Effect of increased potassium intake on blood pressure and potential adverse effects in children

World Health Organization

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Contents

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Abbreviations and acronyms

CHD	coronary heart disease
CI	confidence interval
CVD	cardiovascular disease
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
ITT	intention to treat
LDL	low-density lipoprotein
LILACS	Latin American and Caribbean Health Science Literature Database
MD	mean difference
NCD	noncommunicable disease
PRISMA	preferred reporting items for systematic reviews and meta-analyses
RCT	randomized controlled trial
SD	standard deviation
WHO	World Health Organization

Symbols

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

1 Introduction

1.1 Background

Noncommunicable diseases (NCDs) are the leading cause of death globally, killing more people each year than all other causes combined (*1*). 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 (*2, 3*). In 2008, 29 million NCD-related deaths (nearly 80%) occurred in low- and middle-income countries; 29% of such deaths in these countries were in people aged < 60 years, and were thus defined as premature. In contrast, in high-income countries, only 13% of the NCD-related deaths were premature. In 2005, cardiovascular disease (CVD) accounted for 30% of all deaths: the equivalent of infectious disease, nutritional deficiency, and maternal and perinatal conditions combined (*2*). Hypertension is considered a major risk factor for CVD, especially heart attack and stroke. Suboptimal systolic blood pressure (> 115 mmHg in adults) is estimated to contribute to 49% of all coronary heart disease (CHD) and 62% of all stroke (*4*). Thus, the burden of morbidity and mortality from hypertension and related NCDs is currently one of the most urgent public health problems globally.

Although NCDs disproportionately affect adults, they and their risk factors are also being detected more frequently in paediatric populations. Diet-related NCDs are chronic and take years or even decades to manifest; thus, delaying the onset of these diseases could improve lives and lead to substantial cost savings (*5*). Blood pressure during childhood has a significant association with blood pressure during adulthood, meaning that children with increased blood pressure are at high risk for hypertension and its related morbidities as adults (*6*). Also, elevated blood pressure in childhood contributes to cardiovascular pathology during childhood itself (*7*). Thus, to combat NCDs, it is crucial to address during childhood the problem of elevated blood pressure and other risk factors for NCDs that could manifest later in life.

Three meta-analyses of trials comparing increased potassium with lower or usual potassium intake in adults found that increased potassium intake lowers blood pressure (*8-10*). However, another meta-analysis that included only studies in adults with hypertension did not detect a significant effect of potassium on blood pressure (*11*).To date, there have been no systematic reviews of the effect of increased potassium on health outcomes in children.

1.2 Need for this review

Much of the human and social impact caused each year by NCD-related morbidity and mortality could be averted through interventions that are well understood, cost effective and feasible (*1*). Increased potassium intake in the population is one such potential public health intervention, which could possibly lead to reduced burden of NCD morbidity and mortality (*5*). Given the ever-increasing importance of NCDs on health-care costs and burden of disease (*1, 3, 5*), and the recent recognition of the importance of preventing NCDs even in childhood, a complete up-to-date systematic review of all available epidemiological evidence on potassium and blood pressure and potential adverse effects (e.g. changes in blood lipids and catecholamine levels in children) is warranted.

1.3 Objectives

The overall objective was to assess the effect, in children (2–15 years of age inclusive), of increased potassium intake compared with lower or usual potassium intake on blood pressure and adverse effects, such as changes in blood lipids and catecholamine levels.

Specific objectives were to assess whether:

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

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 (*12*). 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 potassium intake/day;
- 120 mmol urinary potassium/day equals approximately 156 mmol potassium intake/day.

2 Methods

2.1 Criteria for considering studies for this review

Study type

We prioritized studies according to their design, giving highest priority to randomized controlled trials (RCTs), either individual or cluster randomization. Where there were insufficient numbers of RCTs (i.e. fewer than three), we included quasi-randomized trials, non-randomized trials and prospective, observational cohort studies.

Participants

Studies considered for inclusion were those involving children (2–15 years of age inclusive) 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 pregnant, acutely ill or infected with human immunodeficiency virus (HIV).

Outcome measures

The primary outcome measures were:

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

Secondary outcomes were all other outcomes reported by study authors.

Types of interventions in controlled trials

In relation to controlled trials (randomized or non-randomized), 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 study included multiple follow-up time points, we included data from the last follow-up in the overall analysis. Data from each time point could be used in the subgroup analysis by duration of follow-up, without calculating an overall effect estimate across all subgroups.

We considered other co-interventions (e.g. physical activity), provided that such interventions were identical between the intervention and the control groups. Studies that had lifestyle or dietary intervention arms that resulted in higher potassium intake in one arm were included, provided that the only difference between the study arms was a targeted intervention that resulted in increased potassium intake.

We also included studies in which all participants received some medical treatment (e.g. diuretics or beta blockers), and in which one arm had increased potassium intake and another had usual potassium intake, provided that the only difference between the intervention and control groups was the level of potassium intake.

Types of exposure in cohort trials

For cohort studies, we were interested in comparing outcomes based on exposure to increased potassium intake relative to lower or usual potassium intake. Assessing exposure required an estimation of potassium intake, either through urinary potassium excretion or dietary evaluation at baseline.

2.2 Identification of studies

We searched for studies in three phases. In the first phase, we searched for high-quality systematic reviews in children on increased potassium consumption and the outcomes of interest. If such reviews were found and the inclusion criteria for the reviews were similar or equivalent to those needed to reach the objectives of the current review, we planned to use the references of those reviews as the list of potential studies. If the reviews were high quality but were > 2 years old, we intended to supplement those studies with additional searches. We also planned to contact the original authors of such reviews to request original data in order to explore the data in such a way as to answer our objectives.

The second phase, to be undertaken if high-quality systematic reviews were unavailable or if such reviews were > 2 years old, was to undertake a complete search for data published since the date of publication of the identified systematic review (see *Electronic databases* and *Other resources*, below) for RCTs comparing potassium intake and the outcomes of interest.

The third phase, to be undertaken if fewer than three RCTs for the outcomes of interest were identified, was to:

- undertake a complete search for prospective cohort studies comparing potassium intake as the exposure and the outcomes of interest;
- re-evaluate the list of potential RCTs to include non-RCTs and quasi-experimental trials;
- include trials based on less stringent set of inclusion criteria (see *Selection of studies*, below).

Systematic reviews and meta-analyses

We first searched MEDLINE and the Cochrane Library of Systematic Reviews for high-quality systematic reviews of trials measuring the effect of increased potassium intake on blood pressure and adverse effects such as increased lipids, cholesterol and triglycerides in children.

Electronic databases

We searched the following electronic databases for primary references to original study data:

- the Cochrane Central Register of Controlled Trials (searched 6 September 2011);
- MEDLINE (PubMed searched on 28 August 2011 for RCTs and on 21 September 2011 for cohort studies);
- EMBASE (searched on 25 August 2011 for RCTs and on 21 September 2011 for cohort studies);
- World Health Organization (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 strategy used for the electronic search is given in **Annex 1**.

Other resources

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

2.3 Data collection and analysis

2.3.1 Selection of studies

During the first and second phases of the systematic review, a full article was retrieved when the information given in the title, abstract and keywords suggested that the study:

- included the random allocation of participants (individually or within clusters) to the intervention or control group;
- included an intervention that targeted or achieved an increased potassium intake (provided that an achieved increase in potassium was documented);
- had a prospective design and a control group;
- had a measure of potassium intake through 24-hour urinary potassium excretion;
- did not specifically target individuals identified as being infected with HIV, acutely ill, hospitalized or pregnant;
- reported results of at least one of the outcomes of interest;
- had an intervention with a duration of ≥ 4 weeks;
- included children and adolescents 2–15 years of age (inclusive).

