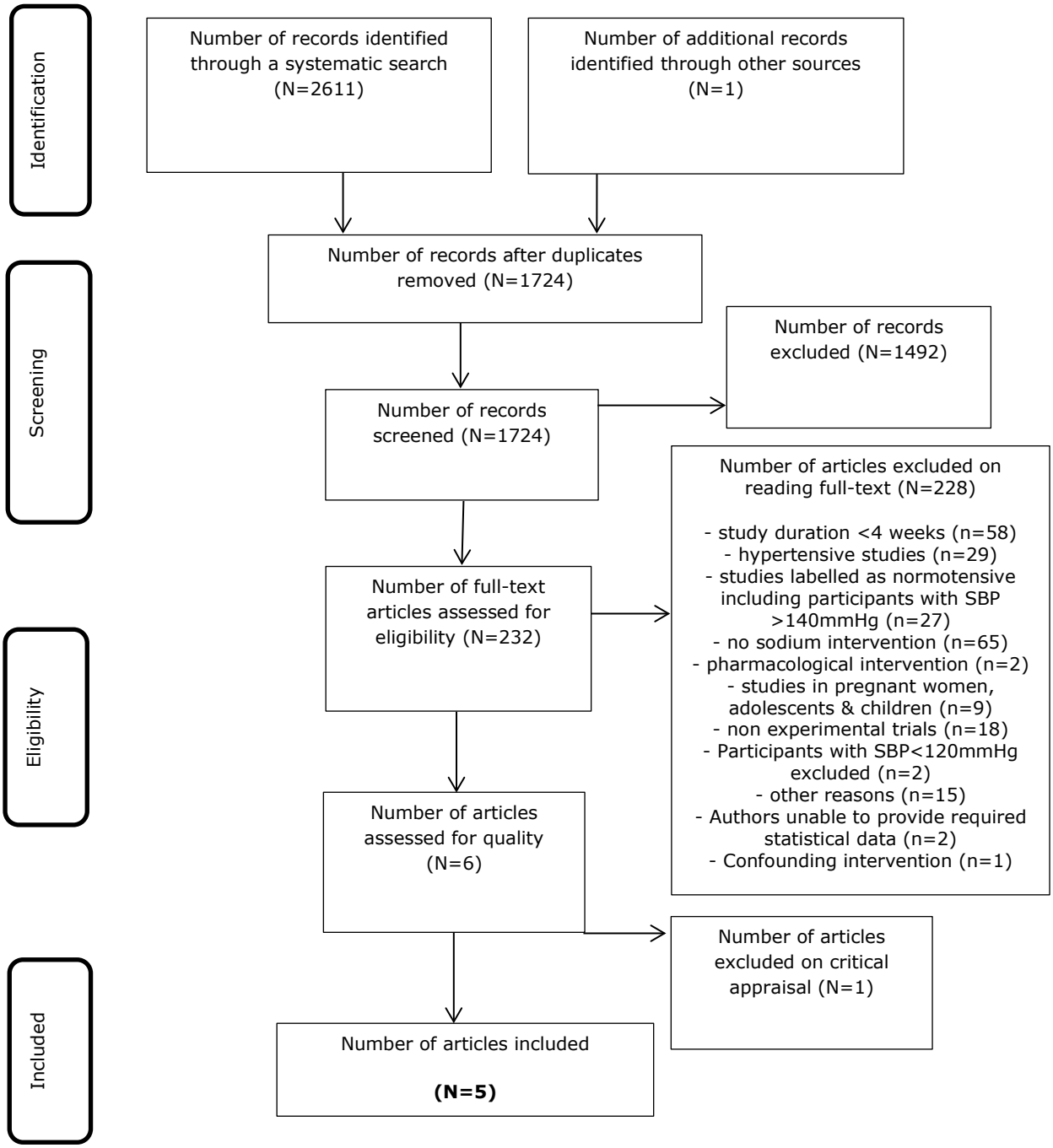

Figure 1: Flow-chart for the search and study selection process

Description of studies

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Of the five articles retrieved and included in the meta-analysis, four were crossover designs,[10, 11, 20, 34] and one was a parallel study design.[12] Three studies were in Caucasians,[10, 11, 20] one was in a African American population,[34] and one was mixed race.[12] All studies utilised different BMI cut-offs, two included obese participants[12, 20] and two were in non-obese participants.[10, 11] One study did not include BMI as an inclusion or exclusion criteria.[34] Two studies[10, 11] implemented four week duration interventions, one implemented a six week intervention,[20] another an eight week intervention.[34] The longest study ran for 48 months, with data collected on all participants for a minimum of 36 months.[12] All five articles reported SBP and DBP, two studies reported PWV,[11, 20] and one study reported FMD.[20] Physical activity was not reported in the five included studies.

Methodological quality

Methodological quality was moderate-to-high across all included studies (see Table 1). Randomisation procedures were adequate in the majority of the included studies and all treatment groups were comparable at entry and treated identical throughout the treatment period. Blinding of study personnel was only possible in one study, although blinding of the participant was only done in two of the included studies, achieving this type of blinding is generally difficult in dietary studies,[35] and is reduced by ensuring all outcome assessors are blind to the randomisation allocation, which was done adequately in four of the five studies.

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Table 1: Quality assessment of the included studies.

Citation	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
Dickinson, Keogh JB, Clifton PM, 2014	N	N	Y	Y	Y	Y	Y	Y	Y	Y
Flack J, Grimm Jr R, Staffileno B, Elmer P, Yunis C, Hedquist L, et. al, 2001	Y	Y	U	U	Y	Y	Y	Y	Y	U
Ruppert M, Overlack A, Kolloch R, Kraft K, Göbel B, Stumpe KO, 1993	Y	Y	U	Y	N	Y	Y	Y	Y	U
Todd AS, MacGinley RJ, Schollum JB, Williams SM, Sutherland WH, Mann JI, Walker RJ, 2012	Y	N	N	Y	Y	Y	Y	Y	Y	Y
Trials of Hypertension Prevention Collaborative Research Group, 1997	Y	N	U	Y	U	Y	Y	Y	Y	Y
% Total	80%	40%	20%	80%	80%	100%	100%	100%	100%	60%

Results of the quantitative analysis

Effects of sodium reduction interventions*:*

A total of five trials with eight comparisons encompassed 1214 participants. The characteristics of studies included in this meta-analysis are presented in Appendix V. The mean blood pressure in the control/high sodium intake groups was 119.4/76.9mmHg. Estimated sodium excretion on usual sodium intake based on 24-hour collections and dietary intervention targets, was 175mmol (10 g/day salt), ranging from 134 to 190mmol (8-

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11g/day salt). The estimated change in dietary sodium from the usual to the reduced salt intake was -75mmol/day (range -37 to -136mmol), equivalent to a reduction in sodium intake 4 g/day (range 2-8g/day).

High sodium versus low sodium for blood pressure in all participants

Five trials (n=1214) were retrieved with data available for SBP; with a mean difference (MD) of -0.71mmHg (95% CI: -2.62, 1.20). There was no significant change in SBP following reduction of dietary sodium over the period of four weeks to 36 months (p=0.48 see Figure 2). The data displayed a moderate degree of heterogeneity (Chi^2 =8.77, p=0.07; I^2=54%) likely due to study design factors, such as the recruitment of obese subjects in two studies.[12, 20]

