Effect of increased potassium intake on cardiovascular disease, coronary heart disease and stroke

World Health Organization

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Contents

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Abbreviations and acronyms

BMI	body mass index
CCNFSDU	the Codex Committee on Nutrition and Food for Special Dietary Uses
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
HR	hazard ratio
MI	myocardial infarction
NCD	noncommunicable disease
NUGAG	the Nutrition Guidance Expert Advisory Group
PRISMA	preferred reporting items for systematic reviews and meta-analyses
RCT	randomized controlled trial
RR	risk ratio
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 about 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 (CHD) 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. Three meta-analyses of randomized controlled trials (RCTs) comparing increased potassium to 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 in exclusively hypertensive individuals concluded that increased potassium had no effect on blood pressure (Dickinson et al., 2006). Several large cohort studies have found an inverse association between potassium intake and risk of stroke (Ascherio et al., 1998; Khaw & Barrett-Connor, 1987); however, other studies have reported no relationship between potassium intake and stroke (Geleijnse et al., 2007; Green et al., 2002). The results from studies reporting all CHD and CVD are also contradictory (Cook et al., 2009; Geleijnse et al., 2007; Umesawa et al., 2008).

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 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).

The 2002 joint WHO/Food and Agriculture Organization of the United Nations 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, provided that 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. Since that time, the results of numerous studies exploring the direct relationship between potassium intake and CVD, stroke and CHD have been published. In light of these recent publications and the ever

increasing importance of NCDs globally, WHO undertook this review. NUGAG will make use of this document when generating WHO guidelines on potassium intake.

1.3 Objectives

The overall objective of the review was to assess the effect of increased potassium intake compared to usual potassium intake on CVD, stroke and CHD in adults.

Specific objectives were to assess whether there is any effect on CVD, stroke and CHD in adults of consuming:

- more potassium compared to consuming less potassium;
- potassium at a level resulting in a urinary potassium excretion of at least 70 mmol/day (see box below) compared to consuming less potassium;
- potassium at a level resulting in a urinary potassium excretion of at least 90 mmol/day compared to consuming less potassium;
- potassium at a level resulting in a urinary potassium excretion of at least 120 mmol/day compared 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 (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 RCTs and prospective cohort studies.

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 also considered studies in people with chronic conditions such as overweight or obesity, diabetes or chronic nephrolithiasis (a chronic form of kidney stones). We excluded studies targeting those who were acutely ill or infected with human immunodeficiency virus (HIV).

Outcome measures

The primary outcome measures were:

- all CVD events (fatal and non-fatal);
- all stroke events (fatal and non-fatal);
- all CHD events (fatal and non-fatal).

Secondary outcomes were all-cause mortality and all other outcomes reported by the authors of the original study.

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 published subsequent to the search date used in that review.

In the second phase, we undertook a complete search for data published since the date of the search performed in the identified systematic review (see *Electronic databases* and *Other resources*, below) for RCTs comparing higher to usual or lower potassium intake, or prospective cohort studies comparing potassium intake as the exposure to the outcomes of interest.

Systematic reviews

In August 2011, we searched the PubMed database and The Cochrane Library for systematic reviews on potassium intake and CVD, stroke and CHD. We considered systematic reviews of RCTs and cohort studies, and contacted authors of the systematic reviews to consult about any other systematic reviews that may have been published.

Electronic databases

In September 2011, we conducted a literature search of PubMed database, to retrieve any primary studies published in the scientific literature. 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 in the reference lists of identified papers. For assistance in identifying continuing or unpublished studies, we contacted the WHO Department of Nutrition for Health and Development and other international partners, such as academic and research institutions with a known interest in this field.

2.3 Data collection and analysis

2.3.1 Selection of studies

Identified references were independently assessed for potential relevance by two reviewers. The title, abstract and keywords of every record retrieved were scanned independently by two authors to determine which studies required further assessment.

A full article was retrieved when the information given in the title, abstract and keywords suggested that the study:

- included a quantitative measure of exposure (potassium intake) and compared this to an outcome of interest, or compared groups consuming different levels of potassium;
- had a prospective design;
- did not target HIV-infected or acutely ill patients;
- had a duration of at least 8 weeks in the case of RCTs and 1 year in the case of cohort studies;
- reported an outcome of interest.

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

Differences in opinion were resolved by discussion, to reach consensus. Two review authors independently assessed for inclusion all the potentially eligible studies, according to the above prespecified inclusion criteria. Where studies were published only as abstracts, or references contained little information on methods, we attempted to contact the authors to obtain further details of study design and results.

Where 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 (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

[1] www.who.int/nutrition

Annex 2), with any disagreements resolved through discussion and consensus. Any relevant missing information on the study was sought from the authors of the original reference. 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 and duration of follow-up.
- *Participants* – selection of participants, exclusion criteria, total number, sex, age, baseline characteristics, diagnostic criteria, similarity of groups at baseline (including any co-morbidity), 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 to control blood pressure.
- *Outcomes* – outcomes specified above, any other outcomes assessed, other events, length of follow-up and quality and completeness of reporting of outcomes.
- *Results* – outcomes specified above and including a measure of variation (if necessary, converted to the measures of effect specified below).

Duplicate publications

In the case of duplicate publications and companion references of a primary study, we attempted to maximize the yield of information by simultaneously evaluating all available data. In cases of doubt, the original reference (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 (version 2008) and checked for accuracy by a second author. In cases of disagreement, a third party was consulted, and a judgement was made based on consensus. We used the broad categories for assessment of risk of bias recommended in the *Cochrane handbook for systematic reviews of interventions 5.0.2* (Higgins et al., 2009) for randomized trials and non-randomized studies. In the case of cohort studies, we also took into account particular sources of bias associated with this study design.

Deeks et al (2003) 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 quality domains by recording in detail the characteristics of the sample, the intervention and its implementation, completeness of follow-up, and methods used in the analysis to adjust for possible confounding factors.

We assessed the potential sources of bias described below.

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

For each included study, and for each outcome or class of outcomes, we described the completeness of the data, including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total at baseline), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Methods were categorized as:

- *adequate* – trials where few drop-outs or losses to follow-up were noted and, in the case of RCTs, an intention-to-treat analysis was possible;
- *inadequate* – the rate of exclusion was at least 20%, or there were wide differences in exclusions between groups;
- *unclear*.

Selective reporting bias

For each included study, we described how we investigated the possibility of selective outcome reporting bias and what we found. Methods were categorized as:

- *adequate* – where it was clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review had been reported;
- *inadequate* – where not all the study's prespecified outcomes had been reported, one or more reported primary outcomes were not prespecified, outcomes of interest were reported incompletely and so could not be used, or the study failed to include results of at least one 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, where 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 are drawn and, where applicable, to determine whether groups were drawn from comparable populations. 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

We recorded the manner in which exposure was measured and the method or methods used to define exposure groups. Where groups were followed up over time at 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, and noted whether there was blinding of outcome assessment.

Collection of outcome data and loss to follow-up

We assessed whether the characteristics of those remaining to follow-up were comparable with the original sample recruited, and 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 exposed and unexposed groups. For each study, we noted which factors were used to adjust for possible confounding, because these may vary between studies considering the same outcome and may be an important source of between-study heterogeneity.

Other sources of bias

For each included study, we described 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, recording answers as “yes”, “no” or “unclear”.

2.3.4 Measures of treatment effect

Dichotomous data were expressed as risk ratio (RR) or hazard ratio (HR) with 95% confidence intervals (CI). The reference group was always the group with the lowest intake of potassium, and the comparison groups were those with higher potassium intakes. Thus, an RR or HR of less than one signified a protective effect of increased potassium intake on risk of the outcome of interest.

2.3.5 Missing data

We obtained relevant missing data from authors, where feasible.

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 *Cochrane handbook for systematic reviews of interventions* (Higgins et al., 2009). Overall results were calculated based on the random-effects model. Where data were reported in forms that could not easily be converted into standard measures, data were summarized in a narrative format, and different comparisons were analysed separately.

For conducting the meta-analyses, we included RR and HR values from original manuscripts that were generated from models adjusting for the most number of covariates, excluding blood pressure. To reduce potential bias from confounding, we chose the model controlling for the most covariates. We chose the models not controlling for blood pressure, because blood pressure has a strong relationship with CVD, stroke and CHD, and may be on the causal pathway between potassium intake and these outcomes (Lewington et al., 2002). We also performed an additional analysis using the RR or HR generated from the models, adjusting for the most number of covariates (most-adjusted models) presented in the original reference.

Assessment of heterogeneity

In the event of substantial clinical, methodological or statistical heterogeneity, study results were not reported as meta-analytically pooled effect estimates. 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 more indicates a considerable level of inconsistency (Higgins et al., 2009). When heterogeneity was found, we attempted to determine the potential causes by examining individual study and subgroup characteristics.

2.3.7 Subgroup analysis

We conducted both overall analyses and subgroup analyses for each outcome to explore effect size differences between groups, as follows:

- by potassium urinary excretion level in the comparison group (<70 mmol/day vs 70–90 mmol/day vs 90–120 mmol/day vs ≥120 mmol/day);
- by outcome (overall fatal and non-fatal events, fatal events only, non-fatal events only).

2.3.8 Sensitivity analysis

We carried out a sensitivity analysis to examine the effects of removing studies at high risk of bias from the analysis.

2.3.9 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). A "risk of bias summary" (**Annex 3**) and a "risk of bias graph" (**Annex 4**) were generated. We assessed the impact of individual bias domains on study results at end point and study levels. We used the GRADEProfiler (version 3.6) software to assess the quality of the body of evidence according to the methodology outlined in *The grading of recommendations assessment, development and evaluation* (Guyatt et al., 2008).

3 Results

3.1 Results of the search

A recent high-quality systematic review of potassium intake and CVD outcomes was identified in the literature (D'Elia et al., 2011). The outcomes reported in this review were CVD, stroke and CHD. The authors conducted a systematic literature search and used similar inclusion criteria to the current review. They found no RCTs reporting data on the effect of potassium intake on incidence of CVD, stroke and CHD, and instead included cohort studies in the review. We updated the D'Elia review and analysed data from that review in such a way as to address the specific objectives of the current review. We screened the full text of each of the 11 references (coming from 11 studies) included in the D'Elia review against the inclusion criteria of the current review. Investigators involved in the D'Elia review provided data, input and assistance in generating the current systematic review.

The date of the electronic search of the D'Elia systematic review was December 2009. The electronic literature search for the current review was limited to 1999–2011. The time overlap provided added assurance that all primary studies were captured in the current review. This search identified 39 additional cohort studies or RCTs. One additional cohort study was identified through other resources. Thus, a total of 51 references were identified (after removal of duplicates). The title and abstract of those 51 references were screened, and the complete reference was reviewed from 12 prospective cohort studies. All 12 of those references – 11 of which had been included in D'Elia review – were included in the current review. The flow of records through screening, exclusion and inclusion is shown in **Figure 3.1**.

3.2 Retrieval of missing data

Marianne Geleijnse (Geleijnse et al., 2007) and Hugh Tunstall-Pedoe (Tunstall-Pedoe et al., 1997) were contacted; they generously provided additional information about their studies. Also, Francesco Cappuccio provided additional data from the systematic review published in 2011 (D'Elia et al., 2011).

3.3 Included studies

Details of the characteristics of the included studies are shown in Section 3.9 (Tables 3.1–3.24).

3.3.1 Settings

All 12 included studies were prospective cohort studies published in English. Of the 12 studies, six were undertaken in the United States of America (USA) (Ascherio et al., 1998; Bazzano et al., 2001; Cook et al., 2009; Green et al., 2002; Iso et al., 1999; Khaw & Barrett-Connor, 1987), one in the Netherlands (Geleijnse et al., 2007), one in Finland (Larsson et al., 2008), one in Scotland (Tunstall-Pedoe et al., 1997), one in Japan (Umesawa et al., 2008) and one in Taiwan (Weng et al., 2008); one study included participants from 40 countries (O'Donnell et al., 2011).

Ascherio et al. (1998) and Cook et al. (2009) were conducted in normotensive populations. One study was in a heterogeneous population (normotensive and hypertensive), but excluded those with blood pressure >160/100 mmHg (O'Donnell et al., 2011). The remaining studies (Bazzano et al., 2001; Geleijnse et al., 2007; Green et al., 2002; Iso et al., 1999; Khaw

& Barrett-Connor, 1987; Larsson et al., 2008; Tunstall-Pedoe et al., 1997; Umesawa et al., 2008; Weng et al., 2008) did not specify the hypertensive status of the study population. The duration of follow-up ranged from 2 years (Umesawa et al., 2008) to 19 years (Bazzano et al., 2001).

3.3.2 Participants

The number of participants in the trials ranged from 443 (Weng et al., 2008) to 38,726 (Ascherio et al., 1998). There were 127,038 participants in total.

3.3.3 Exposure

All studies were intended to compare health outcomes between groups of participants consuming the lowest reported potassium intake (reference group) to groups consuming increased potassium (comparison groups).

In five studies, there was one comparison between the reference group and a group consuming sufficient potassium to result in a urinary potassium excretion of <70 mmol potassium/day (Bazzano et al., 2001; Cook et al., 2009; Iso et al., 1999; O'Donnell et al., 2011; Umesawa et al., 2008). Five studies reported one comparison between the reference and a group consuming sufficient potassium to result in a urinary potassium excretion of 70–90 mmol potassium/day (Ascherio et al., 1998; Cook et al., 2009; Iso et al., 1999; O'Donnell et al., 2011; Weng et al., 2008). In five studies, there was a comparison between the reference group and a comparison group consuming sufficient potassium to result in a urinary potassium excretion of 90–120 mmol potassium/day (Ascherio et al., 1998; Bazzano et al., 2001; Green et al., 2002; Iso et al., 1999; Larsson et al., 2008). One study reported a comparison between the reference group and a group consuming sufficient potassium to result in a urinary potassium excretion of >120 mmol/day (Larsson et al., 2008). One study reported the effect on outcomes for an increase in intake of 10 mmol potassium/day (Khaw & Barrett-Connor, 1987) and one study reported the effect on outcomes for an increase in intake of 45 mmol potassium/day (one standard deviation) (Geleijnse et al., 2007).

