Effects of reduced sodium intake on cardiovascular disease, coronary heart disease and stroke

World Health Organization

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Contents

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Abbreviations and acronyms

CHD	coronary heart disease
CI	confidence interval
CVD	cardiovascular disease
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HDL	high-density lipoprotein
HR	hazard ratio
NCD	noncommunicable disease
PRISMA	preferred reporting items for systematic reviews and meta-analyses
RCT	randomized controlled trial
RR	relative risk
SD	standard deviation
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 leading cause of mortality and morbidity globally (*2*). The major NCDs currently account for approximately 60% of all deaths and 43% of disease burden globally, and these levels are expected to continue to rise (*2, 3*). In 2008, nearly 80% of NCD-related deaths, 29 million, occurred in low- and middle-income countries; 29% of such deaths in these countries were in people aged < 60 years, and were thus defined as premature. In high-income countries, only 13% of the NCD-related deaths were premature. In 2005, cardiovascular disease (CVD) accounted for 30% of all deaths, the equivalent of infectious disease, nutritional deficiency, and maternal and perinatal conditions combined (*2*).

Sodium has been of interest in public health nutrition for decades, mainly because of its association with hypertension and CVDs, especially coronary heart disease (CHD) and stroke. High blood pressure is a major risk factor for both stroke and CHD. Studies suggest that, for most individuals, the higher their sodium consumption, the higher their blood pressure will be (*4*). In turn, high blood pressure has been shown to account for 62% of strokes and 49% of CHD. Diets that are high in sodium may also have independent, but additive, harmful effects on left ventricular hypertrophy, progression of renal disease, and risk of CVD and stroke. It has been estimated that a reduction in dietary intake of sodium of 50 mmol/day would reduce the number of deaths from stroke by 22% and the number of deaths from CHD by 16% (*5*).

1.2 Need for this review

Much of the human and social impact caused each year by NCD-related morbidity and mortality could be averted through interventions that are well-understood, cost-effective and feasible (*6*). Decreased sodium intake in the population is a cost-effective public health intervention that could potentially lead to a reduced burden of NCD morbidity and mortality (*7*). Because of the ever-increasing importance of NCDs on health-care costs and burden of disease (*2, 3, 7*), Member States of the World Health Organization (WHO) requested that WHO update the guideline on sodium intake for adults, and generate a guideline on sodium intake for children, to inform public policy.

Before a guideline can be generated, it is necessary to assess potential benefits (including those related to patient-relevant outcomes such as CVD, stroke and CHD) and potential harms. Some researchers have reported that reducing sodium intake to levels below those currently recommended by WHO would lead to even greater health benefits (*8*). Conversely, two recently published cohort studies have proposed that sodium intake of < 2 g/day may be associated with increased risk of CVD and stroke (*9, 10*). Owing to the continued debate over the effect of sodium consumption and health outcomes, and the recent research that is adding to the evidence base, a complete systematic review of sodium and CVD, stroke, CHD and all-cause mortality is warranted.

1.3 Objectives

The overall objective was to assess the effect of reduced sodium intake compared with usual sodium intake on CVD, stroke and CHD in adults.

Specific objectives were to assess the effect on CVD, stroke and CHD in adults of consuming:

- less sodium compared with more sodium;
- sodium at a level of < 2 g/day compared with ≥ 2 g/day;
- sodium at a level of < 1.2 g/day compared with ≥ 1.2 g/day or 1.2–2 g/day.

2 Methods

2.1 Criteria for considering studies for this review

Study types

The review included randomized controlled trials (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 individuals 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 stroke events (incident events, fatal events and non-fatal events);
- all CVD events (incident events, fatal events and non-fatal events);
- all CHD events (incident events, fatal events and non-fatal events).

The secondary outcomes were all-cause mortality and all other outcomes reported by the original study authors.

2.2 Identification of studies

We searched for studies in two phases. In the first phase, we searched for high-quality systematic reviews on reduced sodium consumption and the outcomes of interest. Where such reviews were found and the inclusion criteria for the reviews were similar or equivalent to those needed to reach the objectives of the current review, we used the references from those reviews as the list of potential studies. If the reviews were of high quality but were > 2 years old, we supplemented those studies with additional searches. We also contacted the original authors of such reviews to request original data, so that we could explore the data in such a way as to achieve our objectives.

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

2.2.1 Search for systematic reviews and meta-analyses

We searched the PubMed database and The Cochrane Library of Systematic Reviews in August 2011 for systematic reviews on sodium intake and CVD, stroke and CHD. We considered systematic reviews of RCTs and cohort studies. We also contacted authors of the systematic reviews to consult about any other published systematic reviews.

Electronic searches

Because recent, high-quality systematic reviews were found, we did not conduct a separate electronic search for studies on the effect of increased sodium on CVD morbidity and mortality.

Other resources

We searched for further trials on the WHO web site[1] and in the reference lists of identified papers. For assistance in identifying ongoing 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. We also contacted the authors of the systematic reviews on this topic to identify any potentially relevant studies in the recent literature.

2.3 Data collection and analysis

2.3.1 Selection of studies

Identified studies were independently assessed for potential relevance by two reviewers. The reviewers scanned the title, abstract and keywords of every record retrieved 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 (sodium intake) and compared this with an outcome of interest, or compared groups consuming different levels of sodium;
- had a prospective design;
- did not target patients who were acutely ill or infected with HIV;
- had a duration of at least 1 year;
- reported on an outcome of interest.

We also retrieved the full article in cases where there was any doubt about these criteria from scanning the title and abstract.

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

Where differences in opinion existed, they were discussed with a third party. If consensus was not possible, the article 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 for the RCTs and, separately, for the cohort studies (**Figures 3.1** and **3.2**) (*11*).

[1] www.who.int/nutrition

2.3.2 Data extraction and management

For studies that fulfilled inclusion criteria, two reviewers independently abstracted relevant population and intervention characteristics using standard data extraction templates, with any disagreements resolved by discussion. Any relevant missing information on the trial was sought from the authors of the original article. 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 comorbidity), assessment of compliance, withdrawals or losses to follow-up (reasons and description), subgroups, status of blood pressure and status of medication to control blood pressure;
- *outcome*s – outcomes specified above, any other outcomes assessed, other events, length of follow-up and quality of reporting of outcomes;
- *results* – for outcomes specified above and including a measure of variation, and, where necessary, converted to measures of effect specified below.

