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The Effect of a Reduction in Sodium Intake on Blood Pressure as Modified by the Control Group's Sodium Level: A Meta-analysis

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By

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Abstract

The Effect of a Reduction in Sodium Intake on Blood Pressure as Modified by the Control Group's Sodium Level: A Meta-analysis

By Sharnali Das

Background: The link between sodium reduction and decreased blood pressure (BP) has been established through previous studies and meta-analyses. However, the link between usual sodium intake level and its effect on BP has not been investigated.
Objectives: To assess whether the sodium to blood pressure association is different according to initial level of sodium intake and BP status.
Search methods: The Cochrane Central Register of Controlled Trials (January 2005 to August 2011), MEDLINE (January 2005 to June 2011), EMBASE (January 2005 to June 2011), WHO ICTRP, LILACS, and reference lists of articles were searched.
Selection criteria: Randomized controlled trials which allocated at least one group of participants to reduced sodium intake and one to regular sodium intake for a minimum of four weeks and reported results on BP.
Data collection and analysis: Two authors independently assessed trial quality, extracted data, and entered it into the Cochrane Collaboration Review Manager 5.1. Study authors were contacted to obtain missing information.
Main results: Thirty-six studies with 3304 participants in the reduced sodium group and 3432 in the usual sodium group were included in the meta-analysis. The pooled estimates for changes in BP using a random effects model were -3.39 mmHg (95% CI: -4.31, -2.46) [systolic] and -1.55 mmHg (95% CI: -2.11, -0.98) [diastolic]. When studies were divided into quartiles based on the level of sodium intake in the control group (lowest sodium intake in the first quartile and highest sodium intake in the fourth quartile), no statistically significant relationship was found between the control group's sodium intake level and blood pressure reduction. When stratified by BP status, a larger decrease in BP was noted in hypertensives compared to the normotensives. There were no observable patterns when the groups were divided by study design. Sensitivity analysis where three low quality studies were removed showed no difference in the overall estimate.
Authors' conclusions: This meta-analysis of randomized controlled trials illustrates that individuals at both higher and lower initial sodium intake levels benefit in terms of BP reduction when sodium intake is decreased and that those with hypertensive BP status benefit more than normotensives.

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INTRODUCTION

Noncommunicable diseases (NCDs) cumulatively account for 63% of mortality globally, which translated into more than thirty-six million deaths in 2008 [1].Cardiovascular diseases, including coronary heart disease, cerebrovascular disease, and peripheral vascular disease, were the leading cause of mortality (48%) [1]. There are several modifiable risk factors which underlie NCDs, but blood pressure is considered the leading risk factor in terms of being responsible for the greatest proportion (13%) of mortality worldwide, compared to all other risk factors [1]. High blood pressure accounts for 62% of stroke and 49% of coronary heart disease events [2].

Global trends show that while average systolic blood pressure has declined minimally over the past few decades, the highest levels are observed in low and middle income countries [3]. People in North America, western Europe, and Australasia had large systolic blood pressure decreases whereas those in east Africa, south and southeast Asia, and Oceania had increases [3]. The variation in blood pressure may be attributed to variation across countries in terms of consumption of salt, fruits, and vegetables, but also differences in adiposity and access or adherence to antihypertensive use [3].

Sodium is a key component of common table salt and has been linked to blood pressure such that higher sodium consumption leads to higher blood pressure [4-9]. In 2007, in response to the wide variation in and excess sodium consumption worldwide, the World Health Organization (WHO) recommended that the general population should consume

less than 2 grams sodium per day which is the equivalent of 5 grams of sodium chloride (common table salt) daily [10]. However, most adult populations globally have average sodium intakes greater than 2.3 g/day and there is wide variation in sodium intake across countries. For example, in many countries in Asia, the average intake is greater than 4.6 g/day. Several studies have outlined differences in sodium intake among and within countries. One extensive study (INTERSALT) looked at 32 countries to determine standardized estimates of sodium intake [5]. The lowest average sodium excretion (which was used as a proxy for sodium intake) was noted among the Yanomamo Indians of Brazil with men and women having a mean of 0.2 g/day. The highest mean sodium excretion was found in Tianjin, China where men had an average intake of 5.9 g/day and the women, 5.3 g/day. The INTERSALT study found that the most frequent values globally were between 3.4-4.5 g/day for men and 2.3-3.4 g/day for women – still above the 2 g/day recommended by the WHO [11].

A Cochrane Review was published (2004) that focused on the effects of modest salt reduction on blood pressure over the long-term (>6 months) [8]. This review concluded that a maximum intake of 3 grams of salt, which is equivalent to 1.2 grams of sodium per day, would provide further reductions in blood pressure to both hypertensive and non-hypertensive people. It is important to note that this value was based on computer modeling and not empirical evidence. Assuming a linear relationship between decreasing sodium intake and blood pressure, and collateral benefits in terms of reduced risk of cardiovascular disease, WHO considered revising their guidelines [4].

Recognizing the need to improve its processes for the generation of public health recommendations, in 2003, WHO welcomed an evaluation of its practices across the entire organization. One result from this evaluation was a paper published by Oxman et al in 2007, which suggested that the majority of WHO recommendations relied too heavily on expert opinion, rather than the cumulative weight of the published evidence [12]. WHO has subsequently committed to ensuring that future guidelines from the organization would be based more heavily on the available scientific evidence. A review by Charles Wiysonge and Gregory Hussey in 2009 found that all thirty-one publicly available documents prepared by the WHO between January 2009 and March 2011 were based on systematic reviews [13].

However, WHO recommendations for sodium intake had not been updated since 2007. Additionally, in the first decade of the 21st century, there has been mounting interest and pressures from academia plus civil society groups to address the upstream determinants of hypertension [14]. Population-wide sodium measures (i.e., targeting salt reduction) are seen as a cost-effective method to do so [15, 16]. However, sodium is a highly debated issue. There are proponents that advocate higher thresholds in guidelines, such as the Salt Institute. Since one of the primary sources of sodium is salt, there are multiple delivery channels. For example, processed foods, food consumed at restaurants, food prepared at home, and naturally-occurring salt within some foods are all conduits for sodium consumption. Therefore, the sodium issue involves a multitude of stakeholders and guidelines have substantial and widespread impacts. The food processing and restaurant industries, as well as the average consumer, are all affected. Additionally, the majority of

the global population consumes more than the WHO recommended amount of sodium (<2 grams/day), so if the 2004 Cochrane Review's suggested sodium level (<1.2 grams/day) is truly a more beneficial guideline, this could further impact a variety of stakeholders [8, 10].

The Department of Nutrition for Health and Development (NHD) at WHO recently decided to revisit the sodium guideline and to comprehensively review the most up-to-date evidence since the implications for blood pressure control and cardiovascular disease prevention have become particularly important in the public health arena. These guidelines would not only guide individual behaviors, but also set an evidence-based benchmark for negotiating with vested stakeholders (e.g., processed food manufacturers). This systematic review will help develop evidence-informed guidelines and aims to provide results that are both credible and reproducible.

The current analysis is part of a larger systematic review. The NHD's large systematic review examined multiple outcomes (adverse effects and renal disease outcomes in addition to blood pressure) using the same search, extraction, and synthesis methodology. This study does not report results from that larger review and the renal or adverse outcomes. Instead, this meta-analysis examines and reports specifically on changes in blood pressure (primary outcome of interest) in relation to reduction in sodium intake and the influence of the control group's sodium level.

Since populations vary widely in their average sodium intake levels, the purpose of this review is to investigate whether the control group's level of sodium intake and initial blood pressure status each modify the effect of a sodium intake reduction on blood pressure. In other words, this analysis might shed light on the effects on blood pressure in situations where one group starts with a baseline sodium intake of 3 g/day and another starts with 4 g/day, and both undergo sodium intake reduction; or where people with hypertension and normal BP are started on the same intervention. This information would be beneficial towards understanding the difference in blood pressure benefits based on current level of sodium intake and even baseline blood pressure status.

METHODS

The published and unpublished literature was systematically reviewed to find randomized controlled trials, both parallel and crossover designs, which compared a sodium reduction group to a usual sodium intake group in either hypertensive, normotensive, or mixed populations.

Search Methods

First, the Cochrane Library and MEDLINE electronic databases were searched to identify any recent (within the last 10 years) systematic reviews of randomized-controlled trials on the effects of reduced sodium intake compared to usual sodium intake on blood pressure in adults. The inclusion criteria of those reviews were examined and if they were in agreement with or broader than the inclusion criteria defined for the specific objectives

of the current systematic review, the reference list of included studies was examined. There was only one such Cochrane review, titled “Effect of longer-term modest salt reduction on blood pressure” published in 2008 by He and MacGregor, that met this criteria [8]. He and MacGregor’s review searched the MEDLINE and EMBASE electronic databases up to April 2005 and each of the included original articles were reviewed and compared against the inclusion criteria for this review. If any of the articles met the inclusion criteria, they were included in this current review.

Additionally, an electronic search was performed to capture all literature published after He and MacGregor’s search date (which was in April 2005) for their systematic review up to June 2011. Our search included the following databases: MEDLINE (January 2005 to June 2011), EMBASE (January 2005 to June 2011), Cochrane Central Register of Controlled Trials (January 2005 to August 2011), the WHO International Clinical Trials Registry Platform (ICTRP) for ongoing trials, and the Latin American and Caribbean Health Sciences (LILACS). The detailed search strategy can be found in Appendix A.

As part of the larger systematic review, the NHD used the same methodology described above for the adverse effects and renal disease outcomes. The studies which were included for those outcomes and also reported blood pressure were included in this analysis.

Types of Studies

The main purpose of this review is to compare the effects of achieving low sodium intake (through dietary, lifestyle, or educational advice) over a minimum period of 4 weeks to usual sodium intake on blood pressure, with all else held equal between the groups. Therefore, to be included in this review, each study's characteristics and content needed to meet all of the following criteria:

- Prospective design;
- Randomized controlled trials (allocated one group to low sodium intake [intervention group] and one to usual sodium intake [control group]; individual or cluster randomization);
    - Studies with co-interventions, such as non-pharmacological interventions, antihypertensive, or other medications, were also included as long as they were equivalent for both the intervention and control groups and did not constitute the main reason for randomization;
- Reported absolute changes in blood pressure or change from baseline (either systolic, diastolic, or both);
- The low sodium group achieved at least 0.9 g sodium / day (2.4 g salt / day) lower intake compared to the control group; and
- Verification of sodium intake through 24-hour urinary sodium excretion.

Types of Participants

Studies with adult participants, ages 15 and above, of either gender were included. Participants could originate from the general population (free living) or part of specific populations such as refugee populations. Participants from apparently healthy populations who may or may not have been at risk or suffer from hypertension, who were known to be hypertensive, or were known to be normotensive were all included. Studies which specifically targeted HIV-positive populations, acutely ill or hospitalized persons, or pregnant women were excluded.

Outcomes of Interest

The primary outcomes of interest were resting systolic and diastolic blood pressure. Our review evaluated the treatment effect of the trials by noting the mean difference in blood pressure achieved between the control and low sodium groups.

Exposure of Interest

The primary exposure was the mean difference in sodium intake (≥0.9g sodium / day) achieved between the intervention and control groups. The control group (a proxy for the usual intake of the population) served as the reference group with the assumption that unmeasured variables which might affect the outcome were randomly distributed across

the intervention and control groups. Therefore, due to the randomization of the subjects, there would no differential effect on either group.

Data Collection, Extraction, and Management

The titles collected from all of the electronic searches and the previous systematic review were initially screened to identify irrelevant studies and exclude them from further consideration. The articles were included for further consideration when the information given in the abstracts met the following criteria or if there was any doubt regarding these criteria from scanning the abstracts:

- Randomized controlled trial
- Did not target hospitalized, acutely ill, HIV-specific, or pregnant populations
- Minimum duration of four weeks
- Reported results on blood pressure outcome
- Only difference between control and intervention groups was reduced sodium intake

After this screening process, full-texts of the potentially-relevant remaining articles were assessed independently by two reviewers for inclusion using the criteria outlined in the “Types of Studies” section. Any disagreements that arose were resolved by discussion and arrival at consensus. If resolving the disagreement was not possible, the article was added to those 'awaiting assessment' and the authors were contacted for clarification. If studies were published only as abstracts or were missing relevant information, every

attempt (up to September 2011) was made to contact the study authors to obtain further details of study design and results. In cases of duplicate publications or companion papers of a primary study, all of the available data was evaluated to maximize the information available. In cases where there was doubt, the original publication (typically the oldest version) received priority. Articles were excluded after data extraction if, upon closer review, they did not meet the initial inclusion criteria.

The two reviewers independently abstracted relevant population and intervention characteristics using standard data extraction forms which were adapted for this review (Appendix B). This was based on guidelines provided in the Cochrane Handbook for Systematic Reviews of Interventions [17]. If relevant data were missing, the publication authors were contacted and requested to provide relevant information, where possible. The data extraction form included the following items:

- General information: classification as published/unpublished, title, authors, reference/source, contact address, country, language of publication, year of publication, duplicate publications, sponsor.
- Trial characteristics: design, duration of follow up, method of randomization, allocation concealment, blinding (patients, people administering treatment, outcome assessors).
- Intervention(s): placebo or comparison included, interventions(s) (dose, route, timing), co-medication(s) (dose, route, timing), sodium intake achieved at follow-up.
- Participants: inclusion and exclusion criteria of each original study; total number and number in comparison groups; actual sex, age, baseline characteristics, and diagnostic

criteria of participants; similarity of groups at baseline (including any co-morbidity); assessment of compliance, withdrawals/losses to follow-up (reasons/description); subgroups analyzed in original study.