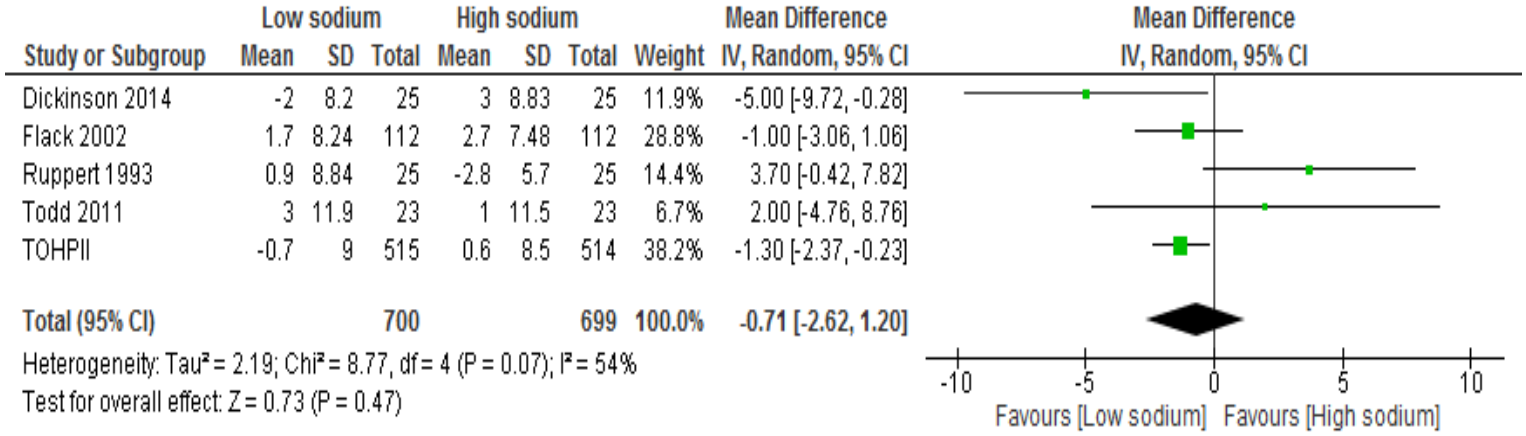

Figure 2: Forest plot of the effect of salt modification on systolic blood pressure. The effectiveness of salt modification is presented using random effect. The mean and SD of changes from baseline are reported for trials. Effects of trial are presented as weight (%) and mean difference (95% CI). The size of the box and its location on horizontal line represents the weight of each study; the variance reported by each study is represented by the horizontal line.

A total of five trials (n=1214) for DBP (Figure 3) had a MD of -0.57 mmHg (95% CI: -1.26, 0.12). There was no significant change in DBP following reduction of dietary sodium over the period of four weeks to 36 months (p=0.10). The data had low heterogeneity (Chi^2 =3.21, p=0.52; I^2=0%). Sensitivity analysis excluded individual studies and assessed the effect on overall results of meta-analysis. No significant effect on meta-analysis was observed by excluding any study on mean difference of DBP.

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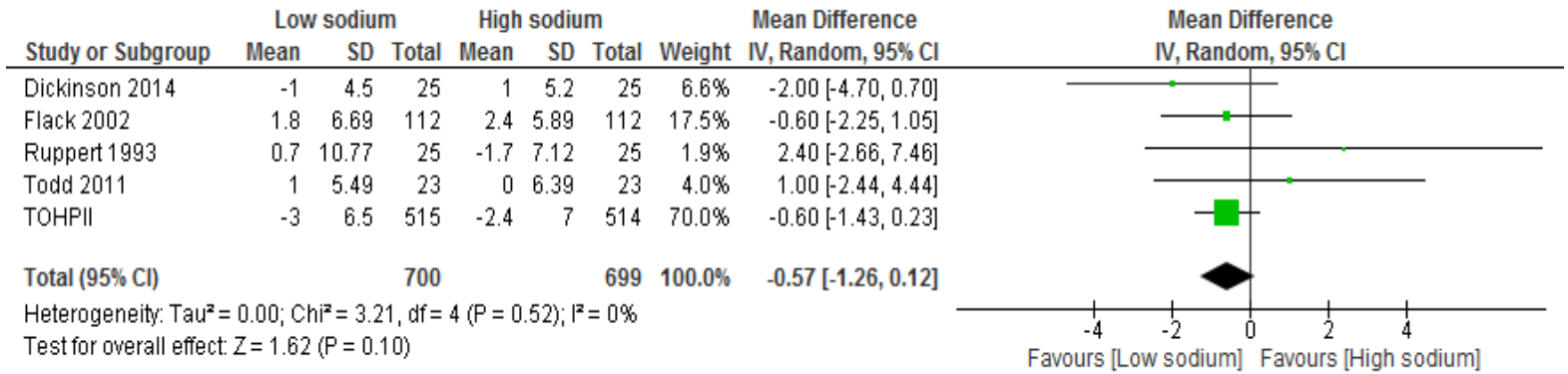

Figure 3: Forest plot of the effect of salt modification on diastolic blood pressure. The effectiveness of salt modification is presented using random effect. The mean and SD of changes from baseline are reported for trials. Effect of trial are presented as weight (%) and mean difference (95% CI). The size of the box and its location on horizontal line represents the weight of each study; the variance reported by each study is presented by the horizontal line

Sub-analysis of four trials with urinary sodium excretion >40mmol/day gave four comparisons encompassing 1102 participants with a MD of -0.40 (95% CI: -3.61, 2.81; p=0.81) (Table2). Sub-group analyses were originally planned to examine studies recruiting participants with SBP ≤130mmHg, participants of different ethnicities, participants with and without diabetes. Only one study was located that presented data for participants with SBP <130mmHg[11] and only one study was included, that presented data for participants of African American ethnicity,[34] therefore sub-analyses were not conducted. No studies were available in participants with diabetes.

Subgroup analysis of the duration of intervention showed a non-significant reduction of SBP and DBP when intervention duration is ≤12 weeks. The subgroup of cross-over design of the study did not show any statistically significant results. We also planned to present between group analyses for study design (parallel versus cross-over), and sodium excretion (>40mmol versus <40mmol/24 hours), however only one study was available for participants with a sodium reduction of <40mmol/24 hours and only one study was of parallel design.

Subgroup analysis also explored the sources of heterogeneity observed in meta-analysis results of SBP. A high heterogeneity was observed with subgroup of studies with intervention duration ≤12 weeks (74%). This may suggest an influence of study duration on the heterogeneity of results, however we are unable to confirm this as as only one study satisfies the ≥12 week study duration criteria. Baseline BMI of participants did not have a statistically significant effect on the meta-analyses of BP. However, a trend was observed with more pronounced reduction of both SBP and DBP in the subgroup of participants with mean baseline BMI >=30 kg/m^2, compared to those with mean BMI <30 kg/m^2 (Table 2).The test for subgroup difference was not significant for the effect of baseline BMI on BP.

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Table 2: Subgroup analysis of normotensive response to sodium modification by duration, achieved sodium reduction and design

Subgroups	Trials, n	Mean difference (95% CI) of SBP, mm Hg	Test for subgroup difference	Mean difference (95% CI) of DBP, mm Hg	Test for subgroup difference
Intervention duration ≤ 12 weeks	*n=4*	-0.24 (-3.62, 3.13; ρ=0.89; I^2=64%)		-0.48 (-1.83, 0.86; ρ=0.95; I^2=6%)	
Baseline BMI ≥30 kg/m²	*n=2*	-2.41 (-5.72, 0.91; ρ=0.16; I^2= 55%)	I^2=51%, ρ=0.15	-0.72 (-1.51, 0.07; ρ=0.07; I^2= 0%)	I^2=0%, ρ=0.45
Baseline BMI <30 kg/m²	*n=3*	-0.71 (-2.62, 1.20; ρ=0.55; I^2= 54%)		-0.09 (-1.51, 1.34; ρ=0.91; I^2= 0%)	
Reduction in sodium excretion ≥ 40 mmol/24 hours	*n=4*	-0.40 (-3.61, 2.81; ρ=0.81; I^2=66%)		-0.55 [-1.14, 0.03; ρ=0.71; I^2=6%)	
Design (Cross-over)	*n=4*	-0.24 (-3.62, 3.13; ρ=0.89; I^2=64%)		-0.48 (-1.83, 0.86; ρ=0.48; I^2=6%)	
All trials (meta-analysis result)	*n=5*	-0.71 (-2.62, 1.20; ρ=0.47; I^2=54%)		-0.57 (-1.26, 0.12; ρ=0.10; I^2=0%)	

1- Abbreviations used in this table: **DBP**: Diastolic blood pressure; **SBP**: Systolic blood pressure, **BMI:** Body-mass index
2- Changes in systolic and diastolic blood pressure are presented as mean difference and 95% confidence interval. Heterogeneity (I^2) is presented by %. A p-value <0.05 is considered significant.