Duplicate publications

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

2.3.3 Assessment of risk of bias in included studies

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

Randomization (checking for possible selection bias)

All RCTs included in the current review were included in the original Cochrane Library publication (*12*). The original review authors assessed risk of bias using the quality criteria specified in *Cochrane handbook for systematic reviews of interventions 5.1.0* (*13*) The results of the assessment of risk of bias for the RCTs can be found in the Cochrane Library publication (*12*).

Cohort studies

To assess risk of bias in non-randomized studies, we used the broad categories recommended for RCTs in the *Cochrane handbook for systematic reviews of interventions* (*13*), but also took into account particular sources of bias associated with specific study designs.

Deeks et al (*14*) 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, the completeness of follow-up, and the methods used in the analysis to adjust for possible confounding factors.

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

For each included study, and for each outcome or class of outcomes, we described the completeness of 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 number of randomized participants), 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 in which few drop-outs or losses to follow-up were noted and 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, whether or not intention-to-treat analysis was used;
- *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 of 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 a key outcome that would have been expected to have been reported;
- *unclear.*

Selection of study participants and creation of treatment groups

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 were drawn and, where applicable, to determine whether groups were drawn from comparable populations. We recorded whether any allocation decisions were based on the preferences of participants, or were dependent on other factors (e.g. clinician choice). We noted which characteristics were used to demonstrate comparability of groups (e.g. age, sex, sociodemographic characteristics and hypertensive status), and considered whether potentially key variables were missing.

Implementing the intervention or defining exposure and collecting outcome data

Where applicable, we recorded the manner in which the intervention was implemented and noted levels of adherence to or coverage of the intervention. In the case of cohort studies, we recorded the manner in which exposure was measured and the methods used to define exposure groups. Where groups were followed up over time in different sites, we considered whether contamination was likely, or whether there were other differences between groups (e.g. exposure to other interventions) that could potentially 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 treatment and control groups, or exposed and unexposed groups. For each study, we recorded the factors used to adjust for possible confounding, because these may vary between studies considering the same outcome and thus may be an important source of between-study heterogeneity.

Other sources of bias

For each included study, we described any important concerns about other possible sources of bias, such as similarity of the groups at baseline. We also assessed whether each study was free of other problems that could put it at risk of bias, recording the 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 (CIs). In RCTs, the reference group was the higher sodium intake; hence, an RR or HR of < 1 indicated a decrease in risk of the outcome with a decrease in sodium intake. In the cohort studies, the reference group was always the group with the lowest intake of sodium; thus, an RR or HR of > 1 signified an increased risk in the outcome with increased sodium intake.

2.3.5 Missing data

We obtained relevant missing data from authors, where feasible.

2.3.6 Data synthesis

If data were available, sufficiently similar and of adequate quality, they were summarized statistically. We performed statistical analyses according to the guidelines referenced in the *Cochrane handbook for systematic reviews of interventions (13)*. Overall, results were calculated based on the random-effects model. Where data were reported in forms that could not easily be converted into a standard measure, they were summarized in a narrative format, and different comparisons were analysed separately.

For conducting the meta-analyses of outcomes reported in the cohort studies, 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 sodium intake and these outcomes (*15*). We also performed a second analysis using the RR or HR generated from the models adjusting for the most number of covariates (most-adjusted models), which may have included blood pressure, presented in the original manuscript.

2.3.7 Subgroup analysis and investigation of heterogeneity

In the event of substantial clinical or 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, by using a standard Chi-squared (χ^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 (*16, 17*), where an I^2 statistic of ≥ 75% indicates a considerable level of inconsistency. Where heterogeneity was found, we attempted to determine the potential causes by examining the characteristics of individual studies and subgroups.

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

- *outcome* – overall (fatal and non-fatal events), fatal only or non-fatal only;
- *sodium intake level in the reference group* – < 1.2 g/day versus > 1.2 g/day, and < 2 g/day versus ≥ 2 g/day;
- *difference in sodium intake level in the reference and comparison group* – < 50 mmol (< 1.15 g/day), versus 50–100 mmol (1.15–2.3 g/day), versus > 100 mmol (2.3 g/day).

2.3.8 Sensitivity analysis

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

Quality of the body of evidence

We used funnel plots to assess the potential existence of small-study bias (*18, 19*). A "risk of bias summary" (**Annex 2**) and "risk of bias graph" (**Annex 3**) were generated. GRADEProfiler software (version 3.6) was used to assess the quality of the body of evidence according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology outlined in *GRADE: an emerging consensus on rating quality of evidence and strength of recommendations* (*20*).

3 Results

3.1 Results of the search

Two systematic reviews were identified through the search for recent systematic reviews on the effect of sodium intake on CVD, stroke, CHD and all-cause mortality (*1, 12*). We collaborated with the authors of the original studies to use the data from these two reviews to complete the current review.

One review included only RCTs (*12*); data from that review were re-analysed based on the inclusion criteria and specific objectives of the current review. Of the seven studies included in that systematic review, one was excluded from the current review because it was conducted in a sample of acutely ill patients (*21*), and another because it manipulated both sodium and potassium intake in the intervention group (*22*), leaving five studies to be included in the current review. The flow of records of RCTs through screening, exclusion and inclusion is shown in **Figure 3.1.** Because of the sparseness of data from RCTs, cohort studies were also considered for inclusion.

The other systematic review included prospective cohort studies (*1*). Based on the reference list of that review, we identified 13 potential cohort studies for the current review. Through scanning the reference lists and communicating directly with study authors, we identified four additional studies, giving 17 potential cohort studies for inclusion in the current systematic review. Screening of abstracts led to the exclusion of one publication for not meeting basic criteria for inclusion (*23*), and a final review of the methods resulted in the exclusion of one publication for lack of quantification of exposure (*24*). The remaining 15 studies were included in the current review. Of these, only 14 contributed to the meta-analysis, because one study did not provide a measure of variance (*25*). The flow of records through screening, exclusion and inclusion is shown in **Figure 3.2**.

3.2 Included studies

3.2.1 Settings

All included studies were published in English. Six were undertaken in the United States of America (USA) (*26-31*), one of which concerned Japanese men living in the State of Hawaii (*31*). One study was undertaken in the Netherlands (*32*), two in Finland (*33, 34*), two in Japan (*35, 36*), one in the United Kingdom of Great Britain and Northern Ireland (Scotland) (*25*), one in Belgium (*10*) and one in Australia (*37*); the remaining study included participants from 40 countries (*9*).

3.2.2 Types of studies

Randomized controlled trials

All RCTs included in the current review were included in the systematic review published in the Cochrane Library (*12*). Details on study design, settings, participants, interventions and outcome measures can be found in that publication (*12*).

Cohort studies

Details of the characteristics of the included studies are shown in **Section 3.6.1**.

