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WHO Library Cataloguing-in-Publication Data

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1.Potassium, Dietary. 2.Blood pressure. 3.Lipids. 4.Kidney. 5.Triglycerides. 6.Cholesterol. 7.Adult. 8.Review literature. 9.Meta-analysis 10.Chronic disease – prevention and control. I. World Health Organization.

ISBN 978 92 4 150488 1 (NLM classification: QV 277)

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Printed by the WHO Document Production Services, Geneva, Switzerland

Contents

Acknowledgements

This systematic review was prepared by Dr Nancy J Aburto, who was working as a scientist at the Nutrition Policy and Scientific Advice Unit (NPU) of the World Health Organization (WHO) Department of Nutrition for Health and Development (NHD), Ms Sarah Hanso, who was working as an intern in NPU at time of the preparation of this review, and Ms Hialy Gutierrez (Independent consultant).

This review was one of three systematic reviews prepared to inform the development of the WHO guideline on potassium. All systematic reviews were presented to the WHO Nutrition Guidance Expert Advisory Group Subgroup on Diet and Health, which assisted WHO in the interpretation of the results and in the generation of the guideline informed by those results.

WHO expresses special appreciation to the Ministry of Health, Labour and Welfare of the Government of Japan and the International Kidney Evaluation Association Japan for providing financial support for undertaking of the systematic reviews.

Technical editing of the document was undertaken by Dr Hilary Cadman from Cadman Editing Services in Australia, and cover design was undertaken by Ms Sue Hobbs from Minimum Graphics in New Zealand.

Abbreviations and acronyms

CCNFSDU	Codex Committee on Nutrition and Food for Special Dietary Uses
CI	confidence interval
CVD	cardiovascular disease
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
ICTRP	International Clinical Trials Registry Platform
ITT	intention-to-treat
LDL	low-density lipoprotein
LILACS	Latin American and Caribbean Health Science Literature Database
MD	mean difference
NCD	noncommunicable diseases
NUGAG	Nutrition Guidance Expert Advisory Group
WHO	World Health Organization

Symbols

>	greater than
<	less than
≥	equal to or greater than
≤	equal to or less than

1 Introduction

1.1 Background

Noncommunicable diseases (NCDs) are the main contributor to mortality and morbidity globally (WHO, 2005). The major NCDs currently account for approximately 60% of all deaths and 43% of disease burden globally, and these levels are expected to continue to rise (Strong et al., 2005; WHO, 2005). In 2005, cardiovascular disease (CVD) itself accounted for 30% of all deaths – the equivalent of infectious disease, nutritional deficiency, and maternal and perinatal conditions combined (WHO, 2005). Hypertension is considered a major risk factor for heart attack, and the most important risk factor for stroke. Suboptimal systolic blood pressure (>115 mmHg) is estimated to contribute to 49% of all coronary heart disease and 62% of all strokes (Mackay & Mensah, 2004).

Potassium consumption is of interest in public health nutrition, mainly due to its association with hypertension and CVDs. Increased consumption of potassium is thought to counteract the negative effects of sodium consumption on blood pressure. The biological plausibility of this theory is based on potassium's role in the physiological mechanisms through which the kidney reduces blood volume. Several large cohort studies have found an inverse association between potassium intake and risk of stroke (Ascherio et al., 1998; Khaw & Barrett-Connor, 1987). Additionally, three meta-analyses of trials comparing increased potassium with lower or usual potassium intake found that, on average, increased potassium intake lowers blood pressure (Cappuccio & MacGregor, 1991; Geleijnse et al., 2003; Whelton et al., 1997). However, another meta-analysis undertaken exclusively in individuals with hypertension did not detect a significant effect of potassium on blood pressure (Dickinson et al., 2006).

1.2 Need for this review

The 32nd Session of the Codex Committee on Nutrition and Food for Special Dietary Uses (CCNFSDU) – held in Santiago, Chile on 1–5 November 2010 – made a special request to the World Health Organization (WHO) to consider establishing daily potassium intake values for the general population on the basis of dietary adequacy or reduction of chronic NCD risk (or both). The CCNFSDU requested that this work be included as part of the update of recommendations on sodium intake by the WHO Nutrition Guidance Expert Advisory Group (NUGAG).

A 2002 joint WHO/Food and Agriculture Organization of the United Nations (FAO) Expert Consultation (WHO, 2003) concluded that the general population should consume a sufficient amount of potassium to maintain the molar ratio of sodium to potassium of 1:1. This ratio can generally be achieved with an intake of 70–80 mmol potassium/day if sodium is consumed at the recommended level. This recommendation is based on an improvement in blood pressure, and a blunting of the detrimental effects of higher sodium consumption on blood pressure. The expert consultation recommended that this intake of potassium be achieved through fruit and vegetable consumption. A report from the Institute of Medicine recommends a much higher level of potassium as an adequate intake – 120.5 mmol/day – based on literature citing benefits in blood pressure, risk of developing kidney stones and possibly decreased bone loss (Institute of Medicine, 2005). The latter two outcomes were not considered by the 2002 joint WHO/FAO Expert Consultation when recommending the level of potassium intake (WHO, 2003). The review presented here was undertaken in light of more recent evidence regarding potassium and blood pressure, and the association with

renal function and potential bone loss, plus the contradictory findings of recent systematic reviews. NUGAG will make use of this document when generating, reviewing and updating WHO guidelines on potassium intake.

1.3 Objectives

The overall objective was to assess the effect, in adults, of increased potassium intake compared with normal, lower or usual potassium intake on blood pressure and renal function, and on adverse effects, such as changes in blood lipids and catecholamine levels,.

Specific objectives were to assess whether:

- consuming more potassium differentially affects blood pressure, renal function and adverse effects such as increased lipids, cholesterol and triglycerides relative to consuming less potassium;
- potassium intake resulting in a urinary potassium excretion at or above 70 mmol/day has a greater effect on blood pressure, renal function and adverse effects such as increased lipids, cholesterol and triglycerides than less potassium intake;
- potassium intake resulting in a urinary potassium excretion at or above 90 mmol/day has a greater effect on blood pressure, renal function and adverse effects such as increased lipids, cholesterol and triglycerides than less potassium intake;
- potassium intake resulting in a urinary potassium excretion at or above 120 mmol/day has a greater effect on blood pressure, renal function and adverse effects such as increased lipids, cholesterol and triglycerides than less potassium intake.

Estimating potassium intake

Urinary potassium excretion is a common and valid form of estimating potassium intake. Data from 4680 men and women from 17 cities in four countries showed that average urinary potassium excretion was approximately 77% of intake (Stamler et al., 2003).Therefore, a factor of 1.30 is used to convert urinary potassium excretion to potassium intake. Because original studies reported urinary potassium excretion, data were analysed based on that value. Using the factor of 1.30:

- 70 mmol urinary potassium/day equals approximately 91 mmol potassium intake/day;
- 90 mmol urinary potassium/day equals approximately 117 mmol intake/day;
- 120 mmol urinary potassium/day equals approximately 156 mmol intake/day.

2 Methods

2.1 Criteria for considering studies for this review

Study types

We included in the review randomized controlled trials (RCTs) – both individual and cluster randomized – that allocated at least one group of participants to increased potassium intake, and at least one control group to lower potassium intake, and that were of at least 4 weeks' duration. We excluded studies that had concomitant interventions (i.e. nonpharmacological interventions, antihypertensive or other medications) in the intervention group unless those interventions were also applied to the control group (i.e. the only difference between the groups was the level of potassium intake).

Participants

Studies considered for inclusion were those involving adults (≥16 years of age) of either gender, from the general population (free living) or specific groups (e.g. refugee populations). We considered studies in apparently healthy populations who may have been at risk of or have had hypertension, were known to have hypertension or were known to have normal blood pressure. We excluded studies targeting those who were acutely ill, infected with human immunodeficiency virus (HIV) or hospitalized.

Interventions

We were interested in comparisons between increased potassium intake achieved through any means (e.g. supplements, food or dietary advice) and lower or usual potassium intake. If a manuscript presented multiple follow-up time points, data from the last follow-up were included in the overall analysis. Data from each time point were used in the subgroup analysis by duration of follow-up, without calculating an overall effect estimate across all subgroups.

Outcome measures

The primary outcome measures were:

- blood pressure (systolic or diastolic, or both);
- renal function;
- adverse effects including:
  - increased total cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides;
  - decreased high-density lipoprotein (HDL) cholesterol;
  - increased adrenaline or noradrenaline (urinary or plasma);
  - any other adverse effects reported by study authors.

As secondary outcome measures, any other outcomes reported in the studies were noted.

2.2 Identification of studies

We searched for studies in two phases. In the first phase, we searched for high-quality systematic reviews on increased potassium consumption that included the outcomes of interest. If the inclusion criteria for an identified review were similar or equivalent to those of the current review, we used the references from that review as a list of potential studies, and completed the list by searching the literature subsequent to the search date used in that review. In some cases, we contacted the original authors of the systematic review and sought to collaborate, to explore the data in such a way as to meet our objectives.

In the second phase, we undertook a complete search for data published since the date of of the search performed in the identified systematic review (see *Electronic databases* and *Other resources*, below).

2.2.1 Search for systematic reviews and meta-analyses

We first identified in the literature any high-quality systematic reviews of RCTs on the effect of increased potassium intake on blood pressure, renal function and adverse effects. If the inclusion criteria were in agreement with, or were broader than, the inclusion criteria defined for the specific objectives of the current literature review, the reference list of included studies was examined. Each of the original references was reviewed and compared against the inclusion criteria for the current review. Those references that met the inclusion criteria were included in the current review.

Electronic databases

We searched the following electronic databases:

- the Cochrane Central Register of Controlled Trials (searched 6 September 2011);
- MEDLINE (PubMed searched 28 August 2011);
- EMBASE (searched 25 August 2011);
- WHO International Clinical Trials Registry Platform (ICTRP) for ongoing trials (searched 1 September 2011);
- the Latin American and Caribbean Health Science Literature Database (LILACS) (searched 1 September 2011).

The detailed search strategy used for the electronic search is given in **Annex 1**.

Other resources

We also searched the web site of WHO,[1] and scanned the reference lists of identified papers for further trials. For assistance in identifying continuing or unpublished studies, we contacted the WHO Department of Nutrition for Health and Development, authors of recent systematic reviews and meta-analyses, and other academics and international partners with a known interest in this field.

[1] www.who.int/nutrition

2.3 Data collection and analysis

2.3.1 Selection of studies

Identified references were independently assessed for potential relevance by two reviewers (HG, SH). These reviewers also independently scanned the title, abstract and keywords of every record retrieved, to determine which studies required further assessment.

In the case of RCTs, the full reference was retrieved when the information given in the title, abstract and keywords suggested that the study:

- included an intervention that targeted or achieved an increased potassium intake (however, to remain in the review, an increase in potassium had to have been documented);
- had a prospective design and a control group;
- included the random allocation of participants (individually or within clusters) to the intervention or control group;
- did not specifically target people identified as being infected with HIV or acquired immunodeficiency syndrome (AIDS), or acutely ill or hospitalized individuals;
- reported results of at least one of the outcomes of interest;
- involved an intervention of at least 4 weeks' duration;
- had a measure of potassium excretion through 24-hour urinary potassium excretion.

We also retrieved the full reference when it was unclear from scanning the title and abstract whether a study met the above criteria.

If studies were published only as abstracts, or study reports contained little information on methods, we attempted to contact the authors to obtain further details of study design and results.

Differences in opinion between the two review authors were resolved by consultation with a third reviewer (NA) and by consensus. If resolving disagreement through consensus was not possible, the reference was added to a list of those "awaiting assessment", and authors were contacted for clarification. An adapted preferred reporting items for systematic reviews and meta-analyses (PRISMA) flowchart of study selection was generated (see **Figure 3.1**) (Liberati et al., 2009).

2.3.2 Data extraction and management

For studies that fulfilled inclusion criteria, two authors independently abstracted relevant population and intervention characteristics using a standard data extraction form (see **Annex 2**), with any disagreements resolved through discussion. Any relevant missing information about a trial was sought from the authors of the original reference.

Data concerning details of study population, intervention and outcomes were extracted independently by two reviewers (HG, SH). Another author (NA) checked extracted data. The data extraction form included the following items:

- *General information* – published or unpublished, title, authors, reference or source, contact address, country, language of publication, year of publication, duplicate publications, sponsor and setting.

- *Trial characteristics* – design, duration of intervention or follow-up, method of randomization, allocation concealment and blinding (patients, people administering treatment and outcome assessors).
- *Interventions or exposure* – placebo or comparison included, interventions (dose, route and timing), comparison interventions (dose, route and timing), co-medications, potassium intake achieved at baseline and follow-up, and method of evaluation of potassium intake.
- *Participants* – sampling and randomization methods, inclusion and exclusion criteria of original study, total number and number in comparison groups, sex, age, baseline characteristics, diagnostic criteria, similarity of groups at baseline (including any co-morbidities), assessment of compliance, withdrawals or losses to follow-up (reasons or description), subgroups analysed in original study, status of blood pressure and status of consumption of medication for controlling blood pressure.
- *Outcomes* – outcomes specified above and any other outcomes assessed, length of follow-up, and quality and completeness of reporting of outcomes.
- *Results* – outcomes, times of assessment, and a measure of variation (if necessary, converted to measures of effect specified below) and intention-to-treat (ITT) analysis.
- *Stated objective of the study*.

Duplicate publications

In the case of duplicate publications and companion papers of a primary study, we attempted to maximize the yield of information by simultaneously evaluating all available data. In cases of doubt, the original publication (usually the oldest version) was given priority.

2.3.3 Assessment of risk of bias in included studies

Data were entered into Review Manager software (RevMan 2008) and checked for accuracy by a second author. In cases of disagreement, a third party was consulted, and a judgement made based on consensus. We assessed risk of bias of RCTs by the quality criteria specified in the *Cochrane handbook for systematic reviews of interventions 5.0.2* (Higgins et al., 2009), outlined below.

Randomization (checking for possible selection bias)

For each included study, we described the method used for randomization in sufficient detail to allow an assessment of whether it should produce comparable groups. Methods of randomization were categorized as one of the following:

- *adequate* – any truly random process (e.g. random number table or computer random number generator);
- *inadequate* – any non-random process (e.g. odd or even date of birth, or hospital or clinic record number);
- *no randomization*;
- *unclear*.

Allocation concealment (checking for possible selection bias)

We gave a detailed description of the method used to conceal the allocation, and determined whether intervention allocation could have been foreseen in advance of, or

during, recruitment, and whether it could have been changed after assignment. Methods were categorized as one of the following:

- *adequate* – for example, telephone or central randomization, or consecutively numbered sealed opaque envelopes;
- *inadequate* – open random allocation, unsealed or non-opaque envelopes, alternation or date of birth;
- *concealment not used or not applicable*;
- *unclear*.

Blinding (checking for possible performance bias)

We described how studies blinded study participants and personnel from knowledge of which intervention a participant received. We judged studies to be at low risk of bias if they were blinded, or if we judged that the lack of blinding was unlikely to have affected the results. We assessed blinding separately for different outcomes or classes of outcomes. Methods were categorized as *adequate, inadequate* or *unclear* – for participants, personnel and outcome assessors.

Incomplete outcome data (checking for possible attrition bias through withdrawals, drop-outs and protocol deviations)

We stated whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total number of randomized participants), reasons for attrition or exclusion when reported, and whether missing data were balanced across groups or were related to outcomes. Methods regarding loss to follow-up or attrition were categorized as one of the following:

- *adequate* – trials where few drop-outs or losses to follow-up were noted, and an ITT analysis was possible;
- *inadequate* – the rate of exclusion was at least 20%, or there were wide differences in exclusions between groups, whether or not ITT was used;
- *unclear.*

Selective reporting bias

Methods regarding attempts to reduce selective reporting bias were categorized as one of the following:

- *adequate* – when it was clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review were reported;
- *inadequate* – when not all of the study's prespecified outcomes were reported, one or more reported primary outcomes were not prespecified, outcomes of interest were reported incompletely and could not be used, or the study failed to include results of a key outcome that would have been expected to have been reported;
- *unclear.*

Other sources of bias

We noted any important concerns we had about other possible sources of bias, such as similarity of the groups at baseline. We assessed whether each study was free of other problems that could put it at risk of bias, and answered *yes*, *no* or *unclear.*

2.3.4 Measures of treatment effect

Dichotomous data were expressed as risk ratio with 95% confidence intervals (CI). Continuous variables were expressed as mean difference (MD) with 95% CI.

2.3.5 Missing data

Where feasible, we obtained relevant missing data from the authors of the original study, and evaluated important numerical data such as screened and randomized patients, as well as ITT.

2.3.6 Data synthesis

Data were summarized statistically if they were available, sufficiently similar and of sufficient quality. Statistical analyses were performed according to the statistical guidelines referenced in the newest version of the *Cochrane handbook for systematic reviews of interventions* (Higgins et al., 2009), using the random-effects model.

Assessment of heterogeneity

In the event of substantial clinical, methodological or statistical heterogeneity, study results were not reported as meta-analytically pooled effect estimates were instead summarized in a narrative format. We identified heterogeneity by visual inspection of the forest plots, and by using a standard Chi-squared (I^2) test and a significance level of $\alpha = 0.1$, in view of the low power of this test. We specifically examined heterogeneity with the I^2 statistic quantifying inconsistency across studies, to assess the impact of heterogeneity on the meta-analysis (Higgins et al., 2002; Higgins & Thompson, 2002) – where an I^2 statistic of 75% or greater indicates a considerable level of inconsistency (Higgins et al., 2009). Where heterogeneity was found, we attempted to determine the potential causes by examining individual study and subgroup characteristics.

Statistical comparisons

For each of the objectives discussed above, we analysed the data through both direct and indirect comparisons:

- *direct comparisons* looked within each study for multiple groups randomized into the different specific potassium levels;
- *indirect comparisons* involved a subgroup analysis of all studies testing the effect of potassium on the specified outcomes by potassium intake achieved in the intervention group.

2.3.7 Subgroup analysis

We conducted both overall analysis and subgroup analyses, to explore effect-size differences between groups, as follows:

- by gender (male vs female vs combined);
- by hypertensive status of participants at baseline (hypertensive vs not hypertensive vs undetermined status or heterogeneous);
- by level of potassium intake achieved in the intervention groups (<70 mmol/day vs 70–90 mmol/day vs 90–120 mmol/day vs ≥120 mmol/day urinary potassium excretion);
- by achieved difference in intake between intervention and control (<30 mmol/day vs 30–60 mmol/day vs ≥60 mmol/day urinary potassium excretion);

- by population average level of potassium intake at baseline (<40 mmol/day vs 40–60 mmol/day vs ≥60 mmol/day urinary potassium excretion);
- by population average level of sodium intake at baseline (≤2 g/day vs 2–4 g/day vs ≥4 g/day);
- by duration of intervention (<2 months vs 2–4 months vs >4 months);
- by type of intervention (diet or feeding vs supplementation vs advice);
- by type of blood pressure device used (automatic, manual);
- by method of measurement of blood pressure (supine office, seated office, standing office, supine home, seated home, standing home);
- by study design (parallel, cross-over).

2.3.8 Sensitivity analysis

Sensitivity analysis was used to examine the effects of removing studies at high risk of bias from the analysis. We considered a study to be of high risk of bias if it was graded as "inadequate" in both the randomization and allocation concealment, and in either blinding or loss to follow-up.

Quality of the body of evidence

We used funnel plots to assess the potential existence of small-study bias, and carefully interpreted the results (Lau et al., 2006; Sterne & Egger, 2001). We generated a "risk of bias summary" (**Annex 4**) and a "risk of bias graph" (**Annex 5**), and assessed the impact of individual bias domains on study results at end point and study levels.

GRADEProfiler software (version 3.6) was used to assess the quality of the body of evidence according to the methodology of *Grading of recommendations assessment, development and evaluation* (Guyatt et al., 2008).

3 Results

3.1 Results of the search

The search for RCTs of potassium intake and outcomes of interest in PubMed, the Cochrane Central Register of Controlled Trials, EMBASE, the WHO ICTRP and LILACS resulted in the identification of 4882 publications and study reports. The scan of the reference lists of previous high-quality systematic reviews and the reference lists of included studies resulted in the identification of another 44 studies of possible interest. Thus, 4926 publications or study reports for possible inclusion in the systematic review were identified, of which:

- 4646 were excluded after review of the titles, due to obvious lack of relevance to this review;
- 50 of the remaining 280 studies were removed for being duplicates or companion papers to primary references to studies, leaving a total of 237 potential studies;
- 172 of the remaining 237 studies were excluded for not meeting basic criteria for inclusion.

The remaining 58 studies were fully reviewed. Of these, 27 were excluded on the basis of the methods and one was identified as a duplicate only after full review, leaving 30 studies for inclusion in the review. Of these, seven are awaiting author communications, and one does not report quantitative data and will thus not contribute to the meta-analysis. Hence, a total of 22 studies, contributed to the meta-analyses. The process of selection of studies is shown in **Figure 3.1**.

3.2 Retrieval of missing data

The following authors were contacted and generously provided additional information about their studies: Anne Barden (Barden et al., 1986), Norman Kaplan (Kaplan et al., 1985) and Thomas Sanders (Berry et al., 2010).

3.3 Included studies

Details of the characteristics of the included studies are shown in Section 3.7.1 (Tables 3.1–3.51).

3.3.1 Settings

All included studies were published in English. Of the 23 included studies, two were undertaken in Australia (Barden et al., 1986; Chalmers et al., 1986), one in Chile (Valdés et al., 1991), one in China (Gu et al., 2001), one in Germany (Overlack et al., 1991), one in India (Patki et al., 1990), two in Italy (Siani et al., 1991; Siani et al., 1987), one in Jamaica (Forrester & Grell, 1988), one in Japan (Kawano et al., 1998), one in Kenya (Obel, 1989), one in the Netherlands (Grobbee et al., 1987), one in New Zealand (Richards et al., 1984), one in South Africa (Matlou et al., 1986), five in the United Kingdom (Berry et al., 2010; Bulpitt et al., 1985; Fotherby & Potter, 1992; He et al., 2010; MacGregor et al., 1982) and four in the United States of America (USA) (Kaplan et al., 1985; Smith et al., 1985; Trial Hyp Prv Col, 1992; Whelton et al., 1995).

3.3.2 Types of studies

All studies reporting blood pressure, renal function, blood lipids or catecholamine levels were RCTs. Eight trials had a parallel design (Bulpitt et al., 1985; Chalmers et al., 1986; Gu et al., 2001; Obel, 1989; Siani et al., 1991; Siani et al., 1987; Trial Hyp Prv Col, 1992; Whelton et al., 1995). The remaining 15 trials had a cross-over design (Barden et al., 1986; Berry et al., 2010; Forrester & Grell, 1988; Fotherby & Potter, 1992; Grobbee et al., 1987; He et al., 2010; Kaplan et al., 1985; Kawano et al., 1998; MacGregor et al., 1982; Matlou et al., 1986; Overlack et al., 1991; Patki et al., 1990; Richards et al., 1984; Smith et al., 1985; Valdés et al., 1991).

The duration of the RCTs ranged from 4 weeks (Barden et al., 1986; Forrester & Grell, 1988; Fotherby & Potter, 1992; He et al., 2010; Kawano et al., 1998; MacGregor et al., 1982; Richards et al., 1984; Smith et al., 1985; Valdés et al., 1991) to 12 months (Siani et al., 1991). Most of the studies (15) had a duration of less than 3 months (Barden et al., 1986; Berry et al., 2010; Forrester & Grell, 1988; Fotherby & Potter, 1992; Grobbee et al., 1987; He et al., 2010; Kaplan et al., 1985; Kawano et al., 1998; MacGregor et al., 1982; Matlou et al., 1986; Overlack et al., 1991; Patki et al., 1990; Richards et al., 1984; Smith et al., 1985; Valdés et al., 1991). The Fotherby (1992) study included a subgroup in which 8 of the 18 original patients were followed up for 3 months of intervention, after the 1-month original study. The Gu (2001) study reported data after 6 weeks of intervention, in addition to the 3-month data. The Matlou (1986) study reported data after 4 and 6 weeks of intervention. The Obel (1989) study reported data after 1, 2, 3 and 4 months of intervention. The Trial Hyp Prv Col (1992) and Whelton (1995) studies reported data after 3 and 6 months of intervention.

Three studies were undertaken in individuals with normal blood pressure (Barden et al., 1986; Trial Hyp Prv Col, 1992; Whelton et al., 1995), 18 in individuals with hypertension (Bulpitt et al., 1985; Chalmers et al., 1986; Forrester & Grell, 1988; Fotherby & Potter, 1992; Grobbee et al., 1987; He et al., 2010; Kaplan et al., 1985; Kawano et al., 1998; MacGregor et al., 1982; Matlou et al., 1986; Obel, 1989; Overlack et al., 1991; Patki et al., 1990; Richards et al., 1984; Siani et al., 1991; Siani et al., 1987; Smith et al., 1985; Valdés et al., 1991), and two in a heterogeneous group of individuals with hypertension or normal blood pressure (Berry et al., 2010; Gu et al., 2001).

Two studies reported on an all-female population (Barden et al., 1986; Matlou et al., 1986). The remaining 21 studies were conducted in a heterogeneous population of men and women (Berry et al., 2010; Bulpitt et al., 1985; Chalmers et al., 1986; Forrester & Grell, 1988; Fotherby & Potter, 1992; Grobbee et al., 1987; Gu et al., 2001; He et al., 2010; Kaplan et al., 1985; Kawano et al., 1998; MacGregor et al., 1982; Obel, 1989; Overlack et al., 1991; Patki et al., 1990; Richards et al., 1984; Siani et al., 1991; Siani et al., 1987; Smith et al., 1985; Trial Hyp Prv Col, 1992; Valdés et al., 1991; Whelton et al., 1995).

3.3.3 Participants

The number of participants in the trials ranged from 12 (Overlack et al., 1991) to 353 (Whelton et al., 1995). There were a total of 1606 participants: 445 in cross-over trials and 1161 in parallel trials, of whom 719 had hypertension, 689 had normal blood pressure and 198 had an undisclosed hypertensive status at baseline.

3.3.4 Interventions

All of the included studies intended to compare health outcomes between a group of participants consuming a normal or usual potassium intake to a group consuming increased potassium. In one study, the intervention was dietary advice or education, plus a tablet

supplement (Berry et al., 2010). In two studies, the intervention was dietary advice or education (Chalmers et al., 1986; Siani et al., 1991). The remaining 20 studies used a supplement intervention (Barden et al., 1986; Bulpitt et al., 1985; Forrester & Grell, 1988; Fotherby & Potter, 1992; Grobbee et al., 1987; Gu et al., 2001; He et al., 2010; Kaplan et al., 1985; Kawano et al., 1998; MacGregor et al., 1982; Matlou et al., 1986; Obel, 1989; Overlack et al., 1991; Patki et al., 1990; Richards et al., 1984; Siani et al., 1987; Smith et al., 1985; Trial Hyp Prv Col, 1992; Valdés et al., 1991; Whelton et al., 1995). Compliance to intervention and control was monitored in all studies using 24-hour urinary potassium excretion.

Twenty-two studies contributed only one comparison between an increased potassium intake group and a corresponding control group (Barden et al., 1986; Bulpitt et al., 1985; Chalmers et al., 1986; Forrester & Grell, 1988; Fotherby & Potter, 1992; Grobbee et al., 1987; Gu et al., 2001; He et al., 2010; Kaplan et al., 1985; Kawano et al., 1998; MacGregor et al., 1982; Matlou et al., 1986; Obel, 1989; Overlack et al., 1991; Patki et al., 1990; Richards et al., 1984; Siani et al., 1991; Siani et al., 1987; Smith et al., 1985; Trial Hyp Prv Col, 1992; Valdés et al., 1991; Whelton et al., 1995). However, one of these studies did not contribute to the meta-analysis, because additional information on outcomes of interest was requested from study authors and had not been received at the time of writing (Overlack et al., 1991). One study contributed two comparisons between two potassium groups and one corresponding control group, with the different interventions administered in a cross-over design (Berry et al., 2010). Thus, the 23 studies contributed 22 comparisons between an increased potassium intake group and a corresponding control group for the generation of overall estimates of effect on health outcomes, with an additional comparison from the Berry (2010) study used only in the subgroup analysis.

In two studies, the achieved potassium intake in the intervention group was less than that necessary for a urinary potassium excretion of 70 mmol/day (Forrester & Grell, 1988; Gu et al., 2001). In five studies, the potassium intake at follow-up in the intervention group was at least equal to that necessary for a urinary potassium excretion of 70 mmol/day, but less than 90 mmol/day (Berry et al., 2010; Kaplan et al., 1985; Patki et al., 1990; Siani et al., 1991; Siani et al., 1987). In 11 studies, the potassium intake at follow-up was at least equal to that necessary for a urinary potassium excretion of 90 mmol/day, but less than 120 mmol/day for the intervention group (Barden et al., 1986; Bulpitt et al., 1985; Chalmers et al., 1986; Fotherby & Potter, 1992; Kawano et al., 1998; MacGregor et al., 1982; Matlou et al., 1986; Obel, 1989; Smith et al., 1985; Trial Hyp Prv Col, 1992; Whelton et al., 1995). In four studies, the potassium intake at follow-up was greater than that necessary for a urinary potassium excretion of 120 mmol/day for the intervention group (Grobbee et al., 1987; He et al., 2010; Richards et al., 1984; Valdés et al., 1991).

One study reported a baseline sodium intake of less than 2 g/day (Smith et al., 1985). At baseline, 18 studies reported a sodium intake of 2–4 g/day (Barden et al., 1986; Berry et al., 2010; Bulpitt et al., 1985; Chalmers et al., 1986; Forrester & Grell, 1988; Fotherby & Potter, 1992; Grobbee et al., 1987; He et al., 2010; Kaplan et al., 1985; Kawano et al., 1998; MacGregor et al., 1982; Matlou et al., 1986; Obel, 1989; Overlack et al., 1991; Siani et al., 1987; Trial Hyp Prv Col, 1992; Valdés et al., 1991; Whelton et al., 1995). Four studies reported a baseline sodium intake of more than 4 g/day (Gu et al., 2001; Kawano et al., 1998; Patki et al., 1990; Siani et al., 1987).