In two studies, participants were not taking any medical therapy to control blood pressure (Bazzano et al., 2001; Cook et al., 2009). In three studies, participants included both treated and untreated individuals (Geleijnse et al., 2007; O'Donnell et al., 2011; Weng et al., 2008). In six studies, the status of consumption of medication to control blood pressure was unspecified or unknown (Ascherio et al., 1998; Iso et al., 1999; Khaw & Barrett-Connor, 1987; Larsson et al., 2008; Tunstall-Pedoe et al., 1997; Umesawa et al., 2008). In one study, participants were divided by status of consumption of diuretics to control blood pressure (Green et al., 2002). Results were reported separately for the group in which no participants consumed diuretics (or any other medication), and the group in which all participants consumed diuretics.

3.3.4 Outcome measures

Most studies divided the population into quartiles or quintiles of potassium intake at baseline, and measured the outcomes of interest over time (Ascherio et al., 1998; Bazzano et al., 2001; Cook et al., 2009; Green et al., 2002; Iso et al., 1999; Larsson et al., 2008; Tunstall-Pedoe et al., 1997; Umesawa et al., 2008; Weng et al., 2008). One study divided the population into three subgroups (of unequal size) based on potassium intake at baseline (O'Donnell et al., 2011). One study followed participants for 10–15 years after having participated for 18 or 36 months in an RCT of sodium intake and blood pressure (Cook et al., 2009). The participants included in the cohort study were those who were in the control group of the RCT.

Cardiovascular disease

Two studies reported data on all CVD (fatal and non-fatal) (Cook et al., 2009; Weng et al., 2008). Two other studies reported data on fatal CVD only (Geleijnse et al., 2007; Umesawa et al., 2008). One study reported data on all CVD (fatal and non-fatal) and on fatal CVD (O'Donnell et al., 2011). No studies reported results of non-fatal CVD separate from fatal CVD.

Stroke

Eight studies reported data on stroke events (fatal and non-fatal) (Ascherio et al., 1998; Bazzano et al., 2001; Geleijnse et al., 2007; Green et al., 2002; Iso et al., 1999; Larsson et al., 2008; O'Donnell et al., 2011; Weng et al., 2008). Two studies reported data on fatal stroke only (Khaw & Barrett-Connor, 1987; Umesawa et al., 2008).

Coronary heart disease

Four studies reported data on CHD (Bazzano et al., 2001; Geleijnse et al., 2007; Tunstall-Pedoe et al., 1997; Umesawa et al., 2008). The Tunstall-Pedoe study, which reported HRs for fatal CHD, did not provide a measure of variance and was not included in the meta-analysis. One study reported incidence rates of fatal CHD (Umesawa et al., (2008). Two studies reported on combined risk of fatal and non-fatal CHD events (Bazzano et al., (2001); Geleijnse et al., (2007).

All-cause mortality

Two studies reported all-cause mortality (Geleijnse et al., 2007; Tunstall-Pedoe et al., 1997).

3.5 Excluded studies

Among the studies identified from the previous review or from other sources that passed the abstract and title screening, none were excluded from the current review.

3.6 Exposure and outcome results

The relationship between potassium intake and the outcomes of interest are summarized in the effect estimate tables (**Table 3.25** and **3.26**), as well as in **Figures 3.2–3.10**.

3.6.1 Cardiovascular disease

The meta-analysis of four studies with four comparisons reporting potassium intake and CVD was inconclusive (RR = 0.88, 95%CI: 0.70, 1.11) (**Table 3.25** and **Figure 3.2**). None of these studies reported an RR or HR for a model adjusting for blood pressure; therefore, no further analysis was conducted.

The meta-analysis of three studies with three comparisons in which the comparison group (high potassium intake) had a urinary potassium excretion of <70 mmol/day was inconclusive (RR = 0.87, 95%CI: 0.71, 1.06). The meta-analysis of two studies with two comparisons in which the comparison group had a urinary potassium excretion of 70–90 mmol potassium/day was also inconclusive (RR = 0.84, 95%CI: 0.61, 1.15). (**Table 3.25** and **Figure 3.3**).

3.6.2 Stroke

The meta-analysis of nine studies with nine comparisons including RRs and HRs calculated from models not adjusting for blood pressure detected a protective effect of increased potassium intake on risk of stroke (RR = 0.76, 95%CI: 0.66, 0.89) (**Table 3.25** and **Figure 3.4**).

Two studies reported models that adjusted for additional covariates including blood pressure, and one study reported only a model adjusting for blood pressure as well as other covariates. Repeating the analysis, including the RR or HR from these fully adjusted models when available, generated a similar result (RR = 0.76, 95%CI: 0.66, 0.88) (**Table 3.26** and **Figure 3.5**).

The meta-analysis of four studies with four comparisons in which the comparison group (high potassium intake) had a urinary potassium excretion of <70 mmol/day detected a protective effect of increased potassium intake on risk of stroke (RR = 0.82, 95%CI: 0.71, 0.93). The meta-analysis of four studies with four comparisons in which the comparison group had a urinary potassium excretion of 70–90 mmol potassium/day detected a protective effect of increased potassium intake on risk of stroke (RR = 0.70, 95%CI: 0.56, 0.88). The meta-analysis of five studies with six comparisons in which the comparison group had a urinary potassium excretion of >90 mmol but ≤120 mmol potassium/day was inconclusive (RR = 0.86, 95%CI: 0.71, 1.05). Only one study had a comparison group with a urinary potassium excretion of >120 mmol potassium/day and the results were also inconclusive (RR = 0.87, 95%CI: 0.77, 0.98) (**Table 3.25** and **Figure 3.6**).

The meta-analysis of seven studies with seven comparisons reporting fatal and non-fatal outcomes combined detected a protective effect of increased potassium intake on risk of stroke (RR = 0.78, 95%CI: 0.66, 0.93). The meta-analysis of two studies with three comparisons that reported fatal stroke detected a protective effect of increased potassium intake on risk of fatal stroke (RR = 0.69, 95%CI: 0.54, 0.88) (**Table 3.25** and **Figure 3.7**).

3.6.3 Coronary heart disease

Three studies with three comparisons reported the relationship between potassium intake and CHD. The meta-analysis conducted using the RR and HR calculated from models not adjusting for blood pressure was inconclusive (RR = 0.96, 95%CI: 0.78, 1.19) (**Table 3.25** and **Figure 3.8**). Only one of the three studies reported a model that adjusted for additional covariates including blood pressure. When the RR from that model was used in the meta-analysis, the result was similar (RR = 0.97, 95%CI: 0.77, 1.24) (**Table 3.26** and **Figure 3.9**).

The meta-analysis of two studies with two comparisons in which the comparison group (high potassium intake) had a urinary potassium excretion of <70 mmol/day was inconclusive (RR = 0.84, 95%CI: 0.64, 1.10). Only one study had a comparison group with urinary potassium excretion of 70–90 mmol potassium/day (RR = 0.97, 95%CI: 0.80, 1.18). (**Table 3.25** and **Figure 3.10**).

3.6.4 All-cause mortality

Two studies reported all-cause mortality (Geleijnse et al., 2007; Tunstall-Pedoe et al., 1997). The results could not be combined in a meta-analysis because the Tunstall-Pedoe study did not report a measure of variance. The results of the Geleijnse study showed an increase in risk with increased potassium intake, but the results were inconclusive (RR = 1.08, 95%CI: 0.91, 1.29). The Tunstall-Pedoe study reported a risk of 0.58 for the 80th percentile versus the 20th percentile of potassium intake.

3.7 Sensitivity analysis

We removed the studies in which exposure to potassium intake was measured through one 24-hour dietary recall, because of potential for confounding (Bazzano et al., 2001; Khaw & Barrett-Connor, 1987). Removal of these studies had little effect on any outcome (**Figures 3.11** and **3.12**).

3.8 Quality of the body of evidence

There was no indication of publication bias detected by examination of funnel plots for each outcome (**Annex 3**). The results of the risk of bias summary (**Annex 4**) and the risk of bias graph (**Annex 5**) suggest that the entire body of evidence is not at risk of serious problems due to bias. Blinding of participants and personnel was unclear for most studies. However, blinding is not generally a characteristic of cohort studies; therefore, study authors often did not report blinding related to participants and personnel. Blinding of outcome assessors was reported in half of the studies, and was not mentioned in the other half. There was little indication of bias due to selective reporting or incomplete outcome. Two studies were at high risk of bias due to confounding, because the models from which the RR and HR were taken did not control for common covariates and potential confounders; however, there was generally little risk of bias due to confounding.

Each Grading of Recommendations Assessment, Development and Evaluation (GRADE) evidence profile contains the assessment of the quality of evidence for a relationship between potassium intake and CVD, stroke and CHD (**Annex 6**). The evidence for a protective effect of increased potassium intake on stroke was low. This rating was due to the fact that the body of evidence came from observational cohort studies that start on the GRADE ranking as low-quality. The quality of the body of evidence was not downgraded for any reason. The quality of evidence for CVD and CHD was very low. In both cases, the quality of evidence began as low because of the observational, cohort-study design, and was then downgraded due to imprecision (i.e. the 95% CI of the effect estimate crossed one).

The evidence for a protective effect of increasing potassium to a level resulting in <70 mmol urinary potassium excretion/day was low for stroke. The same was true for increasing potassium to a level resulting in 70–90 mmol urinary potassium excretion/day. The evidence for a protective effect of increasing potassium to a level resulting in 90–120 mmol urinary potassium excretion/day was very low. The downgrade was due to imprecision. The evidence for a protective effect of increasing potassium to a level resulting in >120 mmol urinary potassium excretion/day was low, but only one study addressed this question and the results should therefore be interpreted with caution. There were too few studies measuring CVD or CHD to conduct a subgroup analysis to address these questions.

3.9 Characteristics of included studies

This section provides tables summarizing the characteristics of each of the included studies in terms of methods, participants, interventions and outcomes, with additional notes on the study, as appropriate. For each study, there is a table summarizing the risk of bias.

Table 3.1 Ascherio 1998

Methods	Cohort study conducted in the United States of America; part of the Health Professionals Follow-up study
Participants	38,726 adult men, age range 40–75 years, normotensive, not specified whether taking BP medication; all participants were health-care professionals
Interventions	Intervention: analysis of K intake in diet • Quintile 1 – 61.4 mmol K/day • Quintile 2 – 76.7 mmol K/day • Quintile 3 – 84.4 mmol K/day • Quintile 4 – 92.1 mmol K/day • Quintile 5 – 109.97 mmol K/day
Outcomes	RR of stroke (fatal and non-fatal) according to intake of K, total fibre, magnesium and calcium, adjusted by energy
Notes	Follow-up of 8 years K measured by food frequency questionnaire Participants followed up directly and medical records used to identify non-fatal stroke and death certificates used to identify fatal stroke Group – normotensive at baseline Fully adjusted models adjusted for age, calories, smoking, alcohol, history of hypertension, history of hypercholesterolemia, parental history of myocardial infarction before age 65 years, profession, BMI, physical activity Models did not control for BP but did control for self-reported hypertension at baseline

BMI, body mass index; BP, blood pressure; K, potassium; RR, relative risk
Reference: (Ascherio et al., 1998)

Table 3.2 Risk of bias table Ascherio 1998

Bias	Authors' judgement	Support for judgement
Selection of participants (selection bias)	Unclear risk	All participants were health-care professionals, which may reduce generalizability of results
Blinding of participants and personnel (performance bias)	Unclear risk	Blinding not specified
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessors blinded to risk factors of participants
Incomplete outcome data (attrition bias)	Low risk	Average response rate >94%
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Defining exposure (confounding)	Unclear risk	Potassium measured by food frequency questionnaire, which was validated against two 1-week diet records
Other confounding	Low risk	Models controlled for common risk factors

Table 3.3 Bazzano 2001

Methods	Cohort study conducted in the United States of America; follow-up on the National Health and Nutrition Examination Survey I
Participants	9805 adult men and women, age range 25–74, BP not specified, not taking BP medication
Interventions	Intervention: analysis of K intake in diet • Quartile 1 – 24.0 mmol K/day • Quartile 2 – 42.3 mmol K/day • Quartile 3 – 58.5 mmol K/day • Quartile 4 – 92.2 mmol K/day
Outcomes	HR and 95%CI of stroke (fatal and non-fatal) and CHD (fatal and non-fatal), according to quartile of dietary K intake
Notes	19-year follow-up K measured through one 24-hour dietary recall End point measured through direct follow-up with participants, obtaining hospital and nursing home records, including pathology reports, and, for decedents, acquiring death certificate Fully adjusted models adjusted for age, race, sex, calories, systolic BP, serum cholesterol, BMI, history of diabetes, physical activity, education, alcohol, smoking, vitamin supplement use, saturated fat intake, cholesterol intake, sodium intake, calcium intake, dietary fibres, and vitamin C and A intake Models controlled for BP Less adjusted models adjusted for age, race, sex and calories

BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio; K, potassium
Reference: (Bazzano et al., 2001)

Table 3.4 Risk of bias table Bazzano 2001

Bias	Authors' judgement	Support for judgement
Selection of participants (selection bias)	Low risk	Sample taken for National Health and Nutrition Examination Survey I
Blinding of participants and personnel (performance bias)	Unclear risk	Blinding not specified
Blinding of outcome assessment (detection bias)	Unclear risk	Blinding not specified
Incomplete outcome data (attrition bias)	Low risk	Loss to follow-up <4%
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Defining exposure (confounding)	High risk	Potassium measured through one 24-hour dietary recall
Other confounding	Low risk	Models controlled for common risk factors (controlled for BP)

BP, blood pressure

Table 3.5 Cook 2009

Methods	Cohort study conducted in the United States of America
Participants	2275 adult men and women, age range 30–54 years, normotensive, not taking BP medication Sample taken from participants in previous RCT on sodium intake who had not been given active sodium treatment
Interventions	Intervention: Analysis of K intake in diet • Quartile 1 – 73 mmol K/day • Quartile 2 – 60 mmol K/day • Quartile 3 – 48 mmol K/day • Quartile 4 – approximately 36 mmol K/day (took inverse of quartile 1 to compare quartile 1 and 4)
Outcomes	Risk of CVD (fatal and non-fatal)
Notes	Follow-up 10–15 years K measured through 24-hour urinary excretion End point measured through direct follow-up with participants, obtaining hospital and nursing home records, including pathology reports and, for decedents, acquiring death certificate Group – normotensive at baseline Fully adjusted models adjusted for clinic, treatment assignment, age, sex, race, education, family history, baseline weight, alcohol, smoking, physical activity, changes in weight, smoking and physical activity Models did not control for BP