High sodium versus low sodium for PWV in all participants

Of two trials, with two comparisons for PWV (Figure 4), 48 participants had a MD of 82 m/s (95% CI -1.26, 0.12). There was no significant change in PWV following reduction of dietary sodium over the period of four to six weeks (p=0.29). We were unable to perform a meta-analysis on FMD, because not enough studies met inclusion criteria.

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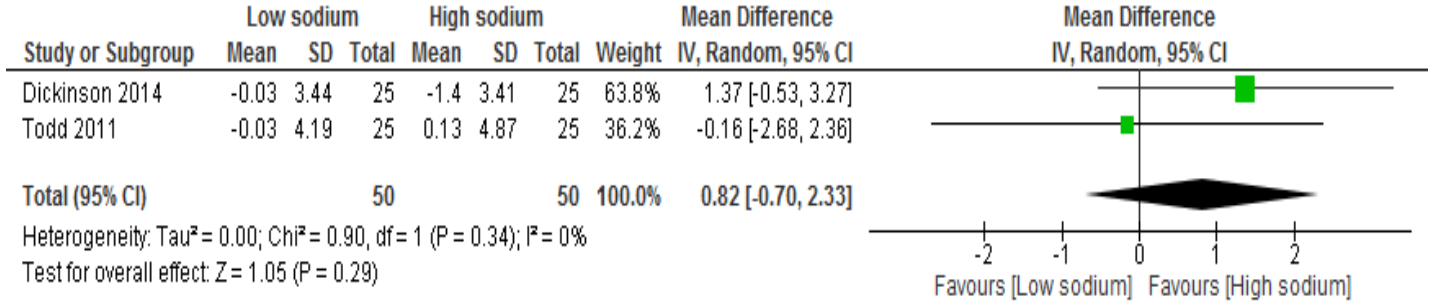

Figure 4: Forest plot of the effect of sodium modification on pulse wave velocity. The effectiveness of sodium modification is presented using random effect. The mean and SD of changes from baseline are reported for trials. The effect of each trial is presented as weight (%) and mean difference (95% CI). The size of the box and its location on horizontal line represents the weight of each study. The variance reported by each study is represented by the horizontal line

Sensitivity analysis

The sensitivity analysis of individual studies showed a significant effect of one study on SBP[10]. This may be due to 19 of the 25 participants in this study being classified as salt-resistant prior to study commencement, reducing the likelihood of a blood pressure response to dietary sodium. Excluding this study showed a more pronounced effect of dietary modification on overall meta-analysis results (-1.34, 95% CI: -2.46, -0.22, p=0.02). However, no significant effect of individual studies was observed on DBP. Sensitivity analysis of alternative correlation coefficients (r = 0.2 and 0.8) also did not report any significant changes using different levels of correlation coefficient. These results suggest the robustness of the analysis using chosen correlation coefficient (r = 0.05) (Appendix VI).

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Discussion

As far as we are aware, this is the first meta-analysis to report the effects of reducing dietary sodium intake on blood pressure as-well as FMD and PWV as markers of arterial function in normotensive participants with SBP equal to or less than 140mmHg; consistent with the current definition of normotension.[36, 37] The finding of this analysis is a reduction following long term sodium modification of just 0.6% of the participants' baseline SBP. This small change in blood pressure is not clinically significant, and indicates that modifying sodium intake in truly normotensive individuals is unlikely to produce a blood pressure benefit. Reduction in sodium intake in those who are high consumers, or those who are pre-hypertensive, or of African American descent may however curb age related rises in blood pressure and help to stem cardiovascular risk independent of blood pressure response.

The lack of blood pressure response to sodium modification in this combined sample of normotensive subjects is consistent with Guyton's hypothesis. This hypothesis provides an explanation for the truly normotensive kidney regulating blood pressure in a setting of dietary sodium loading or modification. Theoretically, acute phases of sodium loading or reduction should cause transient rises or falls in blood pressure, which are corrected by the normal functioning kidney after an initial period between one to two weeks.[7] Blood pressure appears to have been effectively regulated by the kidney in the majority of subjects in this review and a marked increase in blood pressure was not sustained. Although the pooled results show little effect of sodium, it is worth noting that the five included studies varied in their findings, reporting a range of changes to SBP from -5mmHg[20] to +3.7mmHg.[10] This variation can likely be attributed to participant characteristics. Close examination of the methods of the studies included in this analysis indicate that differences in SBP response may be due to factors such as the presence of obesity,[12, 20] or inclusion of participants of African-American ethnicity.[34]

To test the robustness of our primary finding, we performed sub-analyses by intervention duration less than 12 weeks and studies achieving greater (verse less) than 40mmol/day sodium reduction. Both these subgroups had similar non-significant effects on SBP, robust to our primary finding, and thus consistent with Guyton's hypothesis.

Differences between the results of this meta-analysis and previous meta-analyses can be explained by the inclusion of studies. Previous meta-analyses included all studies on participants 'labelled' as normotensive, including those conducted over 20 years ago when the definition of high blood pressure was undergoing review. Many trials labelled as normotensive trials were conducted prior to 1993,[26, 38-42] and the range of blood pressure readings observed in these trials is greater than the range of blood pressure readings observed in more recent studies of normotensive participants.[10, 20] Excluding early studies that include participants with SBP >140mmHg is necessary in order to detect the true effect of sodium reduction in participants with normal or high normal blood pressure.[10] However, exclusion of these studies greatly limits the field of available literature that has previously been described in numerous reviews. We initially planned to include sub-analysis of studies in normotensive participants with absence of pre-hypertension (i.e. SBP <130mmHg), in black populations, and in diabetics; but too few studies were retrieved to enable this.

The inclusion of pre-hypertensive participants in some studies included in this analysis may also account for some of the heterogeneity, as pre-hypertensive participants have previously been shown to have a greater response to sodium than their normotensive counterparts. It is worth noting that the DASH-Sodium study[31] was not included in this meta-analysis as it excluded the main population of interest- those with truly normotensive blood pressure (systolic blood pressure <120mmHg) and ran the intervention concurrently with other dietary changes that significantly altered potassium excretion. This study examined pre-hypertensive participants (SBP 120-140mmHg) and hypertensive participants. A reduction in sodium intake of 77mmol was observed in both the US diet arm and the DASH diet arm and the mean blood pressure on the US diet with high sodium intake was 128/81mmHg and this reduced by -5.6/-2.8mmHg following the low sodium intervention, in the pre-hypertensive subgroup.

Urine sub-analysis

A modest sodium reduction of 30mmol/24 hour has been proven in controlled and free-living situations to elicit a blood pressure response at a significant level.[12, 32, 42, 43] Previous trials have only included

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studies that had a 24-hour sodium urine excretion of >40mmol/day. For consistency with other literature we performed a sub-analysis of trials that achieved a urinary sodium reduction of 40mmol/day was performed and resulted in a non-significant reduction in SBP of -0.40 (95% CI: -3.61, 2.81; p=0.81) (see Table 2). It appears that regardless of the dose of sodium reduction, the normotensive kidney is effective in regulating blood pressure, robust to the primary finding.

Twenty-four hour urine collections to measure sodium excretion are the most accurate marker of dietary sodium intake in both epidemiological and experimental studies of dietary sodium restriction. However, compliance with complete collections is difficult to achieve in participants.[14] Two studies[11, 34] did not measure 24 hour urinary sodium excretion and were not included in this sub-analysis as a result. In Todd et al.,[11] ongoing dietetic review in all interventions in addition to regular early morning spot urine tests were used in place of 24 hour urinary sodium excretion to ensure dietary compliance to the interventions. The other study by Flack et al.[34] utilised a pooled 24 hour urinary (three individual eight hour collections) in addition to sodium pill counts in both interventions. These methods, although not the gold standard, have been shown to elicit significant differences in sodium excretion,[19] and have a role in measuring compliance, while ensuring the relevance in a clinical setting and reducing burden to participants in longer term studies. Both trials detail interventions that would have placed considerable burden on participants, through the complex nature of their design and lengthy durations, of 18 and 26 weeks respectively.