In 16 studies, participants were not taking any medical therapy to control blood pressure (Berry et al., 2010; Chalmers et al., 1986; Fotherby & Potter, 1992; Gu et al., 2001; He et al., 2010; MacGregor et al., 1982; Matlou et al., 1986; Obel, 1989; Overlack et al., 1991; Patki et al., 1990; Richards et al., 1984; Siani et al., 1987; Smith et al., 1985; Trial Hyp Prv Col, 1992;

Valdés et al., 1991; Whelton et al., 1995). In four studies, participants were taking medical therapy to control blood pressure (Bulpitt et al., 1985; Forrester & Grell, 1988; Kaplan et al., 1985; Siani et al., 1991). In one study, participants included both treated and untreated individuals (Kawano et al., 1998). In two studies, the status of consumption of medication to control blood pressure was unspecified or unknown (Barden et al., 1986; Grobbee et al., 1987).

3.3.5 Outcome measures

Resting blood pressure (systolic and diastolic)

Twenty-one studies contributed a total of 21 comparisons to the combined analysis of resting blood pressure (Barden et al., 1986; Berry et al., 2010; Bulpitt et al., 1985; Chalmers et al., 1986; Forrester & Grell, 1988; Fotherby & Potter, 1992; Grobbee et al., 1987; Gu et al., 2001; He et al., 2010; Kaplan et al., 1985; Kawano et al., 1998; MacGregor et al., 1982; Matlou et al., 1986; Patki et al., 1990; Richards et al., 1984; Siani et al., 1991; Siani et al., 1987; Smith et al., 1985; Trial Hyp Prv Col, 1992; Valdés et al., 1991; Whelton et al., 1995). One study was excluded from the resting blood pressure meta-analysis because it introduced excessive heterogeneity ($Tau^2 = 88.59$, $\chi^2 = 555.78$, $P < 0.00001$, $I^2 = 96\%$) (Obel, 1989). The removal of this study from the meta-analysis decreased the heterogeneity ($Tau^2 = 6.52$, $\chi^2 = 56.52$, $P < 0.0001$, $I^2 = 65\%$). Another study was removed from most meta-analyses of resting diastolic blood pressure because it introduced excessive heterogeneity into the statistical analyses (Patki et al., 1990). Ten studies measured resting blood pressure with an automatic device (Barden et al., 1986; Berry et al., 2010; Chalmers et al., 1986; Fotherby & Potter, 1992; He et al., 2010; MacGregor et al., 1982; Richards et al., 1984; Siani et al., 1991; Smith et al., 1985; Valdés et al., 1991). Eleven studies measured blood pressure using a manual device (Bulpitt et al., 1985; Forrester & Grell, 1988; Grobbee et al., 1987; Gu et al., 2001; Kaplan et al., 1985; Kawano et al., 1998; Matlou et al., 1986; Patki et al., 1990; Siani et al., 1987; Trial Hyp Prv Col, 1992; Whelton et al., 1995). Thirteen studies measured supine office blood pressure (Barden et al., 1986; Berry et al., 2010; Forrester & Grell, 1988; Fotherby & Potter, 1992; Grobbee et al., 1987; Kaplan et al., 1985; MacGregor et al., 1982; Patki et al., 1990; Richards et al., 1984; Siani et al., 1991; Siani et al., 1987; Smith et al., 1985; Valdés et al., 1991). Seven studies measured seated office blood pressure (Barden et al., 1986; Chalmers et al., 1986; Gu et al., 2001; Kawano et al., 1998; Matlou et al., 1986; Trial Hyp Prv Col, 1992; Whelton et al., 1995). Eight studies measured standing office blood pressure (Forrester & Grell, 1988; Fotherby & Potter, 1992; MacGregor et al., 1982; Patki et al., 1990; Richards et al., 1984; Siani et al., 1987; Smith et al., 1985; Valdés et al., 1991). Two studies reported resting blood pressure data, but did not specify further the method by which the measurements were taken (Bulpitt et al., 1985; He et al., 2010).

Ambulatory blood pressure (systolic and diastolic)

Four studies measured ambulatory blood pressure (Berry et al., 2010; Fotherby & Potter, 1992; He et al., 2010; Kawano et al., 1998). All four measured 24-hour ambulatory blood pressure, as well as day and night ambulatory blood pressure, and measured ambulatory blood pressure with an automatic device.

Blood lipids

Four studies reported total cholesterol (Berry et al., 2010; Grobbee et al., 1987; Kaplan et al., 1985; Patki et al., 1990). One study reported quantitative data on LDL cholesterol (Berry et al., 2010). Two studies reported quantitative data on total triglycerides (Berry et al., 2010; Kaplan et al., 1985). Two studies reported quantitative data on HDL cholesterol (Berry et al., 2010; Kaplan et al., 1985).

Catecholamine levels

Three studies reported results on plasma adrenaline and noradrenaline (Grobbee et al., 1987; Richards et al., 1984; Valdés et al., 1991). No studies measured urinary catecholamine levels.

Renal function

Renal function was measured by serum creatinine in three studies (Bulpitt et al., 1985; Patki et al., 1990; Smith et al., 1985).

3.4 Excluded studies

Reasons for exclusion of the 28 ineligible studies are given in Section 3.7.4.

In 12 studies, the duration of the intervention was less than 4 weeks (Agnoli et al., 1992a; Agnoli et al., 1992b; Ceglia et al., 2009; Fujita & Ando, 1984; Iimura et al., 1981; Khaw & Thom, 1982; Krishnan, 2010; Lennon & Lemann J, 1968; Parfrey et al., 1981; Poulter & Sever, 1986; Sanclemente, 1987; Smith et al., 1992). In nine studies, 24-hour urinary potassium excretion was not reported (Barcelo et al., 1993; CWP, 1987; Gamarra et al., 1994; Grimm, 1999.; Grimm et al., 1988; Grimm et al., 1990; Jardim et al., 1988; Rahimi et al., 2007; Svetkey et al., 1987). In four studies, other nutrients were manipulated as part of the intervention (Agnoli et al., 1994; Langford et al., 1991; Overlack et al., 1995; WHOICTRP, 2008). In one study, there was no control group (Heller et al., 1998). One study used a child population (Gomez-Marin et al., 1991). One study was a duplicate (MacGregor et al., 1984).

3.5 Effects of interventions

The effects of increased potassium versus control in adults are summarized in Tables 3.53–3.58, and in Figures 3.2–3.27.

3.5.1 Resting blood pressure (systolic and diastolic) – primary findings

Indirect comparisons

The meta-analysis of change in systolic blood pressure is shown in **Figure 3.2** and **Table 3.53**. Systolic blood pressure was reduced by increased potassium intake relative to normal potassium intake by 3.06 mmHg (95%CI: 1.42, 4.70). The reduction in systolic blood pressure in studies specifically targeting individuals with hypertension was 4.68 mmHg (95%CI: 2.40, 6.96), which was statistically significantly greater than the reduction from the trials targeting individuals with normal blood pressure (0.09 mmHg, 95%CI: –0.77, 0.95). The two studies reporting on heterogeneous populations including some individuals with hypertension and some with normal blood pressure showed a reduction in systolic blood pressure of 2.95 mmHg (95%CI: 0.26, 5.65); this reduction was significant, but was not significantly different from that found in individuals with hypertension (**Table 3.54**). After removing the studies in individuals with normal blood pressure, the overall effect of increased potassium on systolic blood pressure was a reduction of 4.77 mmHg (95%CI: 3.14, 6.41).

In studies where the achieved potassium intake of the intervention was that necessary for a urinary potassium excretion of less than 70 mmol/day, the reduction of systolic blood pressure was 3.65 mmHg (95%CI: 0.62, 6.69) (**Figure 3.4** and **Table 3.53**). In studies where the achieved potassium intake of the intervention was equal to that necessary for a urinary potassium excretion of 70–90 mmol/day, the reduction of systolic blood pressure was 5.82 mmHg (95%CI: –0.79, 12.43). In studies where the achieved potassium intake of the intervention was equal to that necessary for a urinary potassium excretion of 90 – 120

mmol/day, the reduction in systolic blood pressure was 1.25 mmHg (95%CI: –0.18, 2.68). In studies where achieved potassium intake was greater than that necessary for a urinary potassium excretion of 120 mmol/day, the change in resting systolic blood pressure was non-significant, at 3.00 mmHg (95%CI: –0.27, 6.28). When the studies in participants with normal blood pressure were removed from the analysis, the reduction in those studies that achieved an intake of potassium equal to that necessary for a urinary potassium excretion of 90–120 mmol/day was 4.69 mmHg (95%CI: 2.56, 6.82); this reduction was significant, but was not significantly different from studies achieving a potassium intake equal to that necessary for a urinary potassium excretion of less than 70 mmol/day or 70–90 mmol/day. No other groups were affected.

The difference in achieved potassium intake between the intervention and control groups had no significant effect on the reduction in systolic blood pressure (**Figure 3.5** and **Table 3.53**). In studies where the difference in achieved potassium intake between the intervention and the control was less than 30 mmol/day, systolic blood pressure was reduced by 3.72 mmHg (95%CI: 0.38, 7.06). In studies where the difference in achieved potassium intake between the intervention and the control was 30–60 mmol/day, systolic blood pressure was reduced by 1.97 mmHg (95%CI: 0.09, 3.85). In studies where the difference in achieved potassium intake between the intervention and the control was greater than 60 mmol/day, systolic blood pressure was reduced by 3.01 mmHg (95%CI: –1.02, 7.03), which was not statistically significant. When the studies in participants with normal blood pressure were excluded from the meta-analysis, the decrease in systolic blood pressure was 4.38 mmHg (95%CI: 1.57, 7.18) in the studies that achieved a difference of 30–60 mmol/day in potassium intake, and 6.02 mmHg (95%CI: 0.99, 11.05) in the studies that achieved a difference of more than 60 mmol/day; however, these reductions were not statistically different from the group with the achieved difference of less than 30 mmol/day.

The meta-analysis of change in diastolic blood pressure is presented in **Figure 3.6** and **Table 3.54**. With increased potassium intake relative to normal potassium intake, diastolic blood pressure was reduced by 2.84 mmHg (95%CI: 1.01, 4.66). The reduction in diastolic blood pressure was not statistically significant in studies specifically targeting individuals with normal blood pressure (0.56 mmHg, 95%CI: –0.42, 1.55) or in studies targeting heterogeneous groups of individuals with hypertension or normal blood pressure (0.17 mmHg, 95%CI: –1.48, 1.82), but had statistical significance in studies targeting those with hypertension with a reduction of 3.65 mmHg (95%CI: 0.91, 6.40) (**Figure 3.7** and **Table 3.54).**

Achieved potassium intake had little effect on the reduction in diastolic blood pressure (**Figure 3.8** and **Table 3.54**). The reduction in diastolic blood pressure was not significant in any of the subgroups of achieved intake (<70 mmol urinary excretion/day 1.35 mmHg [95%CI: –2.60, 5.31]; 70–90 mmol urinary excretion/day 3.52 mmHg [95%CI: –1.24, 8.28]; 90–120 mmol urinary excretion/day 1.47 mmHg [95%CI: 0.27, 2.67]; ≥120 mmol urinary excretion/day 1.75 mmHg [95%CI: –0.74, 4.23]). When only the studies including individuals with hypertension were included in the analysis, the reduction in the group that achieved an intake resulting in 70–90 mmol urinary excretion/day became a statistically significant 7.78 mmHg (95%CI: 1.80, 13.77). No other groups reached statistical significance.

The reduction in diastolic blood pressure was not significantly affected by the difference in achieved potassium intake between the intervention and control groups (**Figure 3.9** and **Table 3.54**). In studies where the difference in achieved potassium intake was less than 30 mmol/day, the reduction in diastolic blood pressure of 1.29 mmHg was not statistically significant (95%CI: –0.54, 3.11). In studies where the difference in achieved potassium

intake was 30–60 mmol/day, diastolic blood pressure was reduced by 1.63 mmHg (95%CI: 0.21, 3.04). In studies where the difference in achieved potassium intake was greater than 60 mmol/day, diastolic blood pressure was reduced by 3.57 mmHg (95%CI: 0.82, 6.32).

When only studies of hypertensive participants were included in the meta-analysis, there was a significant reduction in diastolic blood pressure when the difference in potassium intake was less than 30 mmol/day (3.89 mmHg, 95%CI: 2.34, 5.43) and when the difference in intake was 30–60 mmol/day (2.82 mmHg, 95%CI: 0.46, 5.18).

Direct comparisons

In one study (Berry et al., 2010), participants were randomized into two levels of potassium intake. The dietary advice interventions targeted an increase of 20 mmol/day versus 40 mmol/day of potassium via fruits and vegetables in the two intervention groups. The group with the 40 mmol/day increase in potassium did not achieve a statistically significant reduction in systolic blood pressure (1.90 mmHg, 95%CI: –6.82, 3.02) or diastolic blood pressure (0.70 mmHg, 95%CI: –3.78,2.38) relative to the group with the 20 mmol/day increase in potassium intake. The absolute intake each group achieved was 75 mmol/day versus 84 mmol/day.

3.5.2 Resting blood pressure (systolic and diastolic) – secondary findings

Baseline potassium intake had no statistically significant impact on reduction in systolic blood pressure with increased potassium intake (**Figure 3.10** and **Table 3.53**). In studies where the baseline potassium urinary excretion was less than 40 mmol, systolic blood pressure decreased by 3.89 mmHg (95%CI: 0.74, 7.03). In studies where the baseline potassium urinary excretion was 40–60 mmol/day, systolic blood pressure decreased by 2.95 mmHg (95%CI: 0.82, 5.09). In studies where the baseline potassium urinary excretion was greater than 60 mmol/day, systolic blood pressure decreased by 3.41 mmHg (95%CI: 1.27, 5.56). When only the studies including individuals with hypertension, or heterogeneous populations, were included in the analysis, the group of studies with a baseline potassium urinary excretion of 40–60 mmol/day had a further decrease of 5.78 mmHg (95%CI: 2.86, 8.71), which was not statistically different from the other subgroups.

Baseline sodium intake also had no statistically significant impact on the reduction in systolic blood pressure with increased potassium intake (**Figure 3.11** and **Table 3.53**). In the one study with a baseline sodium value less than 2 g/day, the reduction in systolic blood pressure was not statistically significant (2.00 mmHg, 95%CI: –7.70, 11.70). In studies with baseline sodium intake of 2–4 g/day, systolic blood pressure was reduced by 1.34 mmHg (95%CI: 0.04, 2.64). Studies where the sodium intake at baseline was more than 4 g/day showed a greater (but not statistically significant) reduction in systolic blood pressure (6.91 mmHg, 95%CI: 2.29, 11.53). When studies in individuals with normal blood pressure were excluded from the meta-analysis, the reduction detected in the group of studies with baseline sodium intake of 2–4 g/day was 4.07 mmHg (95%CI: 2.37, 5.76), and the other groups remained unchanged.

There was a decrease in systolic blood pressure of 3.36 mmHg (95%CI: 1.76, 4.94) in the studies with a duration of less than 2 months (**Figure 3.12** and **Table 3.53**). In studies with a duration of 2–4 months, the decrease was 3.53 mmHg (95%CI: 0.78, 6.28). In studies with a duration of more than 4 months, a non-significant increase in systolic blood

pressure was observed (0.16 mmHg, 95%CI: –0.71, 1.03). Removing the studies in individuals with normal blood pressure had little effect on the results.

The reduction in systolic blood pressure was not affected by measurement device (automatic device 2.48 mmHg [95%CI: 0.62, 4.33] vs manual device 3.63 mmHg [95%CI: 1.28, 5.98]). The measurement method also did not affect the reduction in systolic blood pressure (supine office 4.35 mmHg [95%CI: 1.31, 7.40] vs seated office 1.48 mmHg [95%CI: –0.01, 2.97] vs standing office 6.94 mmHg [95%CI: 3.25, 10.63]). When the measurement method was unspecified, the reduction in systolic blood pressure was not significant (2.51 mmHg, 95%CI: –2.85, 7.87) (**Figures 3.13–3.14 and Table 3.53**). The exclusion of studies in only individuals with normal blood pressure had little effect on the results.

The reduction in systolic blood pressure with increased potassium intake was detected in both individuals not taking medication to control blood pressure (4.07 mmHg, 95%CI: 1.96, 6.18) and those taking medication to control blood pressure (0.42 mmHg, 95%CI: –3.97, 4.80). In studies where the medication status was undetermined, the reduction in blood pressure was not statistically significant (1.16 mmHg, 95%CI: –1.43, 3.74) (**Figure 3.15** and **Table 3.53**). When studies in only individuals with normal blood pressure were removed from the analysis, systolic blood pressure in individuals not taking medication to control blood pressure was further reduced by 5.13 mmHg (95%CI: 3.19, 7.06); in those of unspecified medication status, it was further reduced by 2.07 (95%CI: –1.41, 5.56).

The reduction in systolic blood pressure in individuals with increased potassium intake was not affected by type of intervention (supplement 3.31 mmHg [95%CI: 1.55, 5.07] vs dietary advice or education 1.55 mmHg [95%CI: –2.35, 5.44]) (**Figure 3.16** and **Table 3.53**). The exclusion of studies in only individuals with normal blood pressure had little effect on the results.

The reduction in systolic blood pressure in individuals with increased potassium intake was also not affected by study design (parallel design 1.82 mmHg [95%CI: –0.38, 4.02] vs cross-over 3.99 mmHg [95%CI: 1.86, 6.13]) (**Figure 3.17** and **Table 3.53**). The exclusion of studies in only individuals with normal blood pressure increased the reduction detected with both study designs (parallel 5.19 [95%CI: 2.23, 8.16] vs cross-over 4.57 [95%CI: 2.44, 6.70]).
In studies where the baseline potassium urinary excretion was less than 40 mmol/day, the reduction in diastolic blood pressure was not significant (2.41 mmHg, 95%CI: –3.07, 7.90) (**Table 3.54**). However, this reduction became significant with the inclusion of only individuals with hypertension (5.80 mmHg, 95%CI: 0.53, 11.07). In studies where the baseline potassium urinary excretion was 40–60 mmol/day, diastolic blood pressure decreased by 1.53 mmHg (95%CI: 0.25, 2.80). In studies where the baseline potassium urinary excretion was greater than 60 mmol/day, diastolic blood pressure decreased by 3.38 mmHg (95%CI: 2.02, 4.74).

Sodium intake at baseline did not have a significant effect on the reduction of diastolic blood pressure detected with increased potassium intake (**Table 3.54**). In the one study where the sodium intake at baseline was less than 2 g/day, a reduction in diastolic blood pressure was not statistically significant (0.00 mmHg, 95%CI: –6.12, 6.12). In studies where the sodium intake at baseline was 2–4 g/day, the reduction in diastolic blood pressure was 1.96 mmHg (95%CI: 0.76, 3.16). Studies where the sodium intake at baseline was greater than 4 g/day did not have a statistically significant reduction in diastolic blood pressure (2.87 mmHg; 95%CI: –1.22, 6.96).

When only studies including individuals with hypertension were included in the meta-analysis, the diastolic blood pressure was further reduced in those studies where the baseline sodium intake was 2–4 g/day (3.42 mmHg; 95%CI: 2.21, 4.62). There was little change in the other groups.

The reduction in diastolic blood pressure with increased potassium intake was only significant in studies of a duration of less than 2 months (1.99 mmHg, 95%CI: 0.87, 3.11) **(Table 3.54)**. In studies where the duration of intervention was 2–4 months, the reduction in diastolic blood pressure was not statistically significant (1.86 mmHg, 95%CI: –0.02, 3.75). In studies with a duration of more than 4 months, the reduction was 0.35 mmHg (95%CI: –0.35, 1.06). There was no meaningful change in results when only studies with individuals with hypertension were included in the meta-analysis.

Type of device used to measure blood pressure did not affect the reduction in diastolic blood pressure (automatic device 2.84 mmHg [95%CI: 1.71, 3.96] vs manual 1.54 mmHg [95%CI: 0.11, 2.96]) (**Table 3.54**). The measurement method also did not affect the reduction in diastolic blood pressure (supine office 4.34 [95%CI: 1.10, 7.57] vs seated office 1.30 mmHg [95%CI: –0.04, 2.64] vs standing office 4.78 [95%CI: 0.18, 9.38]). When only studies with individuals with hypertension were included in the meta-analysis, the reduction in diastolic blood pressure when measured by the seated office method became statistically significant (3.46 mmHg, 95%CI: 1.22, 5.70).

Status of use of medication to control blood pressure had little effect on the reduction in diastolic blood pressure. The reduction in diastolic blood pressure with increased potassium intake was 1.37 mmHg (95%CI: 0.23, 2.50) in studies of individuals not taking medical therapy to control blood pressure, 3.80 mmHg (95%CI: –0.66, 8.25) in studies of individuals taking medication, and 2.32 mmHg (95%CI: 0.17, 4.46) in studies in which the participants were of undetermined status in relation to blood pressure. When only studies of individuals with hypertension were included in the meta-analysis, the diastolic blood pressure in those not taking medical therapy to control blood pressure was further reduced (4.54 mmHg, 95%CI: 0.69, 8.39).

Type of intervention had little effect on the reduction in diastolic blood pressure (supplement 3.04 mmHg [95%CI: 0.99, 5.09] versus dietary advice or education 2.44 mmHg [95%CI: –0.17, 5.04]). When only individuals with hypertension were included in the meta-analysis, the decrease in diastolic blood pressure in studies administering intervention through dietary advice or education reached statistical significance (3.45 mmHg, 95%CI: 0.85, 6.05).

In studies with a parallel design, the reduction in diastolic blood pressure in those with increased potassium intake was not statistically significant (1.59 mmHg, 95%CI: –0.18, 3.35). In studies with a cross-over design, the reduction in diastolic blood pressure with increased potassium intake was 4.21 mmHg (95%CI: 1.29, 7.12); this reduction was statistically significant, but was not statistically different from the parallel design group. These results were not altered in a meaningful way when only individuals with hypertension were included in the meta-analysis.

3.5.3 Ambulatory blood pressure – primary findings

In the four studies that measured ambulatory blood pressure, an increase in potassium intake resulted in a significant reduction of 3.04 mmHg (95%CI: 0.66, 5.42) in systolic blood pressure, and a non-significant reduction of 1.24 mmHg (95%CI: –0.66, 3.13) in diastolic blood pressure (**Figures 3.18–3.19** and **Tables 3.55–3.56**). The reduction in ambulatory

systolic blood pressure was significant in studies targeting individuals with hypertension (3.37 mmHg, 95%CI: 0.69, 6.05). There were no studies targeting individuals with normal blood pressure, and the reduction was not significant in the one study of heterogeneous populations of individuals with normal blood pressure or hypertension (1.80 mmHg, 95%CI: –3.42, 7.02). The diastolic blood pressure change was non-significant, regardless of blood pressure status.

There were no studies in which the potassium intake in the intervention group resulted in less than 70 mmol urinary potassium excretion/day. The one study with a potassium intake in the intervention group resulting in 70–90 mmol urinary potassium excretion/day reported a non-significant decrease in ambulatory systolic blood pressure (1.80 mmHg, 95%CI: –3.42, 7.02). In the two studies in which the potassium intake of the intervention resulted in 90–120 mmol urinary potassium excretion/day, the reduction of systolic blood pressures was 3.65 mmHg (95%CI: 0.09, 7.21). Only one study had an intake resulting in more than 120 mmol urinary potassium excretion/day; it reported a non-significant decrease in ambulatory systolic blood pressure (3.00 mmHg, 95%CI: –1.07, 7.07) (**Figure 3.20** and **Table 3.56**).

3.5.4 Ambulatory blood pressure – secondary findings

Ambulatory systolic blood pressure was significantly reduced (3.34 mmHg, 95%CI: 0.66, 5.52) by increased potassium intake when 24-hour ambulatory pressure was measured. Daytime ambulatory systolic blood pressure was reduced by 2.74 mmHg (95%CI: 0.28, 5.20), but night-time ambulatory systolic pressure was not reduced significantly with increased potassium (2.37 mmHg, 95%CI: –0.34, 5.09). Studies with a duration of intervention of less than 2 months had a significant reduction in blood pressure of 3.04 mmHg (95%CI: 0.66, 5.42). The one study with a duration of 2–4 months did not have a significant reduction in ambulatory systolic blood pressure (15.00 mmHg, 95%CI:–0.27, 29.73). All studies had a cross-over design.

3.5.5 Blood lipids

Total cholesterol

Total cholesterol was quantified in four studies with 104 participants, but one of these studies (Patki et al., 1990) was not included in the meta-analysis because it introduced excessive heterogeneity (**Figure 3.21** and **Table 3.57**). Increased potassium intake relative to normal potassium intake had no significant effect on total cholesterol (MD: –0.12 mmol/L, 95%CI:-0.33,0.09). The Patki (1990) study reported a significant reduction in total cholesterol with increased potassium intake (1.40 mmol/L, 95%CI: 1.23, 1.56). This result was not affected by blood pressure status, achieved potassium or sodium intake, duration, medication status or study design.

HDL cholesterol

HDL cholesterol was quantified in two studies with 64 participants. Increased potassium intake relative to normal potassium intake had no significant effect on HDL cholesterol (MD: –0.01 mmol/L, 95%CI: -0.13, 0.11) (**Figure 3.22** and **Table 3.57**).

LDL cholesterol

LDL cholesterol was quantified in one study with 48 participants. Increased potassium intake relative to normal potassium intake had no significant effect on LDL cholesterol (MD: –-0.10 mmol/L, 95%CI: -0.38, 0.18) (**Figure 3.23** and **Table 3.57**).

Total triglyceride concentration

Total triglyceride concentration was quantified in two studies with 64 participants. Increased potassium intake relative to normal potassium intake had no significant effect on total triglyceride concentration (-0.11mmol/L, 95%CI: -0.48, 0.26) (**Figure 3.24** and **Table 3.57**).

3.5.6 Catecholamine levels

Plasma adrenaline concentrations were reported in three studies with 76 participants; these studies detected no effect of increased potassium intake on plasma adrenaline (MD:–3.94 pg/mL, 95%CI: –9.22, 1.34) (**Figure 3.25** and **Table 3.58**). These studies also reported on plasma noradrenaline concentration, and again detected no effect of increased potassium intake on plasma noradrenaline (MD:–4.32 pg/mL, 95%CI: –23.78, 15.13) (**Figure 3.26** and **Table 3.58**).

3.5.7 Renal function

No included studies reported quantitative measurements for urinary protein excretion, protein:creatinine ratio, or urinary albumin excretion. Three studies quantified serum creatinine concentrations and found a non-significant decrease of 4.86 µmol/L (95%CI: –0.39, 13.59) with increased potassium intake (**Figure 3.27** and **Table 3.59**).

3.6 Sensitivity analysis and risk of bias

A sensitivity analysis was performed to remove the studies considered to have a high risk of bias. Only one study was determined to be at high risk (Forrester & Grell, 1988). Removal of that study did not greatly alter the effect estimate for systolic (MD: –3.50 mmHg; 95%CI: –5.15, –1.82) or diastolic (MD: –2.95 mmHg; 95%CI: –4.84, –1.06) blood pressure.

3.6.1 Quality of the body of evidence

Funnel plots for each of the main outcomes to assess publication bias indicated little risk of publication bias (**Annex 3**). The risk of bias summary (**Annex 4**) and risk of bias graph (**Annex 5**) suggested that the entire body of evidence is not at risk of serious problems due to bias. Several studies reported that personnel were not blinded, but most reported that participants were blinded. Blinding of outcome assessors was reported in half of the studies and was not mentioned in most of the remaining studies. There was no bias due to selective reporting or incomplete outcomes. One study was assessed as being at high risk of bias in randomization, allocation concealment and blinding. Most studies did not report on how randomization and allocation concealment were achieved.

We generated GRADE evidence profiles for each of the specific objectives of the review. Each profile contained the assessment of the quality of evidence for all indicators of blood pressure, blood lipids, renal function and catecholamine levels (**Annex 6**). The evidence for increased potassium leading to a reduction in blood pressure was of high or moderate quality. The evidence of no effect of increased potassium on renal function, blood lipids and catecholamine levels was all of high quality.

There was high- and moderate-quality evidence that increasing potassium intake to a level resulting in less than 70 mmol urinary excretion/day reduced blood pressure; however, that evidence came from only two studies, and should thus be treated with caution. There was moderate-quality evidence that increased potassium intake resulting in 70–90 mmol urinary excretion/day reduced blood pressure, and high-quality evidence that it had no effect on blood lipids, renal function and catecholamine levels; however, the evidence for these outcomes was all derived from one or two studies and should be treated with caution. There

was moderate-quality evidence that increased potassium intake resulting in 90–120 mmol urinary excretion/day reduced blood pressure, and high-quality evidence that it had no effect on renal function; however, these data came from only two studies. There was moderate-quality evidence that increased potassium intake resulting in greater than 120 mmol/day reduced blood pressure and high-quality evidence of no effect on cholesterol; however, that data came from only one study. There was also high-quality evidence of no effect on catecholamine levels.

3.7 Characteristics of studies

In this section, tables are labelled by the study identifier (e.g. Barden BPARA 1986). The specific references for a particular study are listed below the table. The reference list in Chapter 4 also indicates which references are included in a particular study, and which is the primary reference.