BP, blood pressure; CVD, cardiovascular disease; K, potassium; RCT, randomized controlled trial
Reference: (Cook et al., 2009)

Table 3.6 Risk of bias table Cook 2009

Bias	Authors' judgement	Support for judgement
Selection of participants (selection bias)	Low risk	Participants former participants of RCT and only those who did not take sodium intervention included in follow-up
Blinding of participants and personnel (performance bias)	Unclear risk	Blinding not mentioned
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessors blinded
Incomplete outcome data (attrition bias)	Low risk	70% response rate after 15 years
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Defining exposure (confounding)	Low risk	24-hour urinary excretion
Other confounding	Unclear risk	Controlled for some common risk factors but not for nutritional risk factors

RCT, randomized controlled trial

Table 3.7 Geleijnse 2007

Methods	Case–cohort study conducted in the Netherlands
Participants	1448 adult men and women, mean age 69.2 years, BP status not specified, heterogeneous BP medication population
Interventions	Intervention: analysis of K intake in diet Risk for every one standard deviation increase in K intake (45 mmol/day) reported
Outcomes	Relative risk of incident MI (fatal and non-fatal) Incident stroke (fatal and non-fatal) CVD (fatal) All-cause mortality
Notes	Follow-up 5 years K measured through overnight urinary excretion End point measured through hospital or clinic records and death certificates Fully adjusted models adjusted for age, sex, (urinary K) 24-hour urinary creatinine excretion, BMI, smoking, diabetes, use of diuretics, education, calories, alcohol, calcium, saturated fat, 24-hour sodium excretion Models did not adjust for BP

BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; K, potassium; MI, myocardial infarction
Reference: (Geleijnse et al., 2007)

Table 3.8 Risk of bias table Geleijnse 2007

Bias	Authors' judgement	Support for judgement
Selection of participants (selection bias)	Low risk	Participants selected from Rotterdam Study; controls were randomly selected from individuals who did not have an incident event during the follow-up period
Blinding of participants and personnel (performance bias)	High risk	No blinding
Blinding of outcome assessment (detection bias)	Unclear risk	No description of blinding of outcome assessors
Incomplete outcome data (attrition bias)	Low risk	Reported no loss-to-follow-up and selected a random sample of individuals without an incident event as the control group
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Defining exposure (confounding)	Low risk	Potassium measured through overnight urinary excretion
Other confounding	Low risk	Models tested for significance of common risk factors

Table 3.9 Green 2002

Methods	Cohort study conducted in the United States of America; large cohort with direct follow-up
Participants	5600 adult men and women, mean age 72.8 years, BP status not specified; some participants taking BP medication
Interventions	Intervention: analysis of K intake in diet Diuretics and K measured Not taking diuretic and K measured • noDiuretics quintile 1 (<59.8 mmol K/day) • noDiuretics quintile 2 (60.1–74.7 mmol K/day) • noDiuretics quintile 3 (74.9–88.7 mmol K/day) • noDiuretics quintile 4 (89.0–106.4 mmol K/day) • noDiuretics quintile 5 (>106.4 mmol K/day) • Diuretics quintile 1 (<59.8 mmol K/day) • Diuretics quintile 2 (60.1–74.7 mmol K/day) • Diuretics quintile 3 (74.9–88.7 mmol K/day) • Diuretics quintile 4 (89.0–106.4 mmol K/day) • Diuretics quintile 5 (>106.4 mmol K/day)
Outcomes	Incidence stroke (fatal and non-fatal) Subtypes of strokes
Notes	Follow-up 4–8 years K measured through food frequency questionnaire End points measured by interviews conducted every 6 months, and verification with hospital records Fully adjusted models adjusted for age, sex, history of diabetes, hypertension, coronary artery disease, congestive heart failure, atrial fibrillation , systolic BP, serum creatinine, serum K and K supplement use Models controlled for BP Less adjusted models are not available

BP, blood pressure; K, potassium
Reference: (Green et al., 2002)

Table 3.10 Risk of bias table Green 2002

Bias	Authors' judgement	Support for judgement
Selection of participants (selection bias)	Low risk	Random selection of individuals from households on Medicare eligibility lists in four communities in the United States of America
Blinding of participants and personnel (performance bias)	Unclear risk	No description of blinding presented
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessors blinded
Incomplete outcome data (attrition bias)	Low risk	Reported no loss to follow-up
Selective reporting (reporting bias)	Unclear risk	All outcomes reported
Defining exposure (confounding)	Unclear risk	Potassium intake measured through food frequency questionnaire
Other confounding	Low risk	Models tested for common risk factors and controlled for those that were significant

Table 3.11 Iso 1999

Methods	Cohort study conducted in the United States of America; sample from the Nurses Health Study
Participants	5600 adult women, age range 34–59, BP status not specified, not specified whether taking BP medication
Interventions	Intervention: analysis of K intake in diet • Quintile 1 – 51.6 mmol K/day • Quintile 2 – 61.6 mmol K/day • Quintile 3 – 69.2 mmol K/day • Quintile 4 – 77.5 mmol K/day • Quintile 5 – 90.9 mmol K/day
Outcomes	Relative risk (95%CI) of stroke (fatal and non-fatal) Subtype of stroke
Notes	Follow-up 14 years Potassium measured through food frequency questionnaire validated against 1-week dietary records End points measured through interview and review of medical records Fully adjusted models adjusted for age, smoking, time interval, history of hypertension, BMI, alcohol, menopausal status and postmenopausal hormone use, vigorous exercise, usual aspirin use, multivitamin use, vitamin E use, histories of diabetes and high cholesterol levels, calcium intake Models did not control for BP

BMI, body mass index; BP, blood pressure; CI, confidence interval; K, potassium
Reference: (Iso et al., 1999)

Table 3.12 Risk of bias table Iso 1999

Bias	Authors' judgement	Support for judgement
Selection of participants (selection bias)	Unclear risk	Random selection from multicentre database; all participants were nurses
Blinding of participants and personnel (performance bias)	Unclear risk	No description of blinding of participants and personnel
Blinding of outcome assessment (detection bias)	Low risk	Panel of neurologists were blinded to entry data
Incomplete outcome data (attrition bias)	Low risk	Low loss to follow-up reported (<10%)
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Defining exposure (confounding)	Unclear risk	Exposure to potassium via food frequency questionnaire validated against 1-week dietary records
Other confounding	Low risk	Models controlled for other common risk factors

Table 3.13 Khaw 1987

Methods	Cohort study conducted in the United States of America
Participants	356 men and 503 women aged 50–79 years with no personal history of heart attack, heart failure or stroke at the baseline evaluation
Interventions	Exposure was K intake at baseline Results were presented in terms of 10 mmol increase in K intake
Outcomes	Stroke (fatal)
Notes	Follow-up 12 years on average K measured through 1–24 hour dietary recall and information on supplement use including K supplements was not obtained End points were ascertained through death certificate records and verified with next of kin if the death certificate stated only cardiovascular disease Sex – men and women Fully adjusted models adjusted for age, systolic BP, cholesterol, fasting plasma glucose, BMI, smoking; fully adjusted models were calculated separately for males and females; models did control for BP Less adjusted model adjusted for age, sex, calories; less adjusted model was calculated for males and females combined

BMI, body mass index; BP, blood pressure; K: potassium
Reference: (Khaw & Barrett-Connor, 1987)

Table 3.14 Risk of bias table Khaw 1987

Bias	Authors' judgement	Support for judgement
Selection of participants (selection bias)	Low risk	Randomly selected from population of one community
Blinding of participants and personnel (performance bias)	Unclear risk	No description of blinding of participants and personnel
Blinding of outcome assessment (detection bias)	Unclear risk	No description of blinding of outcome assessors
Incomplete outcome data (attrition bias)	Low risk	Attrition low though not quantified
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported
Defining exposure (confounding)	High risk	1–24 hour dietary recall and information on supplement use not obtained
Other confounding	Low risk	Models controlled for common confounders

Table 3.15 Larsson 2008

Methods	Cohort study conducted in Finland
Participants	26,556 adult men, age range 50–69, BP status not specified, not specified whether taking BP medication
Interventions	Intervention: analysis of K intake in diet • Quintile 1 – 97.5 mmol K/day Quintile 5 – 152.1 mmol K/day
Outcomes	Stroke (fatal and non-fatal) Subtypes
Notes	Follow-up 13.6 years on average K measured through food frequency questionnaire validated through food records End points were ascertained through record linkage with the National Hospital Discharge Register and the National Register of Causes of Death Sex – men only Fully adjusted models adjusted for age, smoking, BMI, systolic BP, diastolic BP, serum total cholesterol, HDL cholesterol, diabetes, history of CHD, physical activities, alcohol and calories Models controlled for BP Less adjusted models adjusted for age, supplementation group

BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; HDL, high-density lipoprotein; K, potassium
Reference: (Larsson et al., 2008)

Table 3.16 Risk of bias table Larsson 2008

Bias	Authors' judgement	Support for judgement
Selection of participants (selection bias)	High risk	Participants had originally agreed to participate in study on effect of alpha-tocopherol or beta-carotene on risk of development of lung cancer; all were smokers at baseline
Blinding of participants and personnel (performance bias)	High risk	No description of blinding of participants and personnel
Blinding of outcome assessment (detection bias)	Unclear risk	No description of blinding of outcome assessor
Incomplete outcome data (attrition bias)	Unclear risk	End points were based on record linkage with the National Hospital Discharge Register and National Register of Causes of Death; emigration not accounted of and if record not found participant considered without outcome
Selective reporting (reporting bias)	Low risk	All outcomes reported
Defining exposure (confounding)	Unclear risk	Exposure to potassium via food frequency questionnaire validated through food records
Other confounding	Low risk	Adjusted for all common risk factors

Table 3.17 O'Donnell 2011

Methods	Cohort study conducted in 40 countries
Participants	28,880 participants aged 55 years and more from 733 centres from 40 countries with established CVD or high-risk diabetes mellitus; patients were ineligible if they had heart failure, low ejection fraction, significant valvular disease, serum creatinine >3.0 mg/dL, renal artery stenosis, nephrotic range proteinuria, or BP higher that 160/100 mmHg
Interventions	Baseline measurement of K intake and population divided into three subgroups and outcomes compared between subgroups • Subgroup 1 – <1.5 g K/day • Subgroup 2 – 1.5–3 g K/day • Subgroup 3 – >3 g K/day
Outcomes	CVD (fatal and non-fatal combined) CVD (fatal) Stroke (fatal and non-fatal combined)
Notes	Median follow-up was 56 months (25–75 percentiles, 53–60 months) 24-hour K urinary excretion was estimated from a fasting morning urine samples Models are unadjusted Models did not adjust for BP

BP, blood pressure; CVD, cardiovascular disease; K, potassium
Reference: (O'Donnell et al., 2011)

Table 3.18 Risk of bias table O'Donnell 2011

Bias	Authors' judgement	Support for judgement
Selection of participants (selection bias)	Low risk	Participants from other trials from 733 centres from 40 countries with established CVD or high-risk diabetes mellitus who provided a baseline urine sample; two cohorts were combined because both trials recruited participants from the same sites, time period, using the same eligibility criteria, and used the same methods to capture baseline clinical data and outcome measures
Blinding of participants and personnel (performance bias)	Unclear risk	No description of blinding of participants and personnel
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 (0.2%)
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Defining exposure (confounding)	Low risk	24-hour potassium urinary excretion was estimated from a fasting morning urine samples
Other confounding	High risk	Models are unadjusted

CVD, cardiovascular disease

Table 3.19 Tunstall-Pedoe 1997

Methods	Cohort study conducted in Scotland
Participants	11,629 adult men and women, age range 40–65, BP status not specified, not specified if taking BP medication
Interventions	Intervention: analysis of K intake in diet • MQ1 – 47.2 mmol K/day men • MQ2 – 59.5 mmol K/day men • MQ3 – 71.3 mmol K/day men • MQ4 – 86.3 mmol K/day men • MQ5 – 138.1 mmol K/day men • WQ1 – 39.7 mmol K/day women • WQ2 –49.4 mmol K/day women • WQ3 –58.5 mmol K/day women • WQ4 –70.2 mmol K/day women • WQ5 –116.4 mmol K/day women
Outcomes	CHD (fatal and non-fatal combined) CHD (fatal) All-cause mortality
Notes	Follow-up time was 7.6 years K intake measured through 24-hour urinary K excretion Outcomes measured through death certificates and hospital/clinician records Fully adjusted models only adjusted for age Models did not adjust for BP

BP, blood pressure; CHD, coronary heart disease; CVD, cardiovascular disease; K, potassium
Reference: (Tunstall-Pedoe et al., 1997)

Table 3.20 Risk of bias table Tunstall-Pedoe 1997

Bias	Authors' judgement	Support for judgement
Selection of participants (selection bias)	Low risk	Random select of clinics then patients of clinics; selection from the Scottish Heart Health Study
Blinding of participants and personnel (performance bias)	Low risk	Personnel not aware of urinary potassium excretion while conducting other measurements
Blinding of outcome assessment (detection bias)	Low risk	Mortality was outcome and morbidity measured through hospital and clinician records
Incomplete outcome data (attrition bias)	Unclear risk	Loss to follow-up limited to emigration but amount unclear
Selective reporting (reporting bias)	Low risk	All outcomes reported
Defining exposure (confounding)	Low risk	24-hour urinary potassium excretion
Other confounding	High risk	Models only adjusted for age