PWV and FMD Sub-analyses

PWV reflects artery elasticity - the higher the velocity of pulse wave transmission, the less elastic the wall.[44] Studies to date in normotensive participants have not yielded significant results in participants with SBP <140mmHg.[11, 20, 21] Improvements previously reported have been conducted in populations with blood pressure ranges up to 160mmHg.[45] FMD has been shown to be impaired following sodium loading in two previous normotensive studies, the included study by Dickinson et al.[20, 21] These studies both document non- significant correlations between FMD and blood pressure[20, 21] and only moderate correlations to PWV in hypertensive participants (r = 0.52, P<0.05);[19] suggestive of blood pressure independent pathways to endothelial and arterial function.

Relevance of the findings

Despite the World Health Organisation and other government bodies reporting that sodium reduction can reduce blood pressure in normotensive individuals,[2, 16] this is not supported by the current available evidence. Previous analyses of data used to inform public health policy around sodium intake have not acknowledged the limitations of available randomised controlled trials, and have incorrectly included studies with hypertensive participants in normotensive analyses. This has resulted in a greater blood pressure lowering effect than that which actually exists in truly normotensive individuals.

The results of this meta-analysis clearly demonstrates that modifying dietary sodium in healthy normotensive populations is not clinically effective to reduce blood pressure at an individual level over a period of four months to one year. Blood pressure remained within 1% of the subjects baseline readings, and only two studies were included in this subgroup which makes it difficult to draw conclusion on the influence of higher duration of modification. Reducing blood pressure is only of significance if it results in a reduction in CVD,[46, 47] and it has been previously suggested that this does not occur until a sustained change of 2-3mmHg over the long term is achieved.[47]

Despite the lack of effect on blood pressure it is important to note that reducing sodium may still be important in normotensive participants at a population level, as it may help to reduce the age-related rise in blood pressure and cardiovascular risk.[46, 48-51] Although there is good evidence to suggest reduction of sodium intake from high to moderate levels is safe and may benefit public health, recent epidemiological studies have controversially reported an increased CVD risk at very low levels of sodium intake (<1500mg/day).[52-54] This J-shaped association has predominantly been noted in diabetics and those with pre-existing heart disease.[52, 54] Recent data from the NHANES study indicates intakes greater than 1500mg sodium per day are likely to be safe for the majority of the population,[55]

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and this is in line with the magnitude of sodium reduction used in the majority of studies included in this review.

It is worth noting that separate meta-analyses addressing questions around cardiovascular risk reduction and sodium intake are available, but none contain a non-confounded analysis of normotensive participants. Taylor and co-workers,[56] included two trials in the normotensive analysis that recruited individuals with SBP >140mmHg[26, 42] in their meta-analysis of longer term RCT's examining overall mortality, cardiovascular mortality and cardiovascular morbidity. Only three truly normotensive trials were included and no findings were presented for overall or cardiovascular mortality, however a reduction in cardiovascular events was reported (RR 0.71, 95% CI 0.42, 1.20 p=). A second meta-analysis by Strazzullo *et al.*[51] also included both normotensive and hypertensive participants in a meta-analysis that evaluated dietary sodium intake and cardiovascular events. An increased risk of stroke (RR 1.23, 95% CI1.06, 1.43 p=0.007) and a non-significant trend between dietary sodium and CVD (RR 1.14, 95% CI 0.99, 1.32, p=0.07) was observed, however as with the meta-analysis by Taylor and co-workers it is impossible to determine from this analysis if an increased risk of CVD or stroke would be present in a purely normotensive population with SBP ≤140mmHg.

Cardiovascular risk associated with dietary sodium intake is an area in which further long term research is required. In our meta-analysis, four of the five studies included were less than eight weeks duration,[10, 11, 20, 34] and only one trial had a duration greater than a year.[12] In the context of cardiovascular risk, even trials labelled as long term are too short (i.e. less than six months) to measure outcomes in terms of cardiovascular events.

Potential limitations of this systematic review

A limitation of this study, like previous meta-analyses, is the lack of longer term trials with large sample numbers. We excluded studies that did not exclude all participants with hypertension as per the definition set by the JNC-7, and supported by the panel members of JNC-8.[36, 37] This resulted in two long term multi-centre trials being excluded.[26, 42] These two studies recruited a combined total of 1308 participants assigned to either a sodium reduction or control group, however, five percent of participants had SBP greater than 140mmHg.[47, 48] The long term effects of these sodium reduction interventions[26, 42] were -1.69/0.85mmHg and -0.3/0.1mmHg, respectively. Another limitation centres on retrieving the appropriate statistical information for dated and large scale multicentre trials. Because we could not be provided with such detail in some instances, trials were excluded.[32] One trial which had data for subgroups of normotensive populations[31] could not be included because the statistical data concerning mean and standard deviation for SBP/DBP could not be sourced.

Differences Between the Protocol and the Review

Additional exclusion criteria were added to ensure the results of the meta-analysis were consistent with the purpose of the review. Trials in pregnant women and trials that intentionally excluded truly normotensive subjects were excluded. JBI MAStARI was originally specified as the pooling software for the meta-analysis, as reported in our protocol,[23] however MAStARI was not operational at the time, so the review authors elected to use RevMan 5.3.5 consequently to conduct the meta-analysis. Additional sub-analyses were conducted for BMI and study duration, as these were additional study design aspects identified as having the potential to influence outcomes.

Implications for Public Health

- Current public health recommendations for reducing cardiovascular disease emphasise importance of population sodium reduction as a strategy to reduce blood pressure. The studies included in this review suggest modifying dietary sodium in a seemingly healthy normotensive population is not clinically effective to reduce blood pressure over a period of four months to one year at an individual level (JBI Grade B evidence);
- High sodium intake is linked to a higher risk of stroke, left ventricular hypertrophy, renal impairment, and can impair the arterial vasculature and endothelial function.[15, 18, 19, 22, 57] A moderate reduction in dietary sodium, to achieve a sodium intake between 1500-2300mg per day, may be cardio-

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protective independent of the blood pressure pathway; but this is inconclusive. It also may not be safe to recommend sodium restriction in older adults with diabetes or those with established cardiovascular disease. (JBI Grade B evidence).

- Given the lack of data on very low levels of sodium intake (<1500mg/day) in the general population, sodium restriction below this level should not be routinely recommended. (JBI Grade B evidence).

Implications for future research

Further long term clinical trials in normotensive subgroups are warranted to examine the effects of ethnicity, obesity, pre-hypertension, and diabetes. Recent literature suggests blood pressure reduction should not be overzealous in participants with diabetes,[52, 58] and individuals with hypertension and diabetes should be treated to a minimum blood pressure of 130mmHg,[59, 60] however this should be confirmed by well-designed randomised controlled clinical trials. As it is currently unknown what level of sodium reduction is safe for normotensive diabetics, trials should initially err on the side of caution and restrict sodium to a minimum intake of 1500mg/day. Dietary sodium restriction also has the potential to exacerbate glucose intolerance, therefore this outcome should be simultaneously examined, along with effects on the renin-angiotensin-aldosterone system.

To better understand dietary sodium intake, true normotensive blood pressure response, and the impact on CVD risk, studies that examine dietary sodium, blood pressure response and cardiovascular risk in participants with SBP equal to or less than 140mmHg over the longer term (i.e. greater than one year) are required. Randomised controlled trials with long term (greater than four week) duration should also be undertaken to look at other surrogate markers of cardiovascular risk, especially in the absence of longer term clinical trials examining hard outcome measures, which are likely to be logistically difficult, lengthy and very costly to undertake.[61]

Conclusions

Normotensive participants seemingly free of any renal or cardiovascular impairment are efficient in effectively regulating blood pressure to within 1% of their baseline SBP values, following a sodium reduction intervention. Blood pressure alone may not be effectively lowered by reducing dietary sodium in normotensive participants, however reducing cardiovascular disease risk may still be of importance. This review confirms that the blood pressure response of normotensive participants with systolic blood pressure less than or equal to 140mmHg does not significantly change over a period of four weeks or more.