3.7.1 Characteristics of included studies

Table 3.1 Barden BPARA1986

Methods	Cross-over design study of increased K via supplements. Participants randomized to receive KCl supplement tablets or placebo. Conducted in Australia.
Participants	43 adult women, normotensive, not specified if taking BP medication.
Interventions	Group1 – placebo Group2 – K-supplemented diet (80 mmol K/day) via tablets Tablet type: KCl.
Outcomes	Supine BP Treatment-period interaction
Notes	1) K intake in intervention ≥90 mmol/day 2) Na intake at baseline 2–4 g/d 3) Age – adult (15 years or greater) 4) Group – normotensive 5) Duration of follow-up – 1 month (4 weeks) 6) Sex – women only 7) BP device – automatic 8) BP method – supine office SBP/DBP, seated office SBP/DBP

BP, blood pressure; Cl: chloride; DBP: diastolic blood pressure; K, potassium; Na, sodium
References: (Barden et al., 1987; Barden et al., 1986)

Table 3.2 Risk of bias table Barden BPARA1986

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description of method of sequence generation
Allocation concealment (selection bias)	Unclear risk	No description of method of concealment of allocation
Blinding of participants and personnel (performance bias)	Unclear risk	Providers were blinded but the blinding of participants was unclear and unlikely
Blinding of outcome assessment (detection bias)	Unclear risk	Unclear if outcome assessor was blinded
Incomplete outcome data (attrition bias)	Low risk	Low loss to follow-up (2%)
Selective reporting (reporting bias)	Low risk	All outcomes reported

Table 3.3 Berry BPA2010

Methods	Cross-over design study of increased K education or advice to increase fruits and vegetables and via supplements. Participants randomized to receive K-citrate supplemented diet (fruit and vegetable diet), supplement tablets, or placebo. Conducted in the United Kingdom.
Participants	57 adult men and women, hypertensive status not specified, not taking BP medication.
Interventions	Group1 – K-supplemented diet (20 mmol K/day) of fruits and vegetables Group2 – K-supplemented diet (40 mmol K/day) of fruits and vegetables Group3 – K-supplemented diet (20 mmol K/day) via tablets Group4 – K-supplemented diet (40 mmol K/day) via tablets Group5 – unchanged diet (control) tablet type: K-citrate
Outcomes	Resting BP Carotid to femoral pulse wave velocity Radial pulse wave analysis Flow-mediated dilation of the brachial artery Endothelial dilation in response to 25 µg glycerol trinitrate Serum total cholesterol, high-density lipoprotein-cholesterol, triacylglycerol, glucose Plasma adrenaline, plasma noradrenaline
Notes	1) K intake in intervention ≥70 mmol/day 2) Na intake at baseline 2–4 g/d 3) Age – adult (15 years or greater) 4) Group – both 5) Duration of follow-up – 1.5 months (6 weeks) 6) Sex – both (heterogeneous) 7) BP device – automatic 8) BP method – ambulatory SBP/DBP (24-hour/day/night), supine DBP/SBP

BP, blood pressure; DBP, diastolic blood pressure; K, potassium; Na, sodium; SBP, systolic blood pressure
Reference: (Berry et al., 2010)

Table 3.4 Risk of bias table Berry BPA2010

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomized via computer algorithm
Allocation concealment (selection bias)	Low risk	Computer allocation
Blinding of participants and personnel (performance bias)	Low risk	Participants blinded
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessor was blinded
Incomplete outcome data (attrition bias)	Low risk	16% loss to follow-up
Selective reporting (reporting bias)	Low risk	All outcomes reported

Table 3.5 Bulpitt BPA1985

Methods	Parallel design study of increased K via supplements. Participants randomized to receive placebo or KCl supplement. Conducted in the United Kingdom.
Participants	33 adult men and women, hypertensive, taking BP medication
Interventions	Group1 – placebo Group2 – K-supplemented diet (64 mmol K/day) via tablets Type: KCl
Outcomes	Changes in resting BP Change in medication dosage
Notes	1) K intake in intervention ≥90 mmol/day 2) Na intake at baseline 2–4 g/d 3) Age – adult (15 years or greater) 4) Group – hypertensive 5) Duration of follow-up – 3 months (12 weeks) 6) Sex – both (heterogeneous) 7) BP device – manual 8) BP method – SBP (unspecified resting), DBP (unspecified resting)

BP, blood pressure; Cl, chloride; DBP, diastolic blood pressure; K, potassium; Na, sodium; SBP, systolic blood pressure
Reference: (Bulpitt et al., 1985)

Table 3.6 Risk of bias table Bulpitt BPA1985

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description of method of sequence generation
Allocation concealment (selection bias)	Unclear risk	No description of method of concealment of allocation
Blinding of participants and personnel (performance bias)	Unclear risk	Not clear how or if participants and providers blinded
Blinding of outcome assessment (detection bias)	Unclear risk	No description of blinding of outcome assessor
Incomplete outcome data (attrition bias)	Low risk	2% loss to follow-up
Selective reporting (reporting bias)	Low risk	All outcomes reported

Table 3.7 Chalmers BPA1986

Methods	Parallel design study of increased K diet. Participants randomized to receive normal diet or high-K diet. Conducted in Australia.
Participants	107 adult men and women, hypertensive, not taking BP medication
Interventions	Group1 – normal diet Group2 – high K diet through diet advice or education
Outcomes	Resting BP Urinary Na, K, creatinine excretion Serum K, creatinine, cholesterol, gamma-glutamyl transferase
Notes	1) K intake in intervention ≥90 mmol/day 2) Na intake at baseline 2–4 g/d 3) Age – adult (15 years or greater) 4) Group – hypertensive 5) Duration of follow-up – 3 months (12 weeks) 6) Sex – both (heterogeneous) 7) BP device – automatic 8) BP method – seated office

BP, blood pressure; K, potassium; Na, sodium
Reference: (Chalmers et al., 1986)

Table 3.8 Risk of bias table Chalmers BPA1986

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description of method of sequence generation
Allocation concealment (selection bias)	Unclear risk	No description of method of concealment of allocation
Blinding of participants and personnel (performance bias)	High risk	Participants and providers not blinded
Blinding of outcome assessment (detection bias)	High risk	Outcome assessor not blinded
Incomplete outcome data (attrition bias)	Unclear risk	Loss to follow-up not reported
Selective reporting (reporting bias)	Low risk	All outcomes reported

Table 3.9 Forrester BPA1988

Methods	Cross-over design study of increased K via supplements. Participants randomized to receive bendroflumethiazide or bendroflumethiazide + KCl. Conducted in Jamaica.
Participants	23 adult men and women, hypertensive status, taking BP medication
Interventions	Group1 – bendroflumethiazide Group2 – bendroflumethiazide + K-supplement (600 mg K) via tablets (type: KCl)
Outcomes	Resting BP Mean BP Serum K Blood glucose Serum urate Urine Na Urine K Red cell Na Red cell K
Notes	1) K intake in intervention ≥60 mmol/day 2) Na intake at baseline 2–4 g/d 3) Age – adult (15 years or greater) 4) Group – hypertensive 5) Duration of follow-up – 1 month (4 weeks) 6) Sex – both (heterogeneous) 7) BP device – manual 8) BP method – Supine office SBP, supine office DBP, standing office SBP, standing office DBP

BP, blood pressure; Cl, chloride; DBP, diastolic blood pressure; K, potassium; Na, sodium; SBP, systolic blood pressure
Reference: (Forrester & Grell, 1988)

Table 3.10 Risk of bias table Forrester BPA1988

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Patients were chosen from clinic by volunteering
Allocation concealment (selection bias)	High risk	Allocation not concealed
Blinding of participants and personnel (performance bias)	High risk	Participants and providers not blinded
Blinding of outcome assessment (detection bias)	Unclear risk	No description of blinding of outcome assessor
Incomplete outcome data (attrition bias)	Low risk	4% loss to follow-up reported
Selective reporting (reporting bias)	Low risk	All outcomes reported

Table 3.11 Fotherby BPA1992

Methods	Cross-over design study of increased K via elixir (supplement). Participants randomized to receive KCl supplement tablets or placebo. Conducted in the United Kingdom.
Participants	18 adult men and women, hypertensive, not taking BP medication
Interventions	Group1 – placebo Group2 – K-supplemented diet (60 mmol K/day) via elixir Elixir type: KCl
Outcomes	Resting BP Pulse rate Ambulatory BP (24-hour/day/night) Serum electrolytes Creatinine Plasma renin activity Urinary electrolytes Body weight changes
Notes	1) Potassium intake in intervention ≥90 mmol/day 2) Na intake at baseline 2–4 g/d 3) Age – adult (15 years or greater) 4) Group – hypertensive 5) Duration of follow-up – 1 month (4 weeks) 6) Sex – both (heterogeneous) 7) BP device – automatic 8) BP method – ambulatory SBP (24-hour/day/night), ambulatory DBP (24-hour/day/night), supine office systolic BP, supine office DBP, standing office SBP, standing office DBP

BP, blood pressure; Cl, chloride; DBP, diastolic blood pressure; K, potassium; Na, sodium; SBP, systolic blood pressure
References: (Fotherby & Potter, 1992; Fotherby & Potter, 1997)

Table 3.12 Risk of bias table Fotherby BPA1992

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described
Blinding of participants and personnel (performance bias)	Low risk	Both participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessor blinded
Incomplete outcome data (attrition bias)	Low risk	Low loss to follow-up (0%)
Selective reporting (reporting bias)	Low risk	All outcomes reported

Table 3.13 Grobbee BPA1987

Methods	Cross-over design study of increased K via supplements. Participants randomized to receive KCl supplement tablets or placebo. Conducted in the Netherlands.
Participants	40 adult men and women, hypertensive, not specified if taking BP medication
Interventions	Group1 – placebo Group2 – K-supplemented diet (8 mmol K) via slow-release tablets Tablet type: slow-KCl
Outcomes	Urinary excretion SBP, DBP Urinary electrolyte excretion Body weight Pulse rate Plasma catecholamine levels Plasma renin Cardiac output Cardiac index
Notes	1) Potassium intake in intervention ≥120 mmol/day 2) Na intake at baseline 2–4 g/d 3) Age – adult (15 years or greater) 4) Group – hypertensive 5) Duration of follow-up – 1.5 months (6 weeks) 6) Sex – both (heterogeneous) 7) BP device – manual 8) BP method – supine office

BP, blood pressure; Cl: chloride; K, potassium; Na, sodium
Reference: (Grobbee et al., 1987)

Table 3.14 Risk of bias table Grobbee BPA1987

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description of method of sequence generation
Allocation concealment (selection bias)	Unclear risk	No description of method of concealment of allocation
Blinding of participants and personnel (performance bias)	Low risk	Participants and providers blinded
Blinding of outcome assessment (detection bias)	Unclear risk	No description of blinding of outcome assessor
Incomplete outcome data (attrition bias)	Unclear risk	No loss to follow-up reported
Selective reporting (reporting bias)	Low risk	All outcomes reported

Table 3.15 Gu BPA2001

Methods	Parallel study of increased K via supplements. Participants randomized to receive KCl supplement tablets or placebo. Conducted in China.
Participants	43 adult women, heterogeneous hypertensive status, not taking BP medication
Interventions	Group1 – placebo Group2 – K-supplemented diet (60 mmol K/day) via tablets Tablet type: KCl
Outcomes	Resting BP Body weight
Notes	1) K intake intervention <70 mmol/day (~57 mmol/day) 2) Na intake at baseline >4 g/d 3) Age – adult (15 years or greater) 4) Group – both 5) Duration of follow-up – 3 months (12 weeks) 6) Sex – women only 7) BP device – manual 8) BP method – seated SBP, seated DBP 9) Subgroup analysis – 6-week timepoint

BP, blood pressure; Cl, chloride; DBP, diastolic blood pressure; Na, sodium; SBP, systolic blood pressure
Reference: (Gu et al., 2001)

Table 3.16 Risk of bias table Gu BPA2001

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Generated by computer program
Allocation concealment (selection bias)	Low risk	Concealed in an ordered set of sealed envelopes
Blinding of participants and personnel (performance bias)	Low risk	Participants and providers blinded
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessor blinded
Incomplete outcome data (attrition bias)	Low risk	Low loss to follow-up reported (<10%)
Selective reporting (reporting bias)	Low risk	All outcomes reported

Table 3.17 He BPA2010

Methods	Cross-over design study of increased K via supplements. Participants randomized to receive supplement tablets or placebo. Conducted in the United Kingdom.
Participants	46 adult men and women, hypertensive, not taking BP medication
Interventions	Group1 – placebo Group2 – K-supplemented diet (64 mmol K/day) via tablets (type KCl) Group3 – K-supplemented diet (64 mmol K/day) via tablets (type $KHCO_3$) Tablet type: KCl and $KHCO_3$
Outcomes	Resting BP Ambulatory BP 24-hour albumin excretion Pulse wave velocity Vascular function: changes in left ventricular geometry and function Change in bone metabolism markers: urinary calcium, pH
Notes	1) K intake in intervention ≥120 mmol/day 2) Na intake at baseline 2–4 g/day 3) Age – adult (15 years or greater) 4) Group – hypertensive 5) Duration of follow-up – 1 month (4 weeks) 6) Sex – both (heterogeneous) 7) BP device – automatic 8) BP method – SBP/DBP (unspecified resting) , ambulatory SBP/DBP (24-hour/day/ night)

BP, blood pressure; Cl, chloride; DBP, diastolic blood pressure; HCO_3, bicarbonate; K, potassium; Na, sodium; SBP, systolic blood pressure
Reference: (He et al., 2010)

Table 3.18 Risk of bias table He BPA2010

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated program by independent company
Allocation concealment (selection bias)	Low risk	Allocated in random order to take intervention capsules or placebo capsules; all were blinded to treatment allocation
Blinding of participants and personnel (performance bias)	Low risk	Participants and providers blinded
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessor blinded
Incomplete outcome data (attrition bias)	Low risk	Low loss to follow-up reported (<10%)
Selective reporting (reporting bias)	Low risk	All outcomes reported

Table 3.19 Kaplan BPA1985

Methods	Cross-over design study of increased K via supplements. Participants randomized to receive KCl supplement tablets or placebo. Conducted in the United States of America.
Participants	16 adult men and women, hypertensive, taking BP medication
Interventions	Group1 – placebo Group2 – K-supplemented diet (60 mmol K/day) via tablets Tablet type: KCl
Outcomes	Resting BP Serum K and Na levels Plasma renin activity Plasma aldosterone Body weight
Notes	1) Potassium intake in intervention ≥70 mmol/day 2) Na intake at baseline 2–4 g/d 3) Age – adult (15 years or greater) 4) Group – hypertensive 5) Duration of follow-up – 1.5 months (6 weeks) 6) Sex – both (heterogeneous) 7) BP device – manual 8) BP method – supine office SBP, supine office DBP

BP, blood pressure; Cl, chloride; DBP, diastolic blood pressure; K, potassium; Na, sodium; SBP, systolic blood pressure
Reference: (Kaplan et al., 1985)

Table 3.20 Risk of bias table Kaplan BPA1985

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description of method of sequence generation
Allocation concealment (selection bias)	Unclear risk	No description of method of concealment of allocation
Blinding of participants and personnel (performance bias)	Low risk	Participants and providers blinded
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessor blinded
Incomplete outcome data (attrition bias)	High risk	20% loss to follow-up reported
Selective reporting (reporting bias)	Low risk	All outcomes reported

Table 3.21 Kawano BPA1998

Methods	Cross-over design study of increased K via supplements. Participants randomized to receive KCl supplement tablets or placebo. Conducted in Japan.
Participants	55 adult men and women, hypertensive, heterogeneous medication status
Interventions	Group1 – placebo Group2 – K-supplemented diet (64 mmol K/day) via tablets Tablet type: KCl
Outcomes	Resting BP Ambulatory BP Serum and urinary electrolytes
Notes	1) K intake in intervention ≥90 mmol/day 2) Na intake at baseline >4 g/day 3) Age – adult (15 years or greater) 4) Group – hypertensive 5) Duration of follow-up – 1 month (4 weeks) 6) Sex – both (heterogeneous) 7) BP device – automatic (ambulatory), manual (resting) 8) BP method – ambulatory SBP/DBP (24-hour/day/night), seated office SBP, seated office DBP

BP, blood pressure; Cl, chloride; DBP, diastolic blood pressure; K, potassium; Na, sodium; SBP, systolic blood pressure
Reference: (Kawano et al., 1998)

Table 3.22 Risk of bias table Kawano BPA1998

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description of method of sequence generation
Allocation concealment (selection bias)	Unclear risk	No description of method of concealment of allocation
Blinding of participants and personnel (performance bias)	Unclear risk	Unclear if participants and providers blinded
Blinding of outcome assessment (detection bias)	Unclear risk	No description of blinding of outcome assessor
Incomplete outcome data (attrition bias)	Low risk	Low loss to follow-up reported (<10%)
Selective reporting (reporting bias)	Low risk	All outcomes reported

Table 3.23 MacGregor AEBPA1982

Methods	Cross-over design study of increased K via supplements. Participants randomized to receive KCl tablets or placebo. Conducted in the United Kingdom.
Participants	23 hypertensive men and women, not taking BP medication
Interventions	Group1 – control (placebo) Group2 – supplement (64 mmol K/day) Tablet type: KCl
Outcomes	Resting BP Pulse rate Weight 24-hour urinary sodium, potassium, creatinine, urea, creatinine, electrolytes, plasma renin activity, aldosterone
Notes	1) K intake in intervention ≥90 mmol/day 2) Na intake at baseline 2–4 g/day 3) Age – adult (15 years or greater) 4) Group – hypertensive 5) Duration of follow-up – 1 month (4 weeks) 6) Sex – both (heterogeneous) 7) BP device – automatic 8) BP method – supine office DBP, supine office SBP, standing office SBP, standing office DBP

BP, blood pressure; Cl, chloride; DBP, diastolic blood pressure; K, potassium; Na, sodium; SBP, systolic blood pressure
References: (MacGregor et al., 1982; MacGregor et al., 1984; Smith et al., 1985)

Table 3.24 Risk of bias table MacGregor AEBPA1982

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description of method of sequence generation
Allocation concealment (selection bias)	Unclear risk	No description of method of concealment of allocation
Blinding of participants and personnel (performance bias)	Low risk	Participants and providers blinded
Blinding of outcome assessment (detection bias)	Unclear risk	No description of blinding of outcome assessor
Incomplete outcome data (attrition bias)	Low risk	0% loss to follow-up reported
Selective reporting (reporting bias)	Low risk	All outcomes reported

Table 3.25 Matlou BPA1986

Methods	Cross-over design study of increased K via supplements. Participants randomized to receive KCl tablets or placebo. Conducted in South Africa.
Participants	32 hypertensive women, not taking BP medication
Interventions	Group1 – control (placebo) Group2 – supplement (65 mmol K/day) Tablet type: KCl
Outcomes	Resting BP Serum K, Na Urinary K, Na
Notes	1) K intake in intervention ≥90 mmol/day 2) Na intake at baseline 2–4 g/d 3) Age – adult (15 years or greater) 4) Group – hypertensive 5) Duration of follow-up – 1.5 months (6 weeks) 6) Sex – women only 7) BP device – manual 8) BP method – seated office SBP, seated office DBP 9) Subgroup analyses – 4 week time point

BP, blood pressure; Cl, chloride; DBP, diastolic blood pressure; K, potassium; Na, sodium; SBP, systolic blood pressure
Reference: (Matlou et al., 1986)

Table 3.26 Risk of bias table Matlou BPA1986

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description of method of sequence generation
Allocation concealment (selection bias)	Unclear risk	No description of method of concealment of allocation
Blinding of participants and personnel (performance bias)	High risk	Participants and providers were not blinded
Blinding of outcome assessment (detection bias)	Low risk	Reported that observer bias was eliminated
Incomplete outcome data (attrition bias)	Low risk	Low loss to follow-up reported (10%)
Selective reporting (reporting bias)	Low risk	All outcomes reported

Table 3.27 Obel BPA1989

Methods	Parallel design study of increased K via supplements. Participants randomized to receive KCl tablets or placebo. Conducted in the United Kingdom.
Participants	48 hypertensive men and women, not taking BP medication
Interventions	Group1 – control (placebo) Group2 – supplement (64 mmol K/day) Tablet type: KCl
Outcomes	Standing BP Supine BP
Notes	1) K intake in intervention ≥90 mmol/day 2) Na intake at baseline 2–4 g/d 3) Age – adult (15 years or greater) 4) Group – hypertensive 5) Duration of follow-up – 4 months (16 weeks) 6) Sex – both (heterogeneous) 7) BP device – manual 8) BP method – supine office DBP, supine office SBP, standing DBP, standing office SBP 9) Subgroup analysis – 4-, 8- and 12-week time points

BP, blood pressure; Cl, chloride; DBP, diastolic blood pressure; K, potassium; Na, sodium; SBP, systolic blood pressure
Reference: (Obel, 1989)

Table 3.28 Risk of bias table Obel BPA1989

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description of method of sequence generation
Allocation concealment (selection bias)	Unclear risk	No description of method of concealment of allocation
Blinding of participants and personnel (performance bias)	Low risk	Participants and providers blinded
Blinding of outcome assessment (detection bias)	Unclear risk	No description of blinding of outcome assessor
Incomplete outcome data (attrition bias)	Low risk	0% loss to follow-up reported
Selective reporting (reporting bias)	Low risk	Most outcomes reported; urinary K and Na not reported for subanalyses (4, 8, 12 week time points)

K, potassium; Na, sodium

Table 3.29 Overlack BPARAAEA1991

Methods	Cross-over design study of increased K via supplements. Participants randomized to receive K tablets or placebo. Conducted in Germany.
Participants	12 hypertensive men and women, not taking BP medication
Interventions	Group1 – control (placebo) Group2 – supplement (120 mmol K/day) Tablet type: K + citrate + bicarbonate
Outcomes	Mean arterial BP Serum Na, K concentrations Intracellular Na, K concentrations Plasma renin activity Plasma aldosterone
Notes	1) K intake in intervention ≥120 mmol/day 2) Na intake at baseline 2–4 g/d 3) Age – adult (15 years or greater) 4) Group – hypertensive 5) Duration of follow-up – 2 months (8 weeks) 6) Sex – both (heterogeneous) 7) BP device – not specified 8) BP method – SBP, DBP 9) Other – Does not contribute to meta-analyses. Waiting on author reply

BP, blood pressure; Cl, chloride; DBP, diastolic blood pressure; K, potassium; Na, sodium; SBP, systolic blood pressure
Reference: (Overlack et al., 1991)

Table 3.30 Risk of bias table Overlack BPARAAEA1991

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description of method of sequence generation; stated that there was a "randomization plan"
Allocation concealment (selection bias)	Unclear risk	No description of method of concealment of allocation
Blinding of participants and personnel (performance bias)	High risk	Participants and providers not blinded
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessor blinded
Incomplete outcome data (attrition bias)	Low risk	0% loss to follow-up reported
Selective reporting (reporting bias)	Low risk	All outcomes reported

Table 3.31 Patki BPARA1990

Methods	Cross-over design study of increased K via supplements. Participants randomized to receive KCl tablets or placebo. Conducted in India.
Participants	37 hypertensive men and women, not taking BP medication
Interventions	Group1 – control (placebo) Group2 – supplement (30 mmol K/day) Tablet type: KCl
Outcomes	Resting BP Serum cholesterol Serum creatinine Serum urea
Notes	1) K intake in intervention ≥70 mmol/day 2) Na intake at baseline >4 g/day 3) Age – adult (15 years or greater) 4) Group – hypertensive 5) Duration of follow-up – 2 months (8 weeks) 6) Sex – both (heterogeneous) 7) BP device – manual 8) BP method – supine SBP, supine DBP, standing office SBP, standing office DBP

BP, blood pressure; Cl, chloride; DBP, diastolic blood pressure; K, potassium; Na, sodium; SBP, systolic blood pressure
Reference: (Patki et al., 1990)

Table 3.32 Risk of bias table Patki BPARA1990

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description of method of sequence generation
Allocation concealment (selection bias)	Unclear risk	No description of method of concealment of allocation
Blinding of participants and personnel (performance bias)	Low risk	Participants and providers blinded
Blinding of outcome assessment (detection bias)	Unclear risk	No description of blinding of outcome assessor
Incomplete outcome data (attrition bias)	Unclear risk	Loss to follow-up not reported
Selective reporting (reporting bias)	Low risk	All outcomes reported

Table 3.33 Richards BPAAEA1984

Methods	Cross-over design study of increased K via supplements. Participants randomized to receive KCl tablets or placebo. Conducted in New Zealand.
Participants	12 hypertensive men and women, not taking BP medication
Interventions	Group1 – control (placebo) Group2 – supplement (200 mmol K/day) Tablet type: KCl
Outcomes	Resting BP Plasma renin activity Anguitensin II Aldosterone Noradrenaline Adrenaline Urine Na, K, creatinine excretions
Notes	1) K intake in intervention ≥120 mmol/day 2) Na intake at baseline >4 g/d (estimate based on figure) 3) Age – adult (15 years or greater) 4) Group – hypertensive 5) Duration of follow-up – 1 month (4 weeks) 6) Sex – both (heterogeneous) 7) BP device – automatic 8) BP method – supine SBP, supine DBP, standing office SBP, standing office DBP

BP, blood pressure; Cl, chloride; DBP, diastolic blood pressure; K, potassium; Na, sodium; SBP, systolic blood pressure
Reference: (Richards et al., 1984)

Table 3.34 Risk of bias table Richards BPAAEA1984

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description of method of sequence generation
Allocation concealment (selection bias)	Unclear risk	No description of method of concealment of allocation
Blinding of participants and personnel (performance bias)	High risk	Providers and participants were not blinded
Blinding of outcome assessment (detection bias)	Unclear risk	Unclear if outcome assessors were blinded
Incomplete outcome data (attrition bias)	High risk	25% loss to follow-up
Selective reporting (reporting bias)	Low risk	All outcomes reported

Table 3.35 Siani BPA1987

Methods	Parallel study of increased K via supplements. Participants randomized to receive KCl tablets or placebo. Conducted in Italy.
Participants	37 hypertensive men and women, not taking BP medication
Interventions	Group1 – control (placebo) Group2 – supplement (24 mmol K/day) Tablet type: KCl
Outcomes	Resting BP Urinary creatinine excretion
Notes	1) K intake in intervention ≥70 mmol/day 2) Na intake at baseline >4 g/d 3) Age – adult (15 years or greater) 4) Group – hypertensive 5) Duration of follow-up – 3.75 months (7 weeks) 6) Sex – both (heterogeneous) 7) BP device – manual 8) BP method – supine office SBP, supine office DBP, standing office SBP, standing office DBP

BP, blood pressure; Cl, chloride; DBP, diastolic blood pressure; K, potassium; Na, sodium; SBP, systolic blood pressure
Reference: (Siani et al., 1987)

Table 3.36 Risk of bias table Siani BPA1987

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description of method of sequence generation
Allocation concealment (selection bias)	Low risk	Concealment of allocation through pre-packaged identical containers
Blinding of participants and personnel (performance bias)	Low risk	Providers and participants were blinded
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessor was blinded
Incomplete outcome data (attrition bias)	Unclear risk	Loss to follow-up not reported
Selective reporting (reporting bias)	Low risk	All outcomes reported

Table 3.37 Siani BPARA1991

Methods	Parallel design study of increased K diet. Participants randomized to receive regular (unchanged) diet or high K diet. Conducted in Italy.
Participants	47 hypertensive men and women, taking BP medication
Interventions	Group1 – control (unchanged diet) Group2 – high K diet (≥30 mmol K/day) Tablet type: N/A
Outcomes	Resting BP Mean energy and nutrient intake Urinary K and Na Rate of treatment discontinuation Pills per day (drug consumption)
Notes	1) K intake in intervention ≥70 mmol/day 2) Na intake at baseline 2–4 g/day 3) Age – adult (15 years or greater) 4) Group – hypertensive 5) Duration of follow-up – 12 months (52 weeks) 6) Sex – both (heterogeneous) 7) BP device – automatic 8) BP method – Supine office SBP, supine office DBP

BP, blood pressure; Cl, chloride; DBP, diastolic blood pressure; K, potassium; Na, sodium; SBP, systolic blood pressure
Reference: (Siani et al., 1991)

Table 3.38 Risk of bias table Siani BPARA1991

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description of method of sequence generation
Allocation concealment (selection bias)	Unclear risk	No description of method of concealment of allocation
Blinding of participants and personnel (performance bias)	High risk	Providers and participants were not blinded
Blinding of outcome assessment (detection bias)	Unclear risk	Unclear if outcome assessors were blinded
Incomplete outcome data (attrition bias)	Low risk	13% loss to follow-up
Selective reporting (reporting bias)	Low risk	All outcomes reported

Table 3.39 Smith BPARA1985

Methods	Cross-over design study of increased K via supplements. Participants randomized to receive KCl tablets or placebo. Conducted in the United States of America.
Participants	20 hypertensive men and women, not taking BP medication
Interventions	Group1 – control (placebo) Group2 – supplement (64 mmol K/day) Tablet type: KCl
Outcomes	Resting BP Supine heart rate Weight Urinary Na, K, creatinine Plasma renin activity Plasma aldosterone, K Blood creatinine
Notes	1) K intake in intervention ≥90 mmol/day 2) Na intake at baseline <2 g/d 3) Age – adult (15 years or greater) 4) Group – hypertensive 5) Duration of follow-up – 1 month (4 weeks) 6) Sex – both (heterogeneous) 7) BP device – automatic 8) BP method – Supine SBP, supine DBP, standing SBP, standing DBP

BP, blood pressure; Cl, chloride; DBP, diastolic blood pressure; K, potassium; Na, sodium; SBP, systolic blood pressure
Reference: (Smith et al., 1985)

Table 3.40 Risk of bias table Smith BPARA1985

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description of method of sequence generation
Allocation concealment (selection bias)	Unclear risk	No description of method of concealment of allocation
Blinding of participants and personnel (performance bias)	Low risk	Providers and participants were blinded
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessors was blinded
Incomplete outcome data (attrition bias)	Low risk	10% loss to follow-up
Selective reporting (reporting bias)	Low risk	All outcomes reported

Table 3.41 Trial Hyp Prv Col BPA1992

Methods	Parallel design study of increased K via supplements. Participants randomized to receive KCl tablets or placebo. Conducted in the United States of America.
Participants	286 normotensive men and women, not taking BP medication
Interventions	Group1 – control (placebo) Group2 – supplement (60 mmol K/day) Tablet type: KCl
Outcomes	Resting BP Na reduction Weight reduction Stress management Incidence of hypertension
Notes	1) K intake in intervention ≥90 mmol/day 2) Na intake at baseline 2–4 g/d 3) Age – adult (15 years or greater) 4) Group – normotensive 5) Duration of follow-up – 6 months (24 weeks) 6) Sex – both (heterogeneous) 7) BP device – manual 8) BP method – Seated office SBP, seated office DBP 9) Subgroup analysis – 3-month time point

BP, blood pressure; Cl, chloride; DBP, diastolic blood pressure; K, potassium; Na, sodium; SBP, systolic blood pressure
Reference: (Trial Hyp Prv Col, 1992)

Table 3.42 Risk of bias table Trial Hyp Prv Col BPA1992

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sequence generation by telephone
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes
Blinding of participants and personnel (performance bias)	Low risk	Providers and participants were blinded
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessors were blinded
Incomplete outcome data (attrition bias)	Low risk	18–20% loss to follow-up among groups
Selective reporting (reporting bias)	Low risk	All outcomes reported

Table 3.43 Valdes BPA1991

Methods	Cross-over design study of increased K via supplements. Participants randomized to receive KCl tablets or placebo. Conducted in Chile.
Participants	24 hypertensive men and women, not taking BP medication
Interventions	Group1 – control (placebo) Group2 – supplement (64 mmol K/day) Tablet type: KCl
Outcomes	Mean arterial BP Serum Na, K concentrations Intracellular Na, K concentrations Plasma renin activity Plasma aldosterone activity
Notes	1) K intake in intervention ≥120 mmol/day 2) Na intake at baseline 2–4 g/d 3) Age – adult (15 years or greater) 4) Group – hypertensive 5) Duration of follow-up – 1 month (4 weeks) 6) Sex – both (heterogeneous) 7) BP device – automatic 8) BP method – supine office SBP, supine office DBP, standing office SBP, standing office DBP