Fifteen studies had a prospective, cohort design; of these, one was a case–cohort study (*32*) and 14 were simple cohort studies (*9, 10, 25-31, 33-37*). Nine of the studies used representative data from a large geographical region and relied on health statistics for outcome measures (*9, 10, 25, 27, 28, 30, 32-34, 36*), one was worksite based (*26*), one followed participants who had previously participated in an RCT of dietary intervention to reduce sodium intake (*29*), and two measured baseline variables and directly followed the cohort over the course of study (*31, 35*). The duration of follow-up varied from 3.8 years (*26*) to 22 years (*30*) (with the latter varying by participant, from 11 to 22 years).

3.2.3 Participants

The number of participants in the trials ranged from 1448 (*32*) to 58 730 (*36*), with a total of 200 855 participants. Three studies reported results for men and women separately (*26, 34, 35*), two included only men (*31, 33*), and the rest reported men and women combined (*9, 10, 25, 27-30, 32, 36, 37*). One study reported results separately for overweight participants and non-overweight participants (*30*).

3.2.4 Measure of exposure

All studies had some measure of sodium intake at baseline, and compared this exposure with the outcomes. Six studies measured exposure through 24-hour urinary sodium excretion (*10, 25, 26, 29, 34, 37*), one measured overnight urinary sodium excretion (*32*), one measured morning fasting urine sodium excretion (*9*), three used food frequency questionnaires (*33, 35, 36*) and four used dietary recall over one 24-hour period (*27, 28, 30, 31*).

Most studies divided the population into quartiles or quintiles of sodium intake at baseline, then measured the outcomes of interest over time (*25, 26, 28, 30, 31, 34, 36*). Three studies divided the population into tertiles of sodium intake (*10, 35, 37*), two into higher and lower sodium intake (*27, 33*), and one into seven unequally sized subgroups of sodium intake at baseline (*9*). One study looked at sodium intake as a continuous variable and reported change in risk for one standard deviation (SD) increase in sodium intake (*32*). 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 (*29*).

3.2.5 Outcome measures

Cardiovascular disease

Twelve studies reported CVD (*9, 10, 25-30, 32, 34, 36, 37*). One study did not provide a measure of variance and was not included in the meta-analysis (*25*). Of the 11 studies in the meta-analysis, two reported both fatal and non-fatal events (*26, 29*), two reported fatal events and a combination of fatal and non-fatal CVD events (*9, 10*), and seven reported only fatal events (*27, 28, 30, 32, 34, 36*). There were no studies that reported only non-fatal events.

Stroke

Eleven studies reported stroke (*9, 10, 26, 27, 30-36*). Of these, seven reported both fatal and non-fatal events combined (*9, 10, 26, 31-34*), three reported only fatal events (*27, 35, 36*), and one reported fatal events separately, and fatal and non-fatal events combined (*30*).

Coronary heart disease

Eight studies reported CHD (*10, 25-27, 30, 32, 34, 36*). Of these, one did not provide a measure of variance and was not included in the meta-analysis (*25*). Of the seven studies in

the meta-analysis, three reported both fatal and non-fatal events combined (*10, 26, 32*), two reported only fatal events (*27, 36*), one reported fatal events separately from non-fatal events (*34*) and one reported fatal events separately, and fatal and non-fatal events combined (*30*).

All-cause mortality

Ten studies reported all-cause mortality (*9, 10, 25, 27-30, 32, 34, 37*). Of these, one did not report a measure of variance and was excluded from the meta-analysis (*25*).

Other outcomes

All other outcomes reported by study authors are found in **Section 3.6.1**. No studies reported any adverse effects of low-sodium intake.

3.3 Excluded studies

Reasons for exclusion of the four excluded studies are given in **Section 3.6.2**.

3.4 Effects of interventions

The effects of reduced sodium versus control in RCTs are found in **Table 3.31**, **Figure 3.3**, and **Figure 3.19**. The association of higher sodium exposure with outcomes of interest in cohort studies are summarized in the effect estimate **Tables 3.32–3.35**, and in **Figures 3.4–3.18** and **3.20–3.27**.

3.4.1 Cardiovascular disease

Randomized controlled trials

Only one study reported cardiovascular deaths during the study follow-up, but there were only five deaths overall; hence, there was no power to assess effects of sodium modification on cardiovascular mortality (*38*). Cardiovascular morbidity at trial end was only available for two studies, one conducted over 7–71 months (*38*), the other over 30 months (*39*). Both studies were in individuals with hypertension. There were a total of 720 participants reporting 93 events. There was no statistically significant reduction in cardiovascular morbidity with a low-sodium diet compared with usual diet (RR 0.84, 95%CI: 0.57, 1.23)[1] (**Table 3.31** and **Figure 3.3**).

Cohort studies

The effect estimate of the association of higher sodium intake and all CVD from RRs and HRs calculated from models not adjusting for blood pressure (nine studies with 13 comparisons) was not statistically significant (RR 1.12, 95%CI: 0.93, 1.34)[2] (**Table 3.32** and **Figure 3.4**). There was no statistically significant association of higher sodium intake and risk of combined fatal and non-fatal CVD events (RR 1.08, 95%CI: 0.78, 1.47), nor risk of fatal CVD events (RR 1.08, 95%CI: 0.87, 1.33) (**Table 3.32** and **Figure 3.5**).

The relationship between higher sodium intake and CVD was not statistically significant when the sodium intake of the reference group was < 2 g sodium/day (RR 1.17, 95%CI: 0.91, 1.50) or > 2 g sodium/day (RR 1.16, 95%CI: 0.86, 1.57). In the only study with a reference

[1] In analyses of data from RCTs, RR < 1 indicates protective effect of reduced sodium intake

[2] In analyses of data from cohort studies, RR > 1 indicates positive association of increased sodium and increased risk of outcome

group intake of < 1.2 g sodium/day, the risk of CVD was increased with higher sodium intake (RR 1.42, 95%CI: 1.19, 1.69) (**Table 3.32** and **Figure 3.6**).

There was no statistically significant increase in risk of CVD when the difference in intake between the reference and the higher sodium groups was < 1.15 g sodium/day (50 mmol) (RR 1.15, 95%CI: 0.86, 1.55), or 1.15–2.3 g sodium/day (50–100 mmol) (RR 1.06, 95%CI: 0.81, 1.39). In the two comparisons where the difference between the reference and the higher sodium groups was > 2.3 g sodium/day (100 mmol), there was no statistically significant increase in risk of CVD with higher sodium intake (RR 1.06, 95%CI: 0.84, 1.34) (**Table 3.32** and **Figure 3.7**).