- Outcomes: systolic and diastolic blood pressure (either absolute data or change from baseline if absolute numbers were not available), a measure of variance, any other outcomes assessed, length of follow-up, quality and completeness of reporting of outcomes.
- Results: for systolic and diastolic blood pressure along with other outcomes assessed and times of assessment (including a measure of variation); intention-to-treat analysis.
- Stated objective of the study.

Where there were multiple measures for any variable that was extracted, an a priori criteria was established to determine which values would be used for the overall and subgroup analyses. If several follow-up time points were presented in the manuscript, data from the last follow-up (and documentation of time since randomization) was included in the overall analysis. Where multiple resting blood pressure measurement approaches were used, the order of importance was as follows: combination office (measured in various ways and then averaged), supine office, seated office, standing office, combination home office (measured in various ways and then averaged), supine home, seated home, and standing home. In the case of more than one intervention arm, the main comparison was deemed to be the control versus the group that achieved closest to a 2.3 g difference in sodium intake.

Assessing Risk of Bias in Included Studies

The risk of bias was assessed using the quality criteria outlined in the Cochrane Handbook for Systematic Reviews [17]. Documenting these biases ensures that users of the review are able to benefit from guidance on reliability of the findings of each study included such that distortions are minimized. The Cochrane Collaboration recommends the evaluation of seven domains whose precision would lead to increased validity.

The bias indicators evaluated included the following study design and reporting features:

(1) Random sequence generation (to check for selection bias) – the method used by the original study for participant allocation was documented and evaluated as low risk (any truly random process such as a computer random number generator), high risk (any non random process such as clinic record number or odd/even dates of birth), or unclear risk (it was not documented in the paper).

(2) Allocation concealment (to check for selection bias) – the method used by the original study to conceal the allocation sequence of the intervention and control group participants to ensure that they could not have been predicted by the participants was marked as low risk (telephone or central randomization or consecutively numbered sealed envelopes), high risk (open random allocation, unsealed envelopes, alternation, date of birth), or unclear risk (it was not documented in the paper).

(3) Blinding of participants and personnel (to check for performance bias) – the method used by the original study to hide which intervention a participant received was

marked as low risk (blinded), high risk (not blinded), or unclear risk (it was not documented in the paper).

(4) Blinding of outcome assessment (to check for detection bias) - the method used by the original study to blind the assessors (such that when they measured outcomes, they were unaware as to which group the participant was allocated) was marked as low risk (blinded), high risk (not blinded), or unclear risk (it was not documented in the paper).

(5) Incomplete outcome data (to check for attrition bias) – the completeness of data in the original studies, including withdrawals, dropouts, missing data across groups, and exclusions, was marked as low risk (few losses to follow-up or loss to follow-up which was equal across groups and therefore did not likely affect results), high risk (loss to follow-up >20% or wide differences in losses to follow-up between groups), or unclear risk (it was not documented in the paper).

(6) Selective reporting (to check for reporting bias) – the possibility that original studies might have selectively reported certain outcomes was marked as low risk (all pre-specified outcomes and outcomes of interest were reported), high risk (all pre-specified outcomes were not reported or outcomes of interest were reported incompletely), or unclear risk (it was not documented in the paper).

(7) Other sources of biases – any other sources in each original study which could possibly bias the study were marked as low risk, high risk, or unclear risk.

The two reviewers assessed bias independently and if there were disagreements, the authors were consulted and resolution was achieved.

Data Analysis

Statistical analyses were performed according to the guidelines referenced in the most recently updated version (2011) of the Cochrane Handbook for Systematic Reviews of Interventions [17]. Blood pressure, the primary outcome, was calculated using the random effects model on Cochrane Collaboration Review Manager 5.1 (Copenhagen, 2011) and was expressed in mmHg as the between-group difference in mean blood pressures or difference of the differences in mean blood pressure at the longest point of follow-up. Variance estimates of treatment effect were calculated in the form of standard deviations. If the study reported standard error or 95% confidence intervals, they were converted into standard deviations. Means or difference of the means of blood pressure, standard deviations, and sample sizes were all entered into Review Manager 5.1. The software calculated the treatment effect for each study and the overall estimate of the effect.

The strength of including only randomized controlled trials in this review was that participants in both the control and intervention groups had comparable baseline characteristics (e.g., age and gender). And since the control group acted as the reference with the assumption that nothing changed, this also meant that once the “low sodium intervention” was applied, the incremental differences in outcomes noted between the two groups could be attributed to the intervention itself. More explicitly stated, this meant that the blood pressure change could be attributed to the reductions in sodium intake. According to the Cochrane Handbook for Systematic Reviews of Interventions, a meta-

analysis of the difference of the means (mean blood pressure in the intervention group minus mean blood pressure in the control group) would give the same result as a difference of the differences (difference between baseline and follow-up blood pressure in the intervention group minus the difference between baseline and follow-up in the control group). Additionally, mean differences (instead of standardized mean difference) were used since they were the appropriate statistical method and also allowed studies with difference of means data or difference of differences data to be combined in one meta-analysis. Standardized mean differences were not used since the outcomes in all of the studies were measured on the same (mmHg) scale.

Random Effects Model

This review used a random effects meta-analysis model to evaluate the effects of sodium intake reduction on the change in blood pressure. The random effects model assumes that each of the studies included in the meta-analysis represent populations which differ from one another in ways that could impact the primary treatment effect. For example, participants' age, health status, and duration of the intervention may all have varying consequences on the final effect size and direction. Therefore, the random effects model accounts for these non-identical studies and assumes that heterogeneities in study designs, locations, participant characteristics, or other differences would influence the effect sizes observed. This model also assumes that the underlying effects follow a normal distribution [18]. Consequently, the combined effect estimated by the model reflects the average effect across the distribution of observations included in the analysis.

The fixed effects model presumes that all studies included in the meta-analysis have one true effect size because all of the factors that influence the outcome are the same in all of the study populations. Under this model, studies are assigned weights based on the amount of information which the study provides. This means that a large study sample size would be given a larger weight and smaller studies would be given lower weight.

The fixed effect model was not used here since there was no reason to believe that all of the studies were structurally identical. The subjects and interventions differed across the studies examined and it was believed that these would impact the final results.

Specific Analysis

First, the overall effect of sodium reduction on blood pressure was assessed. Then, studies were grouped into quartiles based on the level of sodium intake achieved by the control group (usual sodium intake). The sodium intake achieved was used instead of the baseline sodium level because several studies had a run-in period where both the usual sodium and low sodium groups would begin on a ‘low-sodium’ diet and then the usual sodium group would be given sodium pills to increase their levels back to the usual intake. Therefore the baseline sodium levels for both groups were low and instead, the sodium intake achieved by the usual sodium group (control) was used. The first quartile included studies with the lowest levels of sodium intake while the fourth quartile included those with the highest levels of sodium intake.

Subgroup Analyses

Along with the overall analysis, subgroup analyses were conducted to test whether the overall effect size varied by hypertension status of participants (hypertensive versus normotensive versus mixed) and study design (crossover versus parallel). This was done since the effect of sodium intake on blood pressure may be inherently different among the hypertensive, normotensive, and mixed populations and this subgroup analysis would take each of the different risk profiles into account. Additionally, crossover studies are designed such that each participant is his/her own control whereas parallel studies have two separate groups (one intervention and one control). This could lead to differences in the effect size of the outcome since the two designs are inherently distinct in the way in which they are conducted. Statistical heterogeneity was also noted through the I^2 statistic as described below.

Assessment of Heterogeneity

The I^2 statistic quantifies the inconsistency among studies and assesses the impact of heterogeneity on the overall meta-analysis summary estimate [19, 20]. An I^2 statistic of 75% or greater suggests that there was a considerable amount of inconsistency among studies [17]. If significant heterogeneity was found, an attempt was made to understand the potential causes by examining individual study and subgroup characteristics. Additionally, sensitivity analysis was performed to understand if certain studies with high risk of biases influenced the magnitude or direction of the final effect estimate.

Risk of Bias, Unit of Analysis Issues, and Assessment of Reporting Biases

We documented studies which had a high risk of bias across multiple dimensions (random sequence generation, allocation concealment, blinding, loss to follow-up, or selective reporting). A study was deemed to be of high quality if it was graded as adequate in allocation concealment and in either loss to follow up or blinding. Poor quality studies were those with a high risk of bias across more than one domain. These poor quality studies were removed during a sensitivity analysis to examine the influence of these lower quality studies on the overall effect. Those with unclear risk of bias were not removed as the rating was likely due to unclear reporting rather than poor study quality.

Since both parallel and crossover studies were considered in this review, subgroup analyses were performed in order to account for potential biases specific to each study design. Additionally, reporting biases arise when the nature and direction of the final results influence whether or not research is published. Funnel plots were used to assess if there was small study bias (smaller studies biased towards the effectiveness of the intervention they are examining).

In this study, we used an adapted PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) standard for reporting the included and excluded studies.

RESULTS

Description of Studies

A total of 1426 articles were identified through the electronic database searches and another 40 were identified through additional sources. Additional sources included twenty-eight published studies identified from the He and MacGregor Cochrane review [8], three from reference lists of He and MacGregor's review, and nine from searches focused on adverse effects and renal function outcomes associated with sodium intake reduction. These queries were part of a larger systematic review to investigate the health effects of sodium intake. Of the studies focused on the adverse effects of sodium, five reported blood pressure results (Andersson 1984, Fagerberg 1984, Howe 1994, McCarron 1997, Sciarrone 1992). Similarly, four studies from the renal function searches (Dodson 1989, Muhlhauser 1996, Suckling 2010, Vogt 2008) reported blood pressure results. These nine studies were incorporated into the blood pressure review.

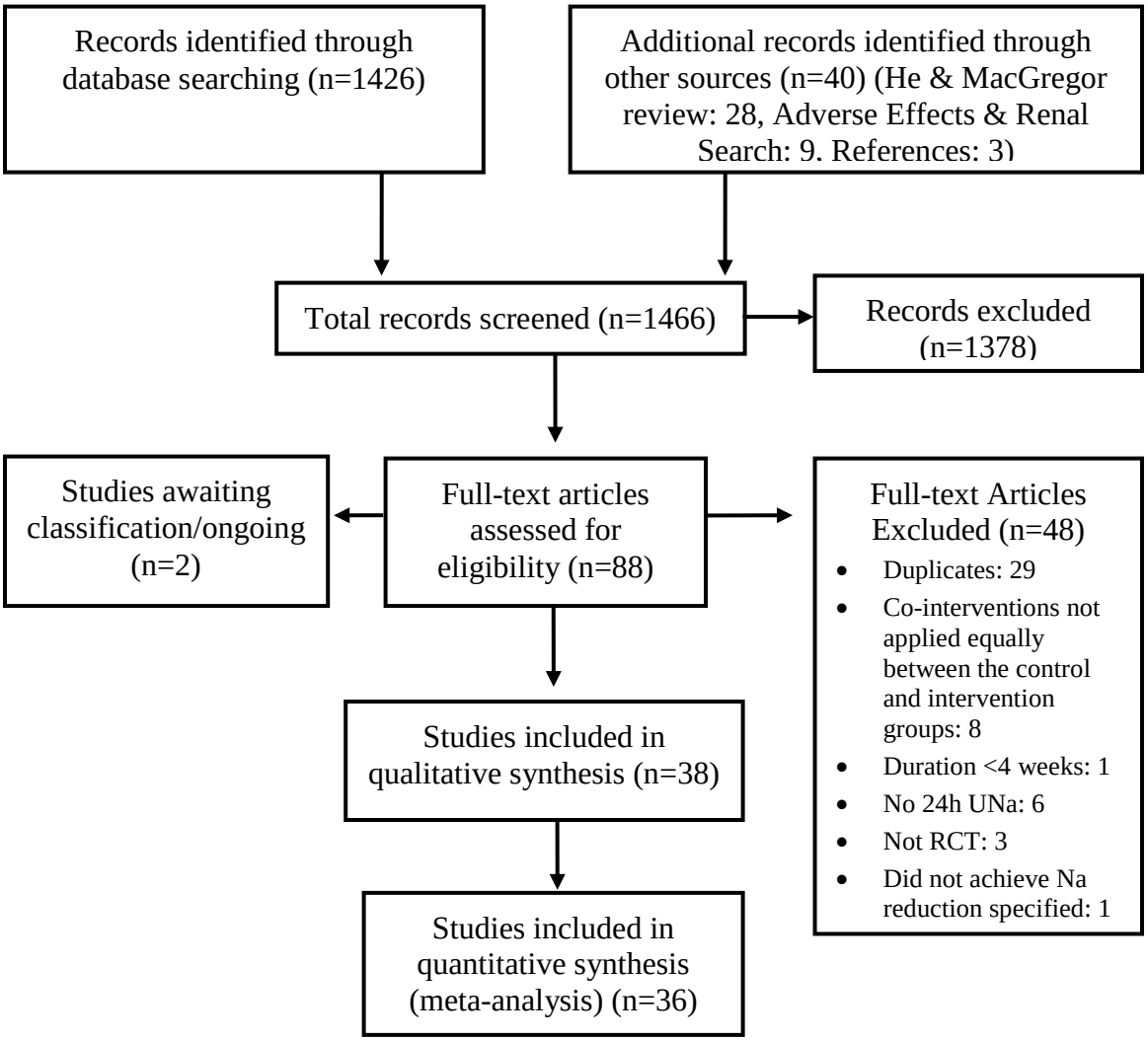
A total of 1466 articles were screened for eligibility and 1378 were excluded. Full texts of the remaining 88 articles were assessed in greater detail, and of these, 48 were excluded, one (Borghi ICTRP) is ongoing, and one (Swift 2006) continues to await classification. Please see Figure 1 below for the PRISMA flow-chart of study selection [21]. Studies were excluded for the following reasons (Appendix C):

- Duplicate publications (n=29)
- Co-interventions not applied equally between the control and intervention groups (n=8)

- 24 hour urinary analysis was not used to determine sodium excretion (n=6)
- Not a randomized control trial (n=3)
- Duration of less than four weeks (n=1)
- Did not achieve the minimum sodium reduction specified (n=1)

Thirty-eight studies met the inclusion criteria and were included in the meta-analysis. However, two of these studies (Gates 2004 and Morgan 1981) were missing outcome data and were therefore excluded from the quantitative synthesis (Appendices D and E). Therefore, a total of 36 studies were included in the meta-analysis. Appendices F (Included Studies), G (Excluded Studies), H (Studies Awaiting Classification), and I (Ongoing Studies) contain references for all studies.