BP, blood pressure; Cl, chloride; DBP, diastolic blood pressure; K, potassium; Na, sodium; SBP, systolic blood pressure
Reference: (Valdés et al., 1991)

Table 3.44 Risk of bias table Valdes BPA1991

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description of method of sequence generation
Allocation concealment (selection bias)	Unclear risk	No description of method of concealment of allocation
Blinding of participants and personnel (performance bias)	Low risk	Providers and participants were blinded
Blinding of outcome assessment (detection bias)	Unclear risk	Unclear if outcome assessors were blinded
Incomplete outcome data (attrition bias)	Unclear risk	No loss to follow-up reported
Selective reporting (reporting bias)	Low risk	All outcomes reported

Table 3.45 Whelton BPA1995

Methods	Parallel design study of increased K via supplements. Participants randomized to receive KCl tablets or placebo. Conducted in the United States of America.
Participants	353 normotensive men and women, not taking BP medication
Interventions	Group1 – control (placebo) Group2 – supplement (60 mmol K/day) Tablet type: KCl
Outcomes	BP Urinary excretion Dietary assessment
Notes	1) K intake in intervention ≥90 mmol/day 2) Na intake at baseline 2–4 g/d 3) Age – adult (15 years or greater) 4) Group – normotensive 5) Duration of follow-up – 6 months (24 weeks) 6) Sex – both (heterogeneous) 7) BP device – manual 8) BP method – SBP, DBP 9) Subgroup analysis – 3-month time point

BP, blood pressure; Cl, chloride; DBP, diastolic blood pressure; K, potassium; Na, sodium; SBP, systolic blood pressure
References: (Whelton et al., 1997; Whelton et al., 1995)

Table 3.46 Risk of bias table Whelton BPA1995

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description of method of sequence generation
Allocation concealment (selection bias)	Unclear risk	No description of method of concealment of allocation
Blinding of participants and personnel (performance bias)	Low risk	Providers and participants were blinded
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessors were blinded
Incomplete outcome data (attrition bias)	Low risk	4–10% loss to follow-up among groups of interest
Selective reporting (reporting bias)	Low risk	All outcomes reported

3.7.2 Characteristics of studies awaiting classification

Table 3.47 Braschi BPA2008

Methods	Parallel design study of increased K diet. Participants randomized to receive placebo, K-citrate supplement, or KCl supplement. Conducted in the United Kingdom.
Participants	90 adult men and women, heterogeneous hypertensive status, heterogeneous BP medication status
Interventions	Group1 – placebo Group2 – K-supplemented diet (30 mmol K/day) via tablets (type: KCl) Group3 – K-supplemented diet (30 mmol K/day) via tablets (type: K-citrate)
Outcomes	BP Urinary electrolyte and creatinine, haematocrit, erythrocyte water and K content
Notes	1) K intake in intervention ≥70 mmol/day 2) Na intake at baseline 2–4 g/d 3) Age – adult (15 years or greater) 4) Group – both 5) Duration of follow-up – 1.5 months (6 weeks) 6) Sex – both (heterogeneous) 7) BP device – automatic 8) BP method – seated office SBP, seated office DBP

BP, blood pressure; Cl, chloride; DBP, diastolic blood pressure; K, potassium; Na, sodium; SBP, systolic blood pressure
Reference: (Braschi & Naismith, 2008)

Table 3.48 Cushman BPA1988

Methods	Parallel design study of increased K diet. Participants randomized to receive placebo or KCl supplement. Conducted in the United States of America.
Participants	58 adult men, hypertensive status, not taking BP medication
Interventions	Group1 – placebo Group2 – K-supplemented diet (80 mmol K/day) via tablets Tablet type: KCl
Outcomes	Urinary K excretion BP (type not specified and data in current form not usable for meta-analysis)
Notes	1) Potassium intake in intervention ≥90 mmol/day 2) Na intake at baseline not reported 3) Age – adult (15 years or greater) 4) Group – hypertensive 5) Duration of follow-up – 2.5 months 6) Sex – men 7) BP device – not specified 8) BP method – SBP, DBP

BP, blood pressure; Cl, chloride; DBP, diastolic blood pressure; K, potassium; Na, sodium; SBP, systolic blood pressure
Reference: (Cushman & Langford, 1988)

Table 3.49 Hilary Green BPA2000

Methods	Cross-over design study of increased K diet. Participants randomized to receive high-calcium milk or high-calcium milk enriched with K. Conducted in New Zealand.
Participants	38 adult men and women, heterogeneous hypertensive status, not taking BP medication
Interventions	Group1 – high-calcium milk Group2 – K-supplemented high-calcium milk (1585 mg K/50 g milk)
Outcomes	Ambulatory BP Resting BP Excretion of calcium, K, Na, magnesium
Notes	1) K intake (as measured by urinary excretion) – Author contacted 2) Na intake at baseline not reported 3) Age – adult (15 years or greater) 4) Group – both 5) Duration of follow-up – 1 month (4 weeks) 6) Sex – both (heterogeneous) 7) BP device – automatic 8) BP method – ambulatory SBP (day), ambulatory DBP (day), seated office DBP, seated office SBP, standing office SBP, standing office DBP

BP, blood pressure; DBP, diastolic blood pressure; K, potassium; Na, sodium; SBP, systolic blood pressure
Reference: (Hilary Green et al., 2000)

The full text was unavailable for the following studies:

- Barros BPA1984 – reference: Barros and Brito (1984);
- Iimura BPA1979 – reference: Iimura et al. (1981);
- Kawano BPA1997 – reference: Kawano et al. (1997);
- Morris BPA 1995 – reference: Morris et al. (1995).

3.7.3 Characteristics of ongoing studies

Table 3.50 Mullan BPA2010

Study name	The renin-angiotensin-aldosterone axis, endothelial function and hypertension: diagnostic strategies, and therapeutic role of K supplementation – a randomized cross-over trial and an observational study. WHO International Clinical Trials Registry Platform. [Other: ISRCTN55798944]
Methods	Study 1: Prospective randomized cross-over investigator-blinded trial Study 2: Observational study
Participants	Study 1: 1.1. Patients (both male and female) aged 40–70 with moderate (>10%) cardiovascular disease risk (Joint British Societies' guidelines) Study 2: Three groups of participants (both male and female, all between age 18–70): 2.1. Patients with essential hypertension 2.2. Patients with hyperaldosteronism 2.3. Healthy volunteers
Interventions	Study 1: Dietary intake of Na and K will be assessed and a 24-hour urine collection for estimation of Na and K excretion will be taken. The participants will be randomized to either placebo or K supplementation (4.8 g/day; oral) for 6 weeks. There will be a 6-week washout period. Participants will be studied at baseline, at the end of washout and after each intervention (four in total). Study 2: The target numbers of participants for the three groups are as follows: i. Patients with essential hypertension: n = 20 ii. Patients with hyperaldosteronism: n = 8 iii. Healthy volunteers: n = 15 43 participants in total Patients with essential hypertension and patients with hyperaldosteronism will undergo a 250-mcg synacthen test with blood and saliva sampled at 0, 30 and 60 minutes for cortisol and aldosterone. This test will be performed after 30 minutes of recumbency. In addition the healthy volunteers and patients with hyperaldosteronism will also undergo a GnRH test to assess aldosterone response.
Outcomes	Study 1 – Global endothelial function assessed by determining the change in augmentation index in response to the administration of nitroglycerin and salbutamol. All primary and secondary outcomes will be assessed at baseline, at the end of washout and after each intervention. Study 2 – Aldosterone response to synacthen/GnRH
Starting date	20/11/2008
Contact information	karen.mullan@hscni.net
Notes	http://www.controlled-trials.com/ISRCTN55798944/ Expected to have ended in 2010, but no publications listed

GnRH, gonadotropin-releasing hormone; K, potassium; Na, sodium

Table 3.51 Turban BPA RA2009

Study name	Potassium intake in patients with chronic kidney disease. Clinicaltrials.gov. [Other: NCT00949585]
Methods	Allocation: randomized Endpoint classification: safety/efficacy study Intervention model: cross-over assignment Masking: double-blind (patient, caregiver, investigator, outcomes assessor) Primary purpose: treatment
Participants	Inclusion criteria: Stage 3 chronic kidney disease (estimated glomerular filtration rate 30–59 mL/min/1.73 m^2 by the 4-variable Modification of Diet in Renal Disease Study Equation Systolic BP 120–159 mmHg and diastolic BP <100 mmHg Willingness to follow strict dietary rules for 9 weeks and to come to the clinical research unit at least 3 weekdays per week for one meal during the two study periods Exclusion criteria: Baseline serum K of at least 5 mEq/L (or history of hyperkalemia) Baseline serum K of less than 3.5 mEq/L (or history of hypokalemia) Insulin-requiring or uncontrolled (HbA1C >9 g/dL) diabetes mellitus Use of K-sparing diuretics, K supplements, non-steroidal anti-inflammatory agents, steroids, digoxin, or calcineurin inhibitors History of any organ transplant Body mass index >40 kg/m^2 Chronic disease(s) that may interfere with trial participation Pregnancy or lactation >14 alcoholic drinks/week Major food allergies or intolerances
Interventions	Participants will be given one of two diets: one contains 100 mmol K/day, the other contains 40 mmol K/day:
Outcomes	Primary outcome measures: 24-hour ambulatory systolic BP [Time frame: at screening, and at the end of each intervention period] [Designated as safety issue: Yes] Secondary outcome measures: other measures of peripheral BP (other types of ambulatory BP measurements as well as clinic BP) [Time frame: ambulatory BP: same as primary outcome. Clinic BP: at screening, run-in, and weekly during intervention] [Designated as safety issue: Yes] Measures of central BP (pulse wave velocity and augmentation index) [Time frame: at screening and at the end of each intervention period] [Designated as safety issue: No] Serum K [Time frame: at screening, run-in, and at least three times during each intervention period] [Designated as safety issue: Yes] Serum inflammatory markers [Time frame: before and at the end of each intervention period] [Designated as safety issue: No]
Starting date	July 2009
Contact information	CKD@jhmi.edu
Notes	http://clinicaltrials.gov/ct2/show/NCT00949585

BP, blood pressure; K, potassium

3.7.4 Excluded studies and reasons for exclusion

The excluded studies, and the reasons for their exclusions, are as shown in Table 3.52, below.

Table 3.52 Excluded studies and reasons for exclusion

Study ID	Reason for exclusion
Agnoli RA 1992	Intervention <4 weeks
Agnoli RA 1992	Intervention <4 weeks
Barcelo RA 1993	24-hour urinary K excretion values not measured
Ceglia RA 2009	Intervention <4 weeks
Fujita AEA 1984	Na levels varied; intervention <4 weeks
Gamarra BPA 1994	24-hour urinary K excretion values not measured
Grimm BPA 1990	24-hour urinary K excretion values not measured
Heller RA 1998	No control
Jardim BPA 1988	24-hour urinary K excretion values not measured
Khaw BPA 1982	Intervention <4 weeks
Krishnan RA 2010	Intervention <4 weeks
Langford BPA 1991	K intake not only difference between control and intervention (Na levels varied)
Lennon RA 1968	Intervention <4 weeks
Med Res CWP BPA 1987	24-hour urinary K excretion values not measured
Overlack BPA RA AEA 1995	K intake not only difference between control and intervention
Parfrey AEA 1981	Intervention <4 weeks
Poulter BPA 1986	Intervention <4 weeks
Rahimi BPA 2007	24-hour urinary K excretion values not measured
Sanclemente BPA 1987	Intervention <4 weeks
Smith BPA 1992	Intervention <4 weeks
Svetkey BPA 1987	24-hour urinary K excretion values not measured
WHO ICTRP RA 2008	K intake not only difference between control and intervention (calcium levels varied)

K, potassium; Na, sodium

3.8 Effect estimate tables

Table 3.53 Resting systolic blood pressure

Outcome or Subgroup*	Studies	Participants	Effect Estimate
1.1 Resting systolic blood pressure (ALL)	22	1892	-3.06 [-4.70, -1.42]
1.2 Resting systolic blood pressure (SUBGROUPS))	22		**Subtotals only**
1.2.1 BP Status (NORMOTENSIVE)	3	757	0.09 [-0.77, 0.95]
1.2.2 BP Status (HYPERTENSIVE)	17	818	-4.68 [-6.96, -2.40]
1.2.3 BP Status (HETEROGENEOUS)	2	233	-2.95 [-5.65, -0.26]
1.2.4 Achieved K intake intervention (<70mmol)	2	183	-3.65 [-6.69, -0.62]
1.2.5 Achieved K in intervention (>=70mmol v <90mmol)	5	286	-5.82 [-12.43, 0.79]
1.2.6 Achieved K in intervention (>=90mmol v <120mmol)	11	1187	-1.25 [-2.68, 0.18]
1.2.7 Achieved K in intervention (>120mmol)	4	236	-3.00 [-6.28, 0.27]
1.2.8 Difference in achieved K intake inter. v control: <30	6	501	-3.72 [-7.06, -0.38]
1.2.9 Difference in achieved K intake inter. v control: 30-60	12	1169	-1.97 [-3.85, -0.09]
1.2.10 Difference in achieved K intake inter. v control: >60	4	222	-3.01 [-7.03, 1.02]
1.2.11 K intake at baseline (lower: <40)	2	169	-3.89 [-7.03, -0.74]
1.2.12 K intake at baseline (intermediate: 40-60)	15	1372	-2.95 [-5.09, -0.82]
1.2.13 K intake at baseline (higher: >60)	5	351	-3.41 [-5.56, -1.27]
1.2.14 Na intake at baseline (<2g/d)	1	40	-2.00 [-11.70, 7.70]
1.2.15 Na intake at baseline (2-4g/d)	16	1470	-1.34 [-2.64, -0.04]
1.2.16 Na intake at baseline (>4g/d)	5	382	-6.91 [-11.53, -2.29]
1.2.17 Duration (<2 months)	15	933	-3.36 [-4.94, -1.78]
1.2.18 Duration (2 - 4 months)	8	1074	-3.53 [-6.28, -0.78]
1.2.19 Duration (> 4 months)	3	718	0.16 [-0.71, 1.03]
1.2.20 Type of BP device (automatic)	10	608	-2.48 [-4.33, -0.62]
1.2.21 Type of BP device (manual)	12	1284	-3.63 [-5.98, -1.28]
1.2.22 Type of BP measure (supine office SBP)	14	692	-4.35 [-7.40, -1.31]
1.2.23 Type of BP measure (seated office SBP)	7	1169	-1.48 [-2.97, 0.01]
1.2.24 Type of BP measure (standing office SBP)	9	351	-6.94 [-10.63, -3.25]
1.2.25 Type of BP measure (unspecified SBP)	2	117	-2.51 [-7.87, 2.85]
1.2.26 Hypertension medication status (not taking medication)	15	1421	-4.07 [-6.18, -1.96]
1.2.27 Hypertension medication status (population taking medication)	4	195	-0.42 [-4.80, 3.97]
1.2.28 Hypertension medication status (not specified/heterogeneous)	3	276	-1.16 [-3.74, 1.43]
1.2.29 Type of intervention (supplement)	20	1744	-3.31 [-5.07, -1.55]
1.2.30 Type of intervention (advice)	3	244	-1.55 [-5.44, 2.35]
1.2.31 Study design (parallel)	8	1026	-1.82 [-4.02, 0.38]
1.2.32 Study design (cross-over)	14	866	-3.99 [-6.13, -1.86]

*Statistical method used: Mean Difference (IV, Random, 95%CI)

Table 3.54 Resting diastolic blood pressure

Outcome or Subgroup*	Studies	Participants	Effect Estimate
1.3 Resting diastolic blood pressure (ALL)	22	1857	-2.84 [-4.66, -1.01]
1.4 Resting diastolic blood pressure (SUBGROUPS))	22		Subtotals only
1.4.1 BP Status (NORMOTENSIVE)	3	722	-0.56 [-1.55, 0.42]
1.4.2 BP Status (HYPERTENSIVE)	17	902	-3.65 [-6.40, -0.91]
1.4.3 BP Status (HETEROGENEOUS)	2	233	-0.17 [-1.82, 1.48]
1.4.4 Achieved K intake in intervention (<70mmol)	2	183	-1.35 [-5.31, 2.60]
1.4.5 Achieved K in intervention (>=70mmol v <90mmol)	5	212	-3.52 [-8.28, 1.24]
1.4.6 Achieved K in intervention (>=90mmol v <120mmol)	10	1051	-1.47 [-2.67, -0.27]
1.4.7 Achieved K in intervention (>120mmol)	4	236	-1.75 [-4.23, 0.74]
1.4.8 Difference in achieved K intake inter. v control: <30	6	427	-1.29 [-3.11, 0.54]
1.4.9 Difference in achieved K intake inter. v control: 30-60	12	1134	-1.63 [-3.04, -0.21]
1.4.10 Difference in achieved K intake inter. v control: >60	4	222	-3.57 [-6.32, -0.82]
1.4.11 K intake at baseline (lower: <40)	2	169	-2.41 [-7.90, 3.07]
1.4.12 K intake at baseline (intermediate: 40-60)	15	1263	-1.53 [-2.80, -0.25]
1.4.13 K intake at baseline (higher: >60)	5	351	-3.38 [-4.74, -2.02]
1.4.14 Na intake at baseline (<2g/d)	1	40	0.00 [-6.12, 6.12]
1.4.15 Na intake at baseline (2-4g/d)	16	1435	-1.96 [-3.16, -0.76]
1.4.16 Na intake at baseline (>4g/d)	5	308	-2.87 [-6.96, 1.22]
1.4.17 Duration (<2 months)	15	933	-1.99 [-3.11, -0.87]
1.4.18 Duration (2 - 4 months)	8	965	-1.86 [-3.75, 0.02]
1.4.19 Duration (> 4 months)	3	683	-0.35 [-1.06, 0.35]
1.4.20 Type of BP device (automatic)	10	608	-2.84 [-3.96, -1.71]
1.4.21 Type of BP device (manual)	12	1175	-1.54 [-2.96, -0.11]
1.4.22 Type of BP measure (supine office DBP)	14	692	-4.34 [-7.57, -1.10]
1.4.23 Type of BP measure (seated office DBP)	7	1134	-1.30 [-2.64, 0.04]
1.4.24 Type of BP measure (standing office DBP)	9	351	-4.78 [-9.38, -0.18]
1.4.25 Type of BP measure (unspecified DBP)	2	117	0.83 [-4.45, 6.11]
1.4.26 Hypertension medication status (not taking medication)	14	1312	-1.37 [-2.50, -0.23]
1.4.27 Hypertension medication status (population taking medication)	5	195	-3.80 [-8.25, 0.66]
1.4.28 Hypertension medication status (not specified/heterogeneous)	3	276	-2.32 [-4.46, -0.17]
1.4.29 Type of intervention (supplement)	20	1709	-3.04 [-5.09, -0.99]
1.4.30 Type of intervention (advice)	3	244	-2.44 [-5.04, 0.17]
1.4.31 Study design (parallel)	8	991	-1.59 [-3.35, 0.18]
1.4.32 Study design (cross-over)	15	903	-4.21 [-7.12, -1.29]

*Statistical method used: Mean Difference (IV, Random, 95%CI)

Table 3.55 Ambulatory systolic blood pressure

Outcome or Subgroup*	Studies	Participants	Effect Estimate
1.5 Ambulatory systolic blood pressure (ALL)	4	322	-3.04 [-5.42, -0.66]
1.6 Ambulatory systolic blood pressure (SUBGROUPS))	4		**Subtotals only**
1.6.1 Achieved K intake inter. v control (both <70mmol)	0	0	Not estimable
1.6.2 Achieved K in intervention (>=70mmol v <90mmol)	1	96	-1.80 [-7.02, 3.42]
1.6.3 Achieved K in intervention (>=90mmol v <120mmol)	2	142	-3.65 [-7.21, -0.09]
1.6.4 Achieved K in intervention (>120mmol)	1	84	-3.00 [-7.07, 1.07]
1.6.5 BP Status (NORMOTENSIVE)	0	0	Not estimable
1.6.6 BP Status (HYPERTENSIVE)	3	226	-3.37 [-6.05, -0.69]
1.6.7 BP Status (HETEROGENEOUS)	1	96	-1.80 [-7.02, 3.42]

*Statistical method used: Mean Difference (IV, Random, 95%CI)

Table 3.56 Ambulatory diastolic blood pressure

Outcome or Subgroup*	Studies	Participants	Effect Estimate
1.7 Ambulatory diastolic blood pressure (ALL)	4	322	-1.24 [-3.13, 0.66]
1.8 Ambulatory diastolic blood pressure (SUBGROUPS))	4		Subtotals only
1.8.1 BP Status (NORMOTENSIVE)	0	0	Not estimable
1.8.2 BP Status (HYPERTENSIVE)	3	226	-1.18 [-3.38, 1.02]
1.8.3 BP Status (HETEROGENEOUS)	1	96	-1.40 [-5.14, 2.34]

*Statistical method used: Mean Difference (IV, Random, 95%CI)

Table 3.57 Blood lipids

Outcome or Subgroup*	Studies	Participants	Effect Estimate
1.9 Total cholesterol (ALL)	4	208	-0.12 [-0.33, 0.09]
1.10 HDL cholesterol (ALL)	2	128	-0.0.1 [-0.13, 0.11]
1.11 LDL cholesterol (ALL)	1	96	-0.10 [-0.38, 0.18]
1.12 Triglycerides (ALL)	2	128	-0.11 [-0.48, 0.26]

*Statistical method used: Mean Difference (IV, Random, 95%CI)

Table 3.58 Catecholamine levels

Outcome or Subgroup*	Studies	Participants	Effect Estimate
1.14 Adrenaline (plasma) (ALL)	3	152	-3.94 [-9.22, 1.34]
1.15 Noradrenaline (plasma) (ALL)	3	152	-4.32 [-23.78, 15.13]

*Statistical method used: Mean Difference (IV, Random, 95%CI)

Table 3.59 Renal function

Outcome or Subgroup*	Studies	Participants	Effect Estimate
1.16 Serum creatinine (ALL)	3	147	-4.86 [-13.59, 3.87]

*Statistical method used: Mean Difference (IV, Random, 95%CI)

3.9 Figures

Figure 3.1 Flow through screening, inclusion, exclusion

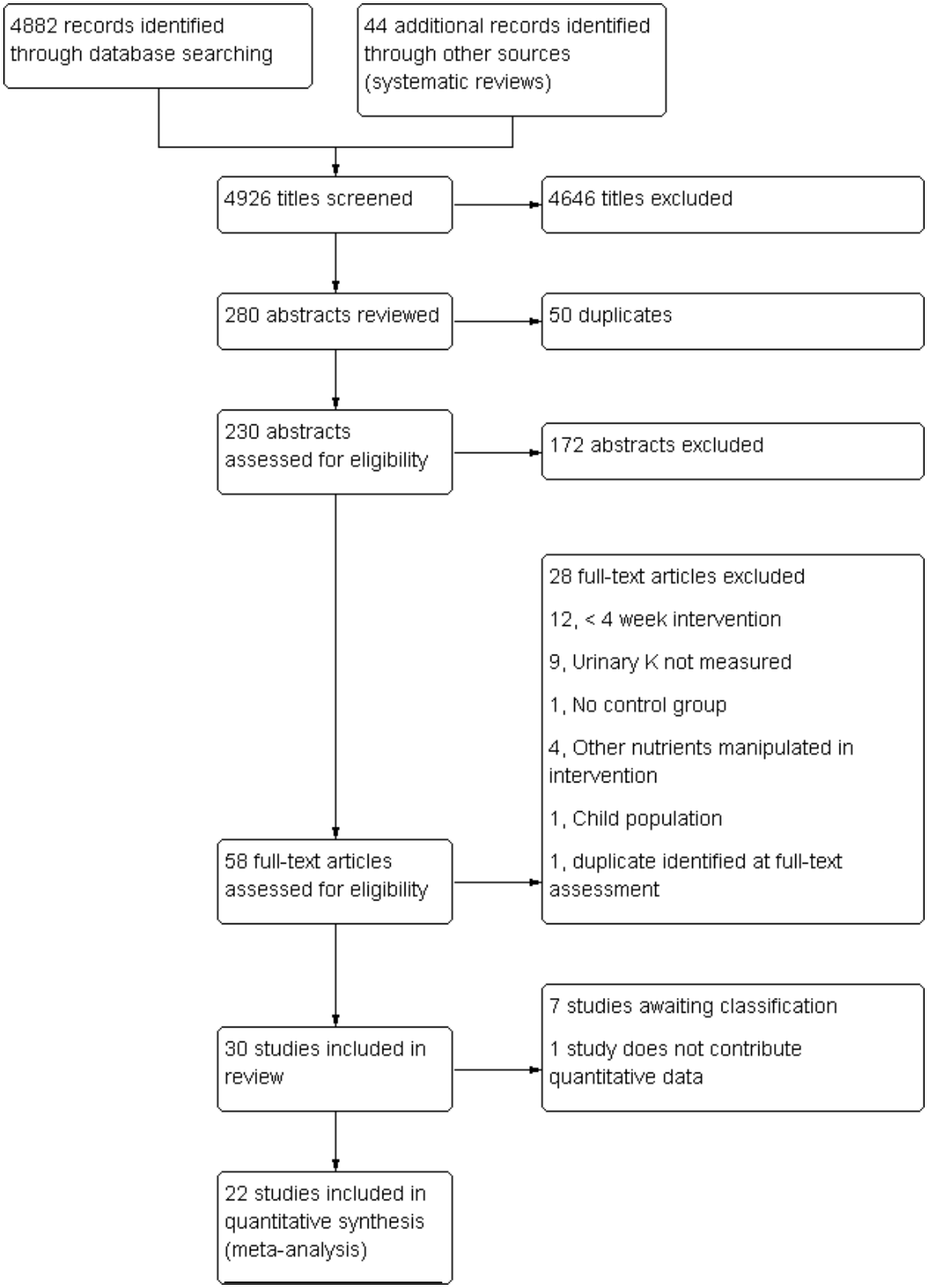


Figure 3.2 Resting systolic blood pressure

Study or Subgroup	Increased potassium Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Barden BPARA1986	113.67	8.87	43	113.69	9.44	43	7.0%	-0.02 [-3.89, 3.85]
Berry BPA2010	120.7	9.9	48	122.2	13	48	6.0%	-1.50 [-6.12, 3.12]
Bulpitt BPA1985	-5.2	27.5	19	-7.5	23.9	14	0.8%	2.30 [-15.30, 19.90]
Chalmers BPA1986	-7.7	7	49	-3.8	7.4	52	8.5%	-3.90 [-6.71, -1.09]
Forrester BPA1988	129.8	13.5	23	133.2	12.7	23	3.3%	-3.40 [-10.97, 4.17]
Fotherby BPA1992	176	20	18	186	24	18	1.2%	-10.00 [-24.43, 4.43]
Grobbee BPA1987	135	13.28	40	135.9	11.38	40	5.1%	-0.90 [-6.32, 4.52]
Gu BPA2001	-13.1	10.7	68	-9.4	9	69	7.8%	-3.70 [-7.01, -0.39]
He BPA2010	142	11	42	145	15	42	4.9%	-3.00 [-8.63, 2.63]
Kaplan BPA1985	127.6	11.6	16	133.2	16.8	16	2.2%	-5.60 [-15.60, 4.40]
Kawano BPA1998	147.9	11.7	55	150.8	12.61	55	6.1%	-2.90 [-7.45, 1.65]
MacGregor AEBPA1982	148	13.91	23	155	14.87	23	2.9%	-7.00 [-15.32, 1.32]
Matlou BPA1986	144	18.1	32	151	19.2	32	2.5%	-7.00 [-16.14, 2.14]
Obel BPA1989	133	4	24	172	7	24	0.0%	-39.00 [-42.23, -35.77]
Patki BPARA1990	143.6	10.8	37	155.7	11.4	37	5.5%	-12.10 [-17.16, -7.04]
Richards BPAAEA1984	148	14.2	12	149.9	14.5	12	1.7%	-1.90 [-13.38, 9.58]
Siani BPA1987	131.8	12.7	18	145.8	11.3	19	3.2%	-14.00 [-21.76, -6.24]
Siani BPARA1991	145.5	9.7	26	142.1	11.5	21	4.3%	3.40 [-2.77, 9.57]
Smith BPARA1985	160	16.1	20	162	15.2	20	2.3%	-2.00 [-11.70, 7.70]
Trial Hyp Prv Col BPA1992	-0.78	5.88	178	-0.84	5.82	175	10.7%	0.06 [-1.16, 1.28]
Valdes BPA1991	138	14.7	24	145	9.8	24	3.6%	-7.00 [-14.07, 0.07]
Whelton BPA1995	-0.87	5.94	161	-1	5.69	157	10.6%	0.13 [-1.15, 1.41]
Total (95% CI)			**952**			**940**	**100.0%**	**-3.06 [-4.70, -1.42]**

Heterogeneity: Tau² = 6.14; Chi² = 54.38, df = 20 (P < 0.0001); I² = 63%

Test for overall effect: Z = 3.66 (P = 0.0003)