Four studies reported RRs or HRs from models that adjusted for additional covariates including blood pressure, and two studies only reported RRs or HRs from models adjusting for blood pressure as well as other covariates. Calculating the effect estimate using the RRs or HRs from the fully adjusted models, where available, generated a result that was similar to estimating the overall effect from the models that did not adjust for blood pressure (RR 1.04, 95%CI: 0.87, 1.25) (**Table 3.32** and **Figure 3.8**).

3.4.2 Stroke

Randomized controlled trials

Only one RCT reported stroke during the study follow-up (*39*). Four stroke events were reported, two in the low-sodium group and two in the usual sodium group. These limited data did not allow for the generation of an effect estimate and did not provide sufficient information to suggest an effect or lack of effect.

Cohort studies

The meta-analysis of 10 studies with 14 comparisons detected a significant association between higher sodium intake and increased risk of all stroke (RR 1.24, 95%CI: 1.08, 1.43) (**Table 3.33** and **Figure 3.9**). There was a statistically significant association between higher sodium intake and increased risk of combined fatal and non-fatal stroke (RR 1.13, 95%CI: 1.01, 1.26), and increased risk of fatal stroke (RR 1.63, 95%CI: 1.27, 2.10) (**Table 3.33** and **Figure 3.10**).

The reference group intake of sodium (< 2 g/day versus > 2 g/day) had little effect on the association between higher sodium intake and stroke events (< 2 g sodium/day, RR 1.30, 95%CI: 1.03, 1.64 versus > 2 g sodium/day, RR 1.24, 95%CI: 1.00, 1.53). In the one comparison with a reference intake of < 1.2 g sodium/day, there was a statistically significant association between higher sodium intake and increased risk of stroke (RR 1.55, 95%CI: 1.20, 2.00) (**Table 3.33** and **Figure 3.11**).

As shown in **Table 3.33** and **Figure 3.12**, when the difference in intake between the reference and the higher sodium intake groups was < 1.15 g sodium/day (50 mmol), there was no statistically significant increase in risk of stroke (RR 1.15, 95%CI: 0.96, 1.38); when it was 1.15–2.3 g sodium/day (50–100 mmol), there was a statistically significant association between higher sodium intake and increased risk of stroke (RR 1.21, 95%CI: 1.05, 1.40); and when it was > 2.3 g sodium/day (100 mmol), there was a borderline statistically significant association between higher sodium intake and increased risk of stroke (RR 1.44, 95%CI: 0.99, 2.12).

Four studies reported RRs or HRs from models that adjusted for additional covariates including blood pressure, and one study only reported an RR from a model adjusting for blood pressure as well as other covariates. The overall effect estimate generated using the

RRs or HRs from the fully adjusted models was less than the effect estimate generated from the models not adjusting for blood pressure; however, the results were not statistically significantly different (RR 1.18, 95%CI: 1.03, 1.36) (**Table 3.33** and **Figure 13**).

3.4.3 Coronary heart disease

Randomized controlled trials

Two RCTs reported myocardial infarction, both fatal and non-fatal events, during the study (*38, 39*). Since there were only seven events, it was not possible to calculate a stable effect estimate or suggest an effect or lack of effect.

Cohort studies

The meta-analysis of six studies with nine comparisons detected a non-significant association between higher sodium intake and increased risk of all CHD (RR 1.04, 95%CI: 0.86, 1.24) (**Table 3.34** and **Figure 3.14**). There was a non-significant association between higher sodium intake and increased risk of combined fatal and non-fatal CHD events (RR 1.02, 95%CI: 0.83, 1.24). However, when only fatal events were considered, there was a significant association between higher sodium intake and risk of fatal CHD (RR 1.32, 95%CI: 1.13, 1.53) (**Table 3.34** and **Figure 3.15**).

There was no statistically significant association between higher sodium intake and increased risk of CHD when the reference group intake of sodium was < 2 g sodium/day, (RR 1.07, 95%CI: 0.94, 1.22) or > 2 g sodium/day (RR 0.86, 95%CI: 0.52, 1.42). In the one comparison with a reference intake of < 1.2 g sodium/day, there was no statistically significant association between higher sodium intake and increased risk of CHD (RR 1.19, 95%CI: 0.82, 1.72) (**Table 3.34** and **Figure 3.16**).

There was no statistically significant association between higher sodium intake and CHD when the difference in intake between the reference and the higher sodium intake groups was < 1.15 g sodium/day (50 mmol) (RR 1.02, 95%CI: 0.87, 1.18), or 1.15–2.3 g sodium/day (50–100 mmol) (RR 1.09, 95%CI: 0.91, 1.30). In the one comparison with a difference between the reference and the higher sodium intake group of > 2.3 g sodium/day (100 mmol), there was a borderline statistically significant association between higher sodium intake and increased risk of CHD (RR 1.35, 95%CI: 0.99, 1.85) (**Table 3.34** and **Figure 3.17**).

Three studies reported RRs and HRs from models that adjusted for additional covariates including blood pressure, and one study only reported an RR from a model adjusting for blood pressure as well as other covariates. The effect estimate generated by using the RRs or HRs from the fully adjusted models was similar to that generated using models that did not control for blood pressure (RR 1.01, 95%CI: 0.86, 1.20) (**Table 3.34** and **Figure 3.18**).

3.4.4 All-cause mortality

Randomized controlled trials

Four RCTs reported all-cause mortality (*38, 40-42*).The effect of reduced sodium intake compared with usual sodium intake on all-cause mortality was not statistically significant (RR 0.70, 95%CI: 0.44, 1.14). However, events were too limited (69 deaths in total) to conclude the presence of or absence of an effect (**Table 3.31** and **Figure 3.19**).

Cohort studies

The meta-analysis of seven cohort studies with 10 comparisons detected a non-significant association between higher sodium intake and increased all-cause mortality (RR 1.06, 95%CI: 0.94, 1.20) (**Table 3.35** and **Figure 3.20**).

There was no statistically significant association between higher sodium intake and increased risk of all-cause mortality when the reference group intake of sodium was < 2 g sodium/day (RR 1.15, 95%CI: 0.95, 1.40) or > 2 g sodium/day (RR 1.03, 95%CI: 0.82, 1.29). There were no comparisons with a reference intake of < 1.2 g sodium/day (**Table 3.35** and **Figure 3.21**).