Figure 1: PRISMA Diagram



From 36 studies that were included in the meta-analysis, data for 50 distinct cohorts were extracted. Eleven of the studies (Cappuccio 1997, Chalmers 1986, Cobiac 1992, Erwteman 1984, Howe 1994, Parijs 1973, Sacks 2001, Sciarrone 1992, TOPH 1997, Vogt 2008, Watt 1985) had multiple control and intervention arms that could each be treated as separate cohorts. For example, the Cobiac 1992 study had 4 distinct arms – (1) sunflower oil + regular diet, (2) sunflower oil + low sodium diet, (3) fish oil + regular diet, and (4) fish oil + low sodium diet. Each of these groups had a unique set of

participants and therefore groups 1 and 2 could be compared while groups 3 and 4 could be compared separately.

Of the 36 studies, 20 involved crossover designs and 16 were parallel study designs. Additionally, 23 included participants who were hypertensive, 5 included participants who were normotensive, and 8 included participants who were a heterogeneous mixture of both normotensive and hypertensive status. Additionally, all of the studies were completed in high-income countries (as defined by the World Bank [22]) – 7 studies originated from Oceania, 5 from North America, and 24 from Western Europe (regions as defined by the United Nations). Please refer to Table 1: Characteristics of Included Studies for further details.

Table 1: Characteristics of Included Studies

Study	Study Design	Sex	Age (years)	Final Sample Size	Final Sample Size	Loss to Follow Up	Duration of Follow-Up (months)	Country	Blood Pressure Status of Participants	Interventions
Andersson 1984	Parallel	M	51	10	13	0.0%	2.5	Sweden	Hypertensive	Group1 -- reduced sodium, fat and CHO diet plus sodium tablets (control), Group2 -- reduced sodium, fat and CHO diet (low sodium)
ANHMRC 1989	Parallel	M/F	58.4	50	53	7.2%	2	Australia	Hypertensive	Group1 -- reduced sodium in diet through counseling + 80mmol sodium per day in sodium chloride tablets and thus no change in sodium intake (control), Group2 -- reduced sodium in diet through counseling + placebo tablets and thus low sodium intake
Benetos 1992	Crossover	M/F	41.5	20	20	9.1%	1	France	Hypertensive	Group1 -- low sodium diet plus 60 mmol sodium in tablets / day (control), Group2 -- low sodium diet plus lactose (placebo) tablets / day

										(low sodium)
Cappuccio 1997	Crossover	M/F	66.8	47	47	2.0%	1	UK	Heterogenous	Group1 -- reduced sodium diet plus 120mmol / day in sodium tablets (control), Group2 -- reduced sodium diet plus placebo tablets (low sodium)
Chalmers 1986	Parallel	M/F	52.3	99	101	5.7%	3	Australia	Hypertensive	Group1 -- Control diet through counseling and education, Group2 -- High potassium diet through counseling and education, Group3 -- Low sodium diet through counseling and education, Group4 -- High potassium/low sodium diet through counseling and education

Cobiac 1992	Parallel	M/F	67	51	55	7.0%	1	Australia	Heterogenous	Group1 -- low sodium diet plus fish oil and 80 mmol sodium / day (fish control), Group2 -- low sodium diet plus fish oil and placebo (fish low sodium), Group3 -- low sodium diet plus sunflower oil and 80 mmol Na / day (sun control), Group4 -- low sodium diet plus sunflower oil and placebo (sun low sodium)
Dodson 1989	Parallel	M/F	62	17	17	0.0%	3	UK	Hypertensive	Group1 - normal diet (control), Group2 - low sodium diet (low sodium)

Erwteman 1984	Parallel	M/F	46	44	50	12.1%	6	UK	Hypertensive	Group1 -- normal sodium diet plus no drug therapy (control), Group2 -- low sodium diet plus no drug therapy (low sodium), Group3 -- normal sodium diet plus beta-blocker (control-B), Group4 -- low sodium diet plus beta-blocker (low sodium-B), Group5 -- normal sodium diet plus diuretic (control-D), Group6 -- low sodium diet plus diuretic (low sodium-D), Group5 -- normal sodium diet plus combination beta-blocker and diuretic (control-C), Group6 -- low sodium diet plus combination beta-blocker and diuretic (low sodium-C)
Fagerberg 1984	Parallel	M	51	15	15	11.7%	2.5	Sweden	Hypertensive	Group1 -- dietary advice for reduced calorie, fat and CHO diet (control), Group2 -- dietary advice for reduced calorie, fat and CHO diet plus reduced sodium diet (low sodium)

Fotherby 1993	Crossover	M/F	73	17	17	5.6%	1.25	UK	Hypertensive	Group1 -- low sodium diet plus 80mmol / day of sodium tablets (control), Group2 -- low sodium diet plus equivalent placebo tablets (low sodium)
Grobbee 1987	Crossover	M/F	24	40	40	0.0%	1.5	Netherlands	Hypertensive	Group1 -- low sodium diet plus 90 mmol sodium / day tablets (control), Group2 -- low sodium diet plus placebo tablets (low sodium)
He 2009	Crossover	M/F	50	169	169	8.6%	1.5	UK	Hypertensive	Group1 -- reduced sodium diet plus 90mmol sodium in tablets / day (control), Group2 -- reduced sodium diet plus placebo tablets (low sodium)
Howe 1994	Parallel	M/F	55	28	28	8.2%	1.5	Australia	Hypertensive	Group1 -- low sodium diet plus olive oil and 80 mmol Na in tablets / day (olive control), Group2 -- low sodium diet plus olive oil and placebo tablets / day (olive low sodium), Group3 -- low sodium diet plus fish oil and 80 mmol sodium in tablets / day (fish control), Group4 -- low sodium diet plus fish oil

										and placebo tablets / day (fish low sodium)
MacGregor 1982	Crossover	M/F	49	19	19	0.0%	1	UK	Hypertensive	Group1 -- low sodium diet plus sodium tablets to restore baseline sodium intake (control), Group2 -- low sodium diet plus placebo tablets (low sodium)
MacGregor 1989	Crossover	M/F	57	20	20	0.0%	1	UK	Hypertensive	Group1 -- low sodium diet plus 160 mmol sodium in tablets / day (control), Group2 -- low sodium diet plus 70mmol sodium + 9 placebo tablets / day (low sodium), Group3 -- low sodium diet plus 16 placebo tablets / day (very low sodium)

McCarron 1997	Crossover	M/F	51.6	97	97	2.0%	1	USA	Hypertensive	Group1 -- dietary advice for reduced calorie, fat and CHO diet (control), Group2 -- dietary advice for reduced calorie, fat and CHO diet plus reduced sodium diet (low sodium)
Meland 1997	Crossover	M/F	50	16	16	0.0%	2	Norway	Hypertensive	Group1 -- low sodium diet plus 50 mmol/day sodium tablets (control), Group2 -- low sodium diet plus placebo (low sodium)
Meland 2009	Parallel	M/F	56	23	23	0.0%	2	Norway	Hypertensive	Group1 -- low sodium diet plus 50 mmol sodium in tablets / day (control), Group2 -- low sodium diet plus placebo tablets / day (low sodium)
Melander 2007	Crossover	M/F	53	39	39	15.2%	1	Sweden	Normotensive	Group1 -- low sodium diet plus 100 mmol/day sodium tablets (control), Group2 -- low sodium diet plus placebo (low sodium)
Muhlhauser 1996	Parallel	M/F	36	8	8	0.0%	1	Germany	Heterogenous	Group1 -- low sodium diet plus 100mmol/day Na tablets (control), Group2 -- low sodium diet plus placebo tablets (low sodium)

Nestel 1993	Parallel	M/F	65	32	34	0.0%	1.5	Australia	Normotensive	Group1 -- low sodium diet plus sodium tablets and DGLA or safflower oil (control), Group2 -- low sodium diet plus placebo tablets and DGLA or safflower oil (low sodium)
Parijs 1973	Crossover	M/F	41.2	17	17	22.7%	1	Belgium	Hypertensive	Group1 -- normal sodium diet plus placebo tablets / day (control-placebo), Group2 -- low sodium diet plus placebo tablets / day (low sodium-placebo), Group3 -- normal sodium diet plus diuretic in tablets / day (control-diuretic), Group4 -- low sodium diet plus diuretic in tablets / day (low sodium-diuretic)
Puska 1983	Parallel	M/F	30 to 50	34	38	5.3%	1.5	Finland	Heterogenous	Group1 -- maintain "normal" diet (control), Group2 -- low sodium diet achieved through counseling and provision of "key" low salt options (low sodium)

Richards 1984	Crossover	M/F	19 to 52	12	12	25.0%	1.25	New Zealand	Hypertensive	Group1 -- control diet with sodium target of 180 mmol/day + 60mmol K/day (control), Group2 -- low sodium diet with sodium target of 80 mmol /day + 60mmol K/day (low sodium)
Ruppert 1993	Crossover	M/F	47	25	25	0.0%	1	Germany	Normotensive	Group1 -- diet of 85 mmol sodium plus 115 mmol sodium/day in tablet (control), Group2 -- deit of 85 mmol sodium plus placebo in tablet (low sodium)
Sacks 2001	Crossover	M/F	48	198	192	5.3%	1	USA	Heterogenous	Group 1 -- DASH diet with sodium target 150 mmol/day (DASH control), Group 2 -- DASH diet with sodium target 100 mmol/day (DASH low Na), Group 3 -- DASH diet with sodium target 50 mmol/day (DASH very low Na), Group 4 -- Normal diet with sodium target 150 mmol/day (control), Group 5 -- Normal diet with sodium target 100 mmol/day (low Na), Group 6 -- Normal diet with sodium target 50 mmol/day (very

										low Na)
Sciarrone 1992	Parallel	M/F	53.5	46	45	4.2%	2	Australia	Hypertensive	Group1 -- low sodium/low fat diet plus 100mmol / day of Na tablets (control low fat), Group2 -- low sodium/low fat diet plus placebo tablets (low sodium low fat), Group3 -- low sodium/normal fat diet plus 100mmol / day of Na tablets (control), Group4 -- low sodium/normal fat diet plus placebo tablets (low sodium)
Silman 1983	Parallel	M/F	50 to 64	10	15	10.7%	12	UK	Hypertensive	Group1 -- healthy lifestyle education (control), Group2 -- education to reach low

										sodium diet plus healthy lifestyle education (low sodium)
Suckling 2010	Crossover	M/F	Not Reported	46	46	Not Reported	1.5	UK	Heterogenous	Group1 -- low sodium diet plus unclear amount /day of sodium tablets (control), Group2 -- low sodium diet plus placebo tablets (low sodium)
Swift 2005	Crossover	M/F	50	40	40	13.0%	1	UK	Hypertensive	Group1 -- low sodium diet plus 120mmol sodium in tablets (control), Group2 -- low sodium diet plus placebo tablets (low sodium)
TOPH 1992	Parallel	M/F	43	327	417	0.0%	18	USA	Normotensive	Group1 -- no intervention (control), Group2 -- educational campaign to reduce sodium intake (low sodium)
TOPH 1997	Parallel	M/F	44	1052	1041	12.1%	36	USA	Normotensive	Group1 -- no intervention (control), Group2 -- educational campaign to reduce sodium intake(low sodium), Group3 -- educational campaign to reduce weight (weight loss), Group4 -- educational campaign to reduce weight and

										sodium intake(low sodium/weight loss)
Vogt 2008	Crossover	M/F	50	33	33	2.9%	1.5	Netherlands	Heterogenous	Group1 -- high sodium diet (~200mmol/day) (control), Group2 -- low sodium diet (~50 mmol/day) (low sodium), Group3 -- high sodium diet (~200mmol/day) + losartan therapy (control-L), Group4 -- low sodium diet (~50 mmol/day) + losartan therapy (low sodium-L), Group5 -- high sodium diet (~200mmol/day) + losartan+ HCT therapy (control-LHCT), Group6 -- low sodium diet (~50 mmol/day) + losartan+ HCT therapy (low sodium-LHCT)

Watt 1983	Crossover	M/F	52	18	18	10.0%	1	UK	Hypertensive	Group1 -- low sodium diet plus 80 mmol sodium in tablets / day (control), Group2 -- low sodium diet plus 8 placebo tablets / day (low sodium)
Watt 1985	Crossover	M/F	22	66	66	12.0%	1	UK	Heterogenous	Group1 -- low sodium diet plus 80 mmol sodium in tablets / day (control), Group2 -- low sodium diet plus 8 placebo tablets / day (low sodium)
Weir 2010	Crossover	M/F	51.5	115	115	12.9%	1	USA	Hypertensive	Group1 -- usual sodium diet plus Aliskiren (control), Group2 -- low sodium diet plus Aliskiren (low sodium)

Effects of Interventions

Overall Effect on Blood Pressure

The meta-analysis consisted of 50 unique cohorts that included a total 3304 participants in the reduced sodium group and 3432 in the usual sodium group. The mean age (not weighted) was 50.6 years (range of 22 to 73 years) and the mean study duration (not weighted) was 3.3 months (range of 1 to 36 months). All of the studies had mixed gender participants except for two (Andersson 1984 and Fagerberg 1984) which included males only.