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

If too few RCTs were identified in the literature, potential studies would be rescreened for inclusion based on less stringent criteria, assessing whether the study:

- was a controlled trial (either randomized or non-randomized);
- included an intervention that targeted or achieved an increased potassium intake of any amount;
- had a measure of potassium intake through 24-hour urinary potassium excretion, overnight urinary potassium excretion, casual urinary potassium excretion or dietary assessment;
- did not specifically target individuals identified as being infected with HIV, acutely ill, hospitalized or pregnant;

[1] www.who.int/nutrition

- reported results of at least one of the outcomes of interest;
- had a duration of ≥ 3 weeks;
- included children and adolescents 2–15 years of age (inclusive).

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

Cohort studies were included if the study:

- had a prospective design;
- had a measure of potassium consumption at baseline to indicate exposure;
- did not specifically target individuals identified as being infected with HIV, acutely ill, hospitalized or pregnant;
- reported results of at least one of the outcomes of interest;
- had a duration of follow-up of ≥ 1 year;
- included children and adolescents 2–15 years of age (inclusive).

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

Two reviewers independently assessed for inclusion all the potentially eligible studies, according to the above prespecified criteria. Where studies were published only as abstracts, or contained little information on methods, we attempted to contact the authors to obtain further details of study design and results.

Where differences in opinion existed, they were resolved by consulting a third party and reaching consensus. If it was not possible to resolve differences of opinion, the reference was added to 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 (**Figures 3.1–3.3**) (*13*).

2.3.2 Data extraction and management

For studies that fulfilled inclusion criteria, two reviewers independently abstracted relevant population and intervention characteristics using standard data extraction templates (**Annex 2**), with any disagreements resolved by discussion and consensus. Any relevant missing information on the study was sought from the authors of the original reference.

Data concerning details of study population, intervention and outcomes were extracted independently by two reviewers. A third reviewer checked all 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 comorbidity), assessment of compliance, withdrawals or losses to follow-up (reasons and description), subgroups analysed in original study, status of blood pressure and status of medication consumption 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); intention-to-treat (ITT) analysis.
- *Objective* – stated objective of the study.

Duplicate publications

In the case of duplicate publications and companion references of a primary study, we tried to maximize yield of information by simultaneously evaluating all available data.

2.2.3 Assessment of risk of bias in included studies

Data were entered into Review Manager software (RevMan 2008) and checked for accuracy by a second reviewer. In cases of disagreement, a third reviewer was consulted and a judgement was made based on consensus.

We assessed risk of bias of RCTs using the broad categories recommended in the *Cochrane handbook for systematic reviews of interventions* (*14*):

Sequence generation (checking for possible selection bias)

For each included study, we described the method used to generate the randomization sequence 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* – trials in which any truly random process was used (e.g. random number table or computer random-number generator);
- *inadequate* – trials in which any non-random process was used (e.g. odd or even date of birth, or hospital or clinic record number);
- *no randomization;*
- *unclear.*

We used these same broad categories to assess risk of bias in non-randomized trials, but also took into account particular sources of bias associated with different study designs. Deeks et al. (*15*) have set out 12 domains for assessing the quality of non-randomized studies:

- background (e.g. whether the research question was clearly stated);
- sample definition and selection;
- interventions (and co-interventions);

- outcomes;
- the creation of treatment groups;
- blinding;
- soundness of information (e.g. protocol deviations);
- follow-up;
- analysis (comparability);
- analysis (outcome);
- interpretation;
- presentation and reporting.

We attempted to collect information on all of these domains by recording in detail the characteristics of the sample, the intervention and its implementation, the completeness of follow-up, and the analytical methods used to adjust for possible confounding factors.

Allocation concealment (checking for possible selection bias)

We described the method used to conceal the allocation sequence in sufficient detail and determined whether intervention allocation could have been foreseen in advance of or during recruitment, or 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* – for example, 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 participants and personnel from knowledge of which intervention a participant received. We judged studies to be at low risk of bias if they included blinding, or if it appeared 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;
- outcome assessors.

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

For each included study, 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:

- *adequate* – trials in which few drop-out or losses to follow-up were noted, and an ITT analysis was possible;
- *inadequate* – trials in which the rate of exclusion was at least 20%, or there were wide differences in exclusions between groups whether ITT analysis 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 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.*

Selection of study participants

We recorded the manner in which study participants were selected and recruited and, when applicable, how treatment and control groups were formed. We provided details of the demographic and other (e.g. physiological) characteristics of participants to assess whether study participants were representative of the wider population from which they were drawn, and to determine whether groups were drawn from comparable populations. We

noted whether any allocation decisions were based on the preferences of participants, or

were dependent on other factors (e.g. clinician choice). We noted which characteristics were used to demonstrate comparability of groups (e.g. age, sex, sociodemographic characteristics and hypertensive status), and considered whether potentially key variables were not included.

Defining exposure and collecting outcome data

In controlled trials, we recorded the manner in which the intervention was implemented, and noted levels of adherence to or coverage of the intervention. In the case of cohort studies, we recorded the manner in which exposure was measured, and the methods used to define exposure groups. In cases of follow-up over time in different sites, we considered whether contamination was likely, or whether there were other differences between groups (e.g. exposure to other interventions) that could confound interpretation of results. We assessed whether the length of follow-up was adequate for the outcomes reported. We also noted whether there was blinding of outcome assessment.

Collection of outcome data and loss to follow-up

We assessed the characteristics of those participants remaining to follow-up and how they compared with the original sample recruited. We also noted whether the loss to follow-up was balanced across groups (in terms of the numbers and characteristics of those lost to follow-up).

Analytical comparability

We recorded the steps taken by investigators to adjust for any possible variation in the characteristics of treatment and control groups, or exposed and unexposed groups. For each study, we recorded the factors used to adjust for possible confounding.

Other sources of bias

For cohort studies, the method of assessment of exposure was considered as a potential source of bias and was thus noted.

For RCTs we noted any important concerns 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, recording answers as "yes", "no" or "unclear".

2.3.4 Measures of treatment effect

Continuous variables were expressed as differences in means (MD) with 95% confidence intervals (CI).

2.3.5 Missing data

We obtained relevant missing data from authors. We also investigated attrition rates (e.g. drop-outs, losses to follow-up and withdrawals).

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 guidelines of the *Cochrane handbook for systematic reviews of interventions* (*14*). Overall results were calculated based on the random-effects model (*16*). Where data were reported in forms that could not easily be converted into a standard measure, data were summarized in a narrative format, and different comparisons were analysed separately.

Assessment of heterogeneity

We identified heterogeneity by visual inspection of the forest plots, and by using a standard Chi squared 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 (*17, 18*),where an I^2 statistic of ≥ 75% indicates a considerable level of inconsistency. Where heterogeneity was found, we attempted to determine the potential causes by examining characteristics of individual studies and subgroups.

Synthesis of data when heterogeneity was found

In the event of substantial clinical, methodological or statistical heterogeneity, study results were summarized in a narrative format rather than being reported as meta-analytically pooled effect estimates. Subgrouping was used to explore potential reasons for heterogeneity.