Conflict of Interest

AT and KD are authors on papers included in this meta-analysis. These authors were not involved in the quality analysis or data extraction of their authored papers.

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Appendix I: Search strategy

MEDLINE (via Pubmed)

The following key words were used (03/03/2014) in the combination

Search	Query
#1	salt
#2	sodium
#3	1 OR 2
#4	normotens*
#5	(normal AND blood pressure)
#6	Diabete
#7	4 OR 5 OR 6
#8	blood pressure
#9	pulse wave
#10	endothelial function
#11	flow mediated
#12	8 OR 9 OR 10 OR 11
#13	randomi*
#14	3 AND 7 AND 12 AND 13

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Appendix II
MAStARI Appraisal instrument

JBI Critical Appraisal Checklist for Randomised Control / Pseudo-randomised Trial

Reviewer _____ Date _____

Author _____ Year _____ Record Number _____

	Yes	No	Unclear	Not Applicable
1. Was the assignment to treatment groups truly random?	☐	☐	☐	☐
2. Were participants blinded to treatment allocation?	☐	☐	☐	☐
3. Was allocation to treatment groups concealed from the allocator?	☐	☐	☐	☐
4. Were the outcomes of people who withdrew described and included in the analysis?	☐	☐	☐	☐
5. Were those assessing outcomes blind to the treatment allocation?	☐	☐	☐	☐
6. Were the control and treatment groups comparable at entry?	☐	☐	☐	☐
7. Were groups treated identically other than for the named interventions	☐	☐	☐	☐
8. Were outcomes measured in the same way for all groups?	☐	☐	☐	☐
9. Were outcomes measured in a reliable way?	☐	☐	☐	☐
10. Was appropriate statistical analysis used?	☐	☐	☐	☐
	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info. ☐

Comments (Including reason for exclusion)

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Appendix III
MAStARI data extraction instrument

JBI Data Extraction Form for Experimental / Observational Studies

Reviewer _____ Date _____

Author _____ Year _____

Journal _____ Record Number _____

Study Method

RCT	☐	Quasi-RCT	☐	Longitudinal	☐
Retrospective	☐	Observational	☐	Other	☐

Participants

Setting _____

Population _____

Sample size

Group A _____ Group B _____

Interventions

Intervention A _____

_____

Intervention B _____

_____

Authors Conclusions:

_____

_____

_____

Reviewers Conclusions:

_____

_____

_____

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Appendix IV: Table of included studies

Table 3: Table of included studies

MAStARI

Study	Methods	Setting	Participants	Intervention A	Intervention B	Outcomes	Notes
Dickinson 2014[18]	RCT X over Duration 6 weeks	Australia Free living	N= 25: Male and female, Overweight (BMI 27-40kg/m2), BP <139/89mmHg	Controlled 6g/day salt diet (+ placebo tablets)	Controlled 6g/day salt diet (+ 3g/day in salt tablets)	**1. BP** 2. Weight **3. FMD** 4. **PWV**, PWA, 5. Urinary Na+, K+, Cr, nitrates 6. Plasma vasoactive hormones (renin, aldosterone, endothelin-1 7. Adhesion molecules (intracellular adhesion molecule-1, endothelium-independent dilatation, vascular cell adhesion molecule-1) 8. Dietary intake	Sample comprised of obese/ participants
Flack	RCT X	United	N= 112: Native	10 individualised dietary	10 individualised dietary	**1. BP**	Participants only included if th

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Study	Methods	Setting	Participants	Intervention A	Intervention B	Outcomes	Notes
2001[34]	over Duration 8 weeks	States Free living	African-American males and females, compliant to urinary Na+ restriction <140mmol/L/day, BP <140/89mmHg, fasting glucose <7.7mmol/L	counselling sessions + 1-2 if required – aimed for a target sodium intake of 75-80mmol/day + sodium tablets	counselling sessions + 1-2 if required – aimed for a target sodium intake of 75-80mmol/day + placebo tablets	2. Weight 3. Urinary Na+, K+, Cr 4. Plasma Na+, K+, Cr, glucose, 5. Dietary intake	<140mmol/day in the eligibil Compliance to intervention th histories and pill cour
Ruppert 1993[10]	RCT X over Duration 4 weeks	Germany Free living , studied in hospital last day of each intervention	N= 25 (6 salt sensitive, 19 salt resistant), Male and female aged 20-65 years, BP <140/90, BMI<30kg/m^2	Standardised diet 85mmol sodium for four weeks	Standardised diet 200mmol sodium for four weeks	**1. BP** 2. Plasma Na+, K+ 3. Lipid profiles (TG, LDL, HDL, TC) 4. Plasma hormones (renin and noradrenaline)	Salt resistant individuals do no great falls in blood pressure follo reduction, compared to salt se sample is unevenly represen resistant participant
Todd 2012[11]	RCT X over Duration 4 weeks	New Zealand Free living	N= 23: Male and female aged 20-65 years, BP <130/85, BMI<30kg/m^2, no clinical signs/diagnosis CVD, renal insufficiency, or diabetes	Low salt (60mmol/day) diet consumed by all participants – in addition consuming a high salt (200-250mmol Na) tomato juice for 4 weeks.	Low salt (60mmol/day) diet consumed by all participants – in addition consuming a no added salt tomato juice (0mmol Na) for 4 weeks	**1. BP** 2. Weight 3. **PWV**, PWA, 4. Urinary Na+, K+, Cr, nitrates 5. Plasma vasoactive hormones (renin, aldosterone, endothelin-1, insulin, atrial natriuretic	Compliance to intervention th histories and spot urine a 4 participants dropped out, only the high salt interventi

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Study	Methods	Setting	Participants	Intervention A	Intervention B	Outcomes	Notes
						peptide, C-natriuretic peptide and N-terminal C-natriuretic peptide 6. Markers of oxidative stress and inflammation (nitrate and nitrite concentrations, lipid peroxides,7 lipofuscin-like fluorophores (LF),8 high-sensitivity C-reactive protein 7. Dietary intake	
TOHP II 1997[12]	RCT Parallel Duration 36 months	United States – multi-centre Free living	Sodium reduction – n= 515 Control – n= 514 Male and female aged 30-54 years, overweight (BMI 24.4-37.4kg/m2), BP <139/89, no clinical	Sodium reduction group (target 80mmol/day)	Control group (no advice)	**1. BP** 2. Weight 3. Urinary Na+, K+, Cr 4. Dietary intake	Large blood pressure changes w in initial 6 months. Over 36 m changes were less prono

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Study	Methods	Setting	Participants	Intervention A	Intervention B	Outcomes	Notes
			signs/diagnosis CVD, renal insufficiency, or diabetes				

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Appendix V: Excluded studies

Adeyemo AA, Prewitt TE, Luke A, Omotade OO, Rotimi CN, Brieger WR, et al. The feasibility of implementing a dietary sodium reduction intervention among free-living normotensive individuals in south west Nigeria. Ethnicity & disease. 2002;12(2):207-12.
Reason for exlcusion: Recruited above 140mmHg (<160mmHg)

Allen AR, Gullixson LR, Wolhart SC, Kost SL, Schroeder DR, Eisenach JH. Dietary sodium influences the effect of mental stress on heart rate variability: a randomized trial in healthy adults. J Hypertens. 2014;32(2):374-82.
Reason for exclusion: Study duration less than 4 weeks

Aro A, Pietinen P, Valsta LM, Salminen I, Turpeinen AM, Virtanen M, et al. Lack of effect on blood pressure by low fat diets with different fatty acid compositions. J Hum Hypertens. 1998;12(6):383-9.
Reason for exclusion: No intervention of interest

Australian National Health & Medical Research Council Dietary Salt Study Management Committee. Fall in blood pressure with modest reduction in dietary salt intake in mild hypertension. Lancet. 1989;1(8635):399-402.
Reason for exclusion: Studies on hypertensives

Australian National Health & Medical Research Council Dietary Salt Study Management Committee. Effects of replacing sodium intake in subjects on a low sodium diet: a crossover study. Clin Exp Hypertens. 1989;11(5-6):1011-24.
Reason for exclusion: Recruited above 140mmHg

Azizi M, Linhart A, Alexander J, Goldberg A, Menten J, Sweet C, et al. Pilot study of combined blockade of the renin-angiotensin system in essential hypertensive patients. J Hypertens. 2000;18(8):1139-47.
Reason for exclusion: Studies on hypertensives

Barba G, Vallance PJ, Strazzullo P, MacAllister RJ. Effects of sodium intake on the pressor and renal responses to nitric oxide synthesis inhibition in normotensive individuals with different sodium sensitivity. J Hypertens. 2000;18(5):615-21.
Reason for exclusion: Study duration less than 4 weeks

Barri YM, Wilcox CS. Salt intake determines the renal response to L-arginine infusion in normal human subjects. Kidney Int. 1998;53(5):1299-304.
Reason for exclusion: Study duration less than 4 weeks

Beerendonk CC, Derkx FH, Schellekens AP, Hop WC, van Dop PA. The influence of dietary sodium restriction on renal and ovarian renin and prorenin production during ovarian stimulation. Hum Reprod. 1996;11(5):956-61.
Reason for exclusion: Study groups not comparable - low sodium group started intervention 10 days before control group.