The pooled summary estimates for between-group differences in blood pressure achieved were -3.41 mmHg (95% CI: -4.33, -2.49) [systolic] and -1.57 mmHg (95% CI: -2.13, -1.00) [diastolic] lower for intervention groups compared to control groups. The I^2 values were 64% for systolic and 59% for diastolic blood pressure.

Please refer to Appendix N for a description of which studies were included in each quartile when divided by the sodium intake achieved by the control group. The number of subjects in each quartile was as follows: Quartile One- 600 (reduced sodium) and 623 (control), Quartile Two - 814 (reduced sodium) and 920 (control), Quartile Three – 1539 (reduced sodium) and 1532 (control), and Quartile Four – 351 (reduced sodium) and 357 (control).

When the 50 cohorts were divided into quartiles based on the level of sodium intake achieved by their control group, the pooled estimates of changes in systolic and diastolic blood pressure using the random effects model generally followed a pattern of increasing effect sizes from quartiles 1 through 4 (especially for diastolic BP) with the last quartile having the greatest effect size (as shown in Table 2). However, the second quartile for systolic blood pressure was lower than the first. Though each quartile had a different effect estimate, they still had overlapping 95% confidence intervals and were therefore not statistically significantly different from each other. Please refer to Appendix L: Forest Plot of Changes in Systolic Blood Pressure Using the Random Effects Model and Appendix M: Forest Plot of Changes in Diastolic Blood Pressure Using the Random Effects Model for the meta-analysis.

Table 2: Overall Pooled Estimates of Changes in Blood Pressure Using the Random Effects Model

	Heterogeneity	Cohorts	Overall	Cohorts	Quartile 1	Cohorts	Quartile 2	Cohorts	Quartile 3	Cohorts	Quartile 4
Overall SBP	I^2 = 64 %	50	-3.41 [-4.33, -2.49]	13	-3.03 [-5.00, -1.06]	12	-2.68 [-3.64, -1.72]	12	-3.39 [-5.24, -1.53]	13	-5.96 [-8.08, -3.83]
Overall DBP	I^2 = 59 %		-1.57 [-2.13, -1.00]		-1.18 [-2.57, 0.21]		-1.52 [-2.42, -0.63]		-1.63 [-2.64, -0.61]		-2.24 [-3.47, -1.00]

*Sodium intake achieved in the control groups: Quartile One (2.9 to 3.28 g Na), Quartile Two (3.31 to 3.73 g Na), Quartile Three (3.75 to 4.16 g Na), and Quartile Four (4.37 to 4.77 g Na).
**All estimates are in mmHg and have 95% CIs in parentheses

Subgroup Analysis by Study Design

The studies were divided into one of two groups depending on whether they had a crossover or parallel design. This subgroup analysis was done to see if the study design influenced the magnitude or direction of the effect. Table 3 provides characteristics of the studies and Table 4 outlines the pooled estimates of changes in systolic and diastolic blood pressure (overall and by quartile).

Table 3: Characteristics of Studies by Type of Study Design

Subgroup	# of Cohorts	# of Participants (Low Sodium/ Control)	Mean # of Participants Per Study (Range)	Mean Age, yrs (Range)	Mean Loss to Follow-up (Range)	Mean Duration, months (Range)
Parallel	24	1978/2103	236 (16-2093)	52.9 (36-67)	5.3% (0-12.1%)	6 (1-36)
Crossover	26	1326/1329	62 (12-390)	48.8 (22-73)	7.7% (0-25%)	1.2 (1-2)

Table 4: Overall Pooled Estimates of Changes in Blood Pressure by Study Design

	Heterogeneity	Cohorts	Overall	Cohorts	Quartile 1	Cohorts	Quartile 2	Cohorts	Quartile 3	Cohorts	Quartile 4
Parallel Design SBP	I^2 = 45 %	24	-2.40 [-3.45, -1.35]	6	-3.86 [-6.46, -1.26]	6	-1.89 [-2.90, -0.87]	6	-4.12 [-6.42, -1.83]	6	-1.63 [-3.65, 0.39]
Parallel Design DBP	I^2 = 53 %		-1.32 [-2.03, -0.60]		-2.07 [-3.96, -0.17]		-0.75 [-1.50, 0.00]		-2.63 [-4.61, -0.65]		-0.55 [-1.59, 0.50]
Crossover Design SBP	I^2 = 64 %	26	-4.15 [-5.51, -2.78]	7	-2.70 [-4.86, -0.54]	6	-5.69 [-7.72, -3.67]	6	-5.47 [-8.36, -2.58]	7	-4.86 [-7.98, -1.74]
Crossover Design DBP	I^2 = 56 %		-1.76 [-2.59, -0.93]		-0.85 [-2.40, 0.69]		-2.84 [-4.13, -1.56]		-2.33 [-3.77, -0.88]		-2.22 [-4.13, -0.32]

*Sodium intake achieved in the control groups: Parallel: Quartile One (2.90-3.13 g Na), Quartile Two (3.22-3.52 g Na), Quartile Three (3.58-3.84 g Na), and Quartile Four (3.95-4.60 g Na). Crossover: Quartile One (2.95-3.31 g Na), Quartile Two (3.73-3.84 g Na), Quartile Three (4.00-4.40 g Na), and Quartile Four (4.44-4.77 g Na).

**All estimates are in mmHg and have 95% CIs in parentheses

When the groups were divided by study design, there was a difference in the overall effect estimates, but they were non-significant as they had overlapping 95% confidence intervals. Additionally, there were no observable sodium-blood pressure reduction patterns when they were separated into quartiles.

Subgroup Analysis by Participant Blood Pressure Status

The studies were also stratified by the blood pressure status of the included participants. This subgroup analysis was done to see if the participants' starting blood pressure status influenced the magnitude or direction of the effect since sodium reduction may affect hypertensive people differently from normotensive people. Table 5 provides characteristics of the studies and Table 6 outlines the pooled estimates of changes in systolic and diastolic blood pressure (overall and by quartile).

Table 5: Characteristics of Studies by Participants' Blood Pressure Status

Subgroup	# of Cohorts	# of Participants (Low Sodium/ Control)	Mean # of Participants Per Study (Range)	Mean Age, yrs (Range)	Mean Loss to Follow-up (Range)	Mean Duration, months (Range)
Hypertensive	30	1088/1127	56 (12-200)	51.2 (24-73)	7.3% (0-25%)	2.3 (1-12)
Normotensive	6	1475/1556	593 (25-2093)	50.4 (43-65)	5.5% (0-15.2%)	11.5 (1-36)
Heterogeneous	13	741/749	97 (16-390)	48.3 (22-67)	4.9% (0-12%)	1.2 (1-1.5)

*49 cohorts are listed here because Cappuccio 1997 was grouped with the heterogeneous studies instead of broken up into its separate hypertensive and normotensive groups

Table 6: Overall Pooled Estimates of Changes in Blood Pressure by Participants' Blood Pressure Status

	Heterogeneity	Cohorts	Overall	Cohorts	Quartile 1	Cohorts	Quartile 2	Cohorts	Quartile 3	Cohorts	Quartile 4
Hypertensive SBP	I^2 = 13 %	31	-4.06 [-5.16, -2.96]	8	-3.09 [-5.16, -1.02]	8	-2.37 [-4.41, -0.33]	7	-5.57 [-7.41, -3.72]	8	-7.31 [-10.02, -4.61]
Hypertensive DBP	I^2 = 29 %		-2.27 [-3.03, -1.51]		-1.72 [-3.22, -0.23]		-1.99 [-3.80, -0.17]		-2.92 [-4.09, -1.75]		-3.28 [-5.03, -1.54]
Normotensive SBP	I^2 = 61 %	7	-1.38 [-2.74, -0.01]	2	-3.49 [-8.40, 1.42]	2	-5.75 [-10.83 -0.68]	1	0.30 [-0.76, 1.36]	2	-1.22 [-2.28, -0.17]
Normotensive DBP	I^2 = 34 %		-0.55 [-1.24, 0.14]		-0.93 [-1.73, -0.13]		-3.18 [-6.30, -0.07]		0.30 [-0.49, 1.09]		-0.55 [-1.36, 0.26]
Heterogeneous SBP	I^2 = 76 %	13	-3.41 [-5.13, -1.69]	4	-2.92 [-5.62, -0.23]	3	-3.46 [-5.61, -1.31]	3	-2.86 [-7.66, 1.93]	3	-6.75 [-11.68, -1.82]
Heterogeneous DBP	I^2 = 73 %		-1.06 [-2.14, 0.02]		-0.75 [-2.89, 1.39]		-0.56 [-1.57, 0.45]		-1.47 [-3.50, 0.56]		-2.08 [-4.72, 0.55]

*Sodium intake achieved in the control groups: Hypertensive: Quartile One (2.90-3.22g Na), Quartile Two (3.28-3.73 g Na), Quartile Three (3.75-4.16 g Na), and Quartile Four (4.37-4.77 g Na). Normotensive: Quartile One (3.22-3.34 g Na), Quartile Two (3.60-3.81 g Na), Quartile Three (3.95 g Na), and Quartile Four (4.08-4.59 g Na). Heterogenous: Quartile One (2.95-3.31 g Na), Quartile Two (3.34-3.8 g Na), Quartile Three (3.84-4.44 g Na), and Quartile Four (4.53-4.60 g Na).
**All estimates are in mmHg and have 95% CIs in parentheses
***There are 51 cohorts since Cappuccio 1997 had results for hypertensives, normotensives, and heterogenous groups separately

There were differences in the estimates between the hypertensive, normotensive, and heterogenous groups with a larger difference in blood pressure in the hypertensives than in the normotensives. However, only the estimates between the hypertensive and nomortensive groups were statistically significantly different as they had non-overlapping 95% confidence intervals. There was no observable pattern in terms of differences

between sodium intake quartiles for the normotensive group, but the quartiles for the hypertensive and heterogeneous groups generally increased in effect size from quartile one to four (though it was not statistically significant).

Study Quality

The mean loss to follow-up among all of the studies was 6.6% (range 0-25%). One article (Suckling 2010) did not report the loss to follow-up percentage, but the author was contacted for further information. Four studies either did not report the participants' average age or provided a range only (Puska 1983, Richards 1984, Silman 1983, and Suckling 2010).

One study (Suckling 2010) was published solely as a conference abstract and therefore risk of bias could not be determined from it. There were three articles which had a 'high risk' of bias across more than one domain (Parijs 1973, Richards 1984, Weir 2010). Please refer to Appendix J for the Risk of Bias Graph and Appendix K for the Risk of Bias Summary for more detail.

Funnel plots (Appendices O and P) were used to determine if there were small study biases. They were symmetrical around the mean effect size line indicating low likelihood of publication bias. Publication bias was also minimized by looking at both published (PUBMED and MEDLINE) and unpublished (ICTRP and Cochrane) literature,

communicating with authors who provided some unpublished papers, and using LILACS to capture literature that was not published in mainstream English language press.

Sensitivity Analyses

Please refer to Appendix K: Risk of Bias Summary. When three studies with a high risk of bias across more than one domain (Parijs 1973, Richards 1984, and Weir 2010) were excluded from the overall meta-analysis, the pooled between-group estimates were -3.24mmHg (95%CI: -4.16, -2.31) [systolic] and -1.54 mmHg (95% CI: -2.11, -0.97) [diastolic] lower for the intervention group compared to the control group. The total number of participants when these three studies were taken out was 3146 for the reduced sodium group and 3271 in the control group. Additionally, the I^2 value changed minimally (systolic: 64% and diastolic: 60%) which suggested that there was no effect from removing these studies.

DISCUSSION

Summary of Main Results

This meta-analysis of randomized controlled trials illustrates that sodium intake reduction affects overall blood pressure changes, but there was no statistically significant relationship between the sodium intake level of the control group and blood pressure reduction. However, it appears that sodium reduction is useful to all since it benefited those with higher and lower relative usual sodium intake levels. When the overall analysis was divided into quartiles based on the control group's sodium intake, the

changes in blood pressure generally followed a pattern of increasing in effect size from quartiles one to four with the last quartile having the greatest effect size. The mean change in blood pressure in the 4th quartile was -5.96/-2.24mmHg compared to -3.03/-1.18mmHg for those in the 1st quartile, though this was not statistically significant. One peculiarity was that the second quartile for systolic blood pressure had a lower mean difference than the first quartile rather than the expected increased difference. This could have been due to specific characteristics (such as age, duration, number of participants) of the study cohorts that were included in that quartile. There was also a moderate level of heterogeneity among these studies in terms of study designs, types of participants, and duration of follow-up.