2.3.7 Subgroup analyses

We planned to perform subgroup analyses for each outcome, to explore effect-size differences between groups by:

- gender (male, versus female, versus heterogeneous group);
- hypertension status (all participants with hypertension, versus all participants without hypertension, versus heterogeneous or unspecified status);
- achieved absolute potassium intake level in intervention group;
- status of medication use to control blood pressure (all participants taking medication, versus no participants taking medication, versus heterogeneous or unspecified medication status);
- duration (< 3 months, versus 3–6 months, versus > 6 months);
- study design (parallel, versus cross-over);
- type of blood pressure device used (automatic, versus manual);
- measurement method for taking blood pressure (supine office, versus seated office, versus standing office, versus combination office, versus supine home, versus seated home, versus standing home, versus combination home).

2.3.8 Sensitivity analysis

We carried out sensitivity analysis 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. Other studies were considered to be at low risk of bias. All non-randomized trials were considered to be at high risk of bias.

2.3.9 Quality of the body of evidence

We planned to generate funnel plots to assess the potential existence of small studies (*19, 20*). A "risk of bias graph" (**Annex 3**) and "risk of bias summary" (**Annex 4**) were generated. We used the GRADE profiler (version 3.6) software to assess the quality of the body of evidence according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology outlined in *GRADE: an emerging consensus on rating quality of evidence and strength of recommendations* (*21*).

3 Results

3.1 Results of the search

The first-phase search resulted in the identification of a systematic review conducted by the Dietary Guidelines Advisory Committee of the United States Department of Agriculture on the effect of potassium on blood pressure in adults (*22*). No reviews were identified on the effect of potassium intake on blood pressure or blood lipids and other potential adverse effects in children.

As shown in **Figure 3.1**, the second-phase search for RCTs resulted in 4882 references. A scan of the reference list of the systematic review of potassium intake and blood pressure in adults (*22*) resulted in the identification of a further three references to potential studies. Thus, a total of 4885 references were identified for potential inclusion in the systematic review. Of these, 4871 were excluded on the basis of the title, due to obvious lack of relevance to the current review or not being conducted in children. Of the remaining 14 references, three were duplicates and were therefore removed. Of the remaining 11 references, 10 were excluded based on the abstracts, which did not meet the basic criteria for inclusion, leaving only one reference to one study that was fully reviewed for inclusion in the review. This study reached inclusion criteria.

As shown in **Figure 3.2**, the expanded search resulted in the identification of 17 references for potential inclusion. Of these, three were excluded because they were duplicates and one had already been identified in the second-phase search. Thus, 13 abstracts were reviewed, of which seven did not meet the inclusion criteria. The remaining six full-text references to six studies were assessed; of these, four were excluded, leaving two studies that met the inclusion criteria for the current review. These two studies had previously been excluded during the second phase search, because of their duration (3 weeks) and non-random allocation to treatment group.

As shown in **Figure 3.3**, the search for cohort studies identified 329 references, and correspondence with an author yielded one additional potential reference. Of these, 306 were excluded on the basis of title because of obvious lack of relevance, participants (i.e. not conducted in children) or study type (i.e. not cohort studies). A further 18 references were excluded based on screening of abstracts, because they did not meet basic inclusion criteria. Of the remaining five full-text references, four were excluded because baseline exposure to potassium was not recorded, outcomes of interest were not reported or the cohort study was not prospective. Thus, only one cohort study was included in the review.

Thus, four studies were included in the review: two RCTs, one non-randomized trial and one cohort study.

3.2 Retrieval of missing data

Dr Dawn Wilson was contacted; she generously provided additional information regarding her studies (*23, 24*).

3.3 Included studies

Details of the characteristics of the included studies are shown in Section 3.7, below.

3.3.1 Settings

All included studies were published in English. The three controlled trials were conducted in the United States of America (*24-26*). The cohort study was undertaken in the Netherlands (*27*).

The two RCTs recruited children either through schools (*26*) or through schools, churches and radio and print advertising for volunteers (*24*). The controlled trial without random allocation to treatment group recruited participants from an existing twin panel (*25*). The cohort study was prospective, with a 7-year follow-up (*27*).

3.3.2 Participants

The two RCTs included a total of 250 male and female participants. One study included 40 African-American children aged 13–15 years without hypertension (*24*); the other included 210 male and female students in grades 5–8, averaging 13 years of age at baseline, whose blood pressure was > 109 mmHg for boys and > 108 mmHg for girls (*26*).

The non-randomized trial included 76 participants, aged 11–14 years (*25*).

The cohort study measured a total of 596 children at baseline, with 233 completing the evaluation and thus included in the analysis. The children were 5–17 years of age at baseline, and were followed for 7 years. Their hypertensive status at baseline was not determined (*27*).

3.3.3 Interventions

In one RCT of 3 weeks duration, the interventions were dietary education, behavioural skills training and feedback on performance (*24*). In the other two controlled trials – one of 4 weeks duration (*25*), the other of 3 years (*26*) – the intervention was the provision of potassium and placebo supplements. The cohort study compared the change in blood pressure over a 7-year period with the average potassium intake during that same period (*27*). The population was divided into tertiles of average potassium intake, and the change in blood pressure over time between the tertiles was compared.

3.3.4 Outcome measures

The outcome measure in one RCT was resting and ambulatory blood pressure, before and after a 3-week dietary intervention (*24*). The outcome in the other RCT was the rate of the change in blood pressure over time, standardized to “change in mmHg per year” (*26*). The outcome in the non-randomized trial was resting blood pressure before and after a 4-week intervention (*25*). The outcome measured in the cohort study was change in resting blood pressure over the 7-year follow-up time, standardized to “change in mmHg per year” (*27*).

3.4 Excluded studies and reasons for exclusion

Reasons for exclusion of the eight ineligible studies are given in **Table 3.9**.

3.5 Effects of interventions and exposure

The effects of increased potassium versus lower or usual potassium intake in children are summarized in **Table 3.10** and in the forest plots **Figures 3. 4–3. 11**.

The meta-analysis of change in systolic blood pressure is found in **Figure 3.4** and **Table 3.10**. Increased potassium intake decreased systolic blood pressure by 0.28 mmHg (95%CI: –0.49, 1.05), which was inconclusive. The meta-analysis found that increased potassium decreased,

though non-significantly, diastolic blood pressure by 0.92 mmHg (95%CI: –0.13, 2.00) (**Figure 3. 6**). The sensitivity analysis of the removal of the non-randomized trial had little effect on the results (systolic blood pressure decreased by 0.27 mmHg [95%CI: –0.62, 1.15]; diastolic blood pressure decreased by 1.00 mmHg [95%CI: –0.11, 2.12]). Only one study with two comparisons measured ambulatory blood pressure (*24*), and the results were inconclusive (**Figures 3. 8–3. 11**).

The results from the observational cohort study suggested a beneficial effect of increased potassium on blood pressure in children. The reported average increase in blood pressure among the children in the lowest tertile of potassium intake was 2.44 mmHg/year (95%CI: 1.99, 2.89), and the average increase among the children in the highest tertile of potassium intake was 1.43 mmHg/year (95%CI: 0.78, 1.88). The study did not provide quantitative results for resting diastolic blood pressure, but did report that potassium was not significantly related to the change in diastolic blood pressure.

There were too few studies to address the question of a differential effect of potassium intake at various levels of intake.

No studies meeting the inclusion criteria reported the effect of increased potassium on blood lipids, catecholamine levels or other minor side effects in children.