Benetos A, Xiao YY, Cuche JL, Hannaert P, Safar M. Arterial effects of salt restriction in hypertensive patients. A 9-week, randomized, double-blind, crossover study. J Hypertens. 1992;10(4):355-60.
Reason for exclusion: Studies on hypertensives

Blumenthal JA, Babyak MA, Hinderliter A, Watkins LL, Craighead L, Lin PH, et al. Effects of the DASH diet alone and in combination with exercise and weight loss on blood pressure and cardiovascular biomarkers in men and women with high blood pressure: the ENCORE study. Arch Intern Med. 2010;170(2):126-35.
Reason for exclusion: Recruited above 140mmHg (<159mmHg)

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https://doi.org/10.11124/JBISRIR-2016-002410

Bompiani GD, Cerasola G, Morici ML, Condorelli M, Trimarco B, De Luca N, et al. Effects of moderate low sodium/high potassium diet on essential hypertension: results of a comparative study. Int J Clin Pharmacol Ther Toxicol. 1988;26(3):129-32.
Reason for exclusion: Studies on hypertensives

Bray GA, Vollmer WM, Sacks FM, Obarzanek E, Svetkey LP, & Appel LJ. A further subgroup analysis of the effects of the DASH diet and three dietary sodium levels on blood pressure: results of the DASH-Sodium Trial. Am J Cardiol, 2004; 94(2): 222-227.
Reason for exclusion: Population not considered suitable for the assessment of the primary outcome as subjects with SBP <120mmHg were excluded. Pre-hypertensive subjects display a heightened response to sodium.

Brier ME, Luft FC. Sodium kinetics in white and black normotensive subjects: possible relevance to salt-sensitive hypertension. Am J Med Sci. 1994;307(Suppl 1):S38-42.
Reason for exclusion: Study duration less than 4 weeks

Buckley MG, Markandu ND, Sagnella GA, MacGregor GA. Brain and atrial natriuretic peptides: a dual peptide system of potential importance in sodium balance and blood pressure regulation in patients with essential hypertension. J Hypertens. 1994;12(7):809-13.
Reason for exclusion: No Sodium intervention; Study duration less than 4 weeks

Bunke M, Gleason JR, Jr., Brier M, Sloan R. Effect of erythropoietin on renal excretion of a sodium load. Clin Pharmacol Ther. 1994;55(5):563-8.
Reason for exclusion: No intervention of interest

Butscher K, Jamali S, Talib R, Ravussin P, Poggi-Bach J, Ecoffey C. [Effects of different loading solutions on plasma osmolality]. Annales francaises d'anesthesie et de reanimation. 1996;15(7):1037-40.
Reason for exclusion: No intervention of interest

Calabrese EJ, Tuthill RW. The Massachusetts Blood Pressure Study, Part 3. Experimental reduction of sodium in drinking water: effects on blood pressure. Toxicol Ind Health. 1985;1(1):19-34.
Reason for exclusion: Studies in paediatrics

Capaldo B, Guardasole V, Pardo F, Matarazzo M, Di Rella F, Numis F, et al. Abnormal vascular reactivity in growth hormone deficiency. Circulation. 2001;103(4):520-4.
Reason for exclusion: No intervention of interest

Cappuccio FP, Kerry SM, Micah FB, Plange-Rhule J, Eastwood JB. A community programme to reduce salt intake and blood pressure in Ghana. BMC Public Health. 2006;6(1):13.
Reason for exclusion: No intervention of interest

Cappuccio FP, Markandu ND, Beynon GW, Shore AC, MacGregor GA. Effect of increasing calcium intake on urinary sodium excretion in normotensive subjects. Clin Sci. 1986;71(4):453-6.
Reason for exclusion: Recruited above 140mmHg

Cappuccio FP, Markandu ND, Carney C, Sagnella GA, MacGregor GA. Double-blind randomised trial of modest salt restriction in older people. Lancet. 1997;350(9081):850-4.
Reason for exclusion: Studies included on hypertensives

Carney SL, Gillies AH, Smith AJ, Smitham S. Increased dietary sodium chloride in patients treated with antihypertensive drugs. Clin Exp Hypertens. 1991;13(3):401-7.
Reason for exclusion: Studies included on hypertensives

Chalmers J, Morgan T, Doyle A, Dickson B, Hopper J, Mathews J, et al. Australian National Health and Medical Research Council dietary salt study in mild hypertension. J Hypertens. 1986

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Dec;4(6):S629-37.
Reason for exclusion: Studies included on hypertensives

Chin-Dusting JP, Alexander CT, Arnold PJ, Hodgson WC, Lux AS, Jennings GL. Effects of in vivo and in vitro L-arginine supplementation on healthy human vessels. Journal of cardiovascular pharmacology. 1996;28(1):158-66.
Reason for exclusion: No intervention of interest

Chopra A, Kumar V, Dutta A. Hypertonic versus normal saline as initial fluid bolus in pediatric septic shock. Indian journal of pediatrics. 2011;78(7):833-7.
Reason for exclusion: Studies in paediatrics

Closas J, Genest J, Larochelle P, Cusson J, Gutkowska J, Hamet P, et al. [Effects of phenylephrine on atrial natriuretic factor and the renin-aldosterone axis in normal patients and essential hypertensive patients]. Archives des maladies du coeur et des vaisseaux. 1988;81:75-8.
Reason for exclusion: No Sodium intervention; Blood pressure not measured

Conlin PR. The dietary approaches to stop hypertension (DASH) clinical trial: implications for lifestyle modifications in the treatment of hypertensive patients. Cardiology in Review. 1999;7(5):284-8.
Reason for exclusion: Reanalysis study

Cook NR, Cohen J, Hebert PR, Taylor JO, Hennekens CH. Implications of small reductions in diastolic blood pressure for primary prevention. Arch Intern Med. 1995;155(7):701-9.
Reason for exclusion: Observational Study

Cooper JN, Tepper P, Barinas-Mitchell E, Woodard GA, Sutton-Tyrrell K. Serum aldosterone is associated with inflammation and aortic stiffness in normotensive overweight and obese young adults. Clin Exp Hypertens. 2012;34(1):63-70.
Reason for exclusion: Not an RCT (Cross sectional)

Cooper R, Van Horn L, Liu K, Trevisan M, Nanas S, Ueshima H, et al. A randomized trial on the effect of decreased dietary sodium intake on blood pressure in adolescents. J Hypertens. 1984 Aug;2(4):361-6.
Reason for exclusion: Study on adolescents (24 day study)

Costa FV, Ambrosioni E, Montebugnoli L, Paccaloni L, Vasconi L, Magnani B. Effects of a low-salt diet and of acute salt loading on blood pressure and intralymphocytic sodium concentration in young subjects with borderline hypertension. Clin Sci. 1981;61 Suppl 7:21s-3s.
Reason for exclusion: Studies on hypertensives