There was no statistically significant increase in risk of all-cause mortality when the difference in intake between the reference and the higher sodium intake groups was < 1.15 g sodium/day (50 mmol) (RR 0.96, 95%CI: 0.69, 1.33), 1.15–2.3 g sodium/day (50–100 mmol) (RR 1.08, 95%CI: 0.91, 1.27) or > 2.3 g sodium/day (100 mmol) (two comparisons) (RR 0.98, 95%CI: 0.76, 1.25) (**Table 3.35** and **Figure 3.22**).

Two studies reported models that adjusted for additional covariates including blood pressure, and two studies only reported RRs or HRs calculated from models adjusting for blood pressure as well as other covariates. The effect estimate generated by repeating the analysis including the RRs or HRs from the fully adjusted models was also non-significant (RR 0.99, 95%CI: 0.87, 1.14) (**Table 3.35** and **Figure 3.23**).

3.5 Sensitivity analysis

We removed four studies due to high risk of confounding, based on the measure of exposure (i.e. the measure of sodium intake). These studies all measured baseline sodium intake using one 24-hour dietary recall (*27, 28, 30, 31*). The results of the effect of the removal of these studies on all CVD, all stroke, all CHD and all-cause mortality are found in **Figures 3.24–3.27**, which indicate that removal of these studies had little effect on any outcome.

3.5.1 Quality of the body of evidence

Few events were reported for CVD, stroke or CHD in the RCTs, and there were too few studies to produce meaningful funnel plots. Given the sparseness of data from RCTs, it was difficult to draw conclusions from that data. The risk of bias assessment for the RCTs can be found in the original review published in the Cochrane Library (*12*).

For the cohort studies, the funnel plots generated for all primary outcomes gave no indication of publication bias (**Annex 1**). One comparison had a higher RR and a much smaller sample size than the other comparisons; however, these results were a subset of results from a larger study and did not indicate that small studies with null results were not published. The results from the risk of bias summary (**Annex 2**) and risk of bias graph (**Annex 3**) suggest that there is some bias present in many studies, but the entire body of evidence is unlikely to be at risk of serious problems due to bias.

In the cohort studies, blinding of participants and personnel was absent from approximately 50% of the studies and unclear for approximately 30% of the studies. Since blinding is not generally a characteristic of cohort studies, it was not surprising that many study authors did not report blinding related to participants and personnel. Blinding of outcome assessors was reported in almost half of the studies and not reported in the rest. There was little indication of bias due to selective reporting or incomplete outcome reporting. Four studies were at high risk of bias due to confounding because of the measure of exposure (i.e. one 24-hour

dietary recall to estimate sodium intake). The sensitivity analysis, however, showed that results did not change significantly with the exclusion of these studies in the meta-analyses. Three 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. Generally, however, most studies were free of risk of bias due to confounding.

The assessments of the quality of evidence for CVD, stroke, CHD and all-cause mortality are found in the GRADE evidence profiles for each of the specific objectives of the review (**Annex 4**). The evidence for an association between sodium intake and CVD was moderate and very low. The evidence from RCTs for reduced sodium reducing risk of CVD was of moderate quality. This evidence started on the GRADE ranking as high quality and was downgraded due to imprecision (the 95%CI crossed one). The body of evidence from observational cohort studies started on the GRADE ranking as low due to study design. The evidence for an association between an increase in risk of CVD and high sodium intake was downgraded for inconsistency (95%CI of studies did not always overlap), and had a GRADE ranking of very low.

There was insufficient evidence from RCTs to generate effect estimates for the effect of sodium intake on stroke or CHD. The evidence for a positive association between sodium intake and risk of stroke from cohort studies was low quality. This evidence started as low due to study design, and was not subsequently downgraded. The quality of evidence for the association between higher sodium intake and increased risk of CHD from cohort studies began as low quality because of study design, and was then downgraded to very low quality because of imprecision for all CHD and combined fatal and non-fatal events. The evidence for an association between sodium intake and fatal CHD events was low quality due to study design and was not downgraded for any reason.

The evidence for an association between sodium intake and all-cause mortality was moderate and very low quality. The evidence for an effect of reduced sodium reducing risk of all-cause mortality from RCTs was of moderate quality, and was then downgraded due to imprecision (the 95%CI crossed one). The body of evidence from observational cohort studies started on the GRADE ranking as low because of study design. The evidence for an increase in risk of all-cause mortality with increased sodium intake was downgraded for imprecision and had a GRADE ranking of very low quality.

Only cohort studies were available to address the question of the effect on the outcomes of consuming < 2 g/day per day versus > 2 g/day. The quality of evidence for an association of sodium intake and CVD or CHD was very low. In both cases, the evidence was initially ranked as low because of study design and was then downgraded because of inconsistency or imprecision. The quality of evidence for an association of sodium intake and stroke was low. This evidence was given this GRADE ranking because of study design and was not downgraded for any reason.

Only cohort studies were available to address the question of the effect on the outcomes of consuming < 1.2 g/day per day versus > 1.2 g/day. The quality of evidence for an association of sodium intake and CVD or stroke was low. In both cases, the evidence was initially low because of study design and was not downgraded for any reason. The quality of evidence for an association of sodium intake and CHD was very low. The evidence was initially ranked as low quality because of study design and was then downgraded because of imprecision. These results, however, came from only one study with one comparison and should be regarded with caution. No studies that reported all-cause mortality addressed this question.

3.6 Tables

3.6.1 Characteristics of included studies

Characteristics of randomized controlled trials

All RCTs included in the current review were included in the systematic review published in the Cochrane Library (*12*). Characteristics of included studies and risk of bias assessments can be found in that publication (*12*).

Characteristics of cohort studies

Table 3.1 Alderman 1995

Methods	Cohort study conducted in the United States; data taken from a union-sponsored hypertensive treatment programme
Participants	2937 mildly and moderately hypertensive adults; worksite-based cohort; participants given antihypertensive medical therapy as part of the programme
Interventions	Participants had a measurement of sodium intake and were divided into sex-specific quartiles of sodium intake and incidence of CVD outcomes compared among quartiles Men: • Quartile 1–2.1 g sodium/day • Quartile 2–2.5 g sodium/day • Quartile 3–3.5 g sodium/day • Quartile 4–4.0 g sodium/day Women: • Quartile 1–1.5 g sodium/day • Quartile 2–1.9 g sodium/day • Quartile 3–2.7 g sodium/day • Quartile 4–3.2 g sodium/day
Outcomes	Stroke Myocardial infarction Outcome results reported for men and women separately
Notes	Follow-up time: 3.8 years average Sodium measured through 24-hour urinary sodium excretion Yearly follow-up Morbid and mortal events assessed through review of hospital charts and death certificates; in some rare cases, data confirmed through physicians outside the programme, family members or friends, or through union records Models were unadjusted Models did not adjust for blood pressure