3.6 Quality of the body of evidence

There were too few studies to generate meaningful funnel plots. The results from the risk of bias graph (**Annex 3**) and risk of bias summary (**Annex 4**) suggest that the entire body of evidence is at risk of serious problems due to bias. Of the four studies, one was a cohort study and one was not randomized. Only one study reported blinding of personnel and participants (*26*), two studies did not blind personnel and participants (*24, 25*), and one did not report blinding (*27*). In all studies it was unclear whether the outcome assessors were blinded.

The GRADE evidence profile (**Annex 5**) was used to assess the quality of the evidence. It demonstrated that the quality of evidence for a reduction in resting systolic and diastolic blood pressure with increased potassium was low. The body of evidence from RCTs starts on the GRADE ranking as high quality. However, the evidence was downgraded because of the high risk of bias (described above) and imprecision (the 95%CI of effect estimate crossed zero). Cohort studies start on the GRADE ranking as low quality. The cohort study was not downgraded for any reason. The evidence for an effect of increased potassium on ambulatory blood pressure was moderate; however, it came from only one study and should therefore be interpreted with caution. It started on the GRADE ranking as high quality due to study design, and was downgraded due to imprecision.

3.7 Tables

3.7.1 Characteristics of included studies

Table 3.1 Geleijnse 1990

Methods	Cohort study with prospective design conducted in the Netherlands
Participants	The total population aged 5–17 years in two districts in Netherlands was invited to participate (mean age 13 years). The study included a total of 596 children at baseline and 233 at follow-up (108 boys and 125 girls).
Interventions	Potassium was measured as urinary potassium excretion. The population was divided, and the third with the lowest urinary potassium excretion was compared with the highest third. Potassium excretion values: • Lower one-third – 21–49 mmol/day • Upper one-third – 62–100 mmol/day
Outcomes	Change in blood pressure over time
Notes	Average follow-up 7 years Potassium measured by urinary potassium excretion Participants followed up directly, and blood pressure measured at yearly intervals Group – no hypertension at baseline. Models adjusted for sex, initial age, change in height and weight, and sodium excretion.

Reference : (*27*)

Table 3.2 Risk of bias table Geleijnse 1990

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Cohort study design
Allocation concealment (selection bias)	High risk	Cohort study design
Blinding of participants and personnel (performance bias)	Unclear risk	No mention of blinding
Blinding of outcome assessment (detection bias)	Unclear risk	No mention of blinding
Incomplete outcome data (attrition bias)	High risk	Very high loss to follow-up (> 50%), with little description of why or from which groups
Selective reporting (reporting bias)	Low risk	All outcomes reported

Table 3.3 Miller 1987

Methods	Controlled trial without random allocation of treatment conducted in the United States of America
Participants	38 families with twin children who were registered in a twin panel at a local medical facility participated. The 38 child participants (24 girls and 14 boys) were aged 11.6±3.8 years
Interventions	Liquid potassium supplement (potassium gluconate and potassium citrate) Non-potassium containing placebo liquid provided, no blinding. Urinary excretion (24-hour) Control 37.1 mmol/day ±15.1 Intervention 48.6 mmol/day ±23.2
Outcomes	Resting systolic and diastolic blood pressure before and after treatment or placebo
Notes	Duration 4 weeks Potassium measured by urinary potassium excretion Participants followed up directly and blood pressure measured before and after treatment or placebo Group – no hypertension at baseline.

Reference: (*25*)

Table 3.4 Risk of bias table Miller 1987

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Not random
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding of participants and personnel (performance bias)	High risk	No blinding
Blinding of outcome assessment (detection bias)	Unclear risk	No mention of blinding
Incomplete outcome data (attrition bias)	Low risk	Reported zero loss to follow-up
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported

Table 3.5 Sinaiko 1993

Methods	Randomized controlled trial conducted in the United States
Participants	210 boys and girls average age 13.3 years. 70 low sodium/71 potassium chloride/69 placebo
Interventions	Potassium tablets (potassium chloride) 1 mmol/kg body weight/24 hours Non-potassium placebo tablets (Also a low-sodium group that was not included in this systematic review) Potassium excretion (24 hour) Boys Control 63mmol/day ±5 Intervention 100 mmol/day ±10 Girls Control 41 mmol/day ±3 Intervention 93 mmol/day ±9
Outcomes	Change in blood pressure over time
Notes	Duration 3 years Potassium measured by urinary potassium excretion Participants followed up directly; blood pressure measured and urinary potassium excretion measured every 3 months Group – hypertension at baseline (defined as having a systolic blood pressure above 109 mmHg for boys and 108 mmHg for girls)

References: (*26, 28*)

Table 3.6 Risk of bias table Sinaiko 1993

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias)	Low risk	Blinding
Blinding of outcome assessment (detection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias)	Low risk	Attrition described and similar between groups
Selective reporting (reporting bias)	Low risk	All outcomes reported

Table 3.7 Wilson 1996

Methods	Randomized controlled trial conducted in the United States of America
Participants	40 African-American adolescents (22 boys and 18 girls), average age 14 years.
Interventions	High potassium or usual potassium diet. Once weekly sessions on dietary education, behavioural skills training and feedback on performance. (control group had once-weekly sessions to discuss food records and urine collections) Potassium excretion (24 hour) Dippers (individuals whose blood pressure declines during sleeping hours) • Control 37mmol/day ±8 • Intervention 62 mmol/day ±19 Non-dippers (individuals whose blood pressure does not decline during sleeping hours) • Control 40 mmol/day ±11 • Intervention 61 mmol/day ±15
Outcomes	Resting systolic and diastolic blood pressure Ambulatory blood pressure (waking hours [day] and sleeping hours [night]) Percentage of participants defined as 'dippers' (i.e. blood pressure declined by at least 10% in sleeping relative to waking hours)
Notes	Duration 3 weeks Potassium measured by urinary potassium excretion Participants followed up directly; blood pressure and urinary potassium excretion measured every 3 months Group – no hypertension at baseline.

Reference: (*24*)

Table 3.8 Risk of bias table Wilson 1996

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	High risk	Not possible because of dietary interventions
Blinding of outcome assessment (detection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias)	Low risk	Zero loss to follow-up
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported

Table 3.9 Excluded studies and reasons for exclusion

Study ID	Reason for exclusion
Aounallah-Skhiri 2011 (*29*)	Retrospective cohort study
He 2008 (*30*)	Cohort study, but baseline exposure to potassium not recorded
Kafatos 2007 (*31*)	Did not report on outcome of interest
Papandreou 2007 (*32*)	Did not report on outcome of interest
Sica 2010 (*33*)	No original data present (review)
Wilson 1999 (*23*)	Did not report on outcome of interest
Wilson 2011 (*34*)	No original data present (review)
Zhu1987 (*35*)	Cross-sectional design

3.7.2 Effect estimate table

Table 3.10 Systolic and diastolic blood pressure

Outcome or subgroup	Studies / comparisons	Participants	Effect estimate[a,b]
1.1 Resting systolic blood pressure	3 / 5	256	–0.28 [–1.05, 0.49]
1.2 Resting diastolic blood pressure	3 / 5	256	–0.92 [–2.00, 0.20]
1.3 Ambulatory systolic blood pressure (day)	1 / 2	40	0.98 [–6.86, 8.82]
1.4 Ambulatory diastolic blood pressure (day)	1 / 2	40	0.85 [–2.74, 4.44]
1.5 Ambulatory systolic blood pressure (night)	1 / 2	40	–0.35 [–6.15, 5.45]
1.6 Ambulatory diastolic blood pressure (night)	1 / 2	40	–0.57 [–4.40, 3.26]