When the studies were divided by blood pressure status, hypertensives had the largest effect size, followed by the heterogeneous group, and then the normotensive group. This result suggests that people with hypertension derive greater benefit (larger blood pressure decreases) from sodium intake reduction in the short term than those that have normal blood pressure. The findings around the overall effect as well as the differences in effect between hypertensives and normotensives were in agreement with previous meta-analyses [8, 23].The pattern remains consistent when these same subgroups are divided into sodium intake quartiles. Exceptions to the general pattern may be due to a small number of studies or variation in study quality within certain quartiles. Additionally, the normotensive and heterogeneous groups had a moderate amount of heterogeneity while studies assessing people with hypertension had a minimal amount.

The studies were also divided by type of study design (crossover versus parallel), but there were no clear patterns visible. There did not seem to be a relationship between the quartile and difference in blood pressure. For the overall estimates, the crossover design studies yielded a larger effect size than the parallel design studies. However, it was not statistically significant which provides support that the effect estimated was true despite including both types of study design. Additionally, there was still a moderate amount of heterogeneity present within both subgroups.

One of the strengths in this review was including studies which used 24 hour urinary sodium excretion to estimate sodium intake. Measurement of 24 hour urinary sodium excretion is considered to be the 'gold standard' for obtaining sodium intake data as 95% of sodium ingested is excreted in urine. Additionally, assessment through dietary surveys has methodological limitations and underestimates the sodium intake. Therefore, using 24 hour urinary sodium excretion is accepted as the most accurate indirect method of determining sodium consumption [24-27].

Quality of the Evidence

The risk of bias was assessed using the quality criteria outlined in the Cochrane Handbook for Systematic Reviews [17]. Removing the three low quality studies during sensitivity analysis did not alter the effect estimates very much.

The Cochrane Handbook for Systematic Reviews also advises the use of funnel plots to check for publication bias and none was found [17]. If there was publication bias that was not picked up by this qualitative method, it would imply that this review picked up a disproportionate amount of studies which showed a beneficial effect estimate which could lead to an overestimation of the effect of sodium reduction on blood pressure.

Additionally, the internal validity of the articles could be affected by methodological limitations covered under the six domains of biases. The risks of biases are shown in Table 7. Though there was a sizeable amount of unclear risk, there was simultaneously little high risk across the domains. The high amount of unclear risk was likely due to unclear reporting rather than poor study quality. Therefore, those studies were not taken out of the analysis.

Table 7: Risk of Biases Among Studies Included in the Meta-Analysis

	Low Risk	Unclear Risk	High Risk
Lack of allocation concealment	11.1%	83.5%	5.6%
Random sequence generation	8.3%	91.7%	0%
Lack of participant/personnel blinding	55.6%	5.6%	38.9%
Lack of blinding of outcome assessor	41.7%	52.8%	5.6%
Incomplete outcome data	72.2%	19.4%	8.3%
Selective reporting	86.1%	11.1%	2.8%

The one ongoing trial, Borghi ICTRP, consists of 350 hypertensives and normotensives with a follow-up period of 12 months. This may influence the heterogeneous subgroup since the average number of participants and duration of those studies was 97 and 1.2

months. However, it is not expected to significantly change the overall findings in this review as it falls within similar characteristics of other studies included.

Other Potential Limitations

Though the search process was very thorough, there is a possibility that some relevant studies were missed. For example, regional databases other than LILACS were not searched and the He and MacGregor review was used as the source to obtain articles from MEDLINE and EMBASE through 2005. This could have resulted in missing articles which were published in alternative regional databases along with those published before 2005. In the future, all of the grey literature along with the other regional databases could be searched. Additionally, outcome data was not obtained from two studies (Gates 2004 and Morgan 1981) despite attempts to contact the authors. Biases may have arisen during data extraction as the longest time point in each study was used even when there may have been several follow-up periods. There was also variation in the total study follow-up durations between studies – as such, effects may have fluctuated across the course of time. This could be resolved in the future by subgroup analysis on the different duration periods.

There was a moderate degree of heterogeneity within the meta-analysis. Since the studies were structurally very different (interventions varied in their use of diet, supplements, and medications), the random effects model was used. There were several factors which could

affect heterogeneity such as differences in the studies in regards to age, duration, health status, design, and overall quality. Only blood pressure status and study design were sub-grouped to understand any inherent differences.

Regional or developed country bias may be another potential limitation since all of the studies were conducted in high income countries [28]. This is especially important since sodium intake varies across countries globally. This bias may affect the external validity, or generalizability, of the results, but there was no apparent reason to believe that people in different parts of the world have separate physiological responses to sodium intake [29, 30] .

Lastly, a meta-regression could have strengthened the review as it would relate the size of the effect to one or more characteristics of the studies involved [31]. However, this was not undertaken since data concerning both baseline and follow-up sodium intake and blood pressure values were not available for all studies.

Implications for Research and Practice

There is a significant amount of evidence linking sodium reduction to decreased blood pressure, but there are certain aspects that could benefit from additional research. First, there are few long-term follow-up studies as these are understandably difficult to carry out as dietary studies are challenging to sustain over a long period of time. The longest study in this review was for 36 months with the average study duration around three months. Therefore, it is unknown whether the size of the blood pressure effect is

sustainable over a period longer than 36 months. Second, all of the studies included in this review were from high-income countries so further research could focus on high quality trials in low- and middle-income countries.

This meta-analysis can be helpful for researchers, policymakers, health care providers, public health agencies, and consumers as it synthesizes a large amount of information and makes it accessible to the general public [32]. Though this review can aid in understanding the benefits of sodium reduction, it does not address the feasibility of how to achieve sodium reduction in the general population.

Increased sodium intake is an important risk factor for increased blood pressure which is a precursor for stroke and coronary heart disease. Low and middle income countries have a higher prevalence of premature deaths from noncommunicable diseases, a higher average systolic blood pressure, and a greater percentage of people with elevated blood pressure when compared to high income countries [1, 3]. Moreover, living in lower socioeconomic status has been associated with higher sodium intake levels [33]. The findings in this review illustrate that populations with varying usual sodium intake levels can benefit from sodium reduction and therefore could help countries and funding organizations prioritize which groups to target first, allocate their resources appropriately, and develop specific implementation plans.

Concluding Remarks

In conclusion, sodium reduction was significantly associated with decreases in blood pressure overall. Additionally, there was no statistically significant relationship between sodium intake in the control group and blood pressure reduction. However, there were statistically significantly larger decreases in blood pressure in hypertensives when compared to normotensives.

Appendix A: Search Strategy

1. PUBMED
    a. Run July 6, 2011
    b. Use He McGregor references until April 2005
    c. Hits: 668
    d. (blood pressure[MeSH] OR hypertension[MeSH] OR blood pressure[tiab] OR hypertension[tiab]) AND (sodium[MeSH] OR salt[MeSH] OR sodium chloride[MeSH] OR sodium[tiab] OR salt[tiab] OR sodium chloride[tiab]) AND (diet[MeSH] OR dietary[MeSH] OR intake[MeSH] OR restriction[MeSH] or reduction[MeSH] OR diet[tiab] OR dietary[tiab] OR intake[tiab] OR restriction[tiab] or reduction[tiab]) AND (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh]), LIMITS: January 1, 2005 – July 6, 2011
2. COCHRANE CENTRAL REGISTER OF CONTROLLED TRIALS
    a. Run on August 24, 2011
    b. Hits: 284
    c. (blood pressure OR hypertension) AND (sodium OR salt) AND (diet OR dietary OR intake OR restriction or reduction) AND (randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR drug therapy randomly OR trial OR groups), LIMITS: January 1, 2005- August 24, 2011
3. WHO CLINICAL TRIALS REGISTRY PLATFORM (ICTRP)
    a. Run on August 23, 2011
    b. Hits: 172 records for 167 trials found
    c. (blood pressure AND sodium) OR (blood pressure AND salt) OR (hypertension AND sodium) OR (hypertension AND salt)
4. LILACS
    a. Run on August 6, 2011
    b. Hits: 2
    c. (blood pressure OR hypertension) AND (sodium OR salt) AND (diet OR dietary OR intake OR restriction or reduction) AND (randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR drug therapy OR randomly OR trial OR groups)
5. EMBASE
    a. Run on 03 August 2011
    b. Hits: 300
    c. Step 1
        i. 'sodium chloride'/exp OR 'sodium'/exp OR salt:ti,ab OR sodium:ti,ab
    d. Step 2
        i. 'diet'/exp OR 'electrolyte intake'/exp OR 'diet restriction'/exp or 'dietary':ti,ab OR 'diet':ti,ab OR intake:ti,ab OR restriction:ti,ab or restricted:ti,ab or restrictive:ti,ab or reduce:ti,ab or reduced;ti, ab OR reduction:ti,ab
    e. Step 3

    i. 'randomized controlled trial'/exp OR 'controlled trial':ab,ti OR 'randomized':ab,ti AND 'randomised':ab,ti OR placebo:ab,ti OR 'drug therapy':ab,ti OR randomly:ab,ti OR trial:ab,ti OR groups:ab,ti

f. Step 4
    i. (Step 1 AND Step 2 AND Step 3) AND [2005-2012]/py
g. Step 5
    i. (Step 1 AND Step 2) AND [randomized controlled trial]/lim AND [2005-2012]/py
h. Step 6
    i. (Step 4 OR Step 5) AND [animals]/lim
i. Step 7
    i. (Step 4 OR Step 5) AND [animals]/lim AND [humans]/lim
j. Step 8
    i. (Step 4 OR Step 5) NOT Step 6
k. Step 9
    i. Step 8 OR Step 7

Appendix B: Data Extraction Form Template

DATA EXTRACTION FORM

1. Participants

Study ID Date

Extractor (initials): Type of report:

Trial title

Authors:

Journal (vol:pages:date):

Language of report: English

Country:

Duplicate publication: YES /

NO

Funding source:

Inclusion Criteria (including sex, age, diagnostic criteria, co-morbidity)	Exclusion criteria (including sex, age, diagnostic criteria, co-morbidity)

Were intervention and control groups comparable at baseline?

Notes:

(CIRCLE FOLLOWING ATTRITUBES OF STUDY)

1) Sodium reduction achieved - <1/3 of control / >1/3 of control / both
- < 2g / d in intervention / >2g/d in intervention
- <1.2 g/d in intervention / > 1.2 g/d in intervention
- <1.2 g/d in intervention / between 1.2 and 2 g/d in control or in other intervention arm

2) Age- Adult (15 yrs or greater) / children (1-14 yrs)

3) Group - Normatensive / hypertensive / both / not specified
4) Duration of follow-up (in months) -
5) Sex - male / female / both (heterogeneous)
6) Blood pressure method - automatic / manual
7) Blood pressure method - supine office / supine home / seated office / seated home / standing office / standing home / combination office / combination home / ambulatory 24 hr / ambulatory day / ambulatory night

2. Methods

Objective as stated in manuscript:

Overview of methods (include detail on method of measurement of sodium intake, study site)

Method of randomization a) Truly random? (computer generated, random numbers, coin toss, shuffle etc.) **A** or b) Not stated or unclear? **B** or c) Quasi-randomized or systematic? (patient number, date of birth, alternate) **C** or d) Allocation not used? **D**	Method:
Allocation concealment a) Adequate? **A** or (central allocation at trials office or pharmacy, sequentially numbered or coded vials, other methods where the trialists allocating treatment could not be aware of the treatment) b) Unclear **B** or c) Inadequate? **C** or (allocation was alternate (by patient, day of the week, admission ward, etc.) or based on information, such as date of birth, already known to the trialists) d) Not used? **D**	
Blinding Subject blinded Yes No Unclear Provider blinded Yes No Unclear Outcome assessor blinded Yes No Unclear A – adequate B- Unclear C - Inadequate	
Loss to follow up <5% 5-9.9% 10-19.9% ≥ 20% Unclear A- Adequate B- Unclear C- Inadequate	

PARTICIPANTS	Group 1	Group 2	Group 3	Group 4	TOTAL
Age (Mean and SD)					
Sex					
N originally randomized					
Final samples					
% Loss to follow up					

3. Interventions

TYPE OF INTERVENTION
Group1 --
Group2 --
Group3 --
Group4 --

COMMENTS:

Intervention/Control	**Group 1**	**Group 2**	**Group 3**	**Group 4**
Name				
Total Duration				
Assessment of compliance				
Sodium intake achieved at follow-up				
Baseline Sodium (mmol/24 h)				
Baseline Potassium (mmol/24 h)				
# of 24 h urine collections				

STARTING TIME OF INTERVENTION:

ENDING TIME OF INTERVENTION:

4. OUTCOMES

OUTCOMES MEASURED IN THE STUDY

ADULTS ALL:
ADULTS NORMATENSIVE:
ADULTS HYPERTENSIVE:
CHILDREN:

COMPARISONS MADE IN STUDY:

SUBGROUP ANALYSES IN STUDY:

OUTCOME – CATEGORICAL	**Group 1**		**Group 2**		**Group 3**		**Group 4**	
	n	***(N)***	**n**	(N)	**n**	(N)	**n**	(N)
ADULTS – ALL								
Elevated systolic blood pressure								
Elevated diastolic blood pressure								
NPS								

ADULTS – normatensive								
Elevated systolic blood pressure								
Elevated diastolic blood pressure								
NPS								
ADULTS –hypertensive								
Elevated systolic blood pressure								
Elevated diastolic blood pressure								
NPS								
CHILDREN								
Elevated systolic blood pressure								
Elevated diastolic blood pressure								
NPS								

OUTCOME - CONTINUOUS	**Group 1**		**Group 2**		**Group 3**		**Group 4**	
	n	***Mean (SD)***	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
ADULTS-ALL								
Systolic blood pressure								
Diastolic blood pressure								
Adrenaline								
Noradrenaline								
Cholesterol								
Triglyceride								
HDL								
LDL								
NPS								
ADULTS – normatensive								
Systolic blood pressure								
Diastolic blood pressure								
Adrenaline								
Noradrenaline								
Cholesterol								
Triglyceride								
HDL								
LDL								
NPS								
ADULTS – hypertensive								
Systolic blood pressure								
Diastolic blood pressure								
Adrenaline								
Noradrenaline								
Cholesterol								
Triglyceride								
HDL								
LDL								
NPS								
CHILDREN								
Systolic blood pressure								

Diastolic blood pressure								
Adrenaline								
Noradrenaline								
Cholesterol								
Triglyceride								
HDL								
LDL								
NPS								

*** NPS = not previously specified**

Contact details
Name
Address (including email)

Investigator contacted for more information YES/NO

Data	Requested	Obtained	Available

GENERAL CONCLUSIONS and information about process variables – costs etc

EXCLUSIONS AFTER DATA EXTRACTION (Check and amend eligibility form)

REASONS FOR EXCLUSION: (Study design? Participants? Intervention? Other?)