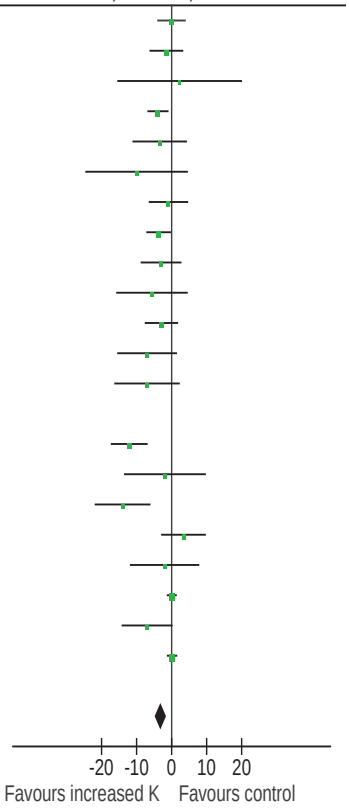


Figure 3.3 Resting systolic blood pressure – blood pressure status subgroups

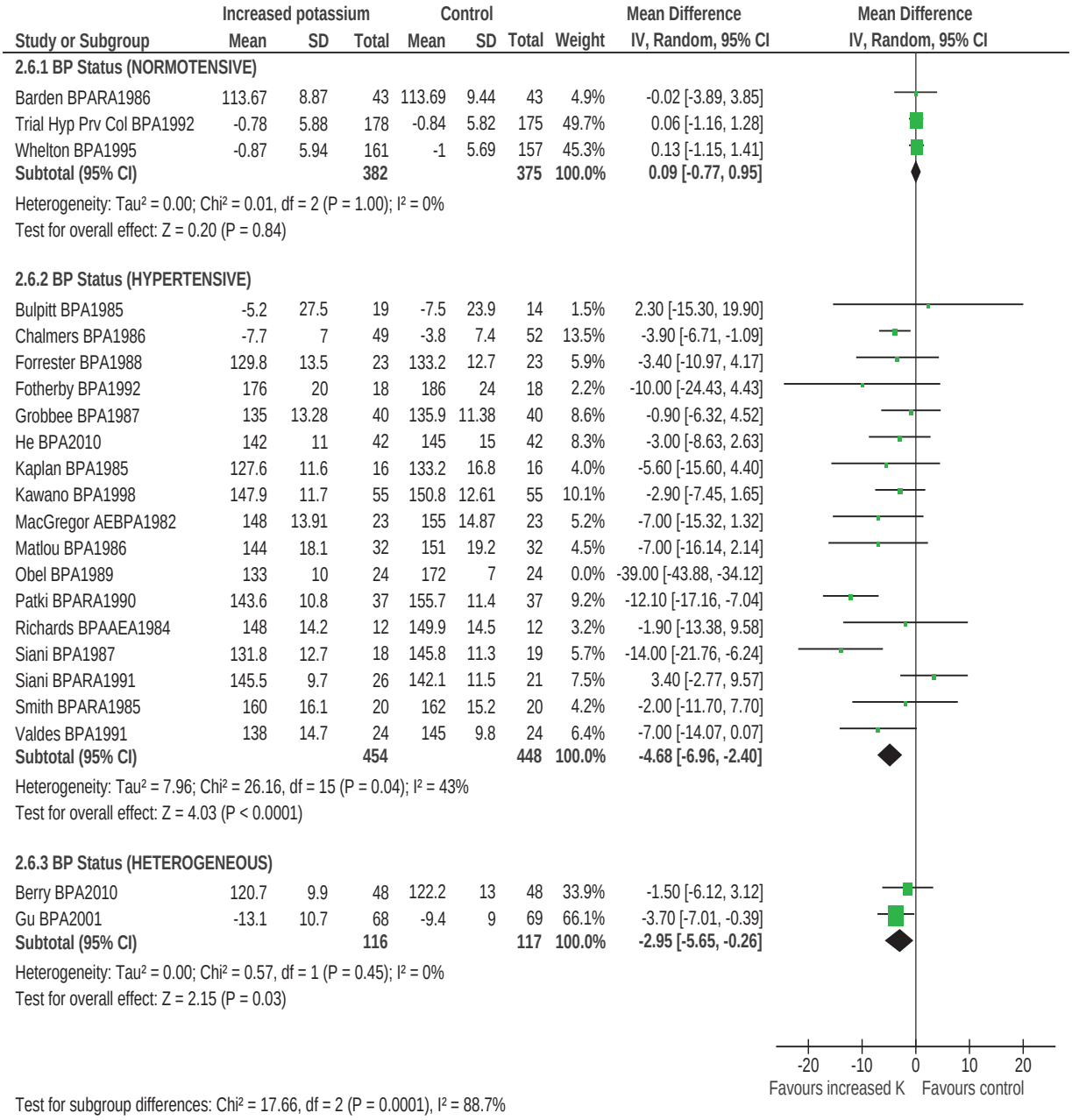
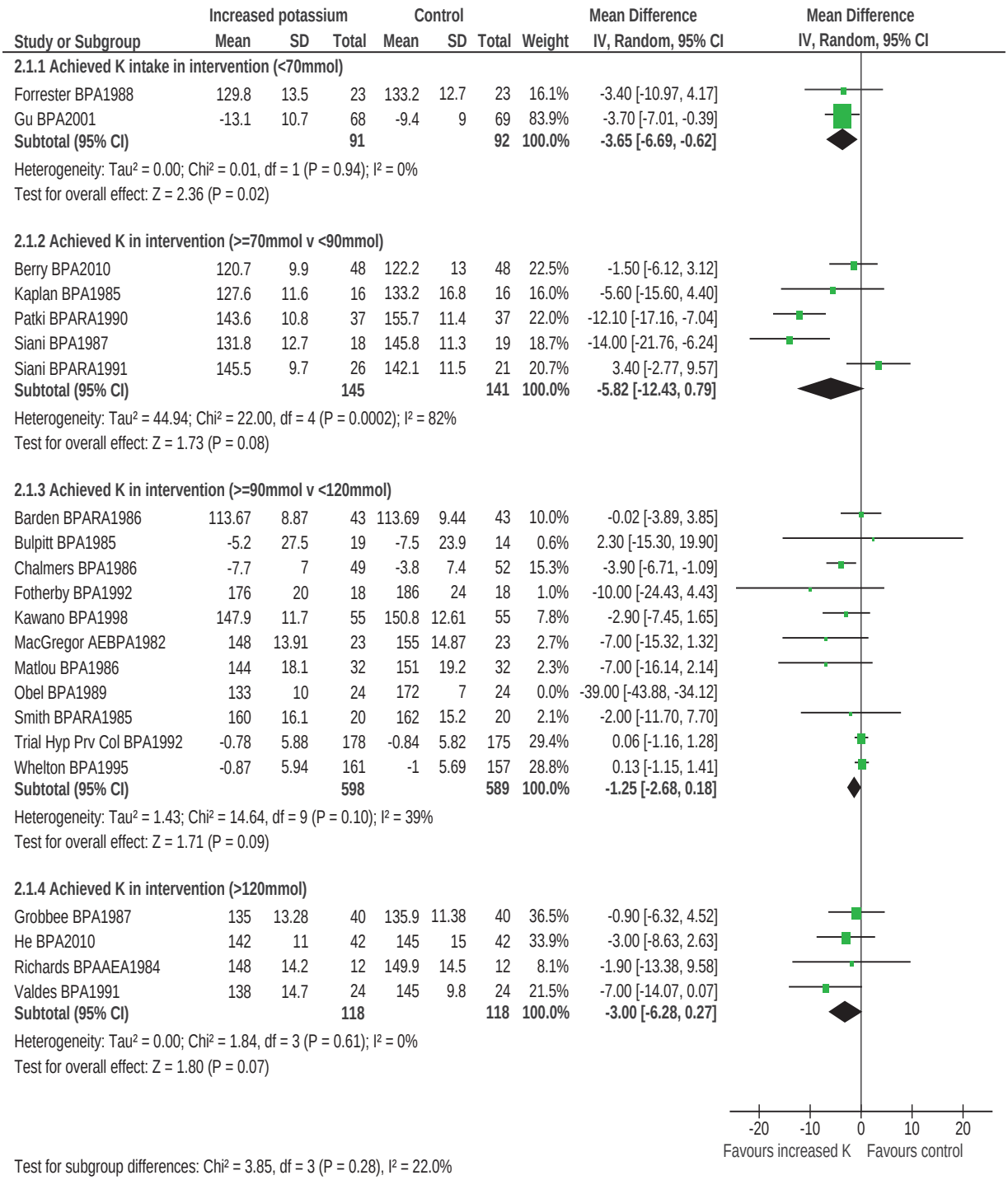
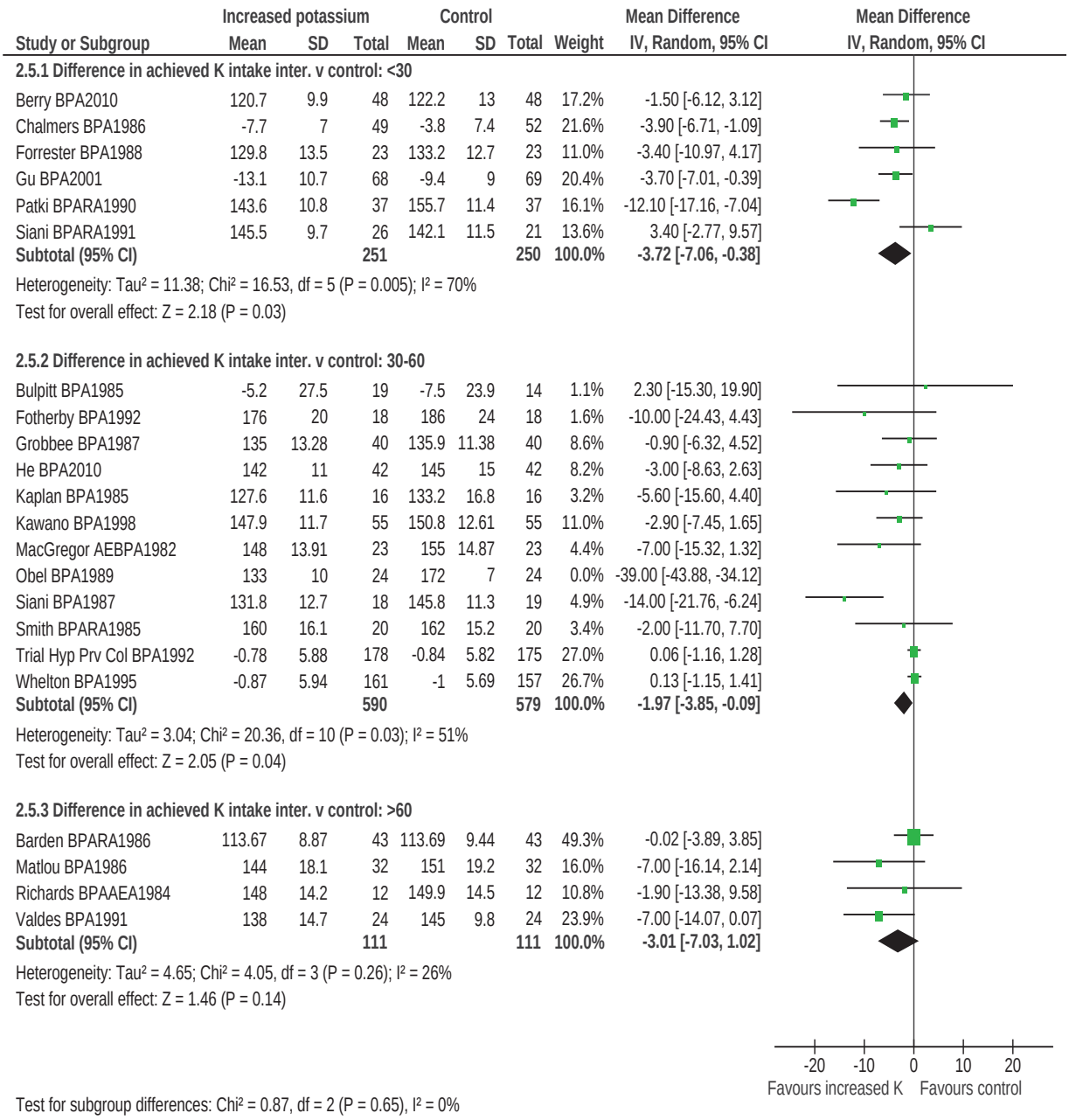


Figure 3.4 Resting systolic blood pressure – achieved intake subgroups (based on urinary potassium excretion*)



* Urinary potassium excretion is a common, valid form of estimating potassium intake. A factor of 1.30 is used to convert urinary potassium excretion to potassium intake (Stamler et al., 2003).

Figure 3.5 Resting systolic blood pressure – achieved difference subgroups (based on urinary potassium excretion*)



* Urinary potassium excretion is a common, valid form of estimating potassium intake. A factor of 1.30 is used to convert urinary potassium excretion to potassium intake (Stamler et al., 2003).

Figure 3.6 Resting diastolic blood pressure – all adults

Study or Subgroup	Increased potassium Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Barden BPARA1986	68.02	7.24	43	71.67	9.68	43	5.4%	-3.65 [-7.26, -0.04]
Berry BPA2010	76.6	6.54	48	76.9	7.5	48	5.9%	-0.30 [-3.12, 2.52]
Bulpitt BPA1985	0.5	11.8	19	-4.3	11.2	14	3.0%	4.80 [-3.11, 12.71]
Chalmers BPA1986	-4.7	4.2	49	-1.6	4.5	52	6.5%	-3.10 [-4.80, -1.40]
Forrester BPA1988	87.7	12.1	23	92.3	9.2	23	3.8%	-4.60 [-10.81, 1.61]
Fotherby BPA1992	94	20	18	100	14	18	1.9%	-6.00 [-17.28, 5.28]
Grobbee BPA1987	71.6	10.75	40	73.7	9.49	40	4.9%	-2.10 [-6.54, 2.34]
Gu BPA2001	-3.8	6.2	68	-3.7	6	69	6.4%	-0.10 [-2.14, 1.94]
He BPA2010	90	9	42	91	9	42	5.3%	-1.00 [-4.85, 2.85]
Kaplan BPA1985	91.9	7.6	16	97.7	7.6	16	4.4%	-5.80 [-11.07, -0.53]
Kawano BPA1998	86.8	8.16	55	88.1	9.64	55	5.6%	-1.30 [-4.64, 2.04]
MacGregor AEBPA1982	95	7.67	23	99	8.15	23	4.8%	-4.00 [-8.57, 0.57]
Matlou BPA1986	144	18.1	32	151	19.2	32	2.5%	-7.00 [-16.14, 2.14]
Obel BPA1989	83	4	24	100	4	24	0.0%	-17.00 [-19.26, -14.74]
Patki BPARA1990	84.5	3.5	37	97.6	5.4	37	6.4%	-13.10 [-15.17, -11.03]
Richards BPAAEA1984	91.4	11.4	12	92.4	12.1	12	2.4%	-1.00 [-10.41, 8.41]
Siani BPA1987	82	8.9	18	92.5	8.7	19	4.1%	-10.50 [-16.18, -4.82]
Siani BPARA1991	84.2	6.6	26	83.1	9.2	21	4.8%	1.10 [-3.58, 5.78]
Smith BPARA1985	103	8.94	20	103	10.73	20	3.9%	0.00 [-6.12, 6.12]
Trial Hyp Prv Col BPA1992	-0.27	4.56	161	0.14	4.64	157	6.8%	-0.41 [-1.42, 0.60]
Valdes BPA1991	89	9.8	24	92	9.8	24	4.2%	-3.00 [-8.54, 2.54]
Whelton BPA1995	-0.29	4.68	161	-0.03	4.5	157	6.8%	-0.26 [-1.27, 0.75]
Total (95% CI)			**935**			**922**	**100.0%**	**-2.84 [-4.66, -1.01]**

Heterogeneity: Tau² = 12.50; Chi² = 156.94, df = 20 (P < 0.00001); I² = 87%

Test for overall effect: Z = 3.05 (P = 0.002)

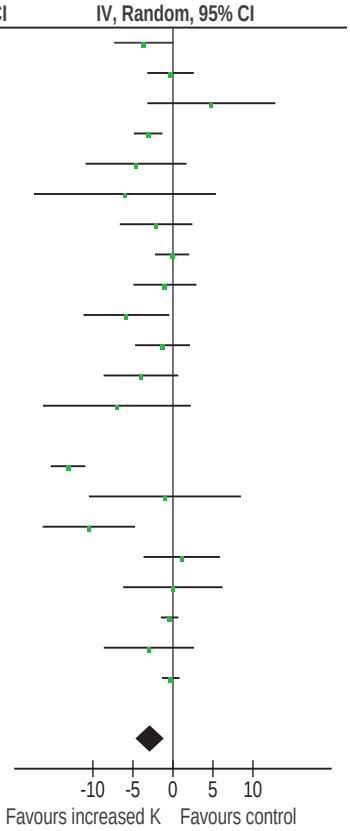


Figure 3.7 Resting diastolic blood pressure – blood pressure status subgroups

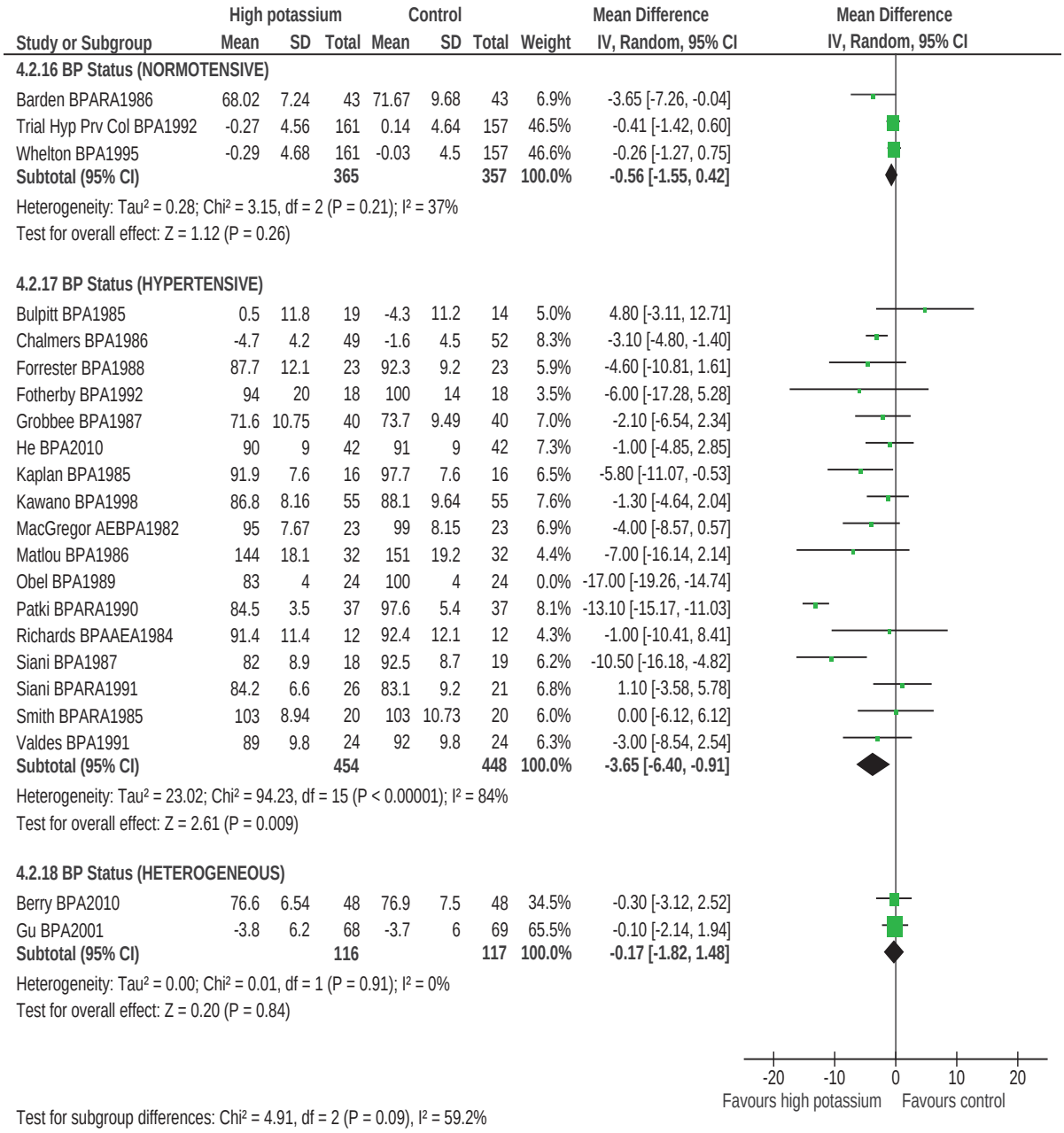
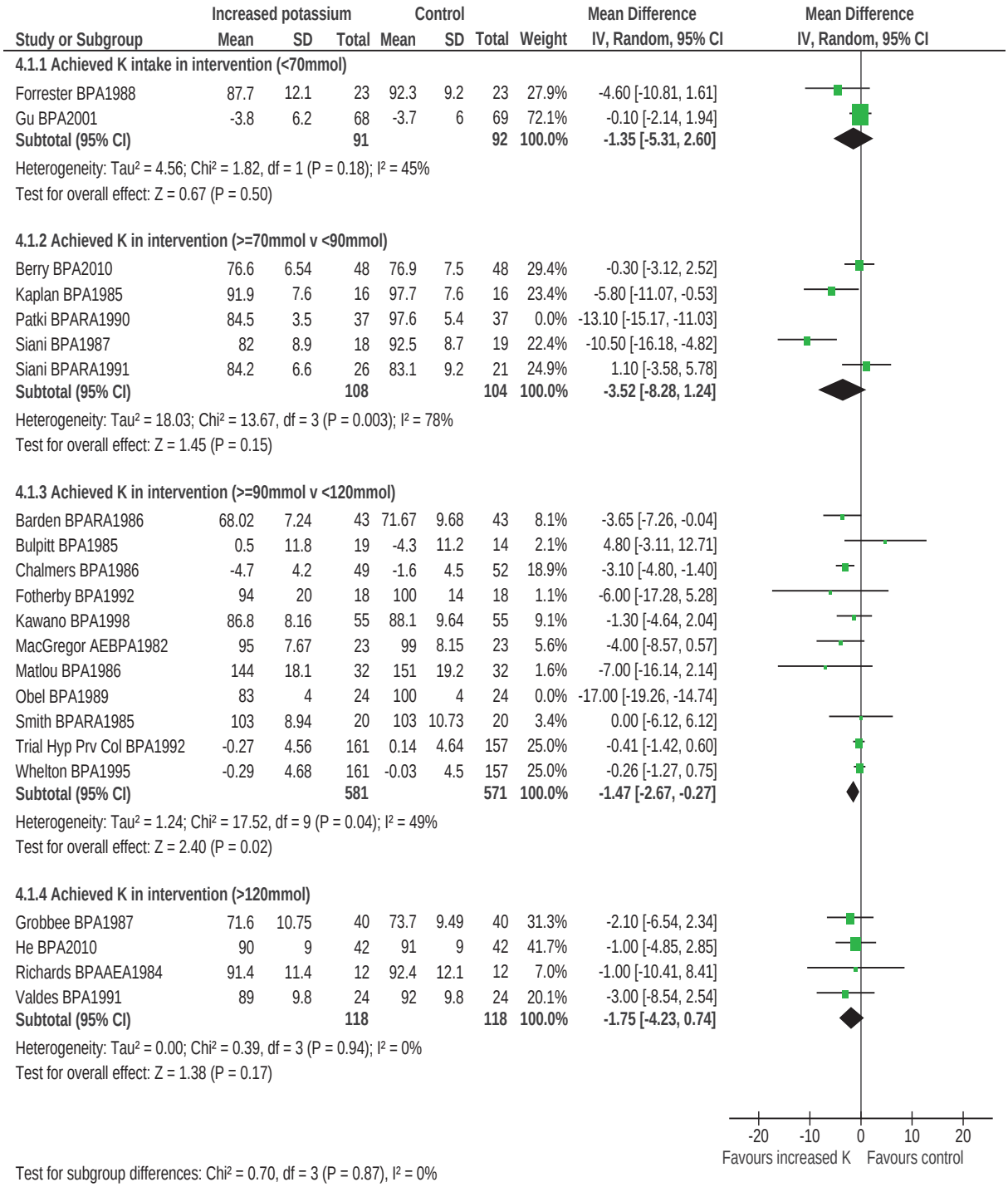
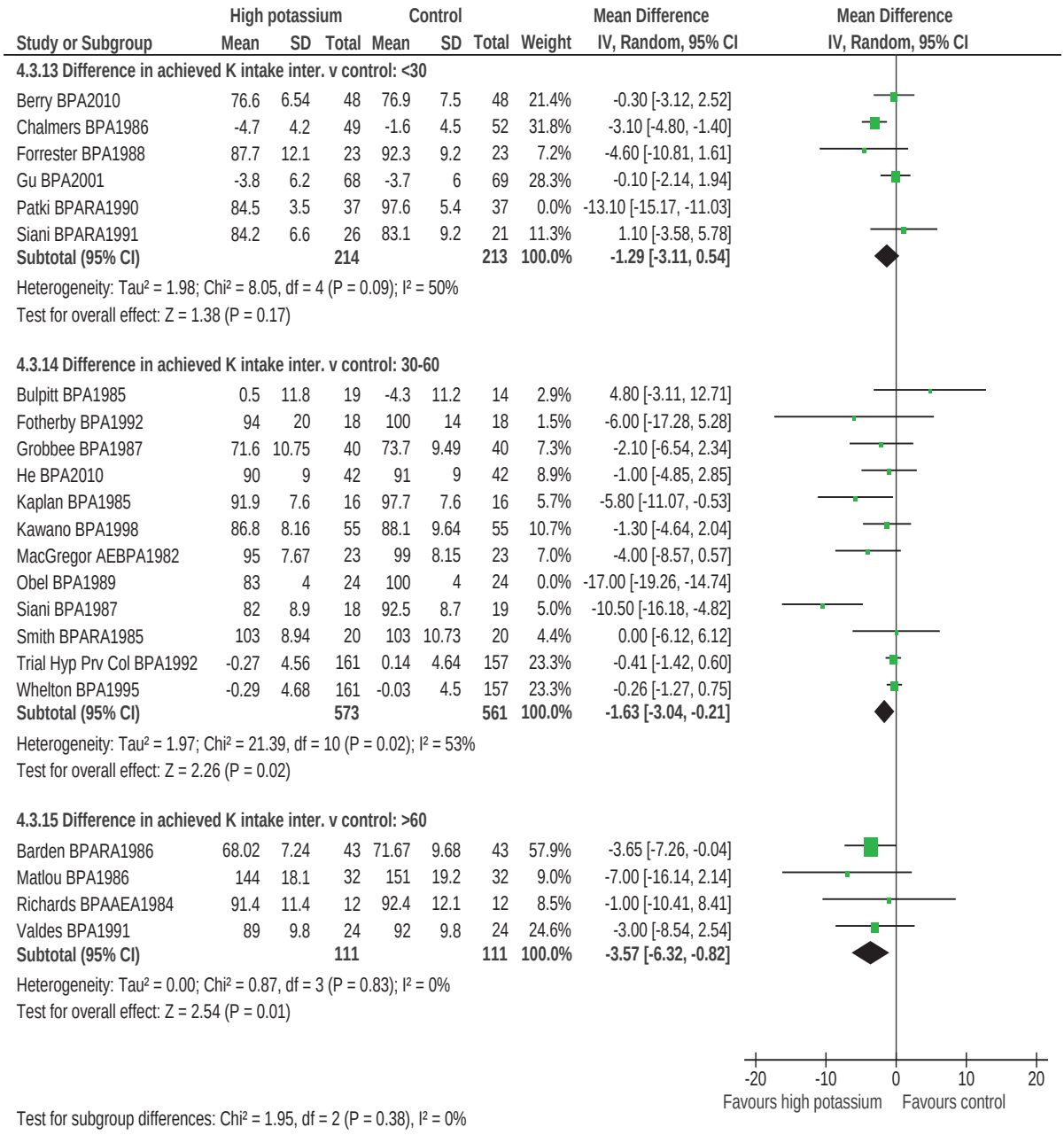


Figure 3.8 Resting diastolic blood pressure – achieved intake subgroups (based on urinary potassium excretion*)



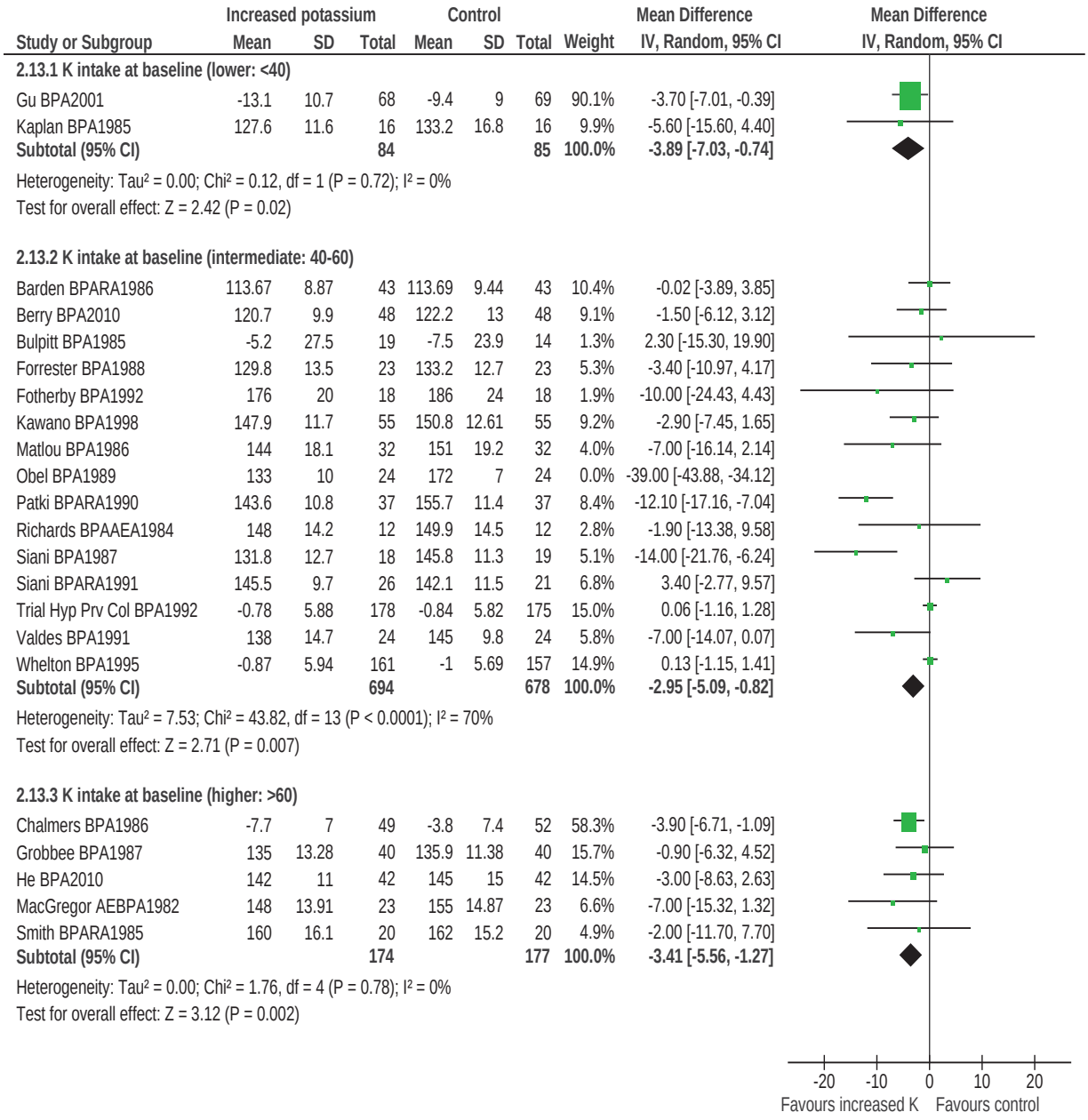
* Urinary potassium excretion is a common, valid form of estimating potassium intake. A factor of 1.30 is used to convert urinary potassium excretion to potassium intake (Stamler et al., 2003).