[a] Statistical method was mean difference (inverse variance random-effects model, 95% confidence interval)
[b] Negative value indicates a lower blood pressure in the increased potassium group versus the usual or lower potassium group

3.8 Figures

Figure 3.1 Flow through screening, inclusion, exclusion – randomized controlled trials

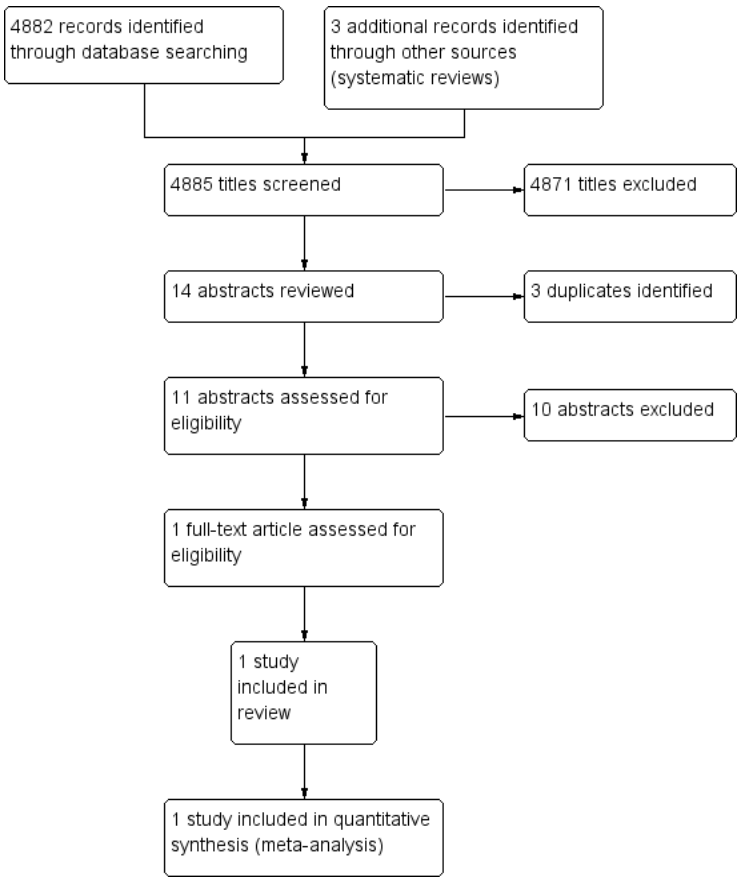


Figure 3.2 Flow through screening, inclusion, exclusion – expanded search

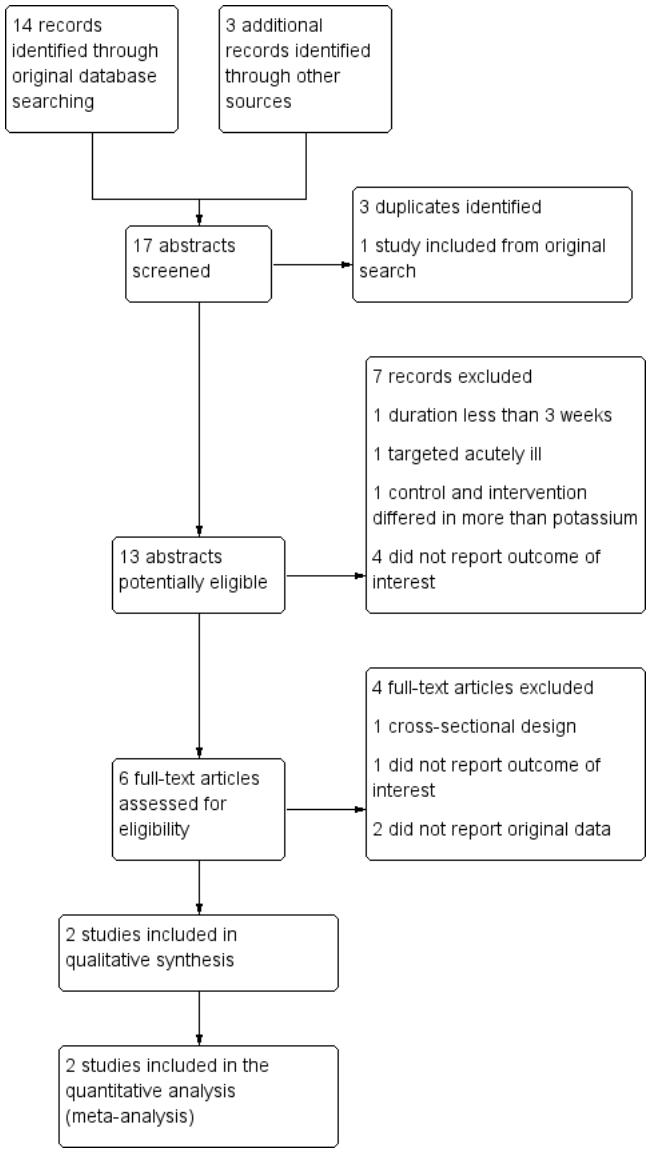


Figure 3.3 Flow through screening, inclusion, exclusion – cohort studies

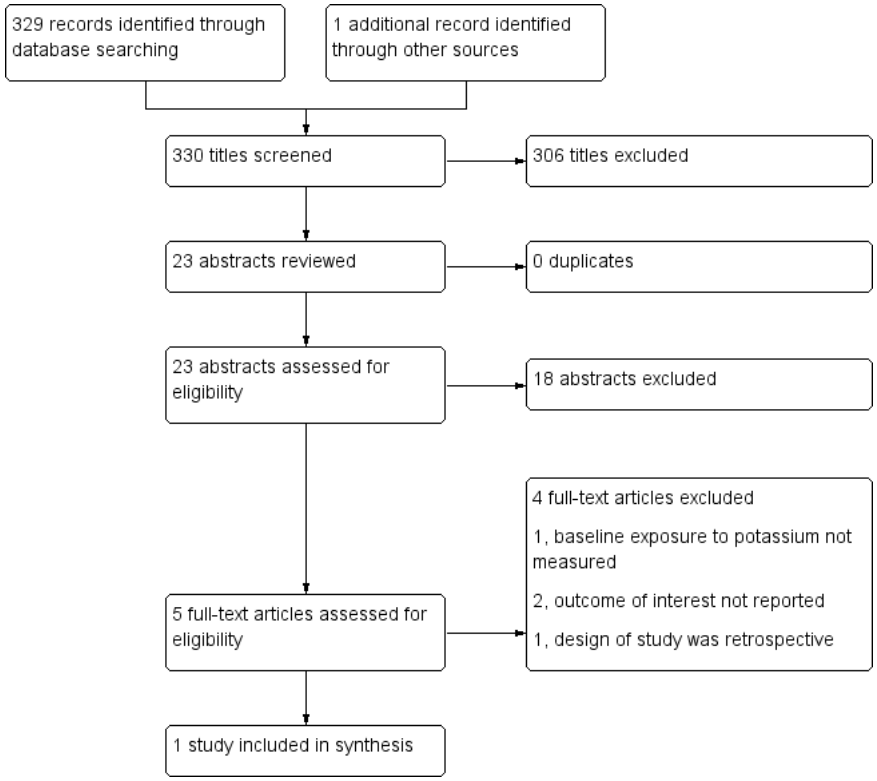


Figure 3.4 Resting systolic blood pressure

Study or Subgroup	Increased potassium Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Miller 1987	1.4	11.5	38	2	11.93	38	2.1%	-0.60 [-5.87, 4.67]
Sinaiko 1993M	1.9	2.4	36	1.6	2.3	34	48.5%	0.30 [-0.80, 1.40]
Sinaiko 1993M	0.5	2.37	35	1.4	2.37	35	47.7%	-0.90 [-2.01, 0.21]
Wilson 1996	-3	11.4	15	-2	8	13	1.1%	-1.00 [-8.22, 6.22]
Wilson 1996	3	9.17	5	-2	8.54	7	0.6%	5.00 [-5.23, 15.23]
Total (95% CI)			**129**			**127**	**100.0%**	**-0.28 [-1.05, 0.49]**