Table 3.21 Umesawa 2008

Methods	Cohort study conducted in Japan; sample derived from 45 communities across Japan
Participants	11,746 adult men and women, age range 40–79 years, BP status not specified, not specified whether taking BP medication
Interventions	Intervention: analysis of K intake in diet • Quintile 1 – 35 mmol K/day • Quintile 2 – 44 mmol K/day • Quintile 3 – 51 mmol K/day • Quintile 4 – 58 mmol K/day • Quintile 5 – 68 mmol K/day
Outcomes	Stroke (fatal) CHD (fatal) CVD (fatal)
Notes	Follow-up time 12.7 year (average) Sodium intake measured through food frequency questionnaire End points measured by death certificate Fully adjusted models adjusted for age, sex, BMI, smoking, alcohol, history of hypertension, diabetes, menopause and hormone replacement therapy (women), sports activities, walking time, education, perceived mental stress, calcium and sodium intake Models did not control for BP but did control for history of hypertension

BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; CVD, cardiovascular disease; K, potassium
Reference: (Umesawa et al., 2008)

Table 3.22 Risk of bias table Umesawa 2008

Bias	Authors' judgement	Support for judgement
Selection of participants (selection bias)	Low risk	Selection from Japanese Collaborative Cohort Study
Blinding of participants and personnel (performance bias)	Unclear risk	Blinding not described
Blinding of outcome assessment (detection bias)	Low risk	Specifically noted that those assessing death certificates were blinded
Incomplete outcome data (attrition bias)	Low risk	Loss to follow-up <5%
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Defining exposure (confounding)	Unclear risk	Exposure to sodium via dietary records
Other confounding	Low risk	Models controlled for common risk factors

Table 3.23 Weng 2008

Methods	Cohort study conducted in Taiwan
Participants	1772 adult men and women, age not specified, BP status not specified, not specified whether taking BP medication
Interventions	Intervention: analysis of K intake in diet • Quartile 1 – >80.6 mmol K/day Quartile 2 – 65.4–80.6 mmol K/day Quartile 3–4 – <65.4 mmol K/day (Inverse of risk in quartile 1 calculated to compare quartile 1 and 4)
Outcomes	Ischaemic stroke (fatal and non-fatal)
Notes	Follow-up time 10.6 year (average) K intake measured through food frequency questionnaire validated against three 5-day food records End points measured by interview and verified through hospital/clinic records or death certificate Fully adjusted models adjusted for age, hypertension, use of antihypertensive drugs, diabetes, obesity, alcohol, smoking, BMI, self-reported heart disease, hypercholesterolemia, hypertriglyceridemia, physical activity, fibrinogen, apolipoprotein B, plasminogen Models did not control for BP but did control for history of hypertension

BMI, body mass index; BP, blood pressure; K, potassium
Reference: (Weng et al., 2008)

Table 3.24 Risk of bias table Weng 2008

Bias	Authors' judgement	Support for judgement
Selection of participants (selection bias)	Low risk	Random selection from multiple townships in Taiwan
Blinding of participants and personnel (performance bias)	Unclear risk	Not reported
Blinding of outcome assessment (detection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Low risk	Reported there was no loss to follow-up
Selective reporting (reporting bias)	Low risk	All outcomes reported
Defining exposure (confounding)	Unclear risk	Potassium intake measured through food frequency questionnaire
Other confounding	Low risk	Models tested for significance of common risk factors

3.10 Effect estimate tables

Table 3.25 Effect estimate of potassium intake and cardiovascular disease, stroke and coronary heart disease[a]

Outcome or subgroup	Studies/comparisons	Effect estimate[b]
Cardiovascular disease	4/4	0.88 [0.70, 1.10]
Cardiovascular disease (Subgroups: urinary excretion in comparison)		Subtotals only
Comparison group excretion (<70 mmol/d)	3/3	0.87 [0.71, 1.06]
Comparison group excretion (70–90 mmol/d)	2/2	0.84 [0.61, 1.15]
Comparison group excretion (90–120 mmol/d)	0/0	Not estimable
Comparison group excretion (>120 mmol/d)	0/0	Not estimable
Stroke	9/9	0.76 [0.66, 0.89]
Stroke (Subgroups: urinary excretion in comparison)		Subtotals only
Comparison group excretion (<70 mmol/d)	4/4	0.82 [0.71, 0.93]
Comparison group excretion (70–90 mmol/d)	4/4	0.70 [0.56, 0.88]
Comparison group excretion (90–120 mmol/d)	4/4	0.86 [0.71, 1.05]
Comparison group excretion (>120 mmol/d)	1/1	0.87 [0.77, 0.98]
Stroke (Subgroup: outcome type)		Subtotals only
Outcome type (all stroke)	7/7	0.78 [0.66, 0.93]
Outcome type (stroke mortality)	2/3	0.69 [0.54, 0.88]
Outcome type (stroke morbidity)	0	Not estimable
Coronary heart disease	3/3	0.96 [0.77, 1.19]
Coronary heart disease (Subgroups: urinary excretion in comparison)		Subtotals only
Comparison group excretion (<70 mmol/d)	2/2	0.84 [0.64, 1.10]
Comparison group excretion (70–90 mmol/d)	0/0	Not estimable
Comparison group excretion (90–120 mmol/d)	1/1	0.97 [0.80, 1.18]
Comparison group excretion (>120 mmol/d)	0/0	Not estimable
All-cause mortality	1/1	1.08 [0.91, 1.29]

[a] Risk ratio and hazard ratio from each original study were calculated from models that adjusted for the most number of covariates **not** including systolic or diastolic blood pressure (or both).
[b] An effect estimate of less than one (1) indicates a protective effect of increased potassium intake on each outcome.

Table 3.26 Effect estimate of potassium intake and cardiovascular disease, stroke, coronary heart disease from meta-analyses using risk ratio and hazard ratio from most-adjusted models[a]

Outcome or subgroup	Studies/comparisons	Effect estimate[b]
Cardiovascular disease	4/4	0.88 [0.70, 1.11]
Stroke	10/12	0.76 [0.66, 0.88]
Coronary heart disease	3/3	0.97 [0.77, 1.24]
All-cause mortality	1/1	1.08 [0.91, 1.29]

[a] Risk ratios and hazard ratios from each original study were calculated from models that adjusted for the most number of covariates including, in some cases, systolic or diastolic blood pressure (or both).
[b] An effect estimate of less than one (1) indicates a protective effect of increased potassium intake on each outcome.

3.11 Figures

Figure 3.1 Flow of studies through screening, inclusion and exclusion

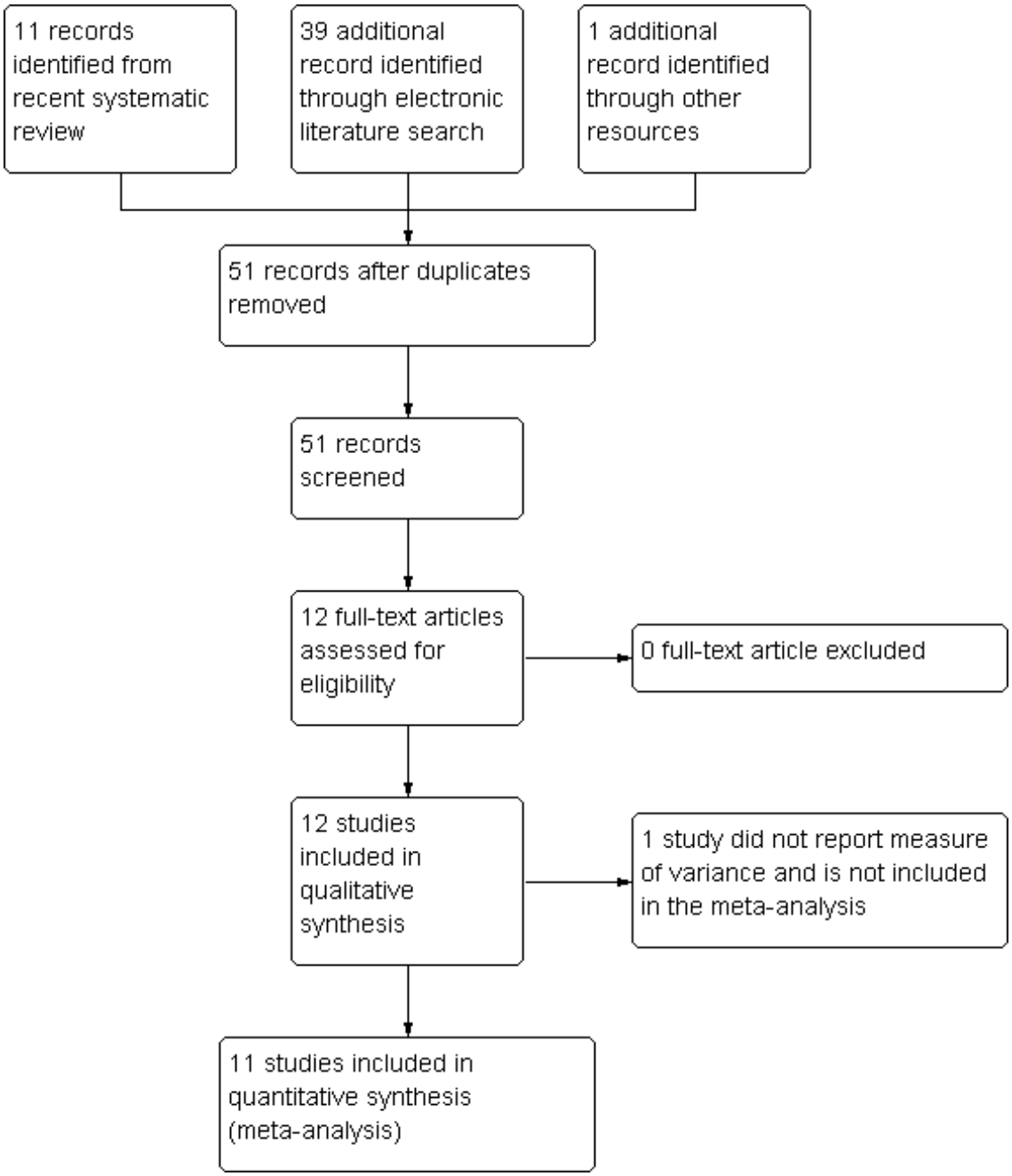
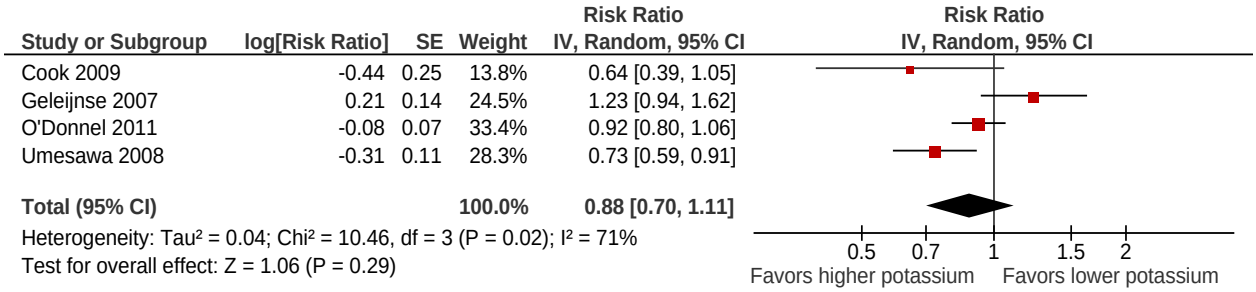


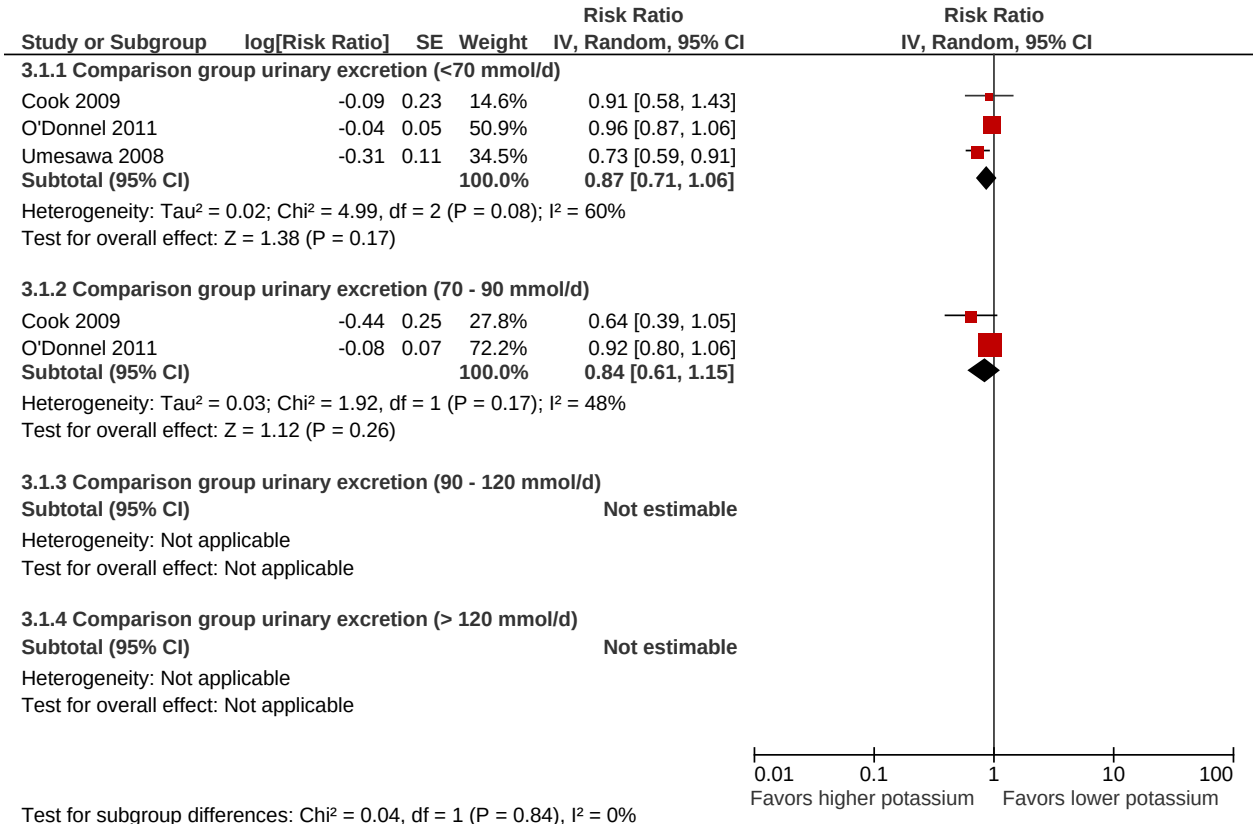
Figure 3.2 Cardiovascular disease – all adults using risk ratio and hazard ratio from less adjusted model[a]