Reference: (*26*)

Table 3.2 Risk of bias table Alderman 1995

Bias	Authors' judgement	Support for judgement
Selection of participants (selection bias)	Unclear risk	Participants were volunteers with high blood pressure in a union-sponsored systematic hypertension treatment programme
Blinding of participants and personnel (performance bias)	Low risk	Personnel were blinded
Blinding of outcome assessment (detection bias)	Low risk	Blinding of outcome assessors
Incomplete outcome data (attrition bias)	Low risk	Reported that there was no loss to follow-up
Selective reporting (reporting bias)	Low risk	The reasons for not reporting some of the prespecified outcomes were explained
Defining exposure (confounding)	Low risk	24-hour urinary sodium excretion
Other confounding	Unclear risk	Models were only adjusted for race and age; therefore, other potential important confounders may have influenced results

Table 3.3 Cohen 2006

Methods	Cohort study conducted in the United States; used data from NHANES II
Participants	7154 men and women 30–74 years old
Interventions	Measured diet and risk factors at baseline and followed for 13.7 years (mean): • Lower half – 1.6 g sodium/day • Upper half – 3.7 g sodium/day
Outcomes	Death from CVD All-cause mortality Death from CHD Death from stroke (cerebrovascular disease)
Notes	Follow-up: 13.7 years (mean) Sodium intake measured using one 24-hour dietary recall Excluded individuals with self-reported history of heart disease or stroke, taking low-salt diet for medical reasons, those who died during ≤ 6 month initial follow-up, and those with the highest or lowest 1% reported intake of sodium or calories Fully adjusted models adjusted for age, sex, race, smoking, alcohol, antihypertension treatment, SBP, body mass index, education, physical activity, potassium intake, history of diabetes, serum cholesterol, calories Models adjusted for SBP Less adjusted models (not adjusted for blood pressure) were not presented.

CHD, coronary heart disease; CVD, cardiovascular disease; NHANES, National Health and Nutrition Examination Survey; SBP, systolic blood pressure
Reference: (*27*)

Table 3.4 Risk of bias table Cohen 2006

Bias	Authors' judgement	Support for judgement
Selection of participants (selection bias)	Unclear risk	Baseline examination part of NHANES II (1976–1980); exclusion of self-reported history of heart disease or stroke
Blinding of participants and personnel (performance bias)	High risk	No blinding
Blinding of outcome assessment (detection bias)	Low risk	Outcome was mortality
Incomplete outcome data (attrition bias)	Unclear risk	Mortality statistics taken from National Death Index and Social Security Administration Death Master File and all those not reported as deceased assumed to be alive; emigration not taken into account
Selective reporting (reporting bias)	Low risk	Prespecified outcomes reported
Defining exposure (confounding)	High risk	Sodium measured through one 24-hour dietary recall
Other confounding	Low risk	Models tested for significance of other common risk factors

NHANES, National Health and Nutrition Examination Survey

Table 3.5 Cohen 2008

Methods	Cohort study conducted in the United States; used data from NHANES III
Participants	8699 male and female adults > 30 years of age
Interventions	Measured diet and risk factors at baseline and followed for 8.7 years (mean): • Quartile 1 – 2.1 g sodium/day • Quartile 2 – 2.5 g sodium/day • Quartile 3 – 3.5 g sodium/day • Quartile 4 – 4.1 g sodium/day
Outcomes	Death from cardiovascular disease All-cause mortality
Notes	Follow-up 8.7 years (mean) Sodium intake measured using one 24-hour dietary recall 13 065 adults over 30 years of age participated in the NHANES III study; analysis excluded individuals with self-reported history of congestive heart failure, heart attack or stroke, taking low-salt diet for medical reasons, those who died during ≤ 6 month initial follow-up, and those with the high or low sodium or calories Fully adjusted models adjusted for age, sex, race, potassium intake, added salt, body mass index, education, smoking, hypertension treatment, SBP, cholesterol, diabetes, cancer, physical activity, alcohol Models adjusted for SBP Less adjusted models adjusted for age, sex, race, calories

NHANES, National Health and Nutrition Examination Survey; SBP, systolic blood pressure
Reference: (*28*)

Table 3.6 Risk of bias table Cohen 2008

Bias	Authors' judgement	Support for judgement
Selection of participants (selection bias)	Unclear risk	Baseline examination part of NHANES III (1988–1994); exclusion of self-reported history of heart disease or stroke and consumption of low salt for health reasons
Blinding of participants and personnel (performance bias)	High risk	No blinding
Blinding of outcome assessment (detection bias)	Low risk	Outcome was mortality
Incomplete outcome data (attrition bias)	Unclear risk	Mortality statistics taken from National Death Index and Social Security Administration Death Master File and all those not reported as deceased assumed to be alive; emigration not taken into account
Selective reporting (reporting bias)	Low risk	Prespecified outcomes reported
Defining exposure (confounding)	High risk	Sodium measured through one 24-hour dietary recall
Other confounding	Low risk	Models tested for significance of other common risk factors

NHANES, National Health and Nutrition Examination Survey

Table 3.7 Cook 2007

Methods	Cohort study conducted in the United States
Participants	2415 (at baseline) men and women 30–54 years of age Cook I = 327 and Cook II = 417
Interventions	Cook I = randomized to low-sodium or control diet; Cook II = randomized to low sodium, low sodium and weight control, weight control only or control; intervention was 18 months in Cook I and 36 months in Cook II Subsequently all participants followed up for a time of 10–15 years post conclusion of the interventions Cook I: • low sodium – 2.29 g sodium/day • higher sodium – 3.34 g sodium/day Cook II: • low sodium – 3.23 g sodium/day • higher sodium – 4.02 g sodium/day
Outcomes	Myocardial infarction Stroke Coronary revascularisation Cardiovascular death
Notes	Follow-up: 10–15 years Sodium intake measured using 24-hour urinary sodium excretion Fully adjusted models adjusted for age, race, sex, weight loss, baseline weight, sodium excretion Models did not adjust for blood pressures

References: (*29, 43*)

Table 3.8 Risk of bias table Cook 2007

Bias	Authors' judgement	Support for judgement
Selection of participants (selection bias)	Low risk	Participants previously participated in RCT and selected from clinics
Blinding of participants and personnel (performance bias)	Unclear risk	Blinded during RCT; unclear whether personnel blinded during follow-up study
Blinding of outcome assessment (detection bias)	Unclear risk	Unclear whether outcome assessors blinded during follow-up study
Incomplete outcome data (attrition bias)	Low risk	> 70% response rate after 10–15 year follow-ups
Selective reporting (reporting bias)	Low risk	Prespecified outcomes reported
Defining exposure (confounding)	Low risk	24-hour urinary sodium excretion
Other confounding	Unclear risk	Controlled for some common confounders but not all