Creager MA, Roddy MA, Holland KM, Hirsch AT, Dzau VJ. Sodium depresses arterial baroreceptor reflex function in normotensive humans. Hypertension. 1991;17(6 Pt 2):989-96.
Reason for exclusion: Study duration less than 4 weeks

Cuneo RC, Espiner EA, Nicholls MG, Yandle TG, Livesey JH. Effect of physiological levels of atrial natriuretic peptide on hormone secretion: inhibition of angiotensin-induced aldosterone secretion and renin release in normal man. J Clin Endocrinol Metab. 1987;65(4):765-72.
Reason for exclusion: Concomitant venous infusion

Damasceno A, Caupers P, Santos A, Lobo E, Sevene E, Bicho M, et al. Influence of salt intake on the daytime-nighttime blood pressure variation in normotensive and hypertensive black subjects. Revista portuguesa de cardiologia. 2000;19(3):315-29.
Reason for exclusion: Study duration less than 4 weeks

Damasceno A, Santos A, Pestana M, Serrao P, Caupers P, Soares-da-Silva P, et al. Acute hypotensive,natriuretic, and hormonal effects of nifedipine in salt-sensitive and salt-resistant black normotensive and hypertensive subjects. J Cardiovasc Pharmacol. 1999;34(3):346-53.
Reason for exclusion: Study duration less than 4 weeks

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Damasceno A, Santos A, Serrao P, Caupers P, Soares-da-Silva P, Polonia J. Deficiency of renal dopaminergic-dependent natriuretic response to acute sodium load in black salt-sensitive subjects in contrast to salt-resistant subjects. J Hypertens. 1999;17(12 Pt 2):1995-2001.
Reason for exclusion: Study duration less than 4 weeks

Del Rio A, Rodriguez-Villamil JL. Metabolic effects of strict salt restriction in essential hypertensive patients. J Intern Med. 1993;233(5):409-14.
Reason for exclusion: Not an RCT (Cross sectional)

Diaz KM, Muntner P, Levitan EB, Brown MD, Babbitt DM, Shimbo D. The effects of weight loss and salt reduction on visit-to-visit blood pressure variability: results from a multicenter randomized controlled trial. J Hypertens. 2014;32(12):840-848.
Reason for exclusion: Studies on hypertensives

Dickinson KM, Clifton PM, Burrell LM, Barrett PH, Keogh JB. Postprandial effects of a high salt meal on serum sodium, arterial stiffness, markers of nitric oxide production and markers of endothelial function. Atherosclerosis. 2014;232(1):211-6.
Reason for exclusion: Reanalysis Study (of TOHP II)

Dickinson KM, Keogh JB, Clifton PM. Effects of a low-salt diet on flow-mediated dilatation in humans. Am J Clin Nutr. 2009;89(2):485-90.
Reason for exclusion: Study duration less than 4 weeks

Dishy V, Sofowora GG, Imamura H, Nishimi Y, Xie HG, Wood AJ, et al. Nitric oxide production decreases after salt loading but is not related to blood pressure changes or nitric oxide-mediated vascular responses. J Hypertens. 2003;21(1):153-7.
Reason for exclusion: Study duration less than 4 weeks

Dodson PM, Stephenson J, Dodson LJ, Kurnik D, Kritzinger EE, Taylor KG, et al. Randomised blind controlled trial of a high fibre, low fat and low sodium dietary regimen in mild essential hypertension. J Hum Hypertens. 1989;3(3):197-202.
Reason for exclusion: Studies on hypertensives

Dorough AE, Winett RA, Anderson ES, Davy BM, Martin EC, & Hedrick V. DASH to wellness: Emphasizing self-regulation through E-health in adults with prehypertension. Health Psychol, 2014:33(3):249-254.

Reason for exclusion: Concomitant intervention

Duarte JD, Zineh I, Burkley B, Gong Y, Langaee TY, Turner ST, et al. Effects of genetic variation in H3K79 methylation regulatory genes on clinical blood pressure and blood pressure response to hydrochlorothiazide. J Transl Med. 2012;10:56.
Reason for exclusion: Studies on hypertensives

Fagerberg B, Andersson OK, Isaksson B, Bjorntorp P. Blood pressure control during weight reduction in obese hypertensive men: separate effects of sodium and energy restriction. BMJ. 1984;288(6410):11-4.
Reason for exclusion: Studies on hypertensives

Farquharson CA, Struthers AD. Aldosterone induces acute endothelial dysfunction in vivo in humans: evidence for an aldosterone-induced vasculopathy. Clin Sci. 2002;103(4):425-31.
Reason for exclusion: No intervention of interest

Fauvel JP, Najem R, Ryon B, Ducher M, Laville M. Effects of rilmenidine on stress-induced peak blood pressure and renal function. J Cardiovasc Pharmacol. 1999;34(1):41-5.
Reason for exclusion: No intervention of interest

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Feldman RD, Logan AG, Schmidt ND. Dietary salt restriction increases vascular insulin resistance. Clin Pharmacol Ther. 1996;60(4):444-51.
Reason for exclusion: Study duration less than 4 weeks

Ferrari P, Gadient G, Cozzio A, Shaw S, Weidmann P. Reduced plasma cyclic GMP but normal renal responses to atrial natriuretic factor in pre-hypertension. Blood Pressure. 1996;5(1):16-26.
Reason for exclusion: No Sodium intervention; Study duration less than 4 weeks

Ferri C, Bellini C, Carlomagno A, Perrone A, Santucci A. Urinary kallikrein and salt sensitivity in essential hypertensive males. Kidney Int. 1994;46(3):780-8.
Reason for exclusion: Studies on hypertensives; Study duration less than 4 weeks

Ferri C, Bellini C, Desideri G, Di Francesco L, De Mattia G, Santucci A, et al. Salt-sensitivity is associated with a hyperinsulinaemic and hyperglycaemic response to atrial natriuretic peptide infusion in human essential hypertension. Diabetologia. 1994;37(3):308-12.
Reason for exclusion: No intervention of interest

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Reason for exclusion: Studies on hypertensives; Study duration less than 4 weeks

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Reason for exclusion: Not an RCT (Review)

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Reason for exclusion: No intervention of interest

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Reason for exclusion: Studies on hypertensives

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Reason for exclusion: Participants on antihypertensive medications

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Reason for exclusion: Recruited above 140mmHg (indicated from baseline measurement)

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Reason for exclusion: Concomitant intervention (Potassium supplement)

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Reason for exclusion: Study duration less than 4 weeks

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Reason for exclusion: Recruited above 140mmHg (mean 159mmHg)

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Reason for exclusion: Not an RCT (Cross sectional)

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Reason for exclusion: Blood pressure not measured

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Reason for exclusion: No Sodium intervention; ANP infused in subjects

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Reason for exclusion: 5% subjects baseline SBP>140mmHg.

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Reason for exclusion: Study duration less than 4 weeks

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Reason for exclusion: Pilot study; no blood pressure results

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Reason for exclusion: No intervention of interest

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Reason for exclusion: No intervention of interest

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Reason for exclusion: Participants with renal deficiency

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Reason for exclusion: Studies on hypertensives

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Reason for exclusion: No intervention of interest

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Reason for exclusion: Study duration less than 4 weeks; Studies on hypertensives

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Reason for exclusion: Study duration less than 4 weeks

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Reason for exclusion: Study report of TOHP II

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Reason for exclusion: Not an RCT (Review)

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Reason for exclusion: Study duration less than 4 weeks

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Reason for exclusion: Wrong style intervention; drug infusions

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Reason for exclusion: Not RCT; Studies on hypertensives

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Reason for exclusion: Not intervention of interest

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Reason for exclusion: Participants with renal deficiency

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Reason for exclusion: Not intervention of interest

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Reason for exclusion: Study duration less than 4 weeks

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Reason for exclusion: Concomitant intervention

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Reason for exclusion: Not intervention of interest

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Reason for exclusion: Studies on hypertensives

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Reason for exclusion: Not an RCT (Viewpoint)

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Reason for exclusion: Not intervention of interest

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Reason for exclusion: Studies on hypertensives

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Reason for exclusion: Study duration less than 4 weeks

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Reason for exclusion: Studies on hypertensives