Heterogeneity: Tau² = 0.00; Chi² = 3.34, df = 4 (P = 0.50); I² = 0%
Test for overall effect: Z = 0.71 (P = 0.47)

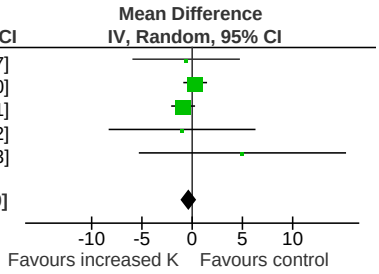


Figure 3.5 Resting systolic blood pressure: sensitivity analysis, removal of non-randomized trials

Study or Subgroup	Increased potassium Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Miller 1987	1.4	11.5	38	2	11.93	38	0.0%	-0.60 [-5.87, 4.67]
Sinaiko 1993M	1.9	2.4	36	1.6	2.3	34	49.2%	0.30 [-0.80, 1.40]
Sinaiko 1993M	0.5	2.37	35	1.4	2.37	35	48.6%	-0.90 [-2.01, 0.21]
Wilson 1996	-3	11.4	15	-2	8	13	1.5%	-1.00 [-8.22, 6.22]
Wilson 1996	3	9.17	5	-2	8.54	7	0.7%	5.00 [-5.23, 15.23]
Total (95% CI)			**91**			**89**	**100.0%**	**-0.27 [-1.15, 0.62]**

Heterogeneity: Tau² = 0.10; Chi² = 3.32, df = 3 (P = 0.34); I² = 10%
Test for overall effect: Z = 0.59 (P = 0.55)

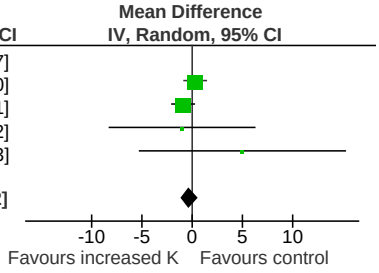


Figure 3.6 Resting diastolic blood pressure

Study or Subgroup	Increased potassium Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Miller 1987	1.6	10.99	38	0.9	10.76	38	4.9%	0.70 [-4.19, 5.59]
Sinaiko 1993M	1.6	4.2	36	3.2	4.1	34	31.0%	-1.60 [-3.54, 0.34]
Sinaiko 1993M	0.9	3	35	1.8	3	35	59.4%	-0.90 [-2.31, 0.51]
Wilson 1996	-2	6.56	15	-4	8.19	13	3.8%	2.00 [-3.55, 7.55]
Wilson 1996	-1	11.53	5	-1	9	7	0.8%	0.00 [-12.11, 12.11]
Total (95% CI)			**129**			**127**	**100.0%**	**-0.92 [-2.00, 0.16]**

Heterogeneity: Tau² = 0.00; Chi² = 1.98, df = 4 (P = 0.74); I² = 0%
Test for overall effect: Z = 1.67 (P = 0.10)

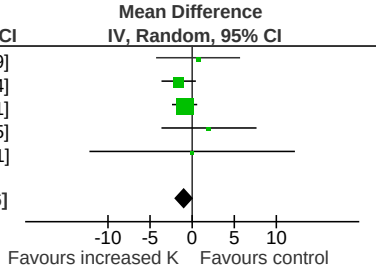


Figure 3.7 Resting diastolic blood pressure: sensitivity analysis, removal of non-randomized trials

Study or Subgroup	Increased potassium Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Miller 1987	1.6	10.99	38	0.9	10.76	38	0.0%	0.70 [-4.19, 5.59]
Sinaiko 1993M	1.6	4.2	36	3.2	4.1	34	32.7%	-1.60 [-3.54, 0.34]
Sinaiko 1993M	0.9	3	35	1.8	3	35	62.5%	-0.90 [-2.31, 0.51]
Wilson 1996	-2	6.56	15	-4	8.19	13	4.0%	2.00 [-3.55, 7.55]
Wilson 1996	-1	11.53	5	-1	9	7	0.8%	0.00 [-12.11, 12.11]
Total (95% CI)			**91**			**89**	**100.0%**	**-1.00 [-2.12, 0.11]**

Heterogeneity: Tau² = 0.00; Chi² = 1.53, df = 3 (P = 0.67); I² = 0%
Test for overall effect: Z = 1.77 (P = 0.08)

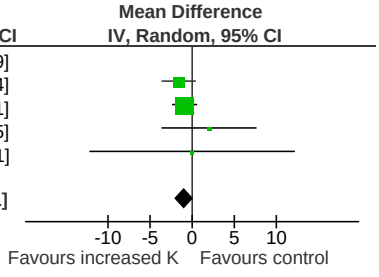


Figure 3.8 Ambulatory systolic blood pressure – day

Study or Subgroup	Increased potassium Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Wilson 1996	-5	9.85	15	-2	9.17	13	50.2%	-3.00 [-10.05, 4.05]
Wilson 1996	9	5.57	5	4	7	7	49.8%	5.00 [-2.12, 12.12]
Total (95% CI)			**20**			**20**	**100.0%**	**0.98 [-6.86, 8.82]**

Heterogeneity: Tau² = 18.93; Chi² = 2.45, df = 1 (P = 0.12); I² = 59%
Test for overall effect: Z = 0.25 (P = 0.81)

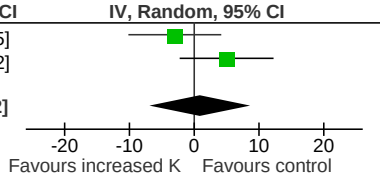


Figure 3.9 Ambulatory systolic blood pressure – night

Study or Subgroup	Increased potassium Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Wilson 1996	4	9.85	15	4	9.54	13	65.0%	0.00 [-7.19, 7.19]
Wilson 1996	0	6.93	5	1	10.39	7	35.0%	-1.00 [-10.81, 8.81]
Total (95% CI)			**20**			**20**	**100.0%**	**-0.35 [-6.15, 5.45]**

Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.87); I² = 0%
Test for overall effect: Z = 0.12 (P = 0.91)

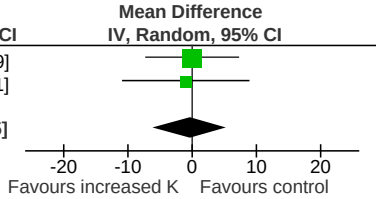


Figure 3.10 Ambulatory diastolic blood pressure – day

Study or Subgroup	Increased potassium Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Wilson 1996	-3	5.57	15	-3	7	13	57.5%	0.00 [-4.74, 4.74]
Wilson 1996	5	3.61	5	3	6.08	7	42.5%	2.00 [-3.50, 7.50]
Total (95% CI)			**20**			**20**	**100.0%**	**0.85 [-2.74, 4.44]**