DATA ENTERED INTO REVMAN BY: ON (date) DATA CHECKED BY: ON (date)

Appendix C: Characteristics of Excluded Studies

Study	Reason for Exclusion
Appel 2006	More than sodium level varied between groups
Cappuccio 2006	Intervention did not achieve a minimum of 40mmol difference in sodium intake relative to control
Charlton 2008	More than sodium level varied between groups
CSSSCG 2007	More than sodium level varied between groups
He 2005	Not RCT
Jessani 2007	Duration < 4 weeks
Keogh ICTRP	Not RCT
Kojuri 2007	Not RCT
Makela 2008	More than sodium level varied between groups
Mascioli 1991	No 24h UNa
Morikawa 2011	No 24h UNa
Rayner 2011	More than sodium level varied between groups
Santos 2010	More than sodium level varied between groups
Saptharishi 2009	No 24h UNa
Schorr 1996	More than sodium level varied between groups
Todd 2010	No 24h UNa
Todd ICTRP	No 24h UNa
Yamakoshi 2006	No 24h UNa
Zhou 2009	More than sodium level varied between groups

Appendix D: Characteristics of Studies Awaiting Classification

Study	Study Design	Sex	Age (years)	Final Sample Size	Loss to Follow Up	Country	Blood Pressure Status of Participants	Interventions	Duration of Follow-Up (months)
Swift 2006	Not known	Not known	Not known	Not known	Not known	Not known	Normotensive	Not known	Not known

Appendix E: Characteristics of Ongoing Studies

Study	Study Design	Sex	Age (years)	Final Sample Size	Loss to Follow Up	Country	Blood Pressure Status of Participants	Interventions	Duration of Follow-Up (months)
Borghi ICTRP	Not known	Male/Female	Not known	Not known	Not known	Italy	Heterogenous	Group 1: Low salt + water therapy diet, Group 2: Water therapy alone	12

Appendix F: References to Included Studies

Andersson 1984

Andersson OK, Fagerberg B, Hedner T. Importance of dietary salt in the hemodynamic adjustment to weight reduction in obese hypertensive men. Hypertension 1984;6:814–9.

ANHMRC 1989

Australian National Health and Medical Research Council Dietary Salt Study Management Committee. Fall in blood pressure with modest reduction in dietary salt intake in mild hypertension. Lancet 1989;1:399–402.

Benetos 1992

Benetos A, Yang Yan X, 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: 355–60.

Cappuccio 1997

Cappuccio FP, Markandu ND, Carney C, Sagnella GA, MacGregor GA. Double-blind randomised trial of modest salt restriction in older people. Lancet 1997;350:850–4.

Chalmers 1986

Chalmers J, Morgan T, Doyle A, Dickson B, Hopper J, Mathews J, Matthews G, Moulds R, Myers J, Nowson C, Scoggins B, Stebbing M. Australian National Health and Medical Research Council dietary salt study in mild hypertension. J Hypertens 1986;4(suppl 6):S629–37.

Cobiac 1992

Cobiac L, Nestel PJ, Wing LMH, Howe PRC. A low-sodium diet supplemented with fish oil lowers blood pressure in the elderly. J Hypertens 1992;10:87–92.

Dodson 1989

Dodson PM, Beevers M, Hallworth R, Webberley MJ, Fletcher RF, Taylor KG. Sodium restriction and blood pressure in hypertensive type II diabetics: randomised blind controlled and crossover studies of moderate sodium restriction and sodium supplementation. BMJ 1989;298:227–30.

Erwteman 1984

Erwteman TM, Nagelkerke N, Lubsen J, Koster M, Dunning AJ. Beta-blockade, diuretics, and salt restriction for the management of mild hypertension: a randomised double blind trial. BMJ 1984; 289:406–9.

Fagerberg 1984

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. Br Med J (Clin Res Ed) 1984;288:11–4.

Fotherby 1993

Fotherby MD, Potter JF. Effects of moderate sodium restriction on clinic and twenty-four-hour ambulatory blood pressure in elderly hypertensive subjects. J Hypertens 1993;11:657–63.

Grobbee 1987

Grobbee DE, Hofman A, Roelandt JT, Boomsma F, Schalekamp MA, Valkenburg HA. Sodium restriction and potassium supplementation in young people with mildly elevated blood pressure. J Hypertens 1987;5:115–9.

He 2009

He FJ, Marciniak M, Visagie E, Markandu ND, Anand V, Dalton RN, MacGregor GA. Effect of modest salt reduction on blood pressure, urinary albumin, and pulse wave velocity in white, black, and Asian mild hypertensives. Hypertension 2009:54:482-488.

Howe 1994

Howe PRC, Lungershausen YK, Cobiac L, Dandy G, Nestel PJ. Effect of sodium restriction and fish oil supplementation on BP and thrombotic risk factors in patients treated with ACE inhibitors. J Hum Hypertens 1994:8(1):43-49.

MacGregor 1982

MacGregor GA, Markandu ND, Best FE, Elder DM, Cam JM, Sagnella GA, Squires M. Double-blind randomised crossover trial of moderate sodium restriction in essential hypertension. Lancet 1982;1:351–5.

MacGregor 1989

MacGregor GA, Markandu ND, Sagnella GA, Singer D, Cappuccio FP. Double-blind study of three sodium intakes and long-term effects of sodium restriction in essential hypertension. Lancet 1989;2:1244–7.

McCarron 1997

McCarron DA,Weder AB, Egan BM, Krishna GG, Morris CD, Cohen M, Oparil S. Blood pressure and metabolic responses to moderate sodium restriction in isradipine-treated hypertensive patients. Am J Hypertens 1997;10:68–76.

Meland 1997

Meland E, Laerum E, Aakvaag A, Ulvik RJ, Hostmark AT. Salt restriction: effects on lipids and insulin production in hypertensive patients. Scand J Clin Lab Invest 1997;57:501–5.

Meland 2009

Meland E, Aamland A. Salt restriction among hypertensive patients: Modest blood pressure effect and no adverse effects. Scandinavian Journal of Primary Health Care 2009 : 27:97-103.

Melander 2007

Melander O, von Wowern F, Frandsen E, Burri P, Willsteen G, Aurell M, Hulthen UL. Moderate salt restriction effectively lowers blood pressure and degree of salt sensitivity is related to baseline concentration of rennin and N-terminal atrial natriuretic peptide in plasma. Journal of Hypertension 2007: 25:619-627.

Muhlhauser 1996

Muhlhauser I, Prange K, Sawicki PT, Bender R, Dworschak A, Schaden W, Berger M. Effects of dietary sodium on blood pressure in IDDM patients with nephropathy. Diabetologia 1996;39: 212–219.

Nestel 1993

Nestel PJ, Clifton PM, Noakes M, McArthur R, Howe PR. Enhanced blood pressure response to dietary salt in elderly women, especially those with small waist:hip ratio. J Hypertens 1993;11: 1387–94.

Parijs 1973

Parijs J, Joossens JV, der Linden LV, Verstreken G, Amery AKPC. Moderate sodium restriction and diuretics in the treatment of hypertension. Am Heart J 1973;85:22–34.

Puska 1983

Puska P, Iacono JM, Nissinen A, Korhonen HJ, Vartiainen E, Pietinen P, Dougherty R, Leino U, Mutanen M, Moisio S, Huttunen J. Controlled, randomised trial of the effect of dietary fat on blood pressure. Lancet 1983;1:1–5.

Richards 1984

Richards AM, Nicholls MG, Espiner EA, Ikram H, Maslowski AH, Hamilton EJ, Wells JE. Blood-pressure response to moderate sodium restriction and to potassium supplementation in mild essential hypertension. Lancet 1984;1:757–61.

Ruppert 1993

Ruppert M, Overlack A, Kolloch R, Kraft K, Gobel B, Stumpe KO. Neurohormonal and metabolic effects of severe and moderate salt restriction in non-obese normotensive adults. J Hypertens 1993; 117:743–9.

Sacks 2001

Sacks FM, Svetkey LR, Vollmer WM, Appel LJ, Bray GA, Harsha D, Obarzanek E, Conlin PR, Miller ER, Simons-Morton DG, Karanja N, Lin PH. Effects on blood pressure of reduced dietary sodium and the dietary approaches to stop hypertension (DASH) diet. N Engl J Med 2001: 344:3–10.

Sciarrone 1992

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;10:287–98.

Silman 1983

Silman AJ, Locke C, Mitchell P, Humpherson P. Evaluation of the effectiveness of a low sodium diet in the treatment of mild to moderate hypertension. Lancet 1983;1:1179–82.

Suckling 2010

Suckling R, He F, Markandu N, MacGregor G. Modest salt reduction lowers blood pressure and urinary albumin excretion in impaired glucose tolerance and type 2 diabetes. J Hypertens 2010: 28: 219.

Swift 2005

Swift PA, Markandu ND, Sagnella GA, He FJ, MacGregor GA. Modest salt reduction reduces blood pressure and urine protein excretion in black hypertensives. Hypertension 2005;46:308–312.

TOPH 1992

The Trials of Hypertension Prevention Collaborative Research Group. The effects of nonpharmarmacologic interventions on blood pressure of persons with high normal

levels: results of the Trials of Hypertension Prevention, phase I. JAMA 1992;267: 1213–20.

TOPH 1997

The Trials of Hypertension Prevention Collaborative Research Group. Effect of weight loss and sodium reduction intervention on blood pressure and hypertension incidence in overweight people with high-normal blood pressure. The Trials of Hypertension Prevention, Phase II. Arch Intern Med 1997;157:657–67.

Vogt 2008

Vogt L, Waanders F, Boomsma F, De Zeeuw D, Navis G. Effects of dietary sodium and hydrochlorothiazide on the antiproteinuric efficacy of losartan. J Am Soc Nephrol 2008: 19: 999–1007.

Watt 1983

Watt GCM, Edward C, Hart JT, Heart M, Walton P, Foy CJW. Dietary sodium restriction for mild hypertension in general practice. BMJ 1983;286:432–6.

Watt 1985

Watt GC, Foy CJ, Hart JT, Bingham G, Edwards C, Hart M, Thomas E, Walton P. Dietary sodium and arterial blood pressure: evidence against genetic susceptibility. BMJ 1985;291:1525–8.

Weir 2010

Weir MR, Yadao AM, Purkayastha D, Charney AN. Effects of High- and Low-Sodium Diets on Ambulatory Blood Pressure in Patients With Hypertension Receiving Aliskiren. J Cardiovascular Pharma and Therapeutics 2010: 15(4) :356-363.

Included, but not contributing to the meta-analysis:

Gates 2004

Gates PE, Tanaka H, Hiatt WR, Seals DR. Dietary sodium restriction rapidly improves large elastic artery compliance in older adults with systolic hypertension. Hypertension 2004;44:35–41.

Morgan 1981

Morgan TO, Myer JB. Hypertension treated by sodium restriction. Med J Aust 1981;2:396–7.

Appendix G: References to Excluded Studies (duplicates not listed)

Appel 2006

Appel LJ, Sacks FM, Carey VJ, Conlin PR, Erlinger TP,Miller ER. The effects of macronutrient intake on blood pressure: Subgroup analyses from the OmniHeart randomized feeding study. J Hypertens 2006: 24 (Suppl 6): 177

Cappuccio 2006

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; 6:13.

Charlton 2008

Charlton KE, Steyn K, Levitt NS, Peer N, Jonathan D, Gogela T, Rossouw K, Gwebushe N, Lombard CJ. A food-based dietary strategy lowers blood pressure in a low socio-economic setting: a randomised study in South Africa. Public Health Nutr. 2008;11(12):1397-406.