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Reason for exclusion: Recruited above 140mmHg

Morgan T, Myers J, Teow BH. The role of sodium and potassium in the control of blood pressure. Aust N Z J Med. 1984;14(4):458-62.
Reason for exclusion: Study duration less than 4 weeks

Moulin B, Fillastre JP, Godin M, Coquerel A, Decoopman E. Renal hemodynamics and sodium excretion after acute and chronic administration of cicletanine in normotensive and hypertensive subjects. J Cardiovasc Pharmacol. 1995;25(2):292-9.
Reason for exclusion: Participants treated with anti-hypertensives (diuretics)

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Reason for exclusion: Not an RCT (Consensus report)

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Reason for exclusion: Study duration less than 4 weeks

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Reason for exclusion: No information on inclusion SBP (authors could not confirm)

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Reason for exclusion: Not intervention of interest

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Reason for exclusion: Recruited above 140mmHg (<160mmHg)

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Reason for exclusion: Wrong style sodium intervention; Drugs used

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Reason for exclusion: Study duration less than 4 weeks

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Reason for exclusion: Studies on Heart failure patients

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Reason for exclusion: Participants all on anti-hypertensives

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Reason for exclusion: No intervention of interest

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Reason for exclusion: Wrong intervention; Drugs used

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Reason for exclusion: Only Hypertensive participants received sodium intervention

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Reason for exclusion: No intervention of interest

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Reason for exclusion: Wrong intervention; Drugs used

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Reason for exclusion: Study duration less than 4 weeks

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Reason for exclusion: Not intervetion of interest.

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Reason for exclusion: Study duration less than 4 weeks

Schrader J, Luders S, Kulschewski A, Hammersen F, Plate K, Berger J, et al. Morbidity and Mortality After Stroke, Eprosartan Compared with Nitrendipine for Secondary Prevention: principal results of a prospective randomized controlled study (MOSES). Stroke. 2005;36(6):1218-26.
Reason for exclusion: Studies on hypertensives

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Reason for exclusion: Study duration less than 4 weeks

Sciarrone SE, Beilin LJ, Rouse IL, Rogers PB. A factorial study of salt restriction and a low-fat/high-fibre diet in hypertensive subjects. J Hypertens. 1992;10(3):287-98.
Reason for exclusion: Recruited above 140mmHg

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Reason for exclusion: Study duration less than 4 weeks

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Reason for exclusion: Study duration less than 4 weeks

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Reason for exclusion: Study duration less than 4 weeks

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Reason for exclusion: Study duration less than 4 weeks

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Reason for exclusion: No intervention of interest

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Reason for exclusion: Study on adolescents

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Reason for exclusion: Studies on hypertensives

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Reason for exclusion: Not an RCT (cross sectional)

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Reason for exclusion: Studies on participants with diabetes

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Reason for exclusion: Studies on hypertensives

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Reason for exclusion: Participants all on anti-hypertensives, discontinued 2 months in

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Reason for exclusion: No Sodium intervention; Study duration less than 4 weeks

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Reason for exclusion: No Sodium intervention; Study duration less than 4 weeks

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Reason for exclusion: Wrong sodium type intervention (one meal)

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Reason for exclusion: Blood pressure not measured/reported

Svetkey LP, Simons-Morton DG, Proschan MA, Sacks FM, Conlin PR, Harsha D, et al. Effect of the dietary approaches to stop hypertension diet and reduced sodium intake on blood pressure control. J Clin Hypertens. 2004;6(7):373-81.
Reason for exclusion: Recruited above 140mmHg

Swift PA, Markandu ND, Sagnella GA, He FJ, MacGregor GA. Modest salt reduction reduces blood pressure and urine protein excretion in black hypertensives: a randomized control trial. Hypertension. 2005;46(2):308-12.
Reason for exclusion: Recruited above 140mmHg

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Reason for exclusion: Not intervention of interest

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Reason for exclusion: Not intervention of interest

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Reason for exclusion: Not intervention of interest

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Reason for exclusion: Studies on hypertensives

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Reason for exclusion: Study duration less than 4 weeks

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Reason for exclusion: Not RCT

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Reason for exclusion: Study duration less than 4 weeks

Tzemos N, Lim PO, Wong S, Struthers AD, MacDonald TM. Adverse cardiovascular effects of acute salt loading in young normotensive individuals. Hypertension. 2008;51(6):1525-30.
Reason for exclusion: Study duration less than 4 weeks

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Reason for exclusion: Not intervention of interest

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Reason for exclusion: Recruited above 140mmHg

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Reason for exclusion: No Sodium intervention; Recruited above 140mmHg

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Reason for exclusion: Study duration less than 4 weeks (3 weeks)

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Reason for exclusion: Not intervention of interest

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Reason for exclusion: Study duration less than 4 weeks

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Reason for exclusion: No Sodium intervention; Study duration less than 4 weeks

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Reason for exclusion: Not intervention of interest

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Reason for exclusion: Studies in sheep (non-human study)

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Reason for exclusion: No Sodium intervention; Study duration less than 4 weeks

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Reason for exclusion: No Sodium intervention; calcium treatment

Weir MR, Dengel DR, Behrens MT, Goldberg AP. Salt-induced increases in systolic blood pressure affect renal hemodynamics and proteinuria. Hypertension. 1995;25(6):1339-44.
Reason for exclusion: Study duration less than 4 weeks

Wenner MM, Edwards DG, Ray CA, Rose WC, Gardner TJ, Stillabower M, et al. Celecoxib does not alter cardiovascular and renal function during dietary salt loading. Clin Exp Pharmacol Physiol. 2011;38(8):543-9.
Reason for exclusion: Wrong intervention; drug infusions

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Reason for exclusion: Included 5% participants >140mmHg at baseline

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Reason for exclusion: Not RCT (report from TOHP I)

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Reason for exclusion: Wrong intervention; on medications

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Reason for exclusion: No Sodium intervention; women using OCP

Wilson DK, Sica DA, Miller SB. Effects of potassium on blood pressure in salt-sensitive and salt-resistant black adolescents. Hypertension. 1999;34(2):181-6.
Reason for exclusion: Studies in adolescents; Study duration less than 4 weeks

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Reason for exclusion: Not intervention of interest

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Reason for exclusion: Study duration less than 4 weeks

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Reason for exclusion: Statisitical data could not be provided by authors regarding non-hypertensive subgroup.

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Reason for exclusion: No compliance measure; no control group; Not RCT

Zabeeda D, Medalion B, Jackobshvilli S, Ezra S, Schachner A, Cohen AJ. Comparison of systemic vasodilators: effects on flow in internal mammary and radial arteries. Ann Thorac Surg. 2001;71(1):138-41.
Reason for exclusion: No Sodium intervention; participants undergoing surgery

Zhou B, Wang HL, Wang WL, Wu XM, Fu LY, Shi JP. Long-term effects of salt substitution on blood pressure in a rural north Chinese population. J Hum Hypertens. 2013;27(7):427-33.
Reason for exclusion: Information on SBP cut off for normotensive subpopulation could not be obtained. included participants with diabtes melittus.

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Reason for exclusion: Concomitant intervention (Potassium supplement)

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Appendix VI: Results of sensitivity analysis using alternative levels of correlation coefficient (r= 0.2, and 0.8) associated with flaxseed meta- analysis of the effect of salt modification on blood pressure and pulse wave velocity.

Alternative r		Mean difference (95% CI), mm Hg	p value	I^2	I^2 of main analysis (with r=0.05)
0.2	SBP	-0.67 (-1.77, 0.43)	0.23	16%	53%
	DBP	-0.56 (-1.19, 0.07)	0.08	0%	0%
	PWV	0.85 (-1.44, 3.13)	0.47	0%	0%
0.8	SBP	-0.38 (-1.93, 1.17)	0.63	69%	53%
	DBP	-0.54 (-1.10, 0.03)	0.06	3%	0%
	PWV	0.73 (-0.75, 2.21])	0.33	30%	0%

Changes in SBP, DBP, and PWV are presented as mean difference and 95% CI. Heterogeneity (I^2) is presented by %. A p-value <0.05 was considered significant.

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