CI, confidence interval; IV, intravenous; SE, standard error

[a] Risk ratio and hazard ratio from each original study calculated from models that adjusted for the most number of covariates **not** including systolic or diastolic blood pressure (or both)

Figure 3.3 Cardiovascular disease by subgroups[a] of urinary potassium excretion[b] in the comparison group (higher potassium group)

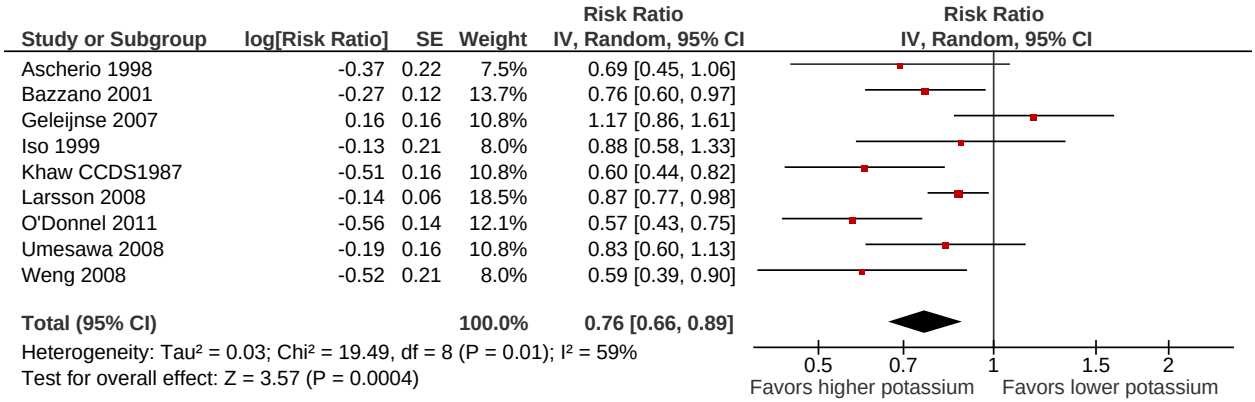


CI, confidence interval; IV, intravenous; SE, standard error

[a] All subgroup analyses conducted using risk ratio and hazard ratio from each original study calculated from models that adjusted for the most number of covariates **not** including systolic or diastolic blood pressure (or both)

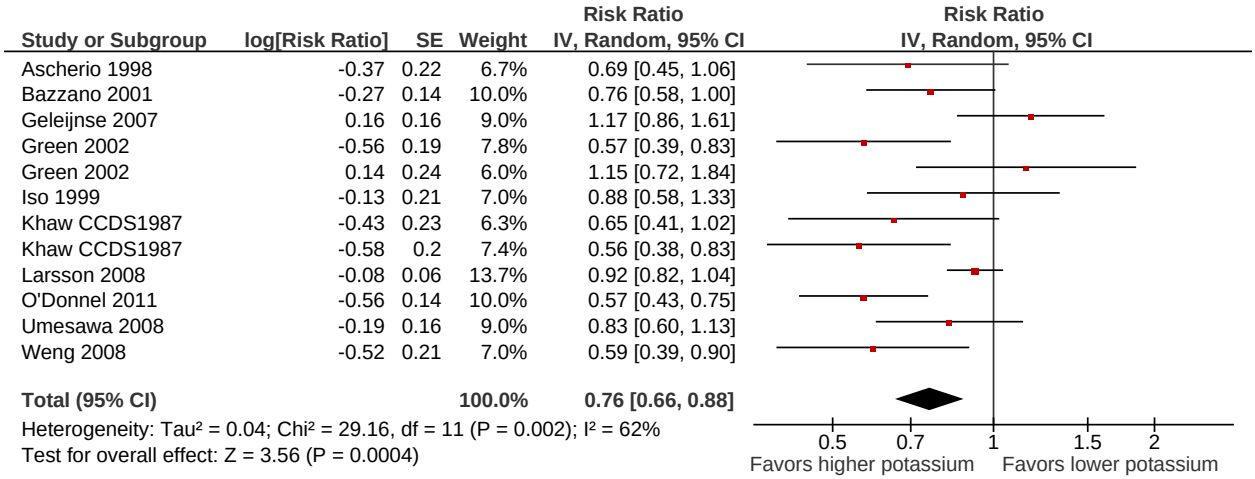
[b] Urinary potassium excretion is a common, valid form of estimating potassium intake. Data from 4680 men and women from 17 cities in four countries showed that average urinary potassium excretion was about 77% of intake. Therefore, a factor of 1.30 was used to convert urinary potassium excretion to potassium intake. Because original studies reported urinary potassium excretion, data was analysed based on that value. Using the factor of 1.30, 70 mmol urinary potassium/day equals about 91 mmol potassium intake/day, 90 mmol urinary potassium/day equals about 117 mmol intake/day; and 120 mmol urinary potassium/day equals about 156 mmol intake/day.

Figure 3.4 Stroke – all adults using risk ratio and hazard ratio from less adjusted model[a]



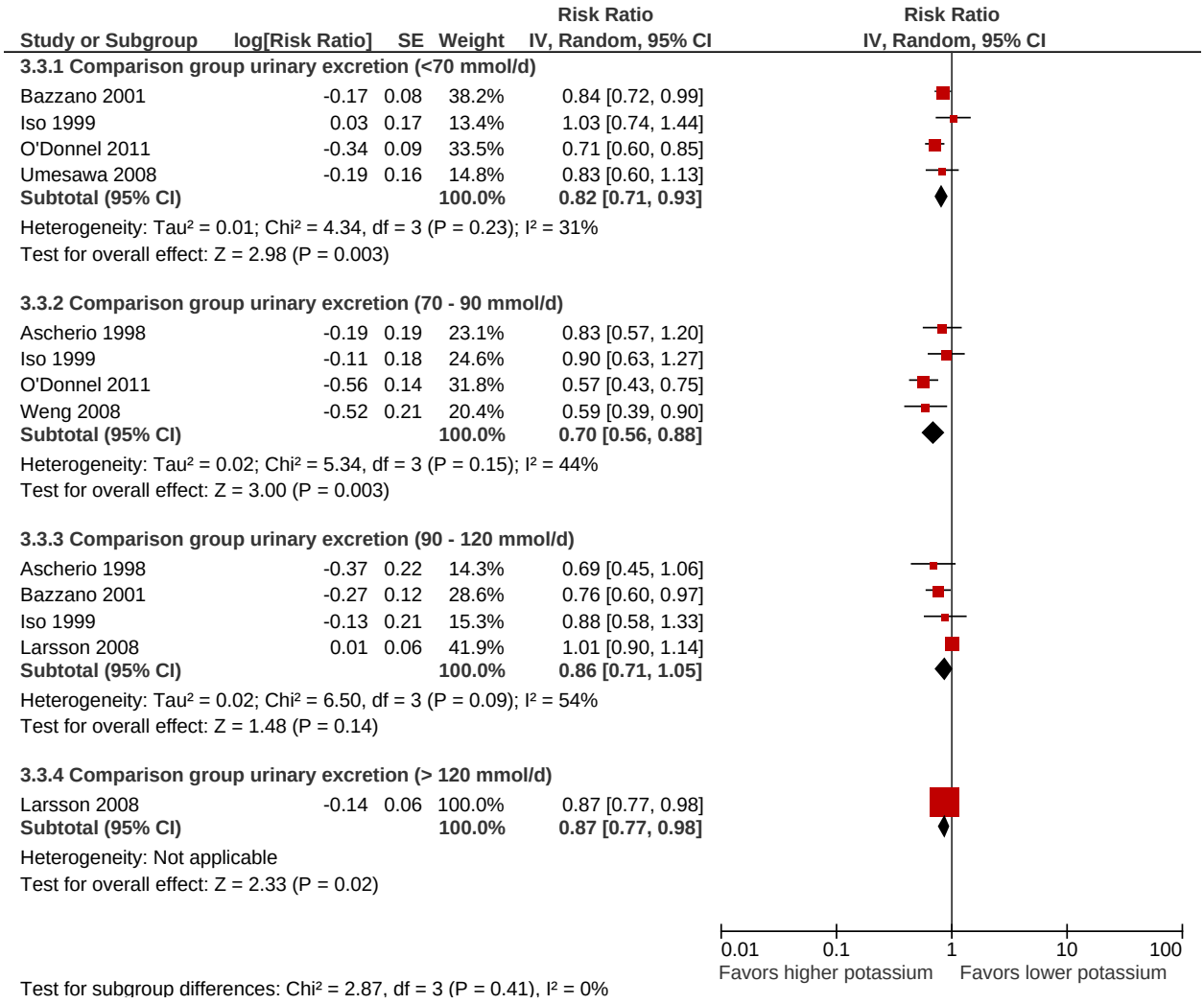
CI, confidence interval; IV, intravenous; SE, standard error
[a] Risk ratio and hazard ratio from each original study calculated from models that adjusted for the most number of covariates **not** including systolic or diastolic blood pressure (or both).

Figure 3.5 Stroke – all adults using risk ratio and hazard ratio from fully adjusted models[a]



CI, confidence interval; IV, intravenous; SE, standard error
a Risk ratio and hazard ratio from each original study calculated from models that adjusted for the most number of covariates including, in some cases, systolic or diastolic blood pressure (or both).

Figure 3.6 Stroke by subgroups[a] of urinary potassium excretion[b] in the comparison group (higher potassium group)

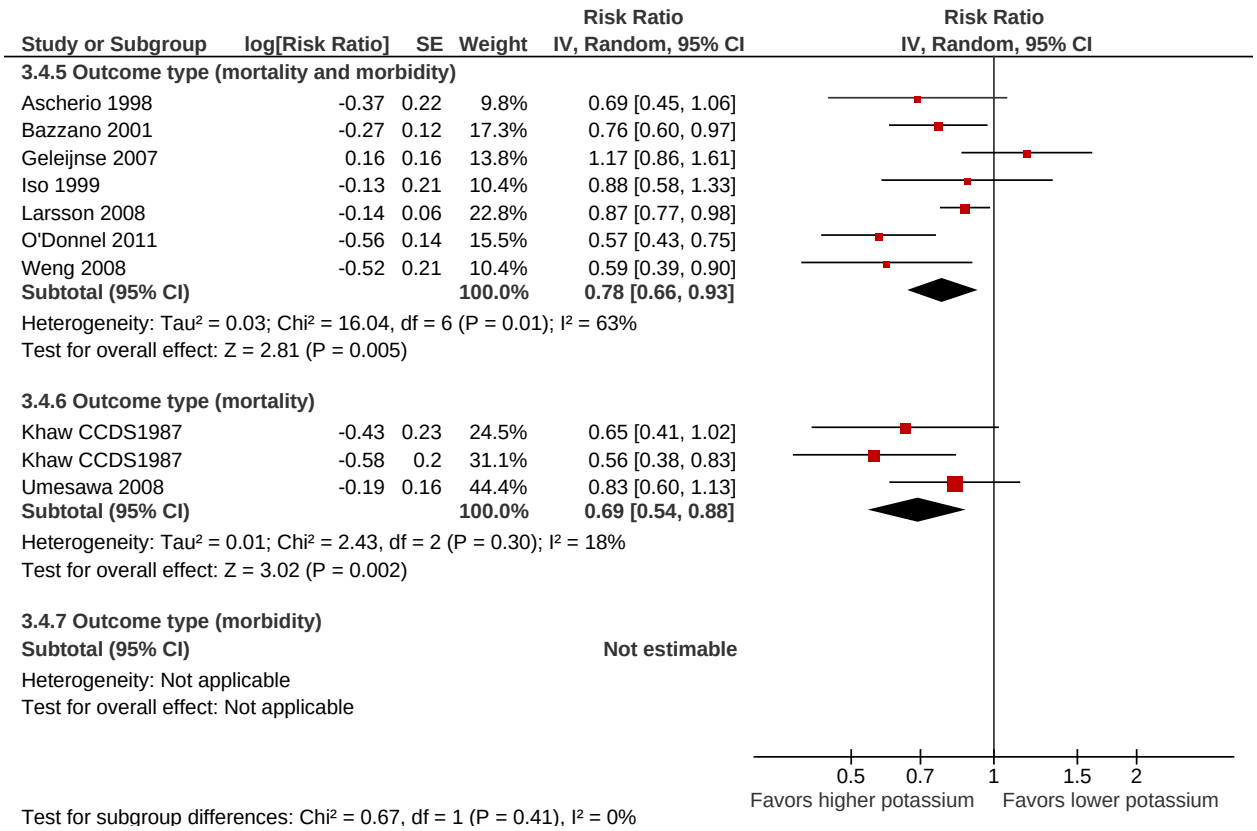


CI, confidence interval; IV, intravenous; SE, standard error

[a] All subgroup analyses conducted using risk ratio and hazard ratio from each original study calculated from models that adjusted for the most number of covariates **not** including systolic or diastolic blood pressure (or both).

[b] Urinary potassium excretion is a common, 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 about 77% of intake. Therefore, a factor of 1.30 was used to convert urinary potassium excretion to potassium intake. Because original studies reported urinary potassium excretion, data was analysed based on that value. Using the factor of 1.30, 70 mmol urinary potassium/day equals about 91 mmol potassium intake/day, 90 mmol urinary potassium/day equals about 117 mmol intake/day; and 120 mmol urinary potassium/day equals about 156 mmol intake/day.

Figure 3.7 Stroke by subgroup[a] of outcome type



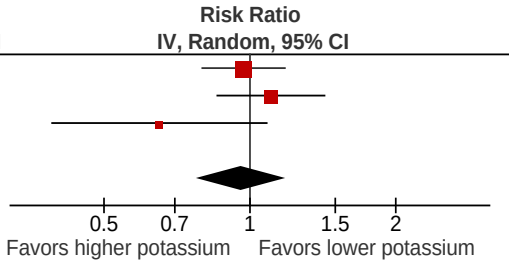
CI, confidence interval; IV, intravenous; SE, standard error

[a] All subgroup analyses conducted using risk ratio and hazard ratio from each original study calculated from models that adjusted for the most number of covariates **not** including systolic or diastolic blood pressure (or both).