CSSSCG 2007

China Salt Substitute Study Collaborative Group. Salt substitution: a low-cost strategy for blood pressure control among rural Chinese. A randomized, controlled trial. J Hypertens. 2007;25(10):2011-8.

He 2005

He FJ, Markandu ND, MacGregor GA. Modest salt reduction lowers blood pressure in isolated systolic hypertension and combined hypertension. Hypertension. 2005;46(1):66-70.

Jessani 2007

Jessani S, Hatcher J,Jafar T. Effects of low salt diet versus high salt diet on blood pressure: A randomized controlled crossover trial. J Hypertens. 2007; 25 (Suppl 2): S156

Keogh ICTRP

A randomised parallel study to assess the effect of dietary education about salt intake compared with usual care in individuals with hypertension who have lost weight following laparoscopic adjustable gastric banding. 2011.

Kojuri 2007

Kojuri J, Rahimi R. Effect of "no added salt diet" on blood pressure control and 24 hour urinary sodium excretion in mild to moderate hypertension. BMC Cardiovasc Disord. 2007;7:34.

Makela 2008

Makela P, Vahlberg T, Kantola I, Vesalainen R, Jula A. The effects of a 6-month sodium restriction on cardiac autonomic function in patients with mild to moderate essential hypertension. Am J Hypertens. 2008;21(11):1183-7.

Mascioli 1991

Mascioli S, Grimm RH, Launer C, Svendsen K, Flack J, Gonzalez N, Elmer P, Neaton J. Sodium chloride raises blood pressure in normotensive subjects: the study of sodium and blood pressure. Hypertension 1991;17(suppl I):I21–6.

Morikawa 2011

Morikawa N, Yamasue K, Tochikubo O, Mizushima S. Effect of salt reduction intervention program using an electronic salt sensor and cellular phone on blood pressure among hypertensive workers. Clin Exp Hypertens. 2011;33(4):216-22.

Rayner 2011

Rayner B, Ramesar R, Steyn K, Levitt N, Lombard C, Charlton K. G-protein-coupled receptor kinase 4 polymorphisms predict blood pressure response to dietary modification in Black patients with mild-to-moderate hypertension. J Hum Hypertens. 2011 May 5.

Santos 2010

Santos A, Martins MJ, Guimaraes JT, Severo M, Azevedo I. Sodium-rich carbonated natural mineral water ingestion and blood pressure. Rev Port Cardiol. 2010;29(2):159-72.

Saptharishi 2009

Saptharishi L, Soudarssanane M, Thiruselvakumar D, Navasakthi D, Mathanraj S, Karthigeyan M, Sahai A. Community-based Randomized Controlled Trial of Non-pharmacological Interventions in Prevention and Control of Hypertension among Young Adults. Indian J Community Med. 2009;34(4):329-34.

Schorr 1996

Schorr U, Distler A, Sharma AM. Effect of sodium chloride- and sodium bicarbonate-rich mineral water on blood pressure and metabolic parameters in elderly normotensive individuals: a randomized double-blind crossover trial. J Hypertens. 1996;14:131–5.

Todd 2010

Todd AS, Macginley RJ, Schollum JB, Johnson RJ, Williams SM, Sutherland WH, Mann JI, Walker RJ. Dietary salt loading impairs arterial vascular reactivity. Am J Clin Nutr. 2010;91(3):557-64.

Todd ICTRP

The impact of dietary sodium chloride intake on arterial wall function in normotensive subjects: a randomised controlled cross-over intervention study. 2009.

Yamakoshi 2006

Yamakoshi J, Shimojo R, Nakagawa S, Izui N, Ogihara T. Hypotensive effects and safety of less-sodium soy sauce containing (gamma)-aminobutyric acid (GABA) on high-normal blood pressure and mild hypertensive subjects. Jpn Pharmacol Ther. 2006; 34(6):691-709.

Zhou 2009

Zhou X, Liu JX, Shi R, Yang N, Song DL, Pang W, Li YM. Compound ion salt, a novel low-sodium salt substitute: From animal study to community-based population trial. Am J Hypertens. 2009;22(9):934-42.

Appendix H: References to Studies Awaiting Classification

Swift 2006

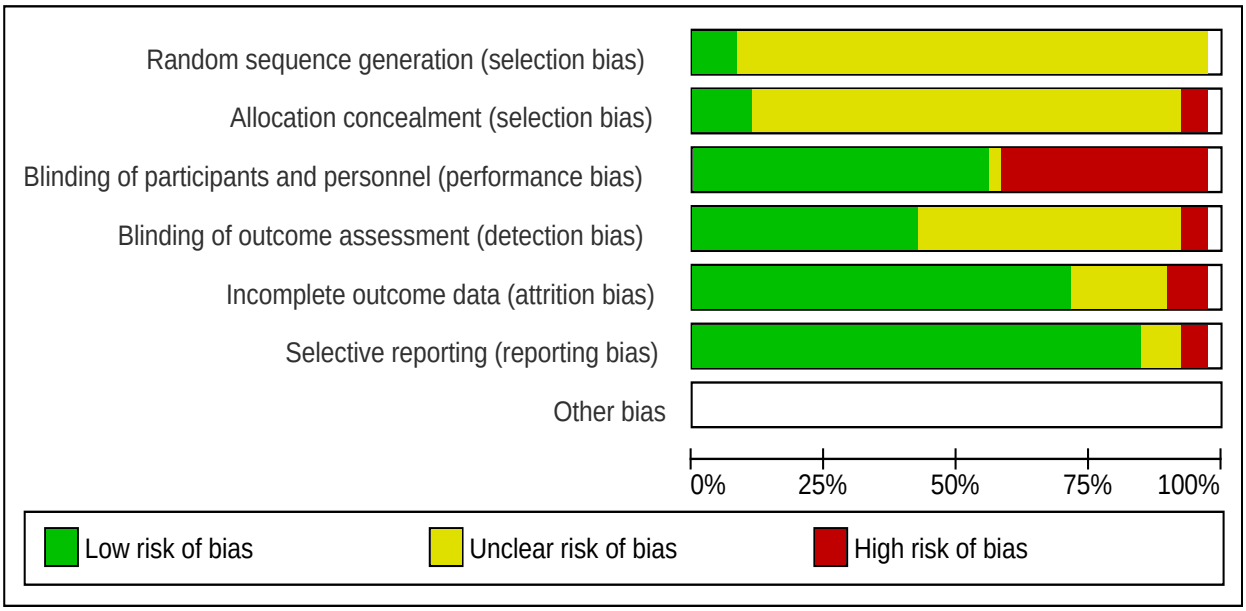
Swift PA, Markandu ND, Sagnella GA, MacGregor GA. A double blind randomised control trial of modest salt reduction in black people with normal blood pressure. Journal of the American Society of Nephrology. 2006; 17:657A.

Appendix I: References to Ongoing Studies

Borghi ICTRP

The Links Between Water and Salt Intake, Body Weight, Hypertension and Kidney Stones: a Difficult Puzzle. 2010.