Figure 3.9 Resting diastolic blood pressure – achieved difference subgroups (based on urinary potassium excretion*)



* Urinary potassium excretion is a common, valid form of estimating potassium intake. A factor of 1.30 is used to convert urinary potassium excretion to potassium intake (Stamler et al., 2003).

Figure 3.10 Resting systolic blood pressure – baseline potassium subgroups (based on urinary potassium excretion*)



Test for subgroup differences: Chi² = 0.25, df = 2 (P = 0.88), I² = 0%

* Urinary potassium excretion is a common, valid form of estimating potassium intake. A factor of 1.30 is used to convert urinary potassium excretion to potassium intake (Stamler et al., 2003).

Figure 3.11 Resting systolic blood pressure – baseline sodium subgroups

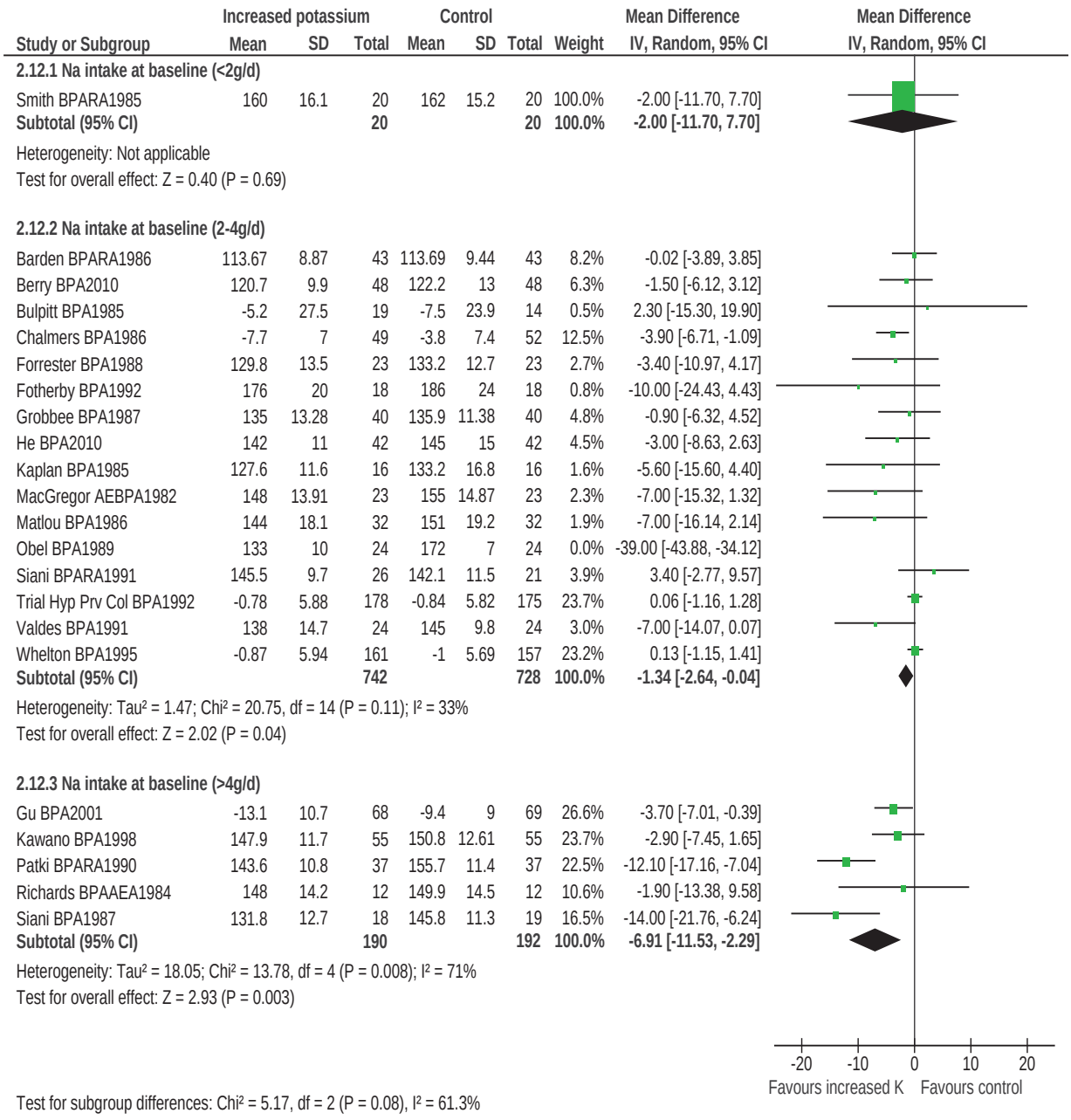


Figure 3.12 Resting systolic blood pressure – duration subgroups

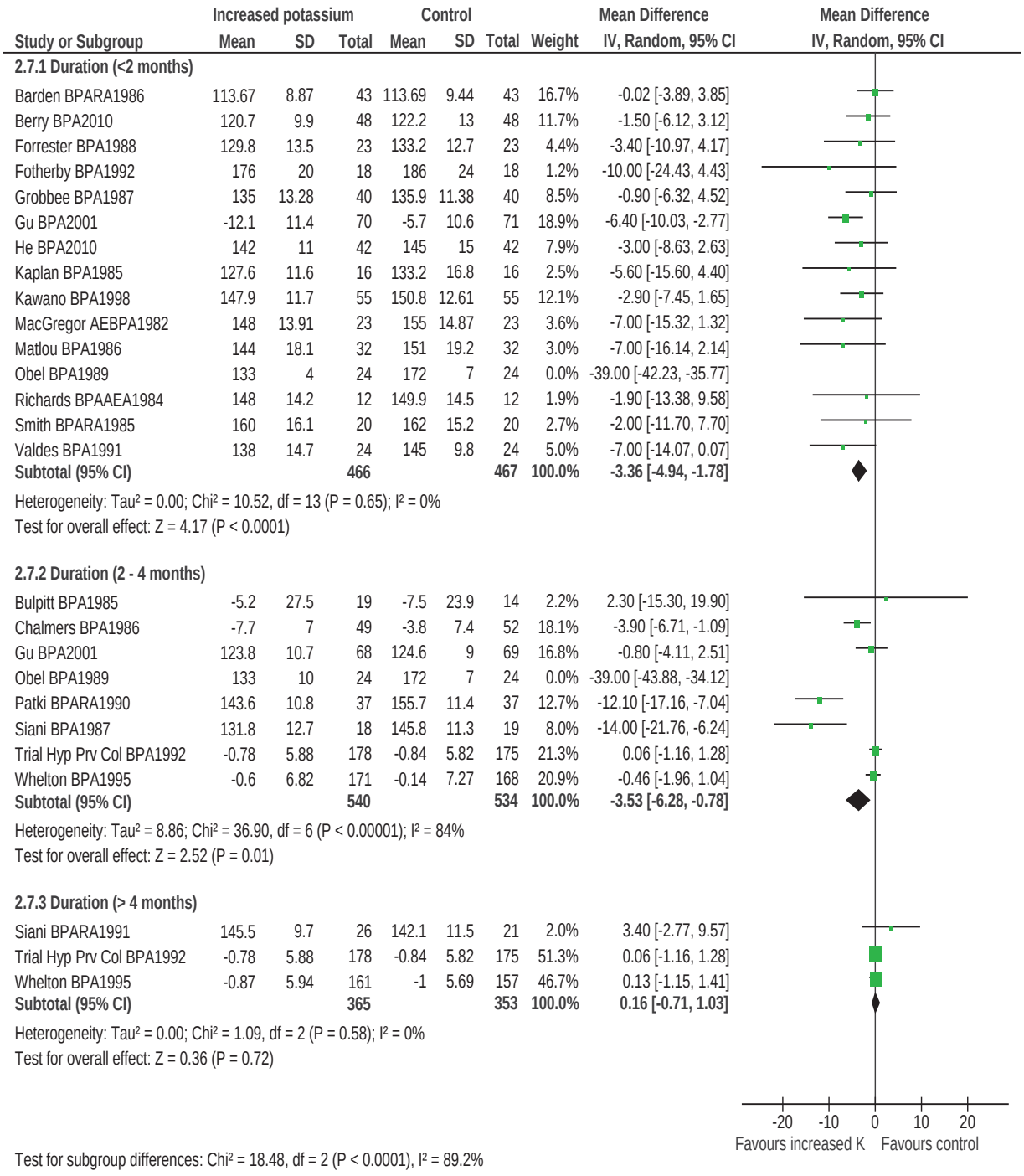
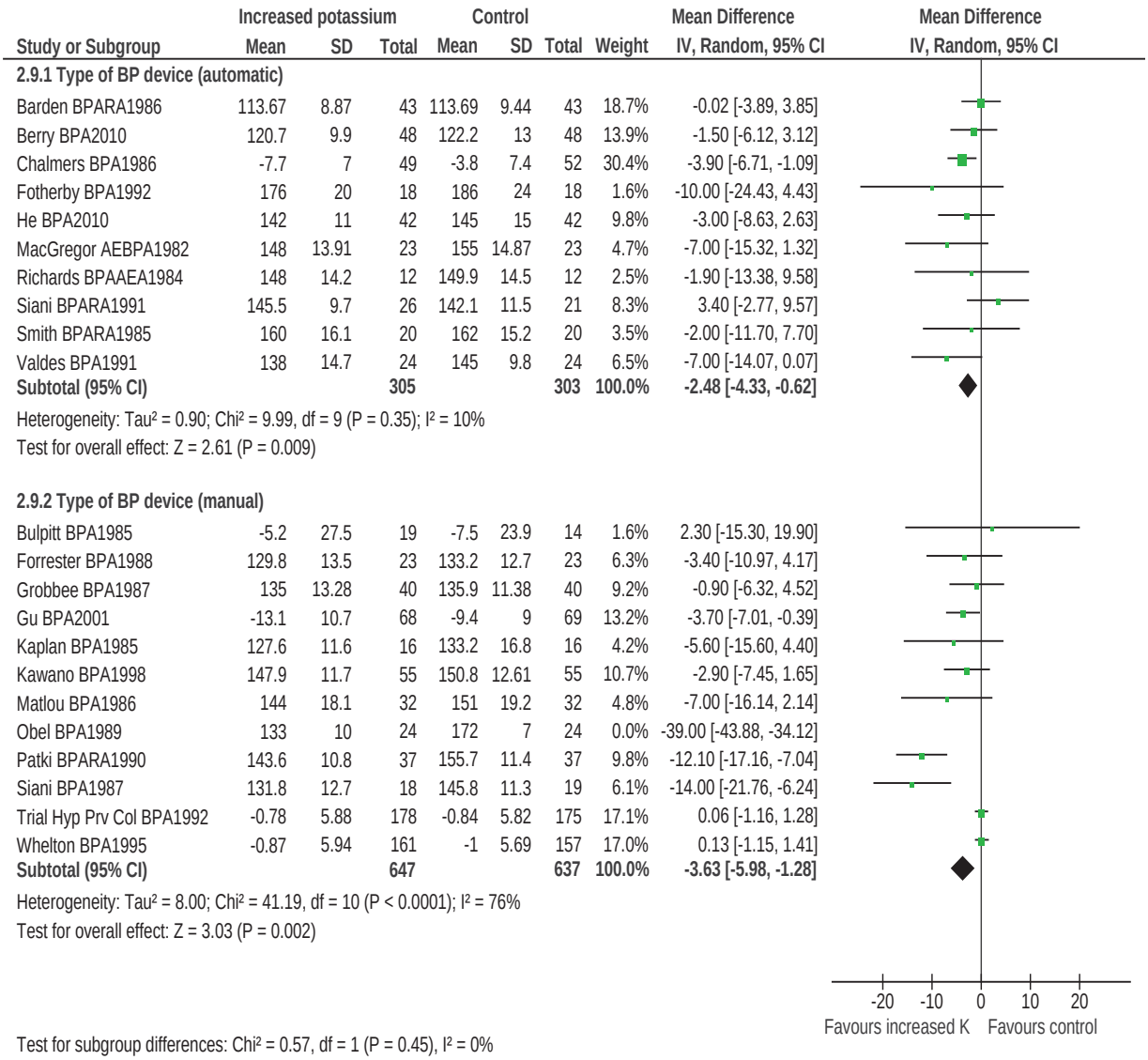


Figure 3.13 Resting systolic blood pressure – device subgroups



Test for subgroup differences: Chi² = 0.57, df = 1 (P = 0.45), I² = 0%

Figure 3.14 Resting systolic blood pressure – method subgroups

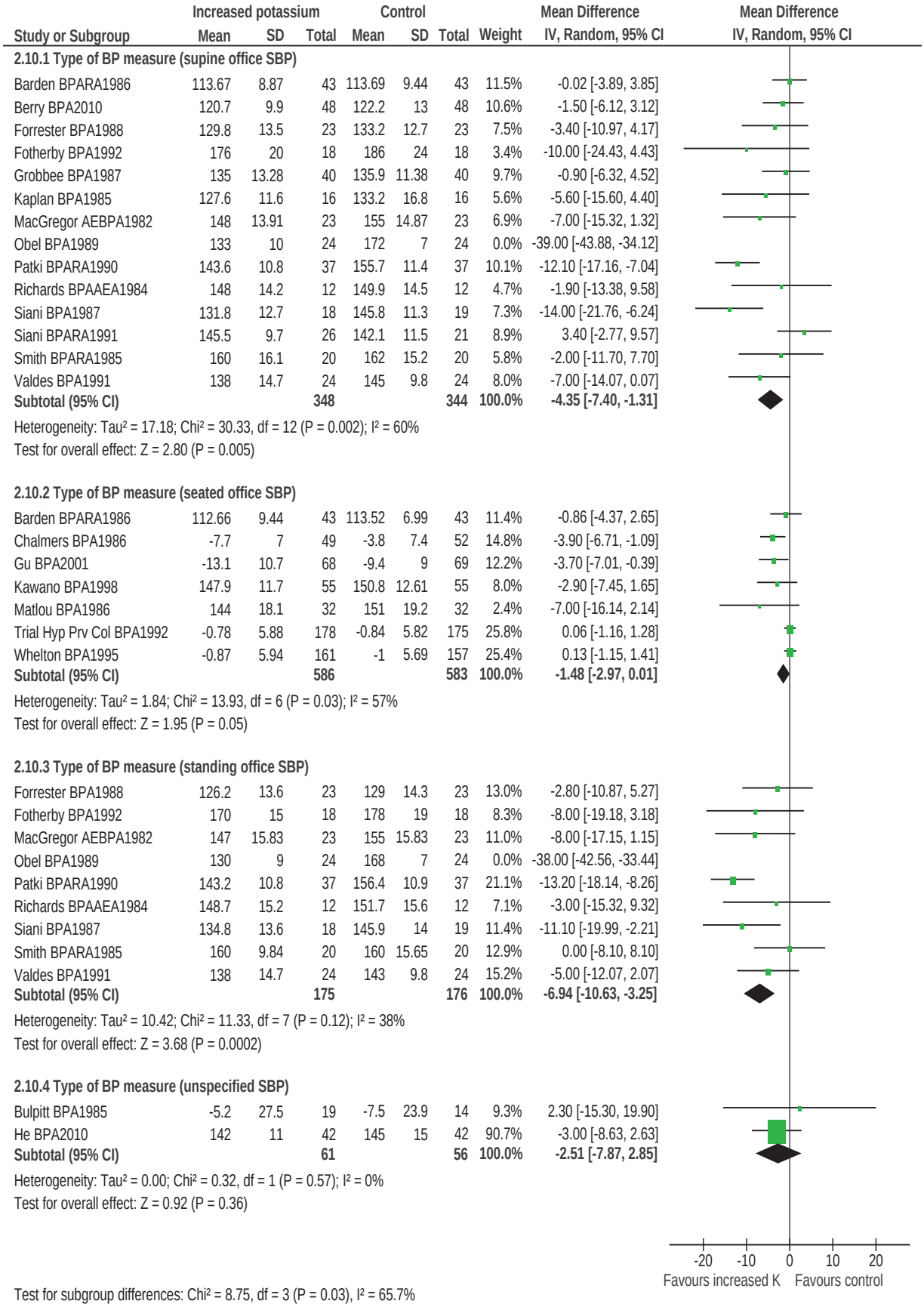


Figure 3.15 Resting systolic blood pressure – medication status subgroups

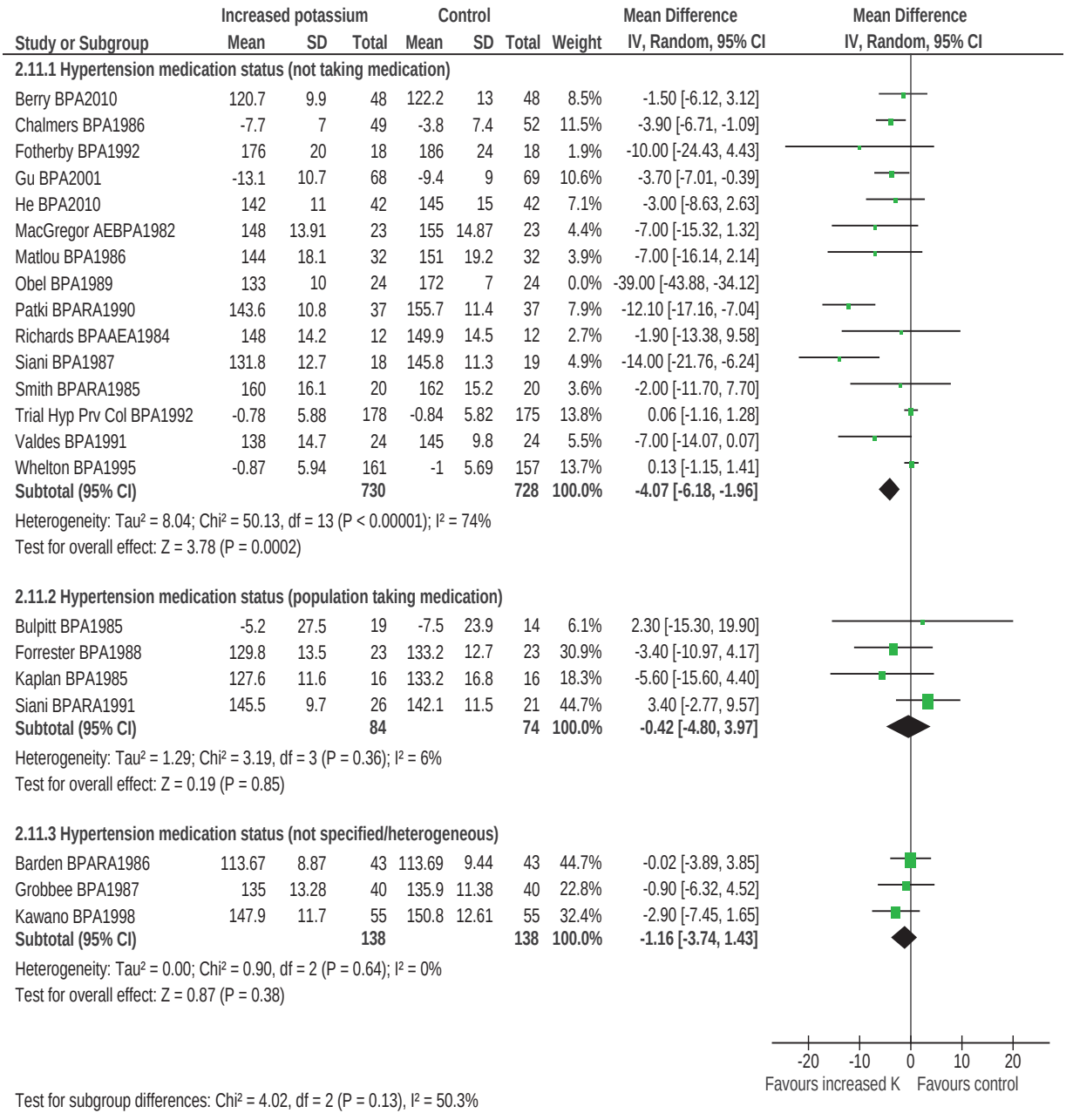
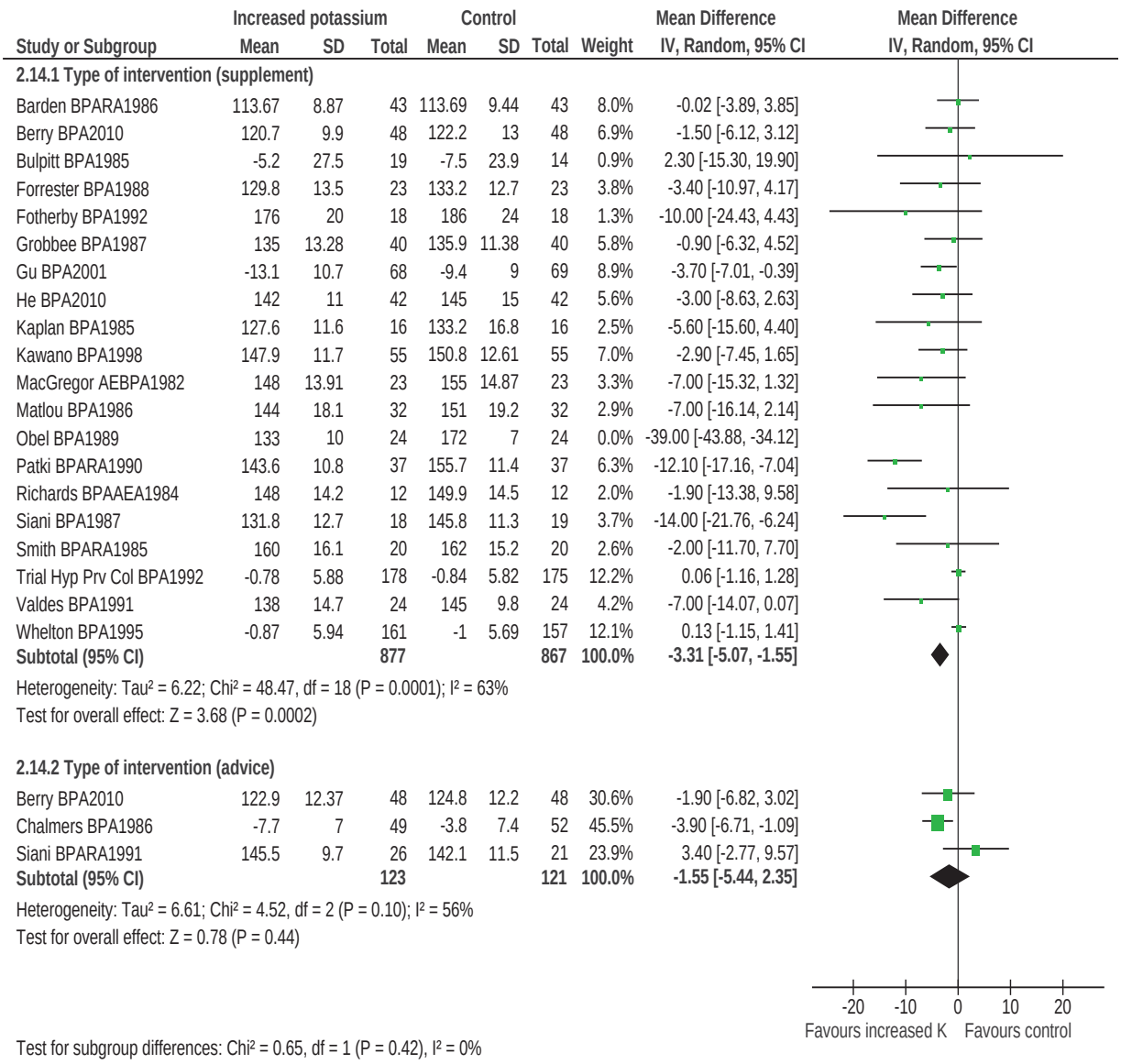


Figure 3.16 Resting systolic blood pressure – type of intervention subgroups



Test for subgroup differences: Chi² = 0.65, df = 1 (P = 0.42), I² = 0%

Figure 3.17 Resting systolic blood pressure – trial design subgroups

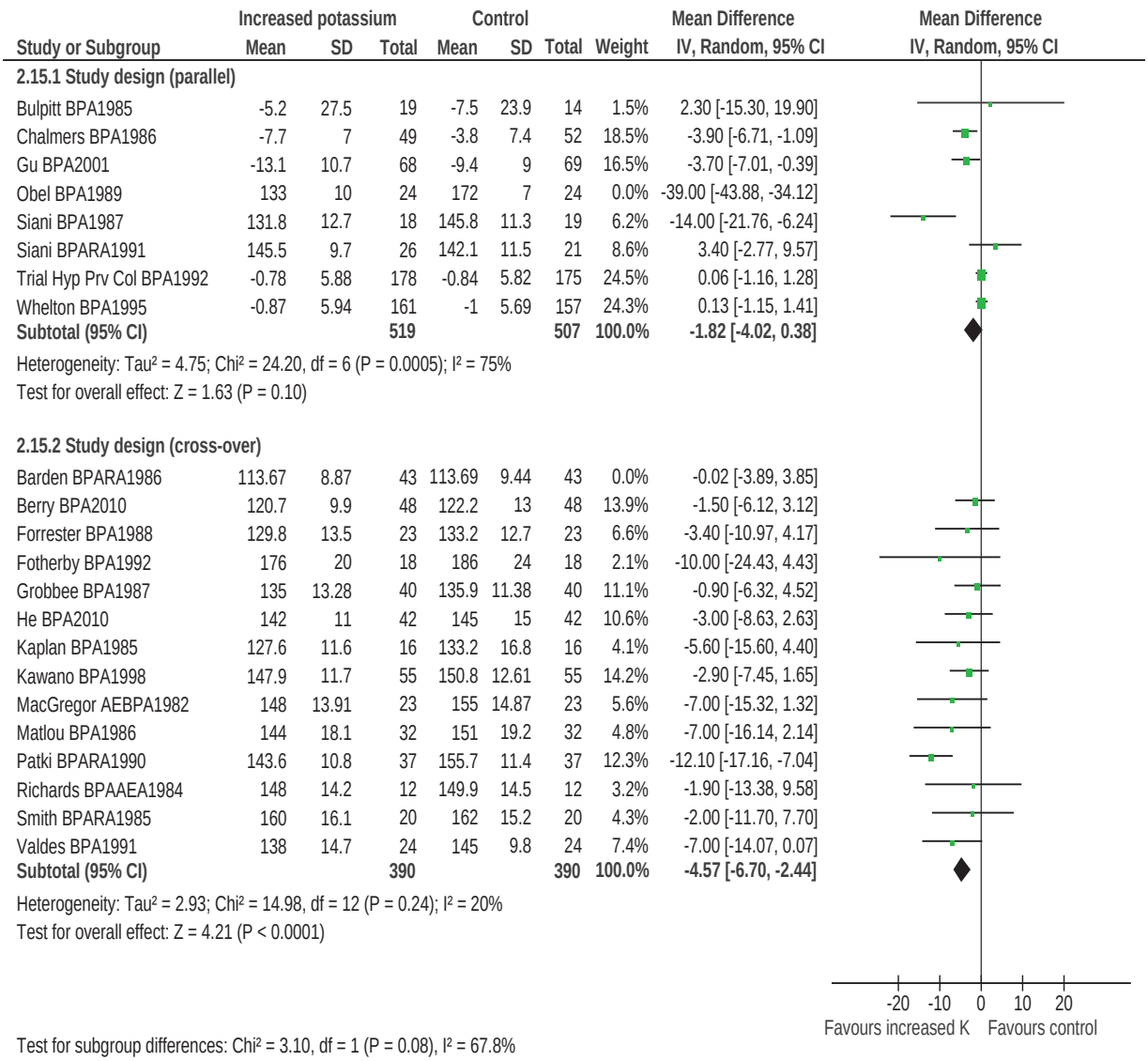


Figure 3.18 Ambulatory systolic blood pressure – all adults

	Increased potassium			Control				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Berry BPA2010	132.3	12	48	134.1	14	48	20.9%	-1.80 [-7.02, 3.42]	
Fotherby BPA1992	154	15	16	160	18	16	4.3%	-6.00 [-17.48, 5.48]	
He BPA2010	139	9	42	142	10	42	34.3%	-3.00 [-7.07, 1.07]	
Kawano BPA1998	133.9	10.4	55	137.3	9.64	55	40.5%	-3.40 [-7.15, 0.35]	
Total (95% CI)			**161**			**161**	**100.0%**	**-3.04 [-5.42, -0.66]**	

Heterogeneity: Tau² = 0.00; Chi² = 0.51, df = 3 (P = 0.92); I² = 0%

Test for overall effect: Z = 2.50 (P = 0.01)

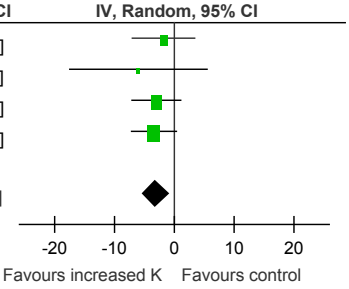


Figure 3.19 Ambulatory diastolic blood pressure – all adults

	Increased potassium			Control				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Berry BPA2010	81.9	10.6	48	83.3	7.9	48	25.7%	-1.40 [-5.14, 2.34]	
Fotherby BPA1992	87	13	16	89	12	16	4.8%	-2.00 [-10.67, 6.67]	
He BPA2010	87	8	42	88	9	42	27.1%	-1.00 [-4.64, 2.64]	
Kawano BPA1998	80.1	8.16	55	81.3	7.42	55	42.4%	-1.20 [-4.11, 1.71]	
Total (95% CI)			**161**			**161**	**100.0%**	**-1.24 [-3.13, 0.66]**	

Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 3 (P = 1.00); I² = 0%

Test for overall effect: Z = 1.28 (P = 0.20)

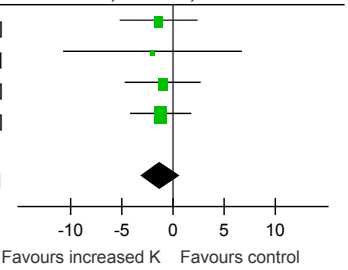
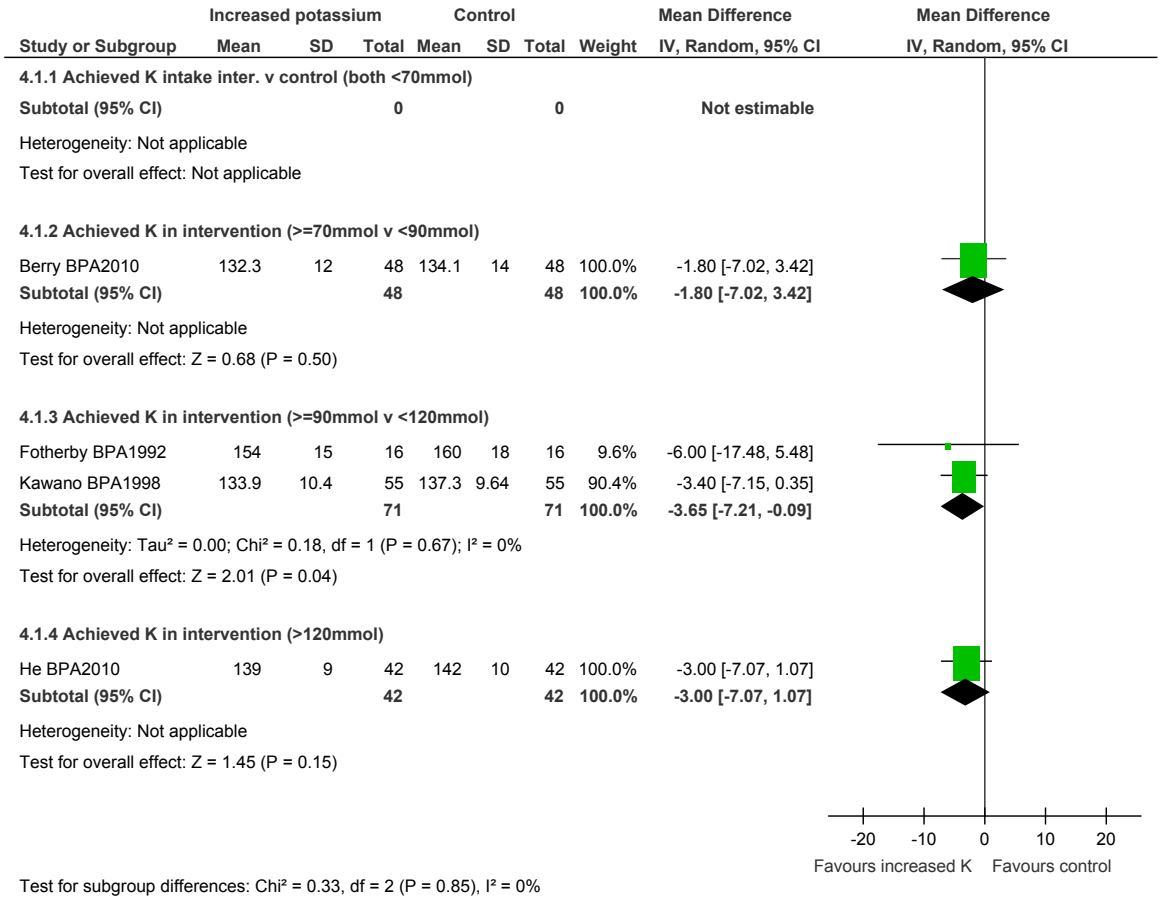


Figure 3.20 Ambulatory systolic blood pressure – achieved intake subgroups (based on urinary potassium excretion*)



* Urinary potassium excretion is a common, valid form of estimating potassium intake. A factor of 1.30 is used to convert urinary potassium excretion to potassium intake (Stamler et al., 2003).