Figure 3.8 Coronary heart disease – all adults using risk ratio and hazard ratio from less adjusted models[a]

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
Bazzano 2001	-0.03	0.1	48.2%	0.97 [0.80, 1.18]
Geleijnse 2007	0.1	0.13	37.5%	1.11 [0.86, 1.43]
Umesawa 2008	-0.43	0.26	14.3%	0.65 [0.39, 1.08]
Total (95% CI)			**100.0%**	**0.96 [0.78, 1.19]**

Heterogeneity: Tau² = 0.01; Chi² = 3.35, df = 2 (P = 0.19); I² = 40%
Test for overall effect: Z = 0.35 (P = 0.72)

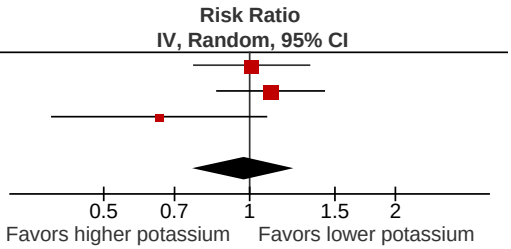


CI, confidence interval; IV, intravenous; SE, standard error
[a] Risk ratio and hazard ratio from each original study calculated from models that adjusted for the most number of covariates **not** including systolic and/or diastolic blood pressure

Figure 3.9 Coronary heart disease – all adults using risk ratio and hazard ratio from fully adjusted models[a]

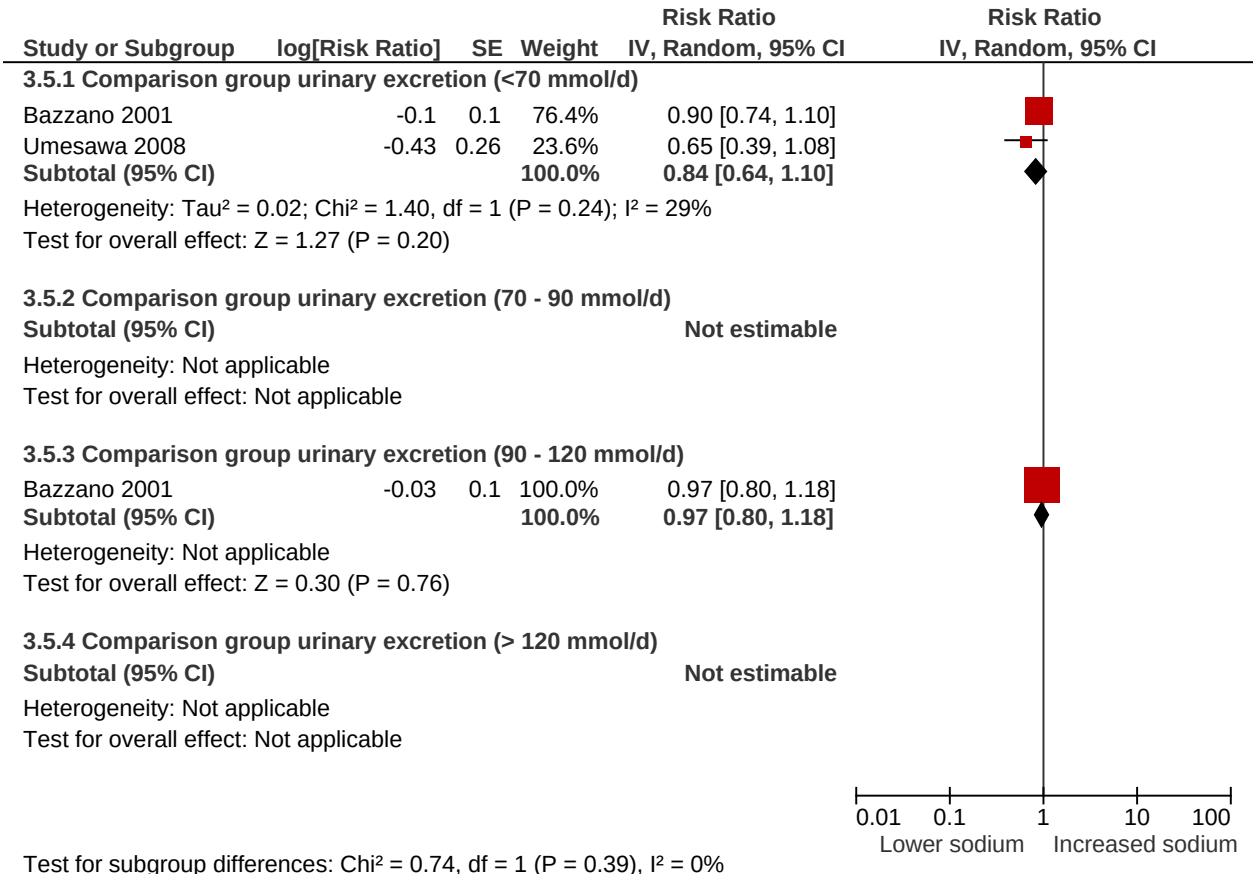
Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
Bazzano 2001	0.01	0.14	39.7%	1.01 [0.77, 1.33]
Geleijnse 2007	0.1	0.13	42.8%	1.11 [0.86, 1.43]
Umesawa 2008	-0.43	0.26	17.4%	0.65 [0.39, 1.08]
Total (95% CI)			**100.0%**	**0.97 [0.77, 1.24]**

Heterogeneity: Tau² = 0.02; Chi² = 3.33, df = 2 (P = 0.19); I² = 40%
Test for overall effect: Z = 0.23 (P = 0.82)



CI, confidence interval; IV, intravenous; SE, standard error
[a] Risk ratio and hazard ratio from each original study calculated from models that adjusted for the most number of covariates including, in some cases, systolic or diastolic blood pressure (or both).

Figure 3.10 Coronary heart disease by subgroups[a] of urinary potassium excretion[b] in the comparison group (higher potassium group)

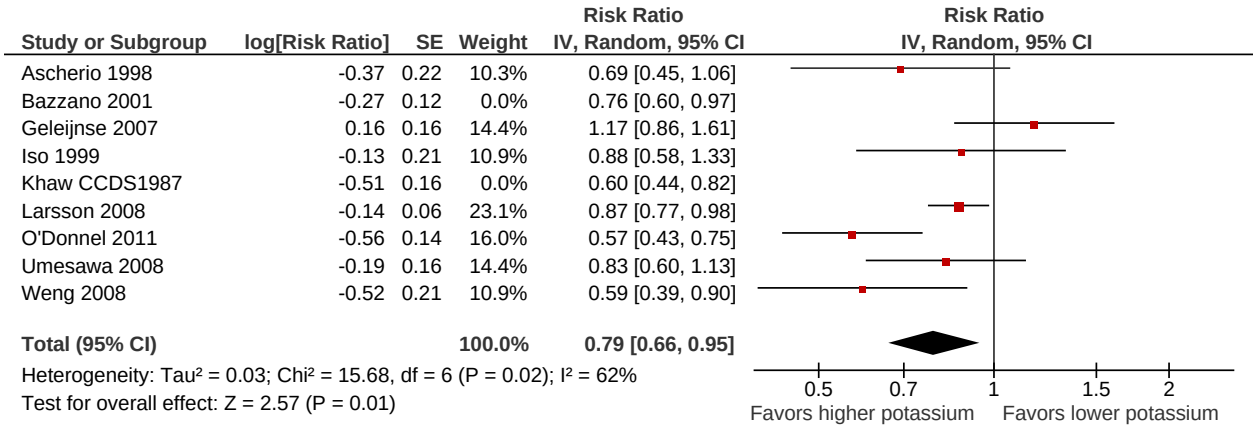


CI, confidence interval; IV, intravenous; SE, standard error

[a] All subgroup analyses conducted using risk ratio and hazard ratio from each original study calculated from models that adjusted for the most number of covariates **not** including systolic or diastolic blood pressure (or both).

[b] Urinary potassium excretion is a common, 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 about 77% of intake. Therefore, a factor of 1.30 was used to convert urinary potassium excretion to potassium intake. Because original studies reported urinary potassium excretion, data was analysed based on that value. Using the factor of 1.30, 70 mmol urinary potassium/day equals about 91 mmol potassium intake/day, 90 mmol urinary potassium/day equals about 117 mmol intake/day; and 120 mmol urinary potassium/day equals about 156 mmol intake/day.

Figure 3.11 Stroke – sensitivity analysis[a] (removal of studies at high risk of confounding due to exposure measure[b])

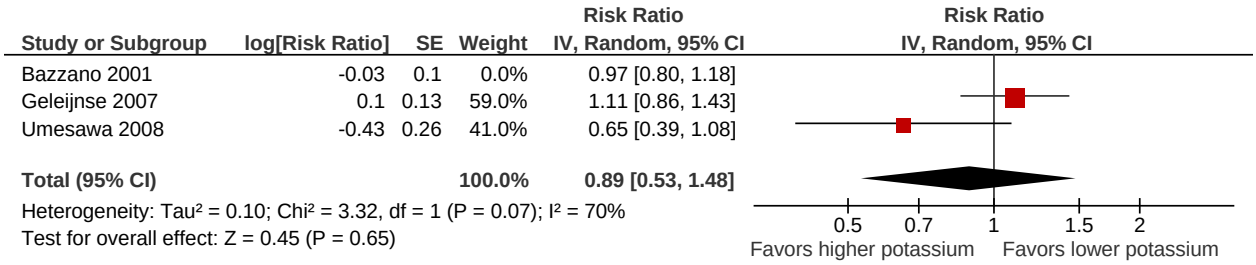


CI, confidence interval; IV, intravenous; SE, standard error

[a] All sensitivity analyses conducted using risk ratio and hazard ratio from each original study calculated from models that adjusted for the most number of covariates **not** including systolic or diastolic blood pressure (or both).

[b] Exposure measure considered high risk of bias if measured through 1–24 hour dietary recall.

Figure 3.12 Coronary heart disease – sensitivity analysis[a] (removal of studies at high risk of bias due to exposure measure[b])



CI, confidence interval; IV, intravenous; SE, standard error

[a] All sensitivity analyses conducted using risk ratio and hazard ratio from each original study calculated from models that adjusted for the most number of covariates **not** including systolic or diastolic blood pressure (or both).

[b] Exposure measure considered high risk of bias if measured through 1–24 hour dietary recall.

4 References to studies

4.1 Included studies

In each case, the reference was the primary reference for the study.

Ascherio 1998

Ascherio A, Rimm EB, Hernán MA et al. Intake of potassium, magnesium, calcium, and fiber and risk of stroke among US men. *Circulation,* 1998, 98:1198–1204.

Bazzano 2001

Bazzano LA, He J, Ogden LG et al. Dietary potassium intake and risk of stroke in US men and women: National Health and Nutrition Examination Survey I epidemiologic follow-up study. *Stroke,* 2001, 32(7):1473–1480.

Cook 2009

Cook NR, Obarzanek E, Cutler JA et al. Joint effects of sodium and potassium intake on subsequent cardiovascular disease: the Trials of Hypertension Prevention follow-up study. *Archives of Internal Medicine,* 2009, 169:32–40.

Geleijnse 2007

Geleijnse JM, Witteman JC, Stijnen T et al. Sodium and potassium intake and risk of cardiovascular events and all-cause mortality: the Rotterdam Study. *European Journal of Epidemiology,* 2007, 22:763–770.

Green 2002

Green DM, Ropper AH, Kronmal RA et al. Serum potassium level and dietary potassium intake as risk factors for stroke. *Neurology,* 2002, 59:314–320.

Iso 2009

Iso H, Stampfer MJ, Manson JE et al. Prospective study of calcium, potassium, and magnesium intake and risk of stroke in women. *Stroke,* 1999, 30:1772–1779.

Khaw 1987

Khaw KT, Barrett-Connor E. Dietary potassium and stroke-associated mortality. A 12-year prospective population study. *New England Journal of Medicine,* 1987, 316:235–240.

Larsson 2008

Larsson SC, Virtanen MJ, Mars M et al. Magnesium, calcium, potassium, and sodium intakes and risk of stroke in male smokers. *Archives of Internal Medicine,* 2008, 168:459–465.

O'Donnell 2011

O'Donnell MJ, Yusuf S, Mente A et al. Urinary sodium and potassium excretion and risk of cardiovascular events. *Journal of the American Medical Association,* 2011, 306(20):2229–2237.

Tunstall-Pedoe 1997

Tunstall-Pedoe H, Woodward M, Tavendale R et al. Comparison of the prediction by 27 different factors of coronary heart disease and death in men and women of the Scottish Heart Health Study: cohort study. *BMJ,* 1997, 315:722–729.

Umesawa 2008

Umesawa M, Iso H, Date C et al. Relations between dietary sodium and potassium intakes and mortality from cardiovascular disease: the Japan Collaborative Cohort Study for Evaluation of Cancer Risks. *American Journal of Clinical Nutrition,* 2008, 88:192–202.

Weng 2008

Weng LC, Yeh WT, Bai CH et al. Is ischemic stroke risk related to folate status or other nutrients correlated with folate intake? *Stroke,* 2008, 39:3152–3158.

4.2 Other references

Cappuccio FP, MacGregor GA. Does potassium supplementation lower blood pressure? A meta-analysis of published trials. *J Hypertens,* 1991, 9(5):465–473.

D'Elia L, Barba G, Cappuccio FP et al. Potassium intake, stroke, and cardiovascular disease a meta-analysis of prospective studies. *J Am Coll Cardiol,* 2011, 57(10):1210–1219.

Deeks JJ, Dinnes J, D'Amico R et al. Evaluating non-randomised intervention studies. *Health Technol Assess,* 2003, 7(27):iii-x, 1–173.

Dickinson HO, Nicolson DJ, Campbell F et al. Potassium supplementation for the management of primary hypertension in adults. *Cochrane Database Syst Rev,* 2006, 3:CD004641.

Geleijnse JM, Kok FJ, Grobbee DE. Blood pressure response to changes in sodium and potassium intake: a metaregression analysis of randomised trials. *J Hum Hypertens,* 2003, 17(7):471–480.