RCT, randomized controlled trial

Table 3.9 Ekinci 2011

Methods	Cohort study conducted in Australia
Participants	638 patients with type 2 diabetes, mean age 64 years, 85% had hypertension (defined by the use of antihypertensive and/or blood pressure > 140/90 mmHg)
Interventions	Baseline measurement of sodium intake and population divided into tertiles and outcomes compared between tertiles: • Low tertile – < 150 mmol/day • Middle tertile – 150–208 mmol/day • High tertile – > 208 mmol/day
Outcomes	All-cause mortality Cardiovascular mortality
Notes	Follow-up: 11 years Sodium intake measured using 24-hour urinary sodium excretion Fully adjusted models adjusted for sex, pre-existing CVD, estimated glomerular filtration rate, atrial fibrillation, urinary albumin excretion rate, SBP, diabetes duration Models adjusted for SBP Less adjusted models (not adjusted for blood pressure) were not presented

CVD, cardiovascular disease; SBP, systolic blood pressure
Reference: (*37*)

Table 3.10 Risk of bias table Ekinci 2011

Bias	Authors' judgement	Support for judgement
Selection of participants (selection bias)	Low risk	638 patients attending a single diabetes clinic
Blinding of participants and personnel (performance bias)	Unclear risk	No blinding described
Blinding of outcome assessment (detection bias)	Unclear risk	No blinding described
Incomplete outcome data (attrition bias)	Low risk	Low loss to follow-up (< 3%)
Selective reporting (reporting bias)	Low risk	Prespecified outcomes reported
Defining exposure (confounding)	Low risk	24-hour urinary sodium excretion
Other confounding	Low risk	Controlled for other common risk factors

Table 3.11 Geleijnse 2007

Methods	Cohort study (case-cohort analysis) conducted in the Netherlands
Participants	1448 adult men and women, mean age 69.2 years, blood pressure status not specified, heterogeneous blood pressure medication population
Interventions	Analysis of sodium in the diet and also analysed potassium intake in diet; results presented as risk per 1 SD change in intake (69 mmol or 1.9 g/day)
Outcomes	Relative risk of incident myocardial infarction Incident stroke CVD mortality All-cause mortality
Notes	Follow-up: 5.5 years Sodium measured by overnight urinary sodium excretion Computerized information system used by general practitioners used to quantify incident events; research physicians verified all information on incident events using records and hospital discharge letters Fully adjusted models adjusted for age, sex, sodium intake, body mass index, smoking, diabetes, use of diuretics, education, calories, alcohol, calcium, saturated fat, potassium intake Models did not adjust for blood pressure

CVD, cardiovascular disease; SD, standard deviation
Reference: (*32*)

Table 3.12 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 assessor
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	Exposure to sodium via urinary excretion
Other confounding	Low risk	Models controlled for other common risk factors

Table 3.13 He 1999

Methods	Cohort study undertaken in the United States; follow-up epidemiological study on the NHANES I
Participants	9485 adults 25–74 years of age during NHANES survey of 1971–1975
Interventions	Assessment of sodium intake as well as overweight and other demographic and physiological indicators were measured at baseline and follow-up measures in 1982, 1984, 1986, 1987, and 1992: • Quartile 1 – 1.4 g sodium/day • Quartile 2 – 1.7 g sodium/day • Quartile 3 – 2.3 g sodium/day • Quartile 4 – 2.6 g sodium/day
Outcomes	Incident CVD Death from CVD Incident stroke Death from stroke Incident CHD Death from CHD Outcomes reported for overweight and non-overweight participants separately
Notes	Follow-up: 11–22 years Sodium intake measured by one 24-hour dietary recall Participants followed up directly Death certificate required to confirm mortality and incident events required documentation for verification Excluded those without exposure data, self-reported history of heart attack, heart failure, or stroke at baseline or were using a low-salt diet at baseline (n from low-salt diet = 337) Fully adjusted models adjusted for age, sex, race, SBP, serum cholesterol level, diabetes, body mass index, diuretic use, physical activity, education, smoking, alcohol, calories Models adjusted for SBP Less adjusted models adjusted for age, sex, race

CHD, coronary heart disease; CVD, cardiovascular disease; NHANES, National Health and Nutrition Examination Survey; SBP, systolic blood pressure
Reference: (*30*)

Table 3.14 Risk of bias table He 1999

Bias	Authors' judgement	Support for judgement
Selection of participants (selection bias)	Unclear risk	Selection from NHANES would be low risk selection through multistage complex random sampling; however, excluded those without exposure data, self-reported history of heart attack, heart failure, or stroke at baseline or using a low-salt diet at baseline (n = 337)
Blinding of participants and personnel (performance bias)	High risk	No blinding
Blinding of outcome assessment (detection bias)	Unclear risk	Not clear whether outcome assessors were blinded
Incomplete outcome data (attrition bias)	Low risk	4% loss to follow-up
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Defining exposure (confounding)	High risk	One 24-hour dietary recall
Other confounding	Low risk	Models controlled for other common risk factors

NHANES, National Health and Nutrition Examination Survey

Table 3.15 Kagan 1985

Methods	Cohort study conducted in the State of Hawaii, the United States of America
Participants	7088 men of Japanese ancestry living in Hawaii, aged 45–68 years; all participants were free of stroke at baseline and individuals with previous CHD or cancer, or those who reported that their previous day's dietary intake was atypical, were excluded
Interventions	Baseline measurement of sodium intake and population divided into quintiles and outcomes compared between quintiles: • Quintile 1 – 1.8 g sodium/day • Quintile 2 – 2.1 g sodium/day • Quintile 3 – 2.7 g sodium/day • Quintile 4 – 3.5 g sodium/day • Quintile 5 – 3.9 g sodium/day
Outcomes	Stroke Stroke subtype Death by stroke
Notes	Follow-up: 10 years Sodium intake measured through 24-hour dietary recall Men followed up directly and surveillance of hospital discharges and death certificates were used for data collection of outcomes Fully adjusted models adjusted for age Models did not adjust for blood pressure

CHD, coronary heart disease
Reference: (*31*)