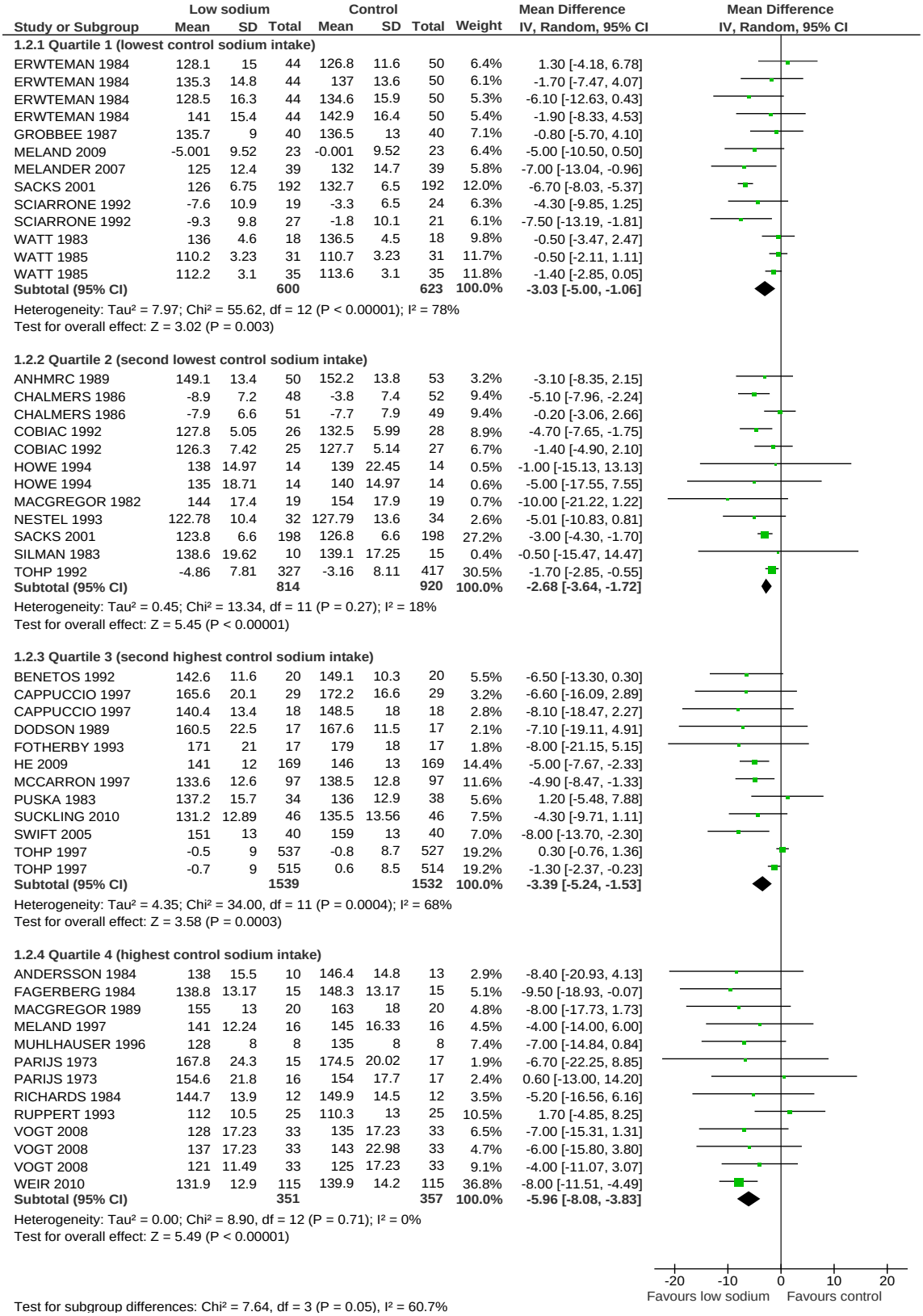
Appendix J: Risk of Bias Graph



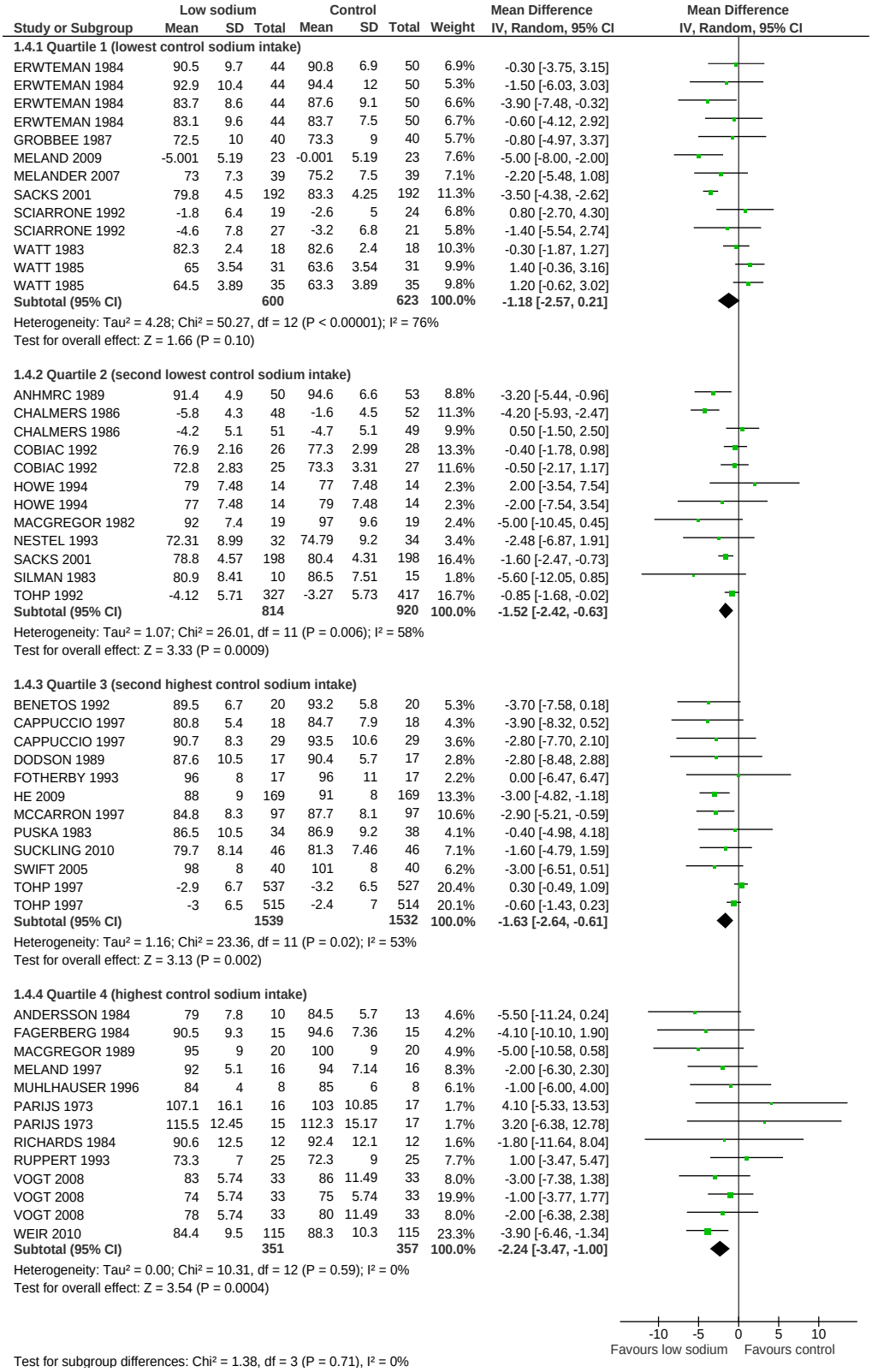
Appendix K: Risk of Bias Summary

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Andersson 1984	Unclear	Unclear	High	Unclear	Low	Low
ANHMRC 1989	Unclear	Unclear	Unclear	Unclear	Low	Low
Benetos 1992	Unclear	Unclear	Low	Unclear	Low	Low
Cappuccio 1997	Low	Low	Low	Unclear	Low	Low
Chalmers 1986	Unclear	Unclear	High	Unclear	Low	Low
Cobiac 1992	Unclear	Unclear	Low	Low	Unclear	Low
Dodson 1989	Unclear	Unclear	High	Unclear	Low	Low
Erwteman 1984	Unclear	Unclear	High	Low	Unclear	Unclear
Fagerberg 1984	Unclear	Unclear	High	Unclear	Unclear	Low
Fotherby 1993	Unclear	Unclear	Low	Unclear	Low	Low
Grobbee 1987	Unclear	Unclear	Low	Unclear	Low	Low
He 2009A	Low	Low	Low	Low	Low	Low
Howe 1994	Unclear	Unclear	Low	Low	Unclear	Low
MacGregor 1982	Unclear	Unclear	Low	Unclear	Low	Low
MacGregor 1989	Unclear	Unclear	Low	Unclear	Low	Low
McCarron 1997	Low	Unclear	Low	Low	Low	Low
Meland 1997	Unclear	Unclear	Low	Low	Low	Low
Meland 2009	Unclear	Unclear	Low	Low	Low	Low
Melander 2007	Unclear	Unclear	Low	Unclear	High	Low
Muhlhauser 1996	Unclear	Unclear	Low	Low	Low	Low
Nestel 1993	Unclear	Unclear	Low	Unclear	Low	High
Parijs 1973	Unclear	High	High	High	High	Low
Puska 1983	Unclear	Unclear	High	Low	Low	Low
Richards 1984	Unclear	Unclear	High	Unclear	High	Low
Ruppert 1993	Unclear	Unclear	Low	Low	Low	Low
Sacks 2001	Unclear	Unclear	High	Low	Low	Low
Sciarrone 1992	Unclear	Unclear	Low	Low	Low	Low
Silman 1983	Unclear	Unclear	High	Unclear	Low	Low
Suckling 2010	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Swift 2005	Unclear	Unclear	Low	Low	Unclear	Low
TOPH 1992	Unclear	Low	High	Low	Low	Low
TOPH 1997	Unclear	Low	High	Low	Low	Low
Vogt 2008	Unclear	Unclear	High	Unclear	Low	Low
Watt 1983	Unclear	Unclear	Low	Unclear	Low	Low
Watt 1985	Unclear	Unclear	Low	Unclear	Unclear	Unclear
Weir 2010	Unclear	High	High	High	Low	Unclear

Appendix L: Forest Plot of Changes in Systolic Blood Pressure Using the Random Effects Model



Appendix M: Forest Plot of Changes in Diastolic Blood Pressure Using the Random Effects Model

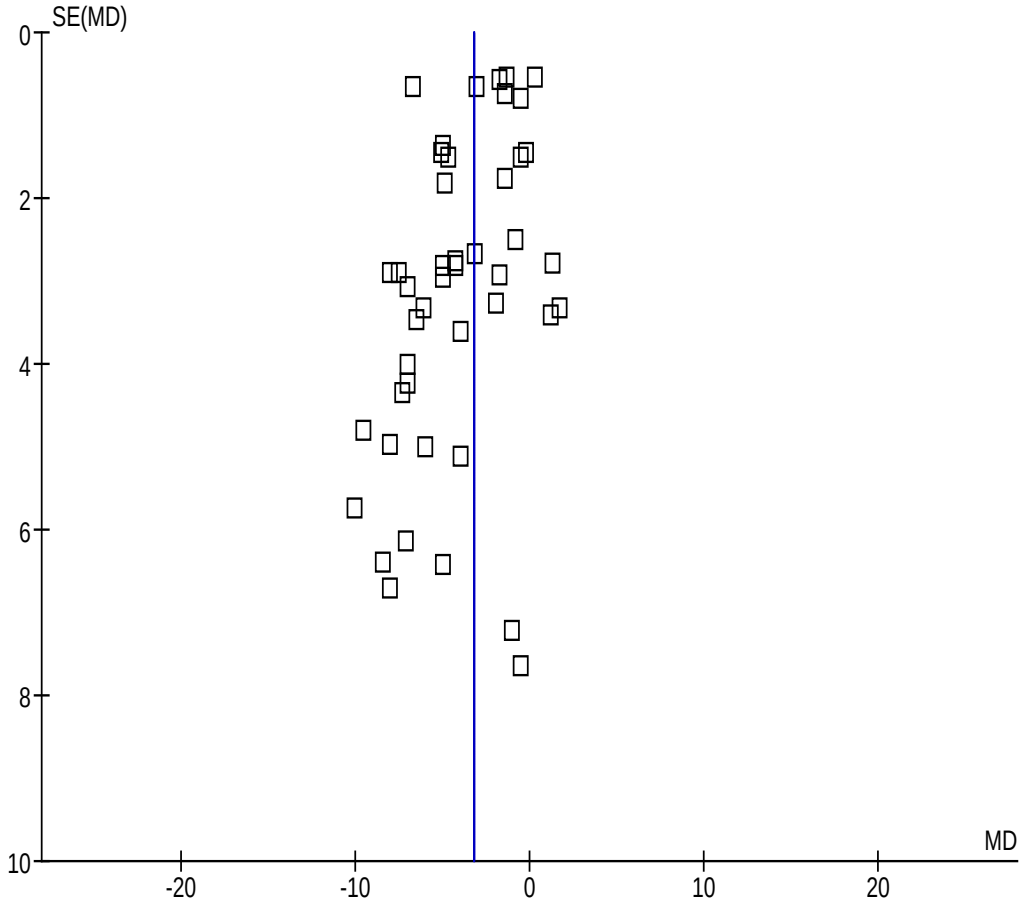


Test for subgroup differences: Chi² = 1.38, df = 3 (P = 0.71), I² = 0%

Appendix N: Division of Cohorts into Quartiles for Overall Analysis

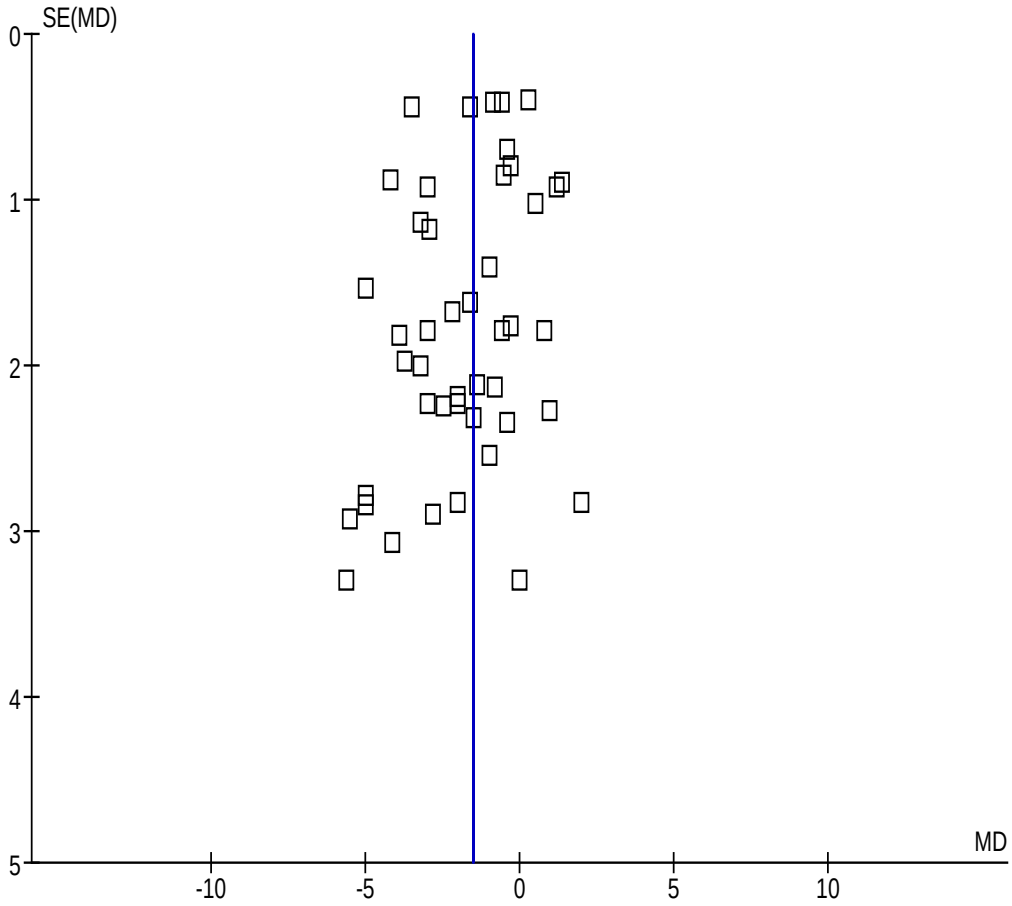
Quartile	Study ID	Group	Sodium (grams)
Quartile 1	Meland 2009	Control	2.90
	Watt 1985	Control - Parents Had Normal BP	2.95
	Sciarrone 1992	Control - Low fat/High fiber diet	2.96
	Erwteman 1984	Control - Beta Blocker	2.97
	Grobbee 1987	Control	2.97
	Erwteman 1984	Control - Placebo	2.99
	Watt 1985	Control - Parents Had High BP	3.00
	Erwteman 1984	Control - Beta-blocker and Diuretic	3.04
	Sciarrone 1992	Control - Normal fat/Normal fiber diet	3.13
	Erwteman 1984	Control - Diuretic	3.22
	Melander 2007	Control	3.22
	Sacks 2001	Control - Normal	3.24
	Watt 1983	Control	3.28
Quartile 2	Sacks 2001	Control - DASH	3.31
	Cobiac 1992	Control - Fish Oil	3.34
	TOPH 1992	Control	3.34
	Chalmers 1986	Control - High Potassium Diet	3.34
	Cobiac 1992	Control - Sunflower Oil	3.50
	ANHMRC 1989	Control	3.52
	Chalmers 1986	Control - Normal Diet	3.58
	Nestel 1993	Control	3.60
	Howe 1994	Control - Olive Oil	3.63
	Howe 1994	Control - Fish Oil	3.63
	Silman 1983	Control	3.67
	MacGregor 1982	Control	3.73
Quartile 3	Benetos 1992	Control	3.75
	He 2009	Control	3.80
	Suckling 2010	Control	3.80
	Cappuccio 1997	Control - Normotensives	3.81
	Puska 1983	Control	3.84
	Swift 2005	Control	3.84
	TOPH 1997	Control - Weight Loss	3.95
	Fotherby 1993	Control	4.00
	McCarron 1997	Control	4.05
	TOPH 1997	Control	4.08
	Cappuccio 1997	Control - Hypertensives	4.15
	Dodson 1989	Control	4.16
Quartile 4	MacGregor 1989	Control	4.37
	Meland 1997	Control	4.39
	Parijs 1973	Control - Placebo	4.40
	Vogt 2008	Control - Losartan/HCT	4.44
	Fagerberg 1984	Control	4.48
	Vogt 2008	Control - Losartan	4.53
	Richards 1984	Control	4.55
	Muhlhauser 1996	Control	4.58
	Ruppert 1993	Control	4.59
	Andersson 1984	Control	4.60
	Vogt 2008	Control	4.60
	Parijs 1973	Control - Diuretic	4.60
	Weir 2010	Control	4.77

Appendix O: Funnel Plot - Systolic Blood Pressure



*Horizontal axis: MD (mean difference) of the effect estimate, Vertical axis: SE (standard error of the mean difference)

Appendix P: Funnel Plot - Diastolic Blood Pressure



*Horizontal axis: MD (mean difference) of the effect estimate, Vertical axis: SE (standard error of the mean difference)

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