Guyatt GH, Oxman AD, Vist GE et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ,* 2008, 336(7650):924–926.

Higgins J, Thompson S, Deeks J et al. Statistical heterogeneity in systematic reviews of clinical trials: a critical appraisal of guidelines and practice. *Journal of Health Services Research & Policy,* 2002, 7(1):51–61.

Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med,* 2002, 21(11):1539–1558.

Higgins JP, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. *Journal of the Royal Statistical Society Series A-Statistics in Society,* 2009, 172(1):137–159.

Lau J, Ioannidis JP, Terrin N et al. The case of the misleading funnel plot. *BMJ,* 2006, 333(7568):597–600.

Lewington S, Clarke R, Qizilbash N et al. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet,* 2002, 360(9349):1903–1913.

Liberati A, Altman DG, Tetzlaff J et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ,* 2009, 339:b2700.

Mackay J, Mensah G. *Atlas of heart disease and stroke.* Geneva, World Health Organization, 2004.

Stamler J, Elliott P, Appel L et al. Higher blood pressure in middle-aged American adults with less education-role of multiple dietary factors: the INTERMAP study. *J Hum Hypertens,* 2003, 17(9):655–775.

Sterne JA, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. *Journal of Clinical Epidemiology,* 2001, 54(10):1046–1055.

Strong K, Mathers C, Leeder S et al. Preventing chronic diseases: how many lives can we save? *Lancet,* 2005, 366(9496):1578–1582.

Whelton PK, He J, Cutler JA et al. Effects of oral potassium on blood pressure. Meta-analysis of randomized controlled clinical trials. *Journal of the American Medical Association,* 1997, 277(20):1624–1632.

WHO. *Preventing chronic disease: A vital investment.* Geneva, World Health Organization (WHO), 2005.

Annex 1: Detailed search strategy

MEDLINE was searched through the PubMed database. All electronic searches were first run to search for RCTs. When fewer than three studies were found, a subsequent search for cohort studies was conducted.

A1.1 Search for randomized controlled trials

- PubMed search terms
- Search date: 15 September 2011
- Limits 1999 – date of search

(potassium [MeSH] OR potassium [tiab]) AND (stroke[MeSH] OR stroke[tiab] OR cerebrovascular disease[MeSH] OR cerebrovascular disease[tiab] OR cardiovascular disease[MeSH] OR cardiovascular disease[tiab], OR coronary heart disease[MeSH] OR coronary heart disease[tiab] OR cerebrovascular accident[MeSH] OR cerebrovascular accident[tiab] OR cerebrovascular disorders[MeSH] OR cerebrovascular disorders[tiab] OR cerebral infarction[MeSH] OR cerebral infarction[tiab] OR cerebral hemorrhage[MeSH] OR cerebral hemorrhage[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 Search for prospective cohort studies

- PubMed search terms
- Search date: 15 September 2011
- Limits 1999 – date of search

(potassium [MeSH] OR potassium [tiab]) AND (stroke[MeSH] OR stroke[tiab] OR cerebrovascular disease[MeSH] OR cerebrovascular disease[tiab] OR cardiovascular disease[MeSH] OR cardiovascular disease[tiab], OR coronary heart disease[MeSH] OR coronary heart disease[tiab] OR cerebrovascular accident[MeSH] OR cerebrovascular accident[tiab] OR cerebrovascular disorders[MeSH] OR cerebrovascular disorders[tiab] OR cerebral infarction[MeSH] OR cerebral infarction[tiab] OR cerebral hemorrhage[MeSH] OR cerebral hemorrhage[tiab]) AND (dietary[MeSH] OR diet[MeSH] OR diets[MeSH] OR restriction[MeSH] OR reduction[MeSH] OR reduce[MeSH] OR restrict[MeSH]) NOT (animals [mh] NOT humans [mh])

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 communication needed?	Author contact	Year	Journal	Vol.	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 generate	Blinding				Incomplete outcome data risk	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		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)
					Hyper tensive	Normo tensive	Both	Unspecified	Adult	Children	Both				

Part 2

Potassium intake at baseline (mmol	Potassium intake achieved at follow-up	Sodium intake at baseline				Starting time of intervention	Ending time of intervention	Duration of follow up (months)
		<2g/d	2-4 g/d	> 4 g/day	Other			

Sheet 5: Outcomes (categorical)

Mortality CHD		Mortality stroke		Mortality renal disease		CVD morbidity		Stroke events (non-fatal)		NPS	
n	N	n	N	n	N	n	N	n	N	n	N

Annex 3: Funnel plots for primary outcomes

Figure A2.1 Funnel plot of studies reporting cardiovascular disease

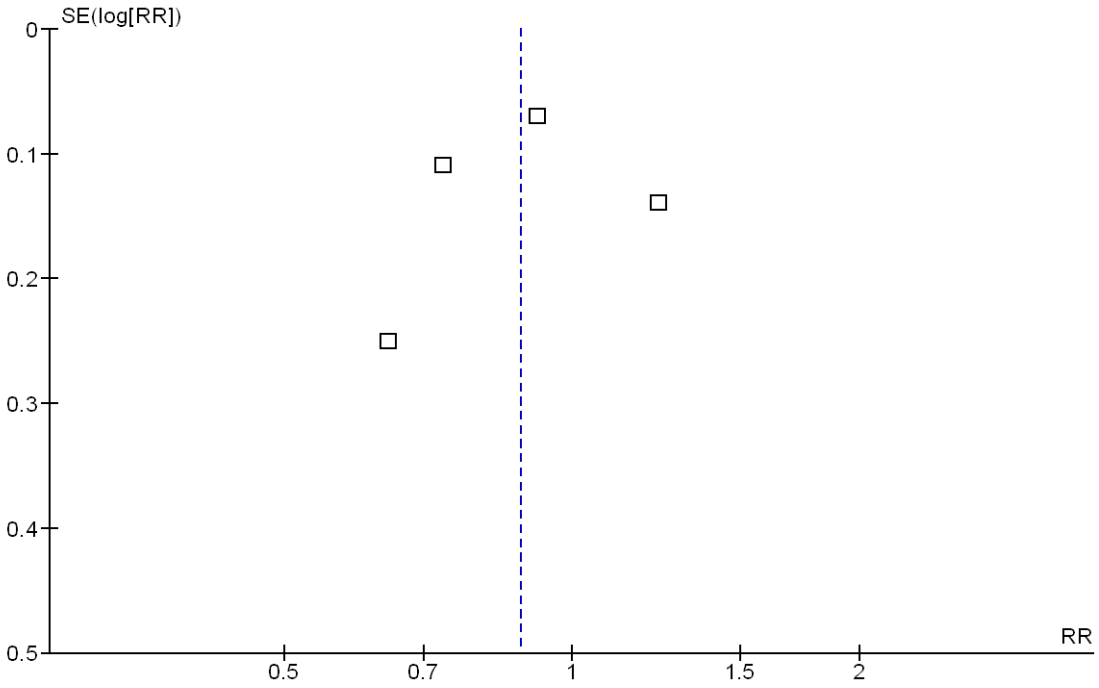


Figure A2.2 Funnel plot of studies reporting stroke

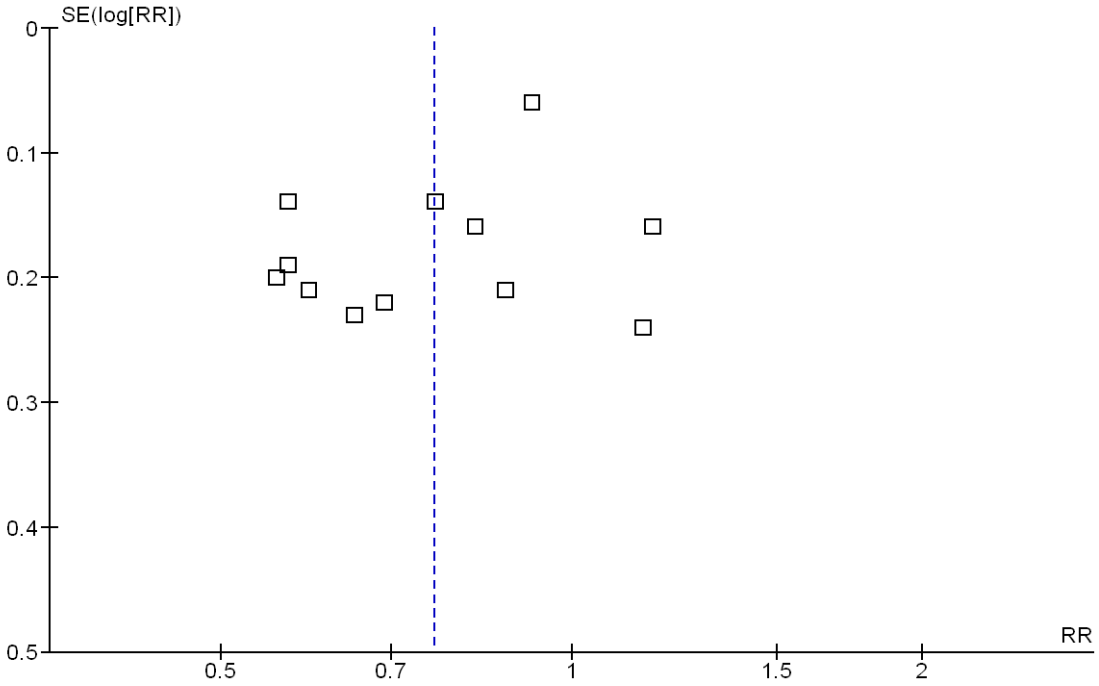
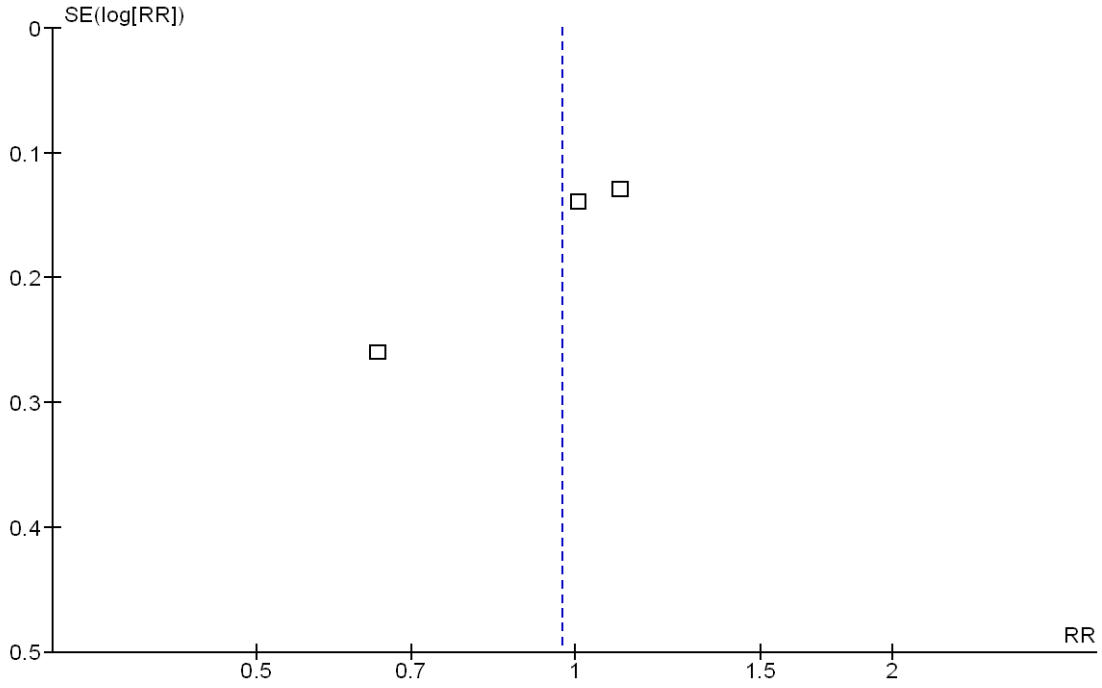
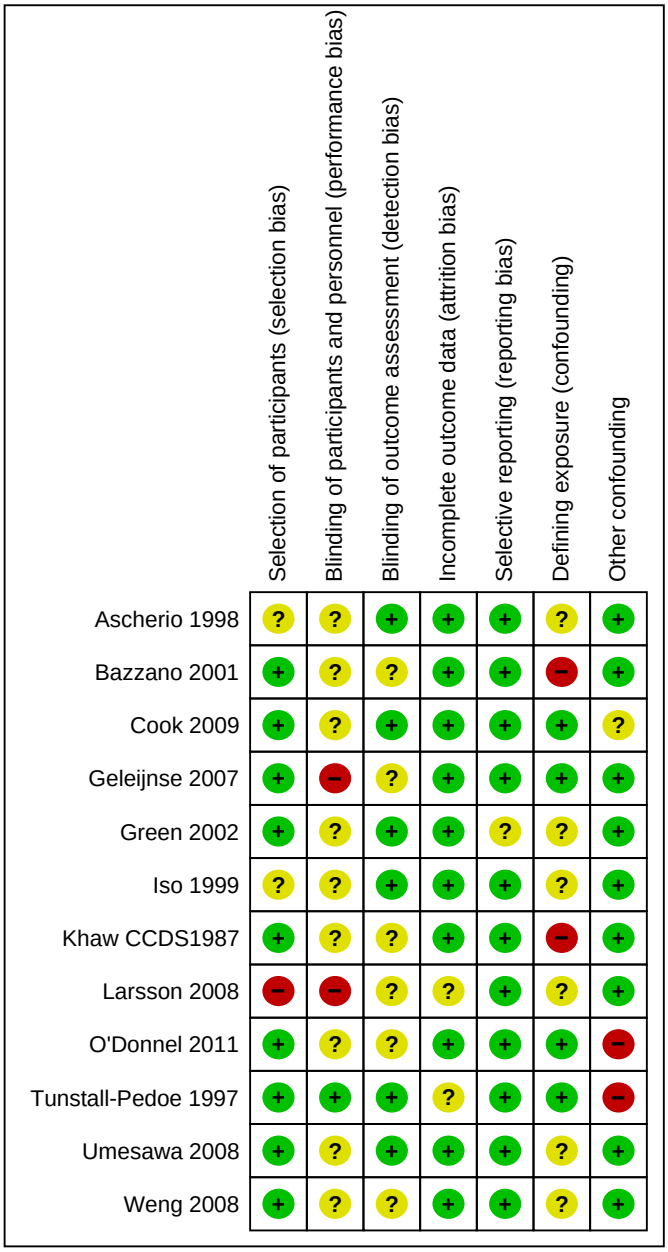