Figure 3.21 Total cholesterol – all adults

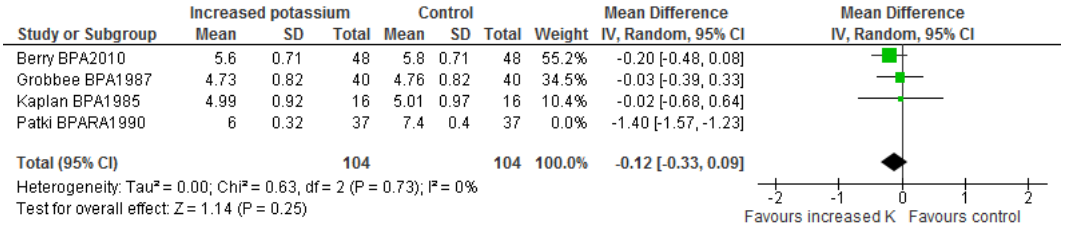


Figure 3.22 HDL cholesterol – all adults

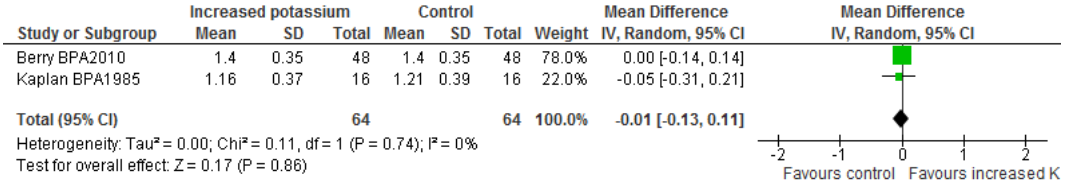


Figure 3.23 LDL cholesterol – all adults

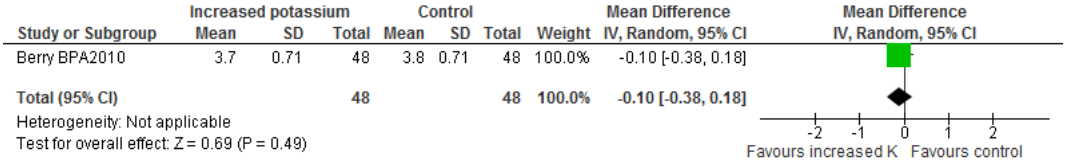


Figure 3.24 Total triglycerides – all adults

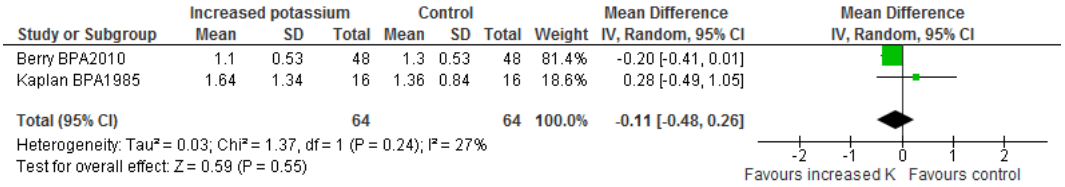


Figure 3.25 Plasma adrenaline – all adults

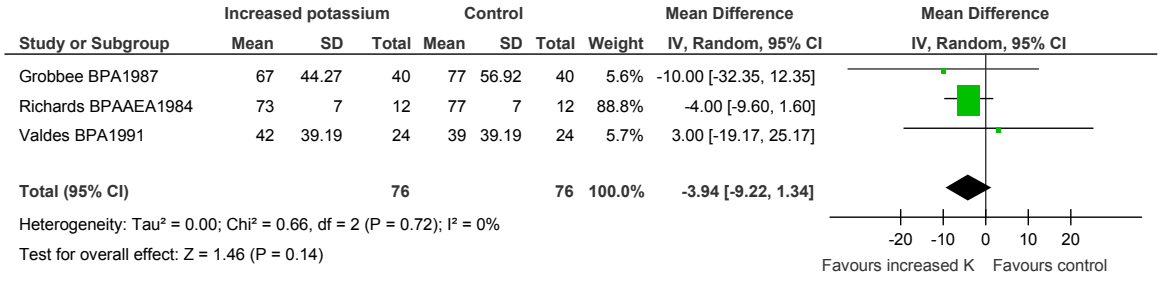


Figure 3.26 Plasma noradrenaline – all adults

Study or Subgroup	Increased potassium Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Grobbee BPA1987	225	132.82	40	239	120.17	40	12.3%	-14.00 [-69.51, 41.51]
Richards BPAAEA1984	404	28	12	405	28	12	75.4%	-1.00 [-23.40, 21.40]
Valdes BPA1991	203	97.98	24	218	97.98	24	12.3%	-15.00 [-70.44, 40.44]
Total (95% CI)			**76**			**76**	**100.0%**	**-4.32 [-23.78, 15.13]**

Heterogeneity: Tau² = 0.00; Chi² = 0.34, df = 2 (P = 0.84); I² = 0%

Test for overall effect: Z = 0.44 (P = 0.66)

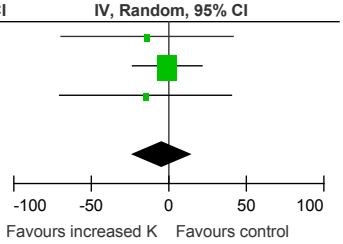
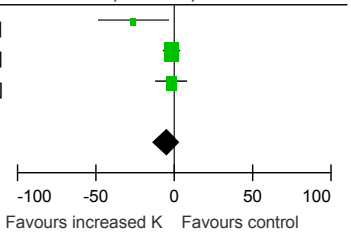


Figure 3.27 Serum creatinine – all adults

Study or Subgroup	Increased potassium Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bulpitt BPA1985	84	18.7	19	110	39.2	14	12.4%	-26.00 [-48.19, -3.81]
Patki BPARA1990	73.38	6.96	37	75.14	14.15	37	52.1%	-1.76 [-6.84, 3.32]
Smith BPARA1985	89	16.99	20	91	14.31	20	35.4%	-2.00 [-11.74, 7.74]
Total (95% CI)			**76**			**71**	**100.0%**	**-4.86 [-13.59, 3.87]**

Heterogeneity: Tau² = 31.33; Chi² = 4.39, df = 2 (P = 0.11); I² = 54%

Test for overall effect: Z = 1.09 (P = 0.28)



4 References to studies

An asterisk indicates that a reference is the primary reference for a study.

4.1 Included studies

Barden BPARA1986

* Barden A, Vandongen R, Beilin LJ. Increases in urinary kallikrein activity and prostanoid synthesis after dietary potassium supplementation. *Clinical and Experimental Pharmacology and Physiology,* 1987, 14:565–572.

Barden AE, Vandongen R, Beilin LJ et al. Potassium supplementation does not lower blood pressure in normotensive women. *Journal of Hypertension,* 1986, 4:339–343.

Berry BPA2010

* Berry SE, Mulla UZ, Chowienczyk PJ et al. Increased potassium intake from fruit and vegetables or supplements does not lower blood pressure or improve vascular function in UK men and women with early hypertension: a randomised controlled trial. *British Journal of Nutrition,* 2010, 104:1839–1847.

Bulpitt BPA1985

Bulpitt CJ, Ferrier G, Lewis PJ et al. Potassium supplementation fails to lower blood pressure in hypertensive patients receiving a potassium losing diuretic. *Annals of Clinical Research,* 1985, 17:126–130.

Chalmers BPA1986

* Chalmers J, Morgan T, Doyle A et al. Australian National Health and Medical Research Council dietary salt study in mild hypertension. *Journal of Hypertension – Supplement,* 1986, 4:S629–S637.

Forrester BPA1988

Forrester TE, Grell GA. Changes in red cell sodium content and blood pressure levels with potassium supplementation in black hypertensive patients. *West Indian Medical Journal,* 1988, 37:92–96.

Fotherby BPA1992

Fotherby MD, Potter JF. Long-term potassium supplementation lowers blood pressure in elderly hypertensive subjects. *International Journal of Clinical Practice,* 1997, 51:219–222.

* Fotherby MD, Potter JF. Potassium supplementation reduces clinic and ambulatory blood pressure in elderly hypertensive patients. *Journal of Hypertension,* 1992, 10:1403–1408.

Grobbee BPA1987

Grobbee DE, Hofman A, Roelandt JT et al. Sodium restriction and potassium supplementation in young people with mildly elevated blood pressure. *Journal of Hypertension,* 1987, 5:115–119.

Gu BPA2001

* Gu D, He J, Wu X et al. Effect of potassium supplementation on blood pressure in Chinese: a randomized, placebo-controlled trial. *Journal of Hypertension,* 2001, 19:1325–1331.

He BPA2010

Effect of potassium bicarbonate and potassium chloride on blood pressure and markers of target organ damage in hypertensives. Clinicaltrials.gov. [Other: NCT00160368]

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Annex 1: Electronic search strategy

A1.1 Overview

For each outcome, two EMBASE searches were conducted: one broad search according to the original protocol and another, more restrictive, search using more specific terms for each concept and an indexer limit for controlled trials. This strategy was supplied by the WHO librarian to facilitate data retrieval.

MEDLINE was searched through the PubMed database for the previous 6 months only, because all references in MEDLINE are also found in EMBASE. EMBASE requires more time to update its database and, therefore, it is possible that some very recent studies could be captured in a PubMed search that would not be captured in EMBASE. All other databases were searched without any date limits. All electronic searches were first run to search for RCTs.

A1.2 Search for randomized controlled trials

A1.2.1 EMBASE searches

Searches conducted on 25 August 2011 in EMBASE version available at http://www.embase.com.
Note EMBASE.COM contains over 24 million indexed records and more than 7500 current, mostly peer-reviewed journals with over 2000 biomedical titles not currently offered by MEDLINE. MEDLINE citations are included in EMBASE.

1) Blood pressure

No language limits; dates needed: Jan 1 2004 to present.

Restricted search

Step	Search terms
Step 1	'potassium'/exp OR 'potassium chloride'/exp
Step 2	('hypertension'/exp OR 'blood pressure'/exp) AND ([cochrane review]/lim OR [controlled clinical trial]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR [systematic review]/lim) AND [2004–2012]/py
Step 3	'dietary intake'/exp OR 'diet'/exp OR restrict*:ab,ti OR reduce*:ab,ti OR 'reduction'/exp OR intake:ab,ti OR diet:ab,ti OR dietary:ab,ti AND [2004–2012]/py
Step 4	Step 1 AND Step 2 AND Step 3

Broader search

Step	Search terms
Step 1	'potassium'/exp OR 'potassium' OR 'potassium chloride'/exp OR 'potassium chloride' OR potassium:ab,ti
Step 2	'hypertension'/exp OR 'blood pressure'/exp OR 'hypertension'/exp OR 'blood pressure':ab,ti OR hypertensive:ab,ti OR 'blood pressure'/exp OR 'intravascular pressure':ab,ti OR normotension:ab,ti OR 'vascular pressure':ab,ti OR 'blood pressure monitoring'/exp
Step 3	'dietary intake'/exp OR 'diet'/exp OR restrict*:ab,ti OR reduce*:ab,ti OR 'reduction'/exp OR intake:ab,ti OR diet:ab,ti OR dietary:ab,ti AND [2004–2012]/py
Step 4	Step 1 AND Step 2 AND Step 3
Step 5	'randomized controlled trial'/exp OR 'controlled trial':ab,ti OR 'randomized':ab,ti OR 'randomised':ab,ti OR placebo:ab,ti OR randomly:ab,ti OR trial:ab,ti
Step 6	Step 4 AND Step 5
Step 7	Step 4 AND ([cochrane review]/lim OR [controlled clinical trial]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR [systematic review]/lim)
Step 8	Step 6 OR Step 7
Step 9	Step 8 NOT [animals]/lim
Step 10	Step 8 AND [animals]/lim AND [humans]/lim
Step 11	Step 9 OR Step 10
Step 12	Step 11 NOT (Citations found in Restricted Search Step 4)

2) Adverse effects

No language limits; no date limits.

Restricted search

Step	Search terms
Step 1	'potassium'/exp OR 'potassium chloride'/exp
Step 2	'noradrenalin'/exp OR 'adrenor':ab,ti OR 'alginodia':ab,ti OR 'arterenal':ab,ti OR 'arterenol':ab,ti OR 'baycain green':ab,ti OR 'd noradrenalin':ab,ti OR 'dextro noradrenalin':ab,ti OR 'dextro noradrenaline':ab,ti OR 'dl arterenol':ab,ti OR 'dl noradrenalin':ab,ti OR 'dl noradrenalin hydrochloride':ab,ti OR 'l alpha aminomethyl 3, 4 dihydroxybenzyl alcohol':ab,ti OR 'l noradrenalin':ab,ti OR 'l noradrenalin hydrochloride':ab,ti OR 'l noradrenaline':ab,ti OR 'l norepinephrine':ab,ti OR 'levarterenol':ab,ti OR 'levo noradrenalin':ab,ti OR 'levo noradrenaline':ab,ti OR 'levo norepinephrine':ab,ti OR 'levonor':ab,ti OR 'levophed':ab,ti OR 'neomelubrin':ab,ti OR 'neurogenic noradrenalin':ab,ti OR 'noradrec':ab,ti OR 'noradrenalin hydrochloride':ab,ti OR 'noradrenalin reduction':ab,ti OR 'noradrenaline':ab,ti OR 'noradrine':ab,ti OR 'norepinephrin':ab,ti OR 'norepinephrine':ab,ti OR 'norepinephrine hydrochloride':ab,ti OR 'norexadrin':ab,ti OR 'revarterenol':ab,ti OR 'sympathin':ab,ti OR 'sympathine':ab,ti OR 'catecholamine'/exp OR 'catechol amine; catecholamin':ab,ti OR 'catecholamines':ab,ti OR 'cathecholamine':ab,ti OR 'dextro pyrocatecholamine':ab,ti OR 'endogenous catecholamine':ab,ti OR 'pyrocatechinamine':ab,ti OR 'pyrocatecholamine':ab,ti OR 'hydroxy 5 cholestene':ab,ti OR '3beta hydroxy 5 cholestene':ab,ti OR '3beta hydroxycholest 5 ene':ab,ti OR '5 cholesten 3beta ol':ab,ti OR 'beta cholesterol':ab,ti OR 'cholest 5 en 3beta ol':ab,ti OR 'cholest 5 ene 3 ol':ab,ti OR 'cholesterin':ab,ti OR 'cholesterine':ab,ti OR 'cholesterol release':ab,ti OR 'dythol':ab,ti OR 'nsc 8798':ab,ti OR 'cholesterol'/exp OR 'riacylglycerol' OR 'acylglycerol, tri':ab,ti OR 'fatty acid triglyceride':ab,ti OR 'triacyl glyceride':ab,ti OR 'triglyceride':ab,ti OR 'triglycerides':ab,ti OR 'tryglyceride':ab,ti OR 'beta lipoprotein':ab,ti OR 'ldl':ab,ti OR 'lipoprotein, beta':ab,ti OR 'lipoprotein, low density':ab,ti OR 'lipoproteins, ldl'/exp OR 'low density lipoprotein'/exp OR 'lpha 7 lipoprotein':ab,ti OR 'alpha lipoprotein':ab,ti OR 'hdl':ab,ti OR 'high density lipoprotein phospholipid':ab,ti OR 'lipoprotein, alpha':ab,ti OR 'lipoprotein, high density':ab,ti OR 'lipoproteins, hdl':ab,ti OR 'pre alpha lipoprotein':ab,ti OR 'very high density lipoprotein'/exp OR 'high density lipoprotein'/exp AND ([cochrane review]/lim OR [controlled clinical trial]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR [systematic review]/lim)
Step 3	Step 1 AND Step 2

Broader search

Step	Search terms
Step 1	'potassium'/exp OR 'potassium chloride'/exp OR potassium:ab,ti
Step 2	'noradrenalin'/exp OR 'adrenor':ab,ti OR 'alginodia':ab,ti OR 'arterenal':ab,ti OR 'arterenol':ab,ti OR 'baycain green':ab,ti OR 'd noradrenalin':ab,ti OR 'dextro noradrenalin':ab,ti OR 'dextro noradrenaline':ab,ti OR 'dl arterenol':ab,ti OR 'dl noradrenalin':ab,ti OR 'dl noradrenalin hydrochloride':ab,ti OR 'l alpha aminomethyl 3, 4 dihydroxybenzyl alcohol':ab,ti OR 'l noradrenalin':ab,ti OR 'l noradrenalin hydrochloride':ab,ti OR 'l noradrenaline':ab,ti OR 'l norepinephrine':ab,ti OR 'levarterenol':ab,ti OR 'levo noradrenalin':ab,ti OR 'levo noradrenaline':ab,ti OR 'levo norepinephrine':ab,ti OR 'levonor':ab,ti OR 'levophed':ab,ti OR 'neomelubrin':ab,ti OR 'neurogenic noradrenalin':ab,ti OR 'noradrec':ab,ti OR 'noradrenalin hydrochloride':ab,ti OR 'noradrenalin reduction':ab,ti OR 'noradrenaline':ab,ti OR 'noradrine':ab,ti OR 'norepinephrin':ab,ti OR 'norepinephrine':ab,ti OR 'norepinephrine hydrochloride':ab,ti OR 'norexadrin':ab,ti OR 'revarterenol':ab,ti OR 'sympathin':ab,ti OR 'sympathine':ab,ti OR 'catecholamine'/exp OR 'catechol amine; catecholamin':ab,ti OR 'catecholamines':ab,ti OR 'cathecholamine':ab,ti OR 'dextro pyrocatecholamine':ab,ti OR 'endogenous catecholamine':ab,ti OR 'pyrocatechinamine':ab,ti OR 'pyrocatecholamine':ab,ti OR 'hydroxy 5 cholestene':ab,ti OR '3beta hydroxy 5 cholestene':ab,ti OR '3beta hydroxycholest 5 ene':ab,ti OR '5 cholesten 3beta ol':ab,ti OR 'beta cholesterol':ab,ti OR 'cholest 5 en 3beta ol':ab,ti OR 'cholest 5 ene 3 ol':ab,ti OR 'cholesterin':ab,ti OR 'cholesterine':ab,ti OR 'cholesterol release':ab,ti OR 'dythol':ab,ti OR 'nsc 8798':ab,ti OR 'cholesterol'/exp OR 'riacylglycerol' OR 'acylglycerol, tri':ab,ti OR 'fatty acid triglyceride':ab,ti OR 'triacyl glyceride':ab,ti OR 'triglyceride':ab,ti OR 'triglycerides':ab,ti OR 'tryglyceride':ab,ti OR 'beta lipoprotein':ab,ti OR 'ldl':ab,ti OR 'lipoprotein, beta':ab,ti OR 'lipoprotein, low density':ab,ti OR 'lipoproteins, ldl'/exp OR 'low density lipoprotein'/exp OR 'lpha 7 lipoprotein':ab,ti OR 'alpha lipoprotein':ab,ti OR 'hdl':ab,ti OR 'high density lipoprotein phospholipid':ab,ti OR 'lipoprotein, alpha':ab,ti OR 'lipoprotein, high density':ab,ti OR 'lipoproteins, hdl':ab,ti OR 'pre alpha lipoprotein':ab,ti OR 'very high density lipoprotein'/exp OR 'high density lipoprotein'/exp
Step 3	'randomized controlled trial'/exp OR 'controlled trial':ab,ti OR 'randomized':ab,ti OR 'randomised':ab,ti OR placebo:ab,ti OR randomly:ab,ti OR trial:ab,ti
Step 4	Step 1 AND Step 2 AND Step 3
Step 5	Step 1 AND Step 2 AND ([cochrane review]/lim OR [controlled clinical trial]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR [systematic review]/lim)
Step 6	Step 4 OR Step 5
Step 7	Step 6 NOT [animals]/lim
Step 8	Step 6 AND [animals]/lim AND [humans]/lim
Step 9	Step 7 OR Step 8
Step 10	Step 9 NOT (Citations found in Restricted Search Step 3

3) Renal function

No language limits; no date limits

Restricted search

Step	Search terms
Step 1	'potassium'/exp OR 'potassium chloride'/exp
Step 2	'kidney diseases':ab,ti OR 'kidney disorder':ab,ti OR 'kidney pathology':ab,ti OR 'nephropathy':ab,ti OR 'perinephritis':ab,ti OR 'perirenal infection':ab,ti OR 'renal disease':ab,ti OR 'renal disorder':ab,ti OR 'unilateral kidney disease':ab,ti OR 'kidney disease'/exp OR renal:ab,ti OR 'analgesic'/exp AND nephropathy:ab,ti OR 'chronic kidney disease':ab,ti OR 'cystinuria':ab,ti OR 'diabetic nephropathy':ab,ti OR 'fabry disease':ab,ti OR 'gitelman syndrome':ab,ti OR 'glomerulopathy':ab,ti OR 'gordon syndrome':ab,ti OR 'hepatorenal syndrome':ab,ti OR 'hiv associated nephropathy':ab,ti OR 'immunoglobulin a nephropathy':ab,ti OR 'kidney amyloidosis':ab,ti OR 'kidney calcification':ab,ti OR 'kidney colic':ab,ti OR 'kidney cyst':ab,ti OR 'kidney dysfunction':ab,ti OR 'kidney failure':ab,ti OR 'kidney fibrosis':ab,ti OR 'kidney hemorrhage':ab,ti OR 'kidney hypertrophy':ab,ti OR 'kidney infarction':ab,ti OR 'kidney infection':ab,ti OR 'kidney injury':ab,ti OR 'kidney ischemia':ab,ti OR 'kidney malformation':ab,ti OR 'kidney necrosis':ab,ti OR 'kidney pain':ab,ti OR 'kidney papilla necrosis':ab,ti OR 'kidney polycystic disease':ab,ti OR 'kidney rupture':ab,ti OR 'kidney scar':ab,ti OR 'kidney tubule acidosis':ab,ti OR 'kidney tubule damage':ab,ti OR 'kidney tubule disorder':ab,ti OR 'kidney tumor':ab,ti OR 'liddle syndrome':ab,ti OR 'lowe syndrome':ab,ti OR 'meckel syndrome':ab,ti OR 'medullary sponge kidney':ab,ti OR 'nephritis':ab,ti OR 'nephrogenic diabetes insipidus':ab,ti OR 'nephrolithiasis':ab,ti OR 'nephronophthisis':ab,ti OR 'nephrosis':ab,ti OR 'nephrotoxicity':ab,ti OR 'perirenal abscess':ab,ti OR 'prune belly syndrome':ab,ti OR 'pyelectasis':ab,ti OR 'reflux nephropathy':ab,ti OR 'renal diabetes':ab,ti OR 'renal graft dysfunction':ab,ti OR 'renovascular disease':ab,ti OR 'silent kidney':ab,ti OR 'uric acid nephropathy':ab,ti OR 'kidney disease'/exp AND ([cochrane review]/lim OR [controlled clinical trial]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR [systematic review]/lim)
Step 3	Step 1 AND Step 2

Broader search

Step	Search terms
Step 1	'potassium'/exp OR 'potassium' OR 'potassium chloride'/exp OR 'potassium chloride' OR potassium:ab,ti
Step 2	'kidney diseases':ab,ti OR 'kidney disorder':ab,ti OR 'kidney pathology':ab,ti OR 'nephropathy':ab,ti OR 'perinephritis':ab,ti OR 'perirenal infection':ab,ti OR 'renal disease':ab,ti OR 'renal disorder':ab,ti OR 'unilateral kidney disease':ab,ti OR 'kidney disease'/exp OR renal:ab,ti OR 'analgesic'/exp AND nephropathy:ab,ti OR 'chronic kidney disease':ab,ti OR 'cystinuria':ab,ti OR 'diabetic nephropathy':ab,ti OR 'fabry disease':ab,ti OR 'gitelman syndrome':ab,ti OR 'glomerulopathy':ab,ti OR 'gordon syndrome':ab,ti OR 'hepatorenal syndrome':ab,ti OR 'hiv associated nephropathy':ab,ti OR 'immunoglobulin a nephropathy':ab,ti OR 'kidney amyloidosis':ab,ti OR 'kidney calcification':ab,ti OR 'kidney colic':ab,ti OR 'kidney cyst':ab,ti OR 'kidney dysfunction':ab,ti OR 'kidney failure':ab,ti OR 'kidney fibrosis':ab,ti OR 'kidney hemorrhage':ab,ti OR 'kidney hypertrophy':ab,ti OR 'kidney infarction':ab,ti OR 'kidney infection':ab,ti OR 'kidney injury':ab,ti OR 'kidney ischemia':ab,ti OR 'kidney malformation':ab,ti OR 'kidney necrosis':ab,ti OR 'kidney pain':ab,ti OR 'kidney papilla necrosis':ab,ti OR 'kidney polycystic disease':ab,ti OR 'kidney rupture':ab,ti OR 'kidney scar':ab,ti OR 'kidney tubule acidosis':ab,ti OR 'kidney tubule damage':ab,ti OR 'kidney tubule disorder':ab,ti OR 'kidney tumor':ab,ti OR 'liddle syndrome':ab,ti OR 'lowe syndrome':ab,ti OR 'meckel syndrome':ab,ti OR 'medullary sponge kidney':ab,ti OR 'nephritis':ab,ti OR 'nephrogenic diabetes insipidus':ab,ti OR 'nephrolithiasis':ab,ti OR 'nephronophthisis':ab,ti OR 'nephrosis':ab,ti OR 'nephrotoxicity':ab,ti OR 'perirenal abscess':ab,ti OR 'prune belly syndrome':ab,ti OR 'pyelectasis':ab,ti OR 'reflux nephropathy':ab,ti OR 'renal diabetes':ab,ti OR 'renal graft dysfunction':ab,ti OR 'renovascular disease':ab,ti OR 'silent kidney':ab,ti OR 'uric acid nephropathy':ab,ti OR 'kidney disease'/exp
Step 3	'randomized controlled trial'/exp OR 'controlled trial':ab,ti OR 'randomized':ab,ti OR 'randomised':ab,ti OR placebo:ab,ti OR randomly:ab,ti OR trial:ab,ti
Step 4	Step 1 AND Step 2 AND Step 3
Step 5	Step 1 AND Step 2 AND ([cochrane review]/lim OR [controlled clinical trial]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR [systematic review]/lim)
Step 6	Step 4 OR Step 5
Step 7	Step 6 NOT [animals]/lim
Step 8	Step 6 AND [animals]/lim AND [humans]/lim
Step 9	Step 7 OR Step 8
Step 10	'dietary intake'/exp OR 'diet'/exp OR restrict*:ab,ti OR reduce*:ab,ti OR reduction
Step 11	Step 9 AND Step 10
Step 12	Step 11 NOT (Citations found in Restricted Search Step 3

A1.2.2 PubMed searches

No language limits; date conducted: 28 Aug 2011; date limit: previous 180 days.