Heterogeneity: Tau² = 0.00; Chi² = 0.29, df = 1 (P = 0.59); I² = 0%
Test for overall effect: Z = 0.46 (P = 0.64)

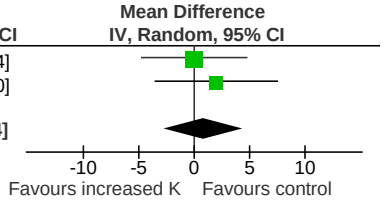
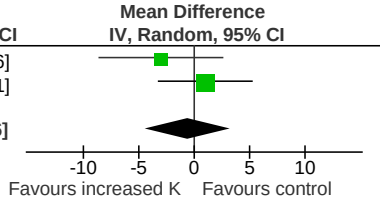


Figure 3.11 Ambulatory diastolic blood pressure – night

Study or Subgroup	Increased potassium Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Wilson 1996	-1	4.58	5	2	5.2	7	39.2%	-3.00 [-8.56, 2.56]
Wilson 1996	1	6.08	15	0	5.29	13	60.8%	1.00 [-3.21, 5.21]
Total (95% CI)			**20**			**20**	**100.0%**	**-0.57 [-4.40, 3.26]**

Heterogeneity: Tau² = 1.66; Chi² = 1.26, df = 1 (P = 0.26); I² = 21%
Test for overall effect: Z = 0.29 (P = 0.77)



4 References to studies

4.1 Included studies

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

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Annex 1: Electronic search strategy

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, as well as, an indexer limit for controlled trials. This strategy was supplied by the WHO librarian to facilitate data retrieval. These searches were run without any age limit; hence, studies reporting on children were recorded manually as they were identified.

Medline was searched through the PubMed database for the previous 6 months only, because all articles 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. Where fewer than three studies were found, a subsequent search for cohort studies was conducted.

A1 Search for randomized controlled trials

A1.1 EMBASE

Searches conducted on 25 August 2011 in EMBASE.[1]

Blood pressure

- Dates needed: 1 January 2004 to present
- No language limits
- Restricted search

Step	Search terms		# Citations
Step 1	'potassium'/exp OR 'potassium chloride'/exp		111,188
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		339
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		324
Step 4	Step 1 AND Step 2 AND Step 3		169

[1] See http://www.embase.com. EMBASE.COM contains over 24 million indexed records and more than 7,500 current, mostly peer-reviewed journals with over 2,000 biomedical titles not currently offered by MEDLINE. Medline citations are included in EMBASE.COM

Broader search

Step	Search terms	# Citations
Step 1	'potassium'/exp OR 'potassium' OR 'potassium chloride'/exp OR 'potassium chloride' OR potassium:ab,ti	301,383
Step 2	'hypertension'/exp OR 'blood pressure'/exp OR 'hypertension'/exp OR 'blood pressure':ab,ti OR hypertensive:ab,ti OR 'blood pressure'/exp AND 'intravascular pressure':ab,ti OR normotension:ab,ti OR 'vascular pressure':ab,ti OR 'blood pressure monitoring'/exp	684,004
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	925,155
Step 4	Step 1 AND Step 2 AND Step 3	62,873
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	833,589
Step 6	Step 4 AND Step 5	1,256
Step 5	Step 4 AND ([cochrane review]/lim OR [controlled clinical trial]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR [systematic review]/lim)	930
Step 6	Step 4 AND Step 5	468
Step 7	Step 6 NOT [animals]/lim	721
Step 8	Step 6 AND [animals]/lim AND [humans]/lim	20
Step 9	Step 7 OR Step 8	741
Step 10	Step 9 NOT (Citations found in Restricted Search Step 3)	575

Adverse effects

- No language limits
- No date limits.
- Restricted search

Step	Search terms		# Citations
Step 1	'potassium'/exp OR 'potassium chloride'/exp		111,188
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 'sympathin e':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)		25,043
Step 3	Step 1 AND Step 2		276

Broader search

Step	Search terms		# Citations
Step 1	sium'/exp OR 'potassium chloride'/exp OR potassium:ab,ti		185.013
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 'sympathin e':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		588,203
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		833,589
Step 4	Step 1 AND Step 2 AND Step 3		731
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)		488
Step 6	Step 4 OR Step 5		842
Step 7	Step 6 NOT [animals]/lim		720
Step 8	Step 6 AND [animals]/lim AND [humans]/lim		22
Step 9	Step 6 OR Step 7		742
Step 10	Step 9 NOT (Citations found in Restricted Search Step 3)		468

A1.2 PubMed

- No language limits
- Date conducted: 28 August 2011
- Date limit: Previous 180 days

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])

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])

A1.3 LILACS

- No language limits
- Date conducted: 1 September 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

A1.4 WHO International Clinical Trials Registry Platform

- No language limits
- Date conducted: 1 September 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)

A1.5 Cochrane Central Register of Controlled Trials

- No language limits
- Date conducted: 6 September 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))**

#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

A2 Search for cohort studies

We conducted a search for cohort studies in children. We scanned the references from the systematic review of potassium in adults from the Dietary Guidelines Advisory Council of the United States Department of Agriculture[1] to locate studies that were excluded because they

[1] www.nutritionevidencelibrary.org

were in children or adolescents. We also conducted electronic searches in EMBASE and Medline.

A2.1 EMBASE

Search conducted on 21 September 2011 in EMBASE.

Step	Search terms	# Citations
#1	'potassium'/exp OR 'potassium' OR 'potassium chloride'/exp OR 'potassium chloride'	302,578
#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	19,596
#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	941,286
#4	#1 AND #2 AND #3	462
#5	'potassium'/exp OR 'potassium chloride'/exp OR potassium:ab,ti	185,607
#6	'hypertension'/exp OR 'blood pressure':ab,ti OR hypertensive:ab,ti OR 'blood pressure'/exp AND 'intravascular pressure':ab,ti OR normotension:ab,ti OR 'vascular pressure':ab,ti OR 'blood pressure monitoring'/exp	19,844
#7	'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	689,437
#8	'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	941,286
#9	'potassium'/exp OR 'potassium chloride'/exp OR potassium:ab,ti	185,607
#10	'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	840,506

Step	Search terms	# Citations
#11	#1 AND #7 AND #8 AND #10	705
#12	#1 AND #7 AND #8	3,722
#13	#1 AND #7 AND #8 AND ([cochrane review]/lim OR [controlled clinical trial]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR [systematic review]/lim)	473
#14	#11 OR #13	821
#15	'child'/exp OR 'children'/exp OR 'youth'/exp OR youth* OR newborn* OR 'newborn'/exp OR 'new born' OR 'childhood disease'/exp OR 'baby'/exp OR babies OR 'infant'/exp OR infant* OR childhood* OR toddler* OR kid OR kids OR 'young patient' OR boy* OR girl* OR 'young age' OR pediatr* OR paediatr* OR 'child death'/exp OR 'child health'/exp OR 'child care'/exp OR 'childhood mortality'/exp OR 'child hospitalization'/exp OR 'pediatric hospital'/exp OR child*	3,445,565
#16	#1 AND #7 AND #8	3,722
#17	#15 AND #16	549
#18	#17 NOT #14	455
#19	#17 NOT #14 AND [2004-2012]/py	455
#20	#6 NOT [animals]/lim	17,690
#21	#19 AND 6 AND [animals]/lim AND [humans]/lim	12
#22	#19 AND [animals]/lim AND [humans]/lim	17
#23	#19 AND [animals]/lim	143
#24	#19 NOT [animals]/lim	311
#25	#22 OR #24	329