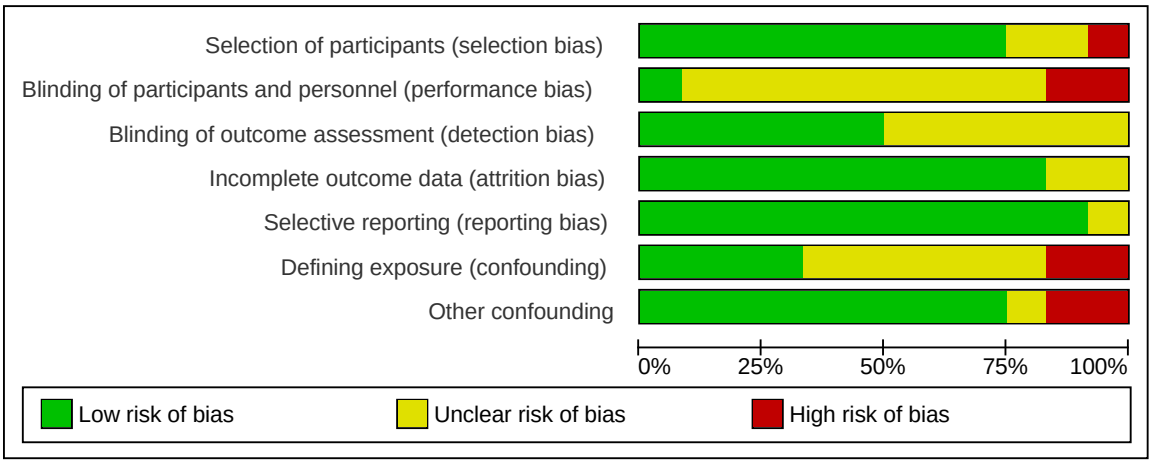
Figure A2.3 Funnel plot of studies reporting coronary heart disease



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 or lower intake in adults (≥16 years) on cardiovascular disease, stroke and coronary heart disease?

Quality assessment							Effect			
No of studies/ comparisons	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Participants	Relative (95% CI)	Quality	Importance
Cardiovascular Disease[1] (RR less than 1 indicates protective effect of increased potassium)										
4 / 4	Observational cohort	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[2]	none	29067	RR = 0.88 (0.70 to 1.11)	⊕ Very Low	CRITICAL
Stroke (RR less than 1 indicates protective effect of increased potassium)										
9 / 9	Observational cohort	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	none	97152	RR = 0.79 (0.68 to 0.93)	⊕⊕ Low	CRITICAL
Coronary Heart Disease (RR less than 1 indicates protective effect of increased potassium)										
3 / 3	Observational cohort	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[2]	none	31162	RR = 0.97 (0.77 to 1.24)	⊕ Very Low	CRITICAL

[1] Composite cardiovascular disease as reported by original study authors. This variable included some or all of the following: fatal and non-fatal stroke, coronary heart disease, myocardial infarction, and/or congestive cardiac failure, or episode of coronary revascularization, bypass grafting, and/or angioplasty.

[2] 95%CI of effect estimate crosses value of one (1).

Research question: What is the effect of increased potassium to a level resulting in <70 mmol/day urinary excretion[1] relative to usual or lower intake in adults (≥16 years) on cardiovascular disease, stroke and coronary heart disease?

Quality assessment							Effect			
No of studies/ comparisons	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	considerations	Participants	Relative (95% CI)	Quality	Importance
Cardiovascular Disease[2] (RR less than 1 indicates protective effect of increased potassium)										
3 / 3	Observational cohort	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[3]	none	26301	RR = 0.87 (0.71 to 1.06)	⊕ Very Low	CRITICAL
Stroke (RR less than 1 indicates protective effect of increased potassium)										
4 / 4	Observational cohort	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	none	64367	RR = 0.82 (0.71 to 0.93)	⊕⊕ Low	CRITICAL
Coronary Heart Disease (RR less than 1 indicates protective effect of increased potassium)										
2 / 2	Observational cohort	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[3]	none	28396	RR = 0.84 (0.64 to 1.10)	⊕ Very Low	CRITICAL

[1] A urinary excretion of 70 mmol/day is equivalent to an approximate intake of 91 mmol/day based on a conversion factor of 1.3 (Stamler 2003).

[2] Composite cardiovascular disease as reported by original study authors. This variable included some or all of the following: fatal and non-fatal stroke, coronary heart disease, myocardial infarction, and/or congestive cardiac failure, or episode of coronary revascularization, bypass grafting, and/or angioplasty.

[3] 95%CI crosses one (1)

[4] Only two studies contributed to estimate

Research question: What is the effect of increased potassium to a level resulting in urinary excretion of 70–90 mmol/day[1] relative to usual or lower intake in adults (≥16 years) on cardiovascular disease, stroke and coronary heart disease?

Quality assessment							Effect			
No of studies/ comparisons	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Participants	Relative (95% CI)	Quality	Importance
Cardiovascular Disease[2] (RR less than 1 indicates protective effect of increased potassium)										
2 / 2	Observational cohort	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[3]	none	2809	RR = 0.84 (0.61 to 1.15)	⊕ Very Low	CRITICAL
Stroke (RR less than 1 indicates protective effect of increased potassium)										
4 / 4	Observational cohort	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	none	54796	RR = 0.70 (0.56 to 0.88)	⊕⊕ Low	CRITICAL
Coronary Heart Disease (RR less than 1 indicates protective effect of increased potassium)										
0 / 0	No studies address this question.									CRITICAL

[1] A urinary excretion value of 70 - 90 mmol/day is the equivalent of an approximate intake of 91 - 117 mmol/day based on a converstion factor of 1.3 (Stamler 2003)

[2] Composite cardiovascular disease as reported by original study authors. This variable included some or all of the following: fatal and non-fatal stroke, coronary heart disease, myocardial infarction, and/or congestive cardiac failure, or episode of coronary revascularization, bypass grafting, and/or angioplasty.

[3] 95%CI crosses one (1)

Research question: What is the effect of increased potassium to a level resulting in urinary excretion of 90–120 mmol/day[1] relative to usual or lower intake in adults (≥16 years) on cardiovascular disease, stroke and coronary heart disease?

Quality assessment							Effect			
No of studies/ comparisons	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Participants	Relative (95% CI)	Quality	Importance
Cardiovascular Disease[2] (RR less than 1 indicates protective effect of increased potassium)										
0 / 0	No studies address this question.									CRITICAL
Stroke (RR less than 1 indicates protective effect of increased potassium)										
4 / 4	Observational cohort	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[3]	none	37328	RR = 0.86 (0.71 to 1.05)	⊕ Very Low	CRITICAL
Coronary Heart Disease (RR less than 1 indicates protective effect of increased potassium)										
1 / 1	Observational cohort	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[3]	none	4904	RR = 0.97 (0.80 to 1.18)	⊕ Very Low[4]	CRITICAL

[1] A urinary excretion value of 90-120 mmol/day is the equivalent of an approximate intake of 117-156 mmol/day based on a converstion factor of 1.3 (Stamler 2003)

[2] Composite cardiovascular disease as reported by original study authors. This variable included some or all of the following: fatal and non-fatal stroke, coronary heart disease, myocardial infarction, and/or congestive cardiac failure, or episode of coronary revascularization, bypass grafting, and/or angioplasty.

[3] 95%CI crosses one (1).

[4] Only one study included in this analysis

Research question: What is the effect of increased potassium to a level resulting in urinary excretion >120 mmol/day[1] relative to usual or lower intake in adults (≥16 years) on cardiovascular disease, stroke and coronary heart disease?

Quality assessment							Effect			
No of studies/ comparisons	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Participants	Relative (95% CI)	Quality	Importance
Cardiovascular Disease[2] (RR less than 1 indicates protective effect of increased potassium)										
0 / 0	No studies address this question.									CRITICAL
Stroke (RR less than 1 indicates protective effect of increased potassium)										
1 /1	Observational cohort	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	none	10622	RR = 0.87 (0.77 to 0.98)	⊕⊕ Low[3]	CRITICAL
Coronary Heart Disease (RR less than 1 indicates protective effect of increased potassium)										
0 / 0	No studies address this question.									CRITICAL

[1] A urinary excretion value of greater than 120 mmol/day is the equivalent of an approximate intake of 156 mmol/day based on a converstion factor of 1.3 (Stamler 2003)

[2] Composite cardiovascular disease as reported by original study authors. This variable included some or all of the following: fatal and non-fatal stroke, coronary heart disease, myocardial infarction, and/or congestive cardiac failure, or episode of coronary revascularization, bypass grafting, and/or angioplasty.

[3] Only one study included in this analysis

Annex 7: Lists of tables and figures

Tables

Figures

Full list of references

Ascherio A, Rimm EB, Hernán MA et al. Intake of potassium, magnesium, calcium, and fiber and risk of stroke among US men. Circulation, 1998, 98:1198–1204.

Bazzano LA, He J, Ogden LG et al. Dietary potassium intake and risk of stroke in US men and women: National Health and Nutrition Examination Survey I epidemiologic follow-up study. Stroke, 2001, 32(7):1473–1480.

Cappuccio FP, MacGregor GA. Does potassium supplementation lower blood pressure? A meta-analysis of published trials. J Hypertens, 1991, 9(5):465–473.

Cook NR, Obarzanek E, Cutler JA et al. Joint effects of sodium and potassium intake on subsequent cardiovascular disease: the Trials of Hypertension Prevention follow-up study. Archives of Internal Medicine, 2009, 169:32–40.

D'Elia L, Barba G, Cappuccio FP et al. Potassium intake, stroke, and cardiovascular disease a meta-analysis of prospective studies. J Am Coll Cardiol, 2011, 57(10):1210–1219.

Deeks JJ, Dinnes J, D'Amico R et al. Evaluating non-randomised intervention studies. Health Technol Assess, 2003, 7(27):iii-x, 1–173.

Dickinson HO, Nicolson DJ, Campbell F et al. Potassium supplementation for the management of primary hypertension in adults. Cochrane Database Syst Rev, 2006, 3:CD004641.

Geleijnse JM, Kok FJ, Grobbee DE. Blood pressure response to changes in sodium and potassium intake: a metaregression analysis of randomised trials. J Hum Hypertens, 2003, 17(7):471–480.

Geleijnse JM, Witteman JC, Stijnen T et al. Sodium and potassium intake and risk of cardiovascular events and all-cause mortality: the Rotterdam Study. European Journal of Epidemiology, 2007, 22:763–770.

Green DM, Ropper AH, Kronmal RA et al. Serum potassium level and dietary potassium intake as risk factors for stroke. Neurology, 2002, 59:314–320.

Guyatt GH, Oxman AD, Vist GE et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ, 2008, 336(7650):924–926.

Higgins J, Thompson S, Deeks J et al. Statistical heterogeneity in systematic reviews of clinical trials: a critical appraisal of guidelines and practice. Journal of Health Services Research & Policy, 2002, 7(1):51–61.

Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med, 2002, 21(11):1539–1558.

Higgins JP, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. Journal of the Royal Statistical Society Series A-Statistics in Society, 2009, 172(1):137–159.

Iso H, Stampfer MJ, Manson JE et al. Prospective study of calcium, potassium, and magnesium intake and risk of stroke in women. Stroke, 1999, 30:1772–1779.

Khaw KT, Barrett-Connor E. Dietary potassium and stroke-associated mortality. A 12-year prospective population study. New England Journal of Medicine, 1987, 316:235–240.

Larsson SC, Virtanen MJ, Mars M et al. Magnesium, calcium, potassium, and sodium intakes and risk of stroke in male smokers. Archives of Internal Medicine, 2008, 168:459–465.

Lau J, Ioannidis JP, Terrin N et al. The case of the misleading funnel plot. BMJ, 2006, 333(7568):597–600.

Lewington S, Clarke R, Qizilbash N et al. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet, 2002, 360(9349):1903–1913.

Liberati A, Altman DG, Tetzlaff J et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ, 2009, 339:b2700.

Mackay J, Mensah G. Atlas of heart disease and stroke. Geneva, World Health Organization, 2004

O'Donnell MJ, Yusuf S, MenteA et al. Urinary sodium and potassium excretion and risk of cardiovascular events. Journal of the American Medical Association, 2011, 306(20):2229–2237.

Stamler J, Elliott P, Appel L et al. Higher blood pressure in middle-aged American adults with less education-role of multiple dietary factors: the INTERMAP study. J Hum Hypertens, 2003, 17(9):655–775.

Sterne JA, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. Journal of Clinical Epidemiology, 2001, 54(10):1046–1055.

Strong K, Mathers C, Leeder S et al. Preventing chronic diseases: how many lives can we save? Lancet, 2005, 366(9496):1578–1582.

Tunstall-Pedoe H, Woodward M, Tavendale R et al. Comparison of the prediction by 27 different factors of coronary heart disease and death in men and women of the Scottish Heart Health Study: cohort study. BMJ, 1997, 315:722–729.

Umesawa M, Iso H, Date C et al. Relations between dietary sodium and potassium intakes and mortality from cardiovascular disease: the Japan Collaborative Cohort Study for Evaluation of Cancer Risks. American Journal of Clinical Nutrition, 2008, 88:192–202.

Weng LC, Yeh WT, Bai CH et al. Is ischemic stroke risk related to folate status or other nutrients correlated with folate intake? Stroke, 2008, 39:3152–3158.

Whelton PK, He J, Cutler JA et al. Effects of oral potassium on blood pressure. Meta-analysis of randomized controlled clinical trials. Journal of the American Medical Association, 1997, 277(20):1624–1632.

WHO. Diet, nutrition and the prevention of chronic disease. Report of a Joint WHO/FAO Expert Consultation. No. 916, Geneva, World Health Organization (WHO), 2003

WHO. Preventing chronic disease: A vital investment. Geneva, World Health Organization (WHO), 2005

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