1) Blood pressure

(blood pressure[MeSH] OR hypertension[MeSH] OR blood pressure[tiab] OR hypertension[tiab]) AND (potassium[MeSH] OR potassium chloride[MeSH] OR potassium[tiab] OR potassium 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])

2) Adverse effects

(potassium[MeSH] OR potassium[tiab]) AND (noradrenaline[MeSH] OR norepinephrine[MeSH] OR noradrenaline[tiab] OR norepinephrine[tiab] OR catecholamine[MeSH] OR catecholamine[tiab] OR cholesterol[MeSH] OR triglycerides[MeSH] OR low density lipoprotein[MeSH] OR high density lipoprotein[MeSH] OR LDL[tiab] OR HDL[tiab] OR cholesterol[tiab] OR triglyceride[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])

3) Renal function

(potassium[MeSH] OR potassium[tiab]) AND (kidney disease[MeSH] OR renal[tiab]) AND (dietary[MeSH] OR diet[MeSH] OR diets[MeSH] OR restriction[MeSH] OR reduction[MeSH] OR reduce[MeSH] OR restrict[MeSH]) 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])

A1.2.3 LILACS searches

No language limits; date conducted: 01 Sept 2011; date limit: none

Query	Search
Blood pressure	potassium AND blood pressure potassium AND hypertension
Adverse effects	potassium AND noradrenaline potassium AND norepinephrine potassium AND catecholamine potassium AND lipoprotein potassium AND hdl potassium AND ldl potassium AND cholesterol potassium AND triglyceride
Renal disease	potassium AND renal

A1.2.4 WHO International Clinical Trials Registry Platform searches

No language limits; date conducted: 01 Sept 2011; date limit: none

Query	Search
Blood pressure	(potassium AND blood pressure) OR (potassium AND hypertension)
Adverse effects	(potassium and noradrenaline) OR (potassium and norepinephrine) OR (potassium and catecholamine) OR (potassium and lipoprotein) OR (potassium and hdl) OR (potassium and ldl) OR (potassium and cholesterol) OR (potassium and triglyceride)
Renal disease	potassium AND renal

A1.2.5 Cochrane Central Register of Controlled Trials searches

No language limits; date conducted: 06 Sept 2011; date limit: none

Query	Search
Blood pressure	((#1 OR #2 OR (blood AND pressure) OR hypertension) AND (#3 OR #4 OR potassium OR (potassium AND chloride)) AND (#5 OR diet OR dietary OR intake OR restriction OR reduction) AND ((randomized AND controlled AND trial) OR (controlled AND clinical AND trial) OR randomized OR placebo OR (drug AND therapy) OR randomly OR trial OR groups))*
Adverse effects	((#3 OR #4 OR potassium OR (potassium AND chloride)) AND (#6 OR #7 OR #8 OR noradrenaline OR norepinephrine OR noradrenaline OR catecholamine OR cholesterol OR triglycerides OR (low AND density AND lipoprotein) OR (high AND density AND lipoprotein) OR LDL OR HDL) AND ((randomized AND controlled AND trial) OR (controlled AND clinical AND trial) OR randomized OR placebo OR (drug AND therapy) OR randomly OR trial OR groups))
Renal disease	(((renal AND disease) OR renal) AND (#3 OR #4 OR potassium OR (potassium AND chloride)) AND (#5 OR diet OR dietary OR intake OR restriction OR reduction) AND ((randomized AND controlled AND trial) OR (controlled AND clinical AND trial) OR randomized OR placebo OR (drug AND therapy) OR randomly OR trial OR groups))

#1 = MeSH descriptor Blood Pressure explode all trees
#2 = MeSH descriptor Hypertension explode all trees
#3 = MeSH descriptor Potassium explode all trees
#4 = MeSH descriptor Potassium Chloride explode all trees
#5 = MeSH descriptor Diet explode all trees
#6 = MeSH descriptor Norepinephrine explode all trees
#7 = MeSH descriptor Cholesterol explode all trees
#8 = MeSH descriptor Triglycerides explode all trees
* “dietary”, “intake”, “reduction”, “restriction” did not retrieve MeSH terms
**”noradrenaline”, “catecholamine”, “low density lipoprotein”, “high density lipoprotein” did not retrieve MeSH terms

Annex 2: Example data extraction template

The data extraction form was an Excel workbook divided into worksheets per topic area. The following sheets are examples demonstrating the data collected in the Excel workbook.

Sheet 1: Reference data

Trial ID	Ref ID	Duplicate	Extract ID	Extract date	Author	Author commu-nication needed?	Author contact	Year	Journal	Volume	Pages	Rep Type	Language	Country	Sponsor	Inclusion	Exclusion	Compa-risons made in study	Final Exclu-sion (Y/N)?

Sheet 2: Risk of bias information

Trial ID	Random sequence generation risk of bias	Allocation concealment risk of bias	Blinding				Incomplete outcome data risk of bias	Selective reporting risk of bias	Risk of other bias	Risk of bias due to systematic differences in care
			Subject	Provider	Outcome assessment	Risk of bias				

Sheet 3: Study design

Trial ID	Parallel design or crossover study	Method of measurement of potassium intake		Description of assessment of compliance	Outcomes measured				Subgroup analyses performed	Type of intervention			
		Dietary	24-hour urinary excretion		Adults - All	Adults - Normotensive	Adults - Hypertensive	Children		Feeding	Supplement	Diet advice / Education	Other

Sheet 4: Participant characteristics

Part 1

Ref ID	Comparison ID	Group	Intervention and control groups comparable at baseline (Y/N)	Group description	BP Group				Age group			Age (Mean and SD)	Sex (%M)	N originally randomized	Final samples (n)	% Loss to follow up (%)
					Hypertensive	Normotensive	Both	Unspecified	Adult	Children	Both					

Part 2

Potassium intake at baseline (mmol K/day)	Potassium intake achieved at follow-up (mmol K/day)	Potassium intake at follow-up				Sodium intake at baseline				Starting time of intervention	Ending time of intervention	Duration of follow up (months)
		≥ 70 mmol/day intervention vs < 70 mmol control	≥ 90 mmol/day intervention vs < 90 mmol control	>120 mmol/day intervention vs < 120 mmol control	Other (if 'Other', see column T: Potassium intake achieved at follow-up)	<2g/d	2-4 g/d	> 4 g/day	Other			

Sheet 5: Outcomes (continuous)

Part 1

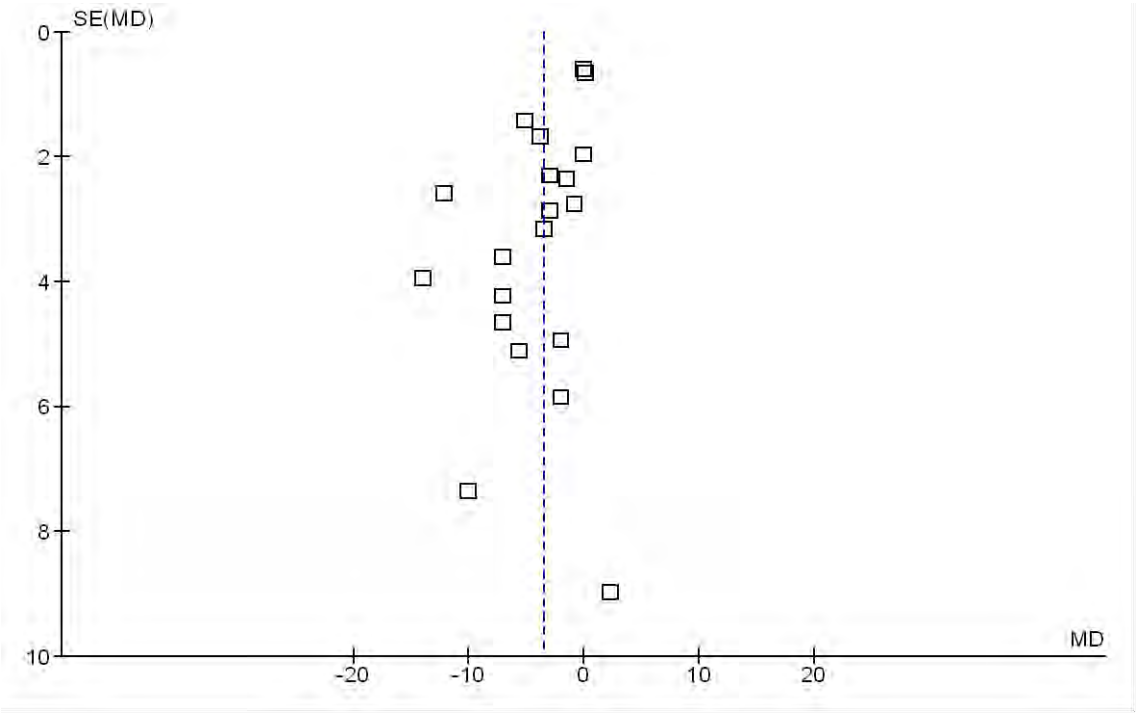
Ref ID	Comparison ID	Group	Systolic blood		Diastolic blood		Adrenaline		Nonadrenaline		Cholesterol	
			n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)

Part 2

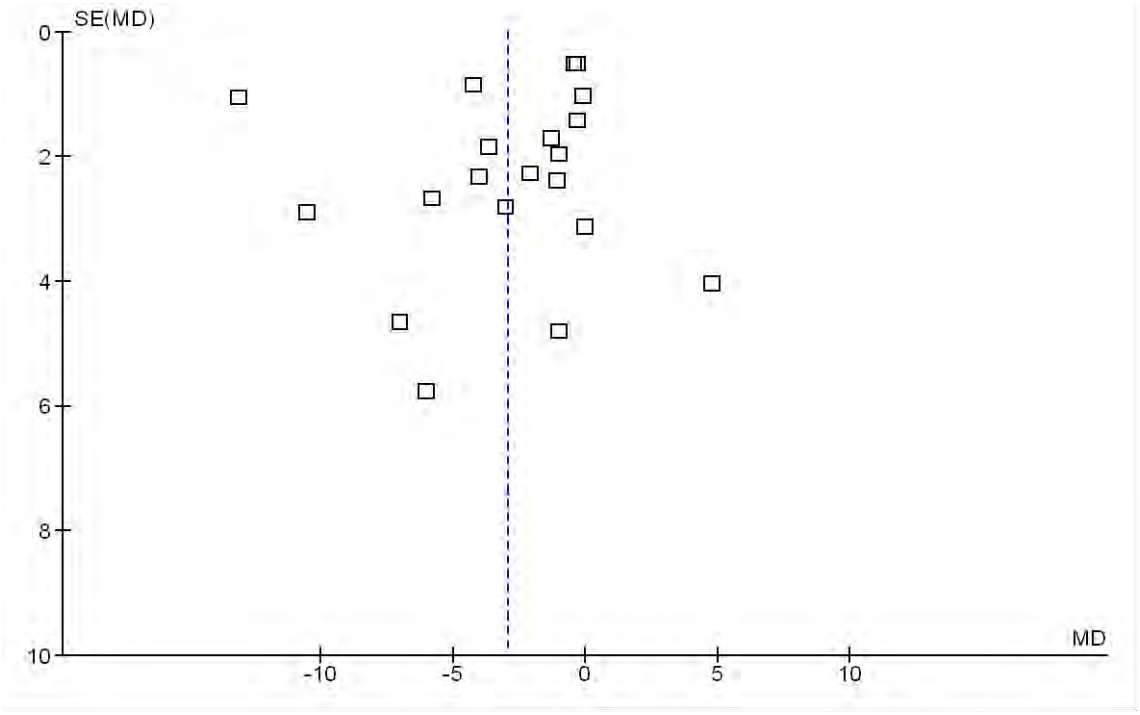
Ref ID	Comparison ID	Group	Triglyceride		HDL		LDL		NPS	
			n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)

Annex 3: Funnel plots

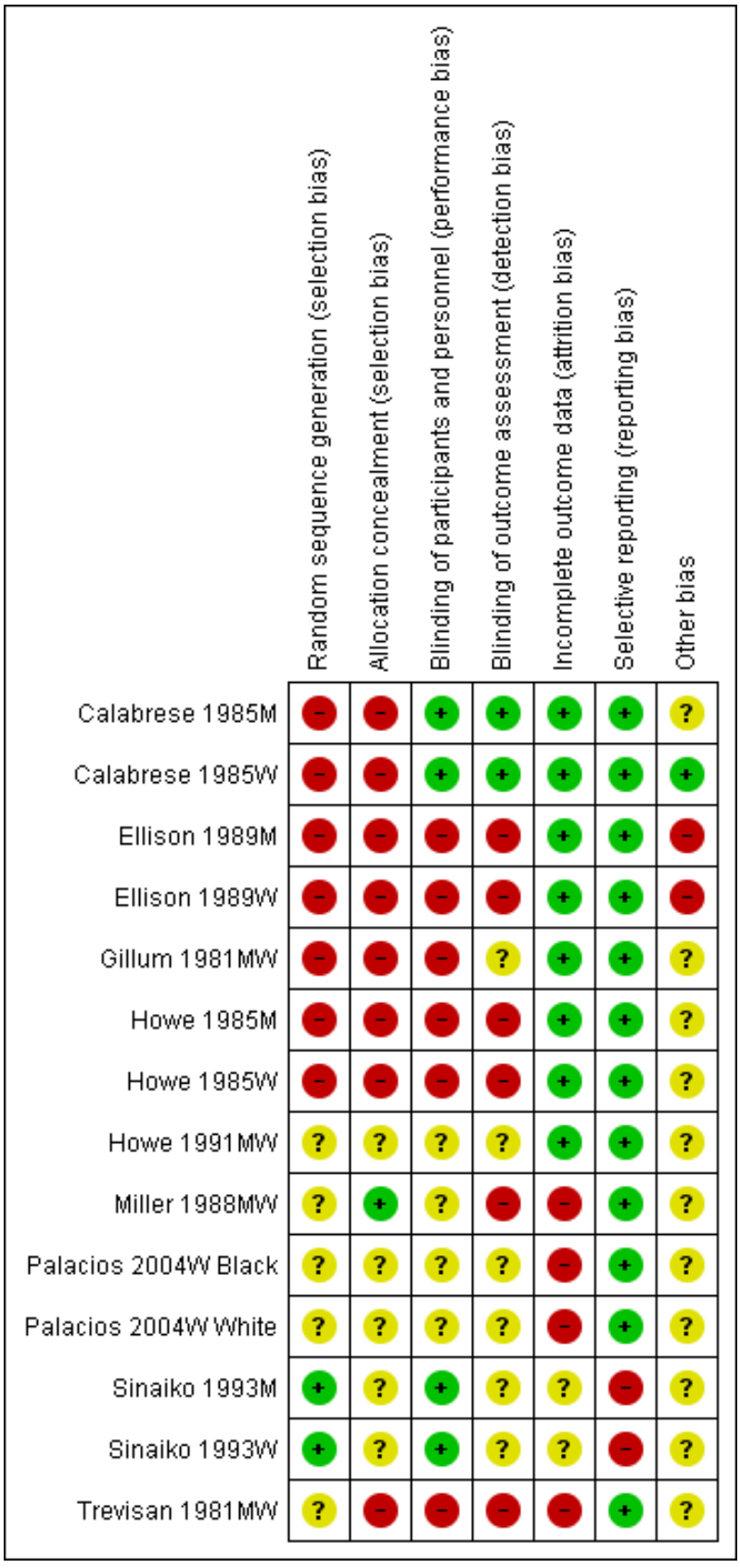
Funnel plot 1: Resting systolic blood pressure



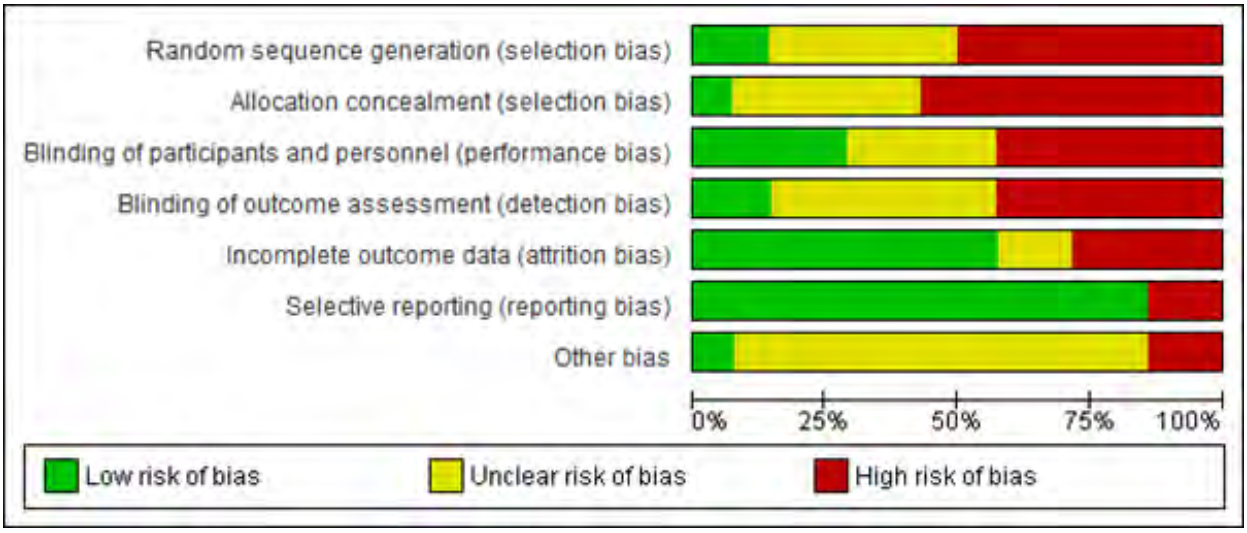
Funnel plot 2: Resting diastolic blood pressure



Annex 4: Risk of bias summary



Annex 5: Risk of bias graph



Annex 6: GRADE evidence profiles

Research question: What is the effect of increased potassium relative to usual intake in adults?

Quality assessment							Participants		Effect		
No of studies/ comparisons	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	considerations	Increased Potassium	Control	Relative (95% CI)	Quality	Importance
Resting systolic blood pressure (follow-up 1 - 36 months; units mmHg; better indicated by lower values)											
21/21	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	947	945	MD 3.06 lower (4.70 to 1.42 lower)	⊕⊕⊕⊕ HIGH	CRITICAL
Resting diastolic blood pressure (follow-up 1 - 36 months; units mmHg; better indicated by lower values)											
21/21	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	930	927	MD 2.84 lower (4.66 to 1.01 lower)	⊕⊕⊕⊕ HIGH	CRITICAL
Ambulatory systolic blood pressure (follow-up 1 - 1.5 months; units mmHg; better indicated by lower values)											
4 / 4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	161	161	MD 3.04 lower (5.42 to 0.66 lower)	⊕⊕⊕O MODERATE	CRITICAL
Ambulatory diastolic blood pressure (follow-up 1 - 1.5 months; units mmHg; better indicated by lower values)											
4 / 4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	161	161	MD 1.24 lower (3.13 lower to 0.66 higher)	⊕⊕⊕O MODERATE	CRITICAL
Serum creatinine (follow-up 1 - 3 months; units µmol/L; better indicated by lower values)											
3 / 3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[3]	none	76	71	MD 4.86 lower (13.6 lower to 3.9 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
Total cholesterol (follow-up 1- 2 months; units mmol/L ; better indicated by lower values)											
3 / 3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[3]	none	104	104	MD 0.12 lower (0.33 lower to 0.09 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
HDL cholesterol (follow-up mean 1.5 months; units mmol/L; better indicated by higher values)											
2 / 2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[3]	none	64	64	MD 0.01 lower (0.13 lower to 0.11 higher)	⊕⊕⊕⊕ HIGH[4]	IMPORTANT
LDL cholesterol (follow-up 1.5 months; units mmol/L; better indicated by lower values)											
1 / 1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[3]	none	48	48	MD 0.10 lower (0.38 lower to 0.18 higher)	⊕⊕⊕⊕ HIGH[5]	IMPORTANT
Triglycerides (follow-up mean 1.5 months; units mmol/L ; better indicated by lower values)											
2 / 2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[3]	none	64	64	MD 0.11 lower (0.48 lower to 0.26 higher)	⊕⊕⊕⊕ HIGH[4]	IMPORTANT
Adrenaline (plasma) (follow-up 1 - 1.5 months; units pg/mL; better indicated by lower values)											
3 / 3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[3]	none	76	76	MD 3.94 lower (9.22 lower to 1.34 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
Noradrenaline (plasma) (follow-up 1 - 1.5 months; units pg/mL; better indicated by lower values)											
3 / 3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[3]	none	76	76	MD 4.32 lower (23.8 lower to 15.1 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT

[1] 95%CI very near zero
[2] 95%CI crosses zero
[3] Outcome is a measure of adverse effect and thus a null value is the perferred value and crossing zero is not considered a matter of imprecision
[4] Only two studies included in generation of estimate
[5] Only one study included in generation of estimate

Research question: What is the effect of increased potassium intake to a level that results in <70 mmol urinary potassium excretion/day relative to usual intake in adults?

Quality assessment							Participants		Effect		
No of studies/ comparisons	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Increased Potassium	Control	Relative (95% CI)	Quality	Importance
Resting systolic blood pressure (follow-up 1.5 - 12 months; units mmHg; better indicated by lower values)											
2 / 2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	91	92	MD 3.65 lower (6.69 to 0.62 lower)	⊕⊕⊕⊕ HIGH[2]	CRITICAL
Resting diastolic blood pressure (follow-up 1.5 - 12 months; units mmHg; better indicated by lower values)											
2 / 2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	91	92	MD 1.35 lower (5.31 lower to 2.60 higher)	⊕⊕⊕O MODERATE[2]	CRITICAL
Ambulatory systolic blood pressure (better indicated by lower values)											
0 / 0											CRITICAL
Ambulatory diastolic blood pressure (better indicated by lower values)											
0 / 0											CRITICAL
Serum creatinine (better indicated by lower values)											
0 / 0											IMPORTANT
Total cholesterol (better indicated by lower values)											
0 / 0											IMPORTANT
HDL cholesterol (better indicated by higher values)											
0 / 0											IMPORTANT
LDL cholesterol (better indicated by lower values)											
0 / 0											IMPORTANT
Triglycerides (better indicated by lower values)											
0 / 0											IMPORTANT
Adrenaline (plasma) (better indicated by lower values)											
0 / 0											IMPORTANT
Noradrenaline (plasma) (better indicated by lower values)											
0 / 0											IMPORTANT

[1] 95%CI crosses zero

[2] Only two studies contributed to the effect estimate

Research question: What is the effect of increased potassium intake to a level that results in 70–90 mmol urinary potassium excretion/day relative to usual intake in adults?

Quality assessment							Participants		Effect		
No of studies/ comparisons	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Increased Potassium	Control	Relative (95% CI)	Quality	Importance
Resting systolic blood pressure (follow-up 1.5 - 12 months; units mmHg; better indicated by lower values)											
5 / 5	randomised trials	no serious risk of bias	serious inconsistency[1]	no serious indirectness	no serious imprecision	none	140	146	MD 5.82 lower (12.43 lower to 0.79 higher)	⊕⊕⊕O MODERATE	CRITICAL
Resting diastolic blood pressure (follow-up 1.5 - 12 months; units mmHg; better indicated by lower values)											
4 / 4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	103	109	MD 4.01 lower (8.44 lower to 0.42 higher)	⊕⊕⊕O MODERATE	CRITICAL
Ambulatory systolic blood pressure (follow-up 1.5 months; units mmHg; better indicated by lower values)											
1 / 1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	48	48	MD 1.8 lower (7.02 lower to 3.42 higher)	⊕⊕⊕O MODERATE[3]	CRITICAL
Ambulatory diastolic blood pressure (follow-up 1.5 months; units mmHg; better indicated by lower values)											
1 / 1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	48	48	MD 1.4 lower (5.14 lower to 2.34 higher)	⊕⊕⊕O MODERATE[3]	CRITICAL
Serum creatinine (follow-up 1 - 3 months; units µmol/L; better indicated by lower values)											
1 / 1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[4]	none	37	37	MD 1.8 lower (6.8 lower to 3.3 higher)	⊕⊕⊕⊕ HIGH[3]	IMPORTANT
Total cholesterol (follow-up 1.5 months; units mmol/L; better indicated by lower values)											
2 / 2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[4]	none	64	64	MD 0.17 lower (0.43 lower to 0.09 higher)	⊕⊕⊕⊕ HIGH[5]	IMPORTANT
HDL cholesterol (follow-up mean 1.5 months; units mmol/L; better indicated by higher values)											
2 / 2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[4]	none	64	64	MD 0.01 lower (0.13 lower to 0.11 higher)	⊕⊕⊕⊕ HIGH[5]	IMPORTANT
LDL cholesterol (follow-up 1.5 months; units mmol/L; better indicated by lower values)											
1 / 1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[4]	none	48	48	MD 0.10 lower (0.38 lower to 0.18 higher)	⊕⊕⊕⊕ HIGH[3]	IMPORTANT
Triglycerides (follow-up mean 1.5 months; units mmol/L ; better indicated by lower values)											
2 / 2	randomised trials	no serious risk of bias	serious inconsistency[6]	no serious indirectness	no serious imprecision[4]	none	64	64	MD 0.11 lower (0.48 lower to 0.26 higher)	⊕⊕⊕ MODERATE[5]	IMPORTANT
Adrenaline (plasma) (better indicated by lower values)											
0 / 0											IMPORTANT
Noradrenaline (plasma) (better indicated by lower values)											
0 / 0											IMPORTANT

[1] 95%CI do not always overlap and effect point estimates fall on both sides of zero

[2] 95%CI crosses zero

[3] Only one study contributed to effect estimate

[4] Outcome is a measure of adverse effect and thus a null value is the perferred value and crossing zero is not considered a matter of imprecision

[5] Only two studies contributed to effect estimate

[6] Effect point estimates fall on both sides of zero

Research question: What is the effect of increased potassium intake to a level that results in 90–120 mmol urinary potassium excretion/day relative to usual intake in adults?

Quality assessment							Participants		Effect		
No of studies/ comparisons	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Increased Potassium	Control	Relative (95% CI)	Quality	Importance
Resting systolic blood pressure (follow-up 1.5 - 12 months; units mmHg; better indicated by lower values)											
10 / 10	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	598	589	MD 1.25 lower (2.68 lower to 0.18higher)	⊕⊕⊕O MODERATE	CRITICAL
Resting diastolic blood pressure (follow-up 1.5 - 12 months; units mmHg; better indicated by lower values)											
9 / 9	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	532	519	MD 0.83 lower (1.82 lower to 0.17 higher)	⊕⊕⊕O MODERATE	CRITICAL
Ambulatory systolic blood pressure (follow-up 1.5 months; units mmHg; better indicated by lower values)											
2 / 2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	71	71	MD 3.65 lower (7.21 to 0.09 lower)	⊕⊕⊕O MODERATE	CRITICAL
Ambulatory diastolic blood pressure (follow-up 1.5 months; units mmHg; better indicated by lower values)											
2 / 2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	71	71	MD 1.28 lower (4.04 lower to 1.48 higher)	⊕⊕⊕O MODERATE[3]	CRITICAL
Serum creatinine (follow-up 1 - 3 months; units µmol/L; better indicated by lower values)											
2 / 2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[4]	none	39	34	MD 11.8 lower (35.0 lower to 11.3 higher)	⊕⊕⊕⊕ HIGH[3]	IMPORTANT
Total cholesterol (better indicated by lower values)											
0 / 0											IMPORTANT
HDL cholesterol (better indicated by higher values)											
0 / 0											IMPORTANT
LDL cholesterol (better indicated by lower values)											
0 / 0											IMPORTANT
Triglycerides (better indicated by lower values)											
0 / 0											IMPORTANT
Adrenaline (plasma) (better indicated by lower values)											
0 / 0											IMPORTANT
Noradrenaline (plasma) (better indicated by lower values)											
0 / 0											IMPORTANT

[1] 95%CI reaches/is very close to zero

[2] 95%CI crosses zero

[3] Only two studies contributed to effect estimate

[4] Outcome is a measure of adverse effect and thus a null value is the perferred value and crossing zero is not considered a matter of imprecision

Research question: What is the effect of increased potassium intake to a level that results in >120 mmol urinary potassium excretion/day relative to usual intake in adults?

Quality assessment							Participants		Effect		
No of studies/ comparisons	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	considerations	Increased Potassium	Control	Relative (95% CI)	Quality	Importance
Resting systolic blood pressure (follow-up 1.5 - 12 months; units mmHg; better indicated by lower values)											
4 / 4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	118	118	MD 3 lower (6.28 lower to 0.27 higher)	⊕⊕⊕O MODERATE	CRITICAL
Resting diastolic blood pressure (follow-up 1.5 - 12 months; units mmHg; better indicated by lower values)											
4 / 4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	118	118	MD 1.75 lower (4.23 lower to 0.74 higher)	⊕⊕⊕O MODERATE	CRITICAL
Ambulatory systolic blood pressure (follow-up 1.5 months; units mmHg; better indicated by lower values)											
1 / 1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	42	42	MD 3 lower (7.07 lower to 1.07 higher)	⊕⊕⊕O MODERATE[2]	CRITICAL
Ambulatory diastolic blood pressure (follow-up 1.5 months; units mmHg; better indicated by lower values)											
1 / 1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	42	42	MD 1 lower (4.64 lower to 2.64 higher)	⊕⊕⊕O MODERATE[2]	CRITICAL
Serum creatinine (better indicated by lower values)											
0 / 0											IMPORTANT
Total cholesterol (follow-up 1.5 months; units mmol/L; better indicated by lower values)											
1 / 1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[3]	none	40	40	MD 0.03 lower (0.39 lower to 0.33 higher)	⊕⊕⊕⊕ HIGH[2]	IMPORTANT
HDL cholesterol (better indicated by higher values)											
0 / 0											IMPORTANT
LDL cholesterol (better indicated by lower values)											
0 / 0											IMPORTANT
Triglycerides (better indicated by lower values)											
0 / 0											IMPORTANT
Adrenaline (plasma) (follow-up 1 - 1.5 months; units pg/mL; better indicated by lower values)											
3 / 3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[3]	none	76	76	MD 3.9 lower (9.2 lower to 1.3 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
Noradrenaline (plasma) (follow-up 1 - 1.5 months; units pg/mL; better indicated by lower values)											
3 / 3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[3]	none	76	76	MD 4.3 lower (23.8 lower to 15.1 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT

[1] 95%CI crosses zero

[2] Only one study contributed to effect estimate

[3] Outcome is a measure of adverse effect and thus a null value is the perferred value and crossing zero is not considered a matter of imprecision

Annex 7: Lists of tables and figures

Tables

Figures

Full list of references

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ISBN 978 92 4 150488 1