A2.2 PubMed

- No language limits
- Date conducted: 21 September 2011
- Date limit: Previous 180 days

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]) NOT (animals [mh] NOT humans [mh])

Annex 2: Example extraction sheet

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 communication needed?	Author contact	Year	Journal	Volume	Pages	RepType	Language	Country	Sponsor	Inclusion	Exclusion	Comparisons made in study	Final Exclusion (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 desgin

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				Salt anion to K+	Notes
		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 (%)
					Hyper tensive	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)

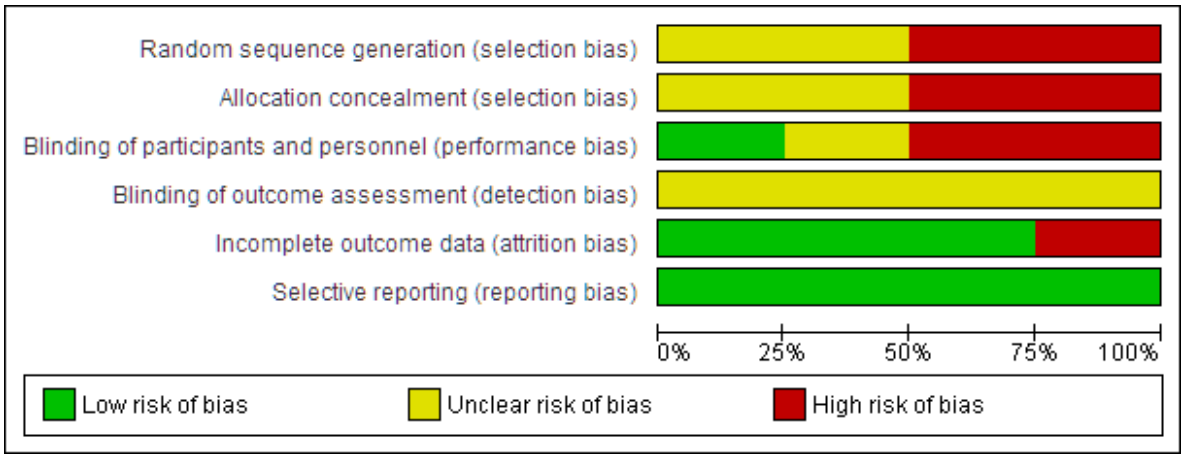
Part 1

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

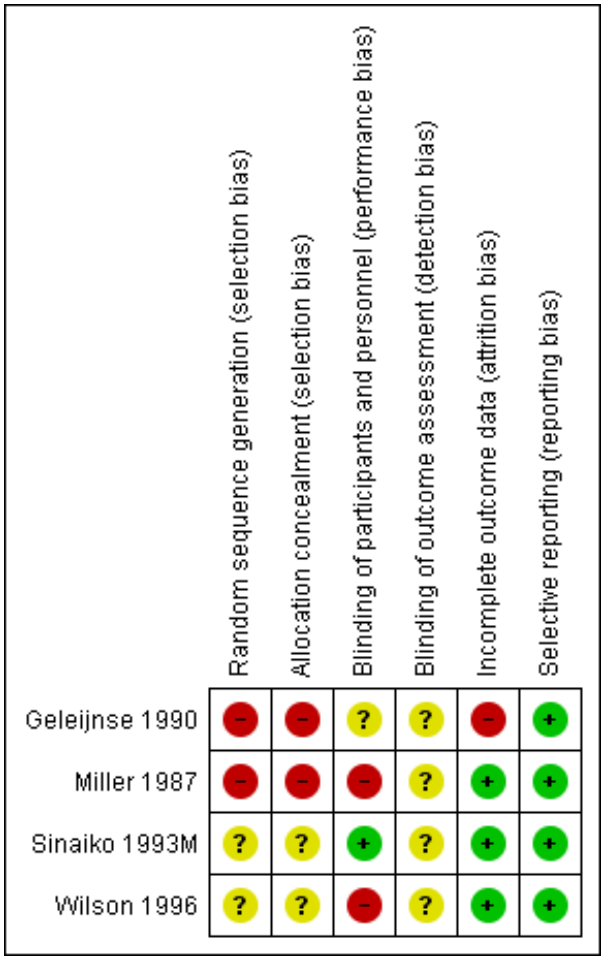
Part 2

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

Annex 3: Risk of bias graph



Annex 4: Risk of bias summary



Annex 5: GRADE evidence profile

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

Quality assessment							No of participants		Effect	Quality	Importance
No of studies / comparisons	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Increased potassium	Control	Absolute		
Resting systolic blood pressure (follow-up 0.75 months - 3 years; units mmHg; better indicated by lower values)											
3 / 5	controlled trials	serious risk of bias[1]	no serious inconsistency	no serious indirectness	serious imprecision[2]	none	129	127	MD 0.28 lower (1.05 lower to 0.49 higher)	⊕⊕ Low	CRITICAL
Resting systolic blood pressure (follow-up 7 years; units mmHg/year; better indicated by lower values)											
1 / 1	observational cohort studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	78	78	MD 1.0 lower (1.7 to 0.4 lower)	⊕⊕ Low[3]	CRITICAL
Resting diastolic blood pressure (follow-up 0.75 months - 3 years; units mmHg; better indicated by lower values)											
3 / 5	controlled trials	serious risk of bias[1]	no serious inconsistency	no serious indirectness	serious imprecision[2]	none	129	127	MD 0.92 lower (2.0 lower to 0.2 higher)	⊕⊕ Low	CRITICAL
Ambulatory systolic blood pressure (DAY) (follow-up 0.75 months; units mmHg; better indicated by lower values)											
1 / 1	randomized controlled trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[2]	none	20	20	MD 0.98 higher (6.9 lower to 8.8 higher)	⊕⊕⊕ Moderate[3]	CRITICAL
Ambulatory diastolic blood pressure (DAY) (follow-up 0.75 months; units mmHg; better indicated by lower values)											
1 / 1	randomized controlled trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[2]	none	20	20	MD 0.85 higher (2.7 lower to 4.4 higher)	⊕⊕⊕ Moderate[3]	CRITICAL
Ambulatory systolic blood pressure (NIGHT) (follow-up 0.75 months; units mmHg; better indicated by lower values)											
1 / 1	randomized controlled trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[2]	none	20	20	MD 0.35 lower (6.2 lower to 5.5 higher)	⊕⊕⊕ Moderate[3]	CRITICAL
Ambulatory diastolic blood pressure (NIGHT) (follow-up 0.75 months; units mmHg; better indicated by lower values)											
1 / 1	randomized controlled trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[2]	none	20	20	MD 0.57 lower (4.4 lower to 3.3 higher)	⊕⊕⊕ Moderate[3]	CRITICAL
Total cholesterol (better indicated by lower values)											
0 / 0	No studies reported blood lipids as an outcome										IMPORTANT
Plasma noradrenaline (better indicated by lower values)											
0 / 0	No studies reported catecholamines as an outcome										IMPORTANT
Minor side effects (better indicated by lower values)											
0 / 0	No studies reported minor side effects such as headache, dizziness, or edema										IMPORTANT

[1] One of three studies was not randomized.

[2] 95%CI crosses zero (0)

[3] Only one study contributed to estimate

Annex 6: List of tables and figures

Tables

Figures

Full list of references

1 WHO. Global status report on noncommunicable diseases. Geneva, World Health Organization (WHO), 2010 (http://whqlibdoc.who.int/publications/2011/9789240686458_eng.pdf).

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