Table 3.16 Risk of bias table Kagan 1985

Bias	Authors' judgement	Support for judgement
Selection of participants (selection bias)	Unclear risk	Selection of participants not clearly described
Blinding of participants and personnel (performance bias)	Unclear risk	Blinding not described
Blinding of outcome assessment (detection bias)	Unclear risk	Blinding not described
Incomplete outcome data (attrition bias)	Unclear risk	Loss to follow-up not reported
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Defining exposure (confounding)	High risk	One 24-hour dietary recall, which did not include use of salt or soy sauce at the table
Other confounding	High risk	Models controlled for age only

Table 3.17 Larsson 2008

Methods	Cohort study conducted in Finland
Participants	26 556 adult men, age range 50–69 years at baseline, blood pressure status not specified, not specified whether taking BP medication; all were smokers at baseline and were excluded if they had a history of cancer or other serious disease, received anticoagulant therapy, used vitamin E, A or beta-carotene supplements, self-reported having experienced stroke, or had incomplete dietary data; all participants had originally been in an RCT of smokers to assess the effect of alpha-tocopherol or beta-carotene on risk of development of lung cancer
Interventions	Intervention: analysis of sodium and potassium intake in diet: • Quintile 1 – 97.5 mmol potassium/day and 3.92 g/sodium • Quintile 2 – 152.1 mmol potassium/day and 5.86 g/sodium
Outcomes	All stroke (fatal and non-fatal) Stroke subtypes according to quintiles of magnesium, potassium and sodium intake
Notes	Follow-up: 13.6 years on average Sodium intake 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, body mass index, SBP, DBP, serum total cholesterol, HDL cholesterol, diabetes, history of CHD, physical activities, alcohol, calories Models adjusted for SBP and DBP Less adjusted models adjusted for age, supplementation group

CHD, coronary heart disease; DBP, diastolic blood pressure; HDL, high-density lipoprotein; RCT, randomized controlled trial; SBP, systolic blood pressure
Reference: (*33*)

Table 3.18 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 blinding
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 for and if record not found participant considered without outcome
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Defining exposure (confounding)	Unclear risk	Exposure to sodium via food frequency questionnaire validated through comparison with food records
Other confounding	Low risk	Models controlled for other common risk factors

Table 3.19 Nagata 2004

Methods	Cohort study conducted in Japan
Participants	13 355 men and 15 724 women in Takayama City, Gifu, Japan ≥ 35 years of age
Interventions	Usual diet including sodium intake was assessed using food frequency questionnaire Men: • Low tertile – 4.1 g/day • Middle tertile – 5.2 g/day • High tertile – 6.6 g/day Women: • Low tertile – 3.8 g/day • Middle tertile – 4.8 g/day • High tertile – 6.0 g/day
Outcomes	Death from stroke Death from ischaemic stroke Death from intracerebral haemorrhage
Notes	Follow-up: 7 years Food frequency questionnaire used to measure sodium intake Data presented separately for men and women End-points ascertained through mandatory death registration Fully adjusted models adjusted for age, marital status, education, body mass index, smoking, alcohol, exercise, hypertension, diabetes, intake of protein, total energy, potassium and vitamin E intake Models did not control for blood pressure but did control for history of hypertension at baseline

Reference: (*35*)

Table 3.20 Risk of bias table Nagata 2004

Bias	Authors' judgement	Support for judgement
Selection of participants (selection bias)	Low risk	All participants of city 35 years and older were eligible and participation rate at baseline was > 85%
Blinding of participants and personnel (performance bias)	High risk	No blinding
Blinding of outcome assessment (detection bias)	Low risk	Mortality was outcome
Incomplete outcome data (attrition bias)	Low risk	< 5% loss to follow-up through emigration
Selective reporting (reporting bias)	Low risk	Death registration required by law and all prespecified outcomes reported
Defining exposure (confounding)	Unclear risk	1-year recall food frequency questionnaire used, which was validated against 3-day diet records, 4-day diet recalls and 12-day diet records over 1 year
Other confounding	Low risk	Models controlled for other common risk factors

Table 3.21 O'Donnell 2011

Methods	Cohort study conducted in 40 countries
Participants	28 880 participants aged ≥ 55 years 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 blood pressure higher than 160/100 mmHg
Interventions	Baseline measurement of sodium intake and population divided into seven subgroups and outcomes compared between subgroups • Subgroup 1 – < 2 g/day • Subgroup 2 – 2–2.99 g/day • Subgroup 3 – 3–3.99 g/day • Subgroup 4 – 4–5.99 g/day • Subgroup 5 – 6–6.99 g/day • Subgroup 6 – 7–8 g/day • Subgroup 7 – > 8 g/day
Outcomes	All-cause mortality Death from CVD Death from non-CVD Incident myocardial infarction Incident congestive heart failure Incident stroke
Notes	Median follow-up: 56 months (25–75 percentiles, 53–60 months) 24-hour sodium and potassium urinary excretion was estimated from a fasting morning urine samples Fully adjusted models are unadjusted Models did not adjust for blood pressure

CVD, cardiovascular disease
Reference: (*9*)

Table 3.22 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 sodium urinary excretion was estimated from a fasting morning urine samples
Other confounding	High risk	Models are unadjusted

CVD, cardiovascular disease

Table 3.23 Stolarz-Skrzypek 2011

Methods	Cohort study conducted in Belgium and other European countries
Participants	3681 participants without CVD from a Flemish cohort (Flemish Study on Environment, Genes, and Health Outcomes) and a cohort across Europe (European Project on Genes in Hypertension)
Interventions	Baseline measurement of sodium intake and the population was divided into tertiles and outcomes compared between tertiles • Low tertile – 50–126 mmol/day for women and 50–158 mmol/day for men • Middle tertile – 127–177 mmol/day for women and 159–221 mmol/day for men • High tertile – 178–400 mmol/day for women and 222–400 mmol/day for men
Outcomes	All-cause mortality Death from CVD Death from non-CVD Incident CVD Incident CHD Incident stroke
Notes	Median follow-up: 7.9 years Sodium intake measured by 24-hour urinary sodium concentration Fully adjusted models adjusted for study population, sex and baseline variables: age, body mass index, systolic blood pressure, 24-hour urinary potassium excretion, antihypertensive drug treatment, smoking and drinking alcohol, diabetes, total cholesterol, and educational attainment Models controlled for blood pressure Less adjusted models, which adjusted for all covariates other than blood pressure or antihypertensive treatment, also available

CHD, coronary heart failure; CVD, cardiovascular disease
Reference: (*10*)

Table 3.24 Risk of bias table Stolarz-Skrzypek 2011

Bias	Authors' judgement	Support for judgement
Selection of participants (selection bias)	Low risk	Participants without cardiovascular disease selected from large Flemish and European cohorts
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	Reported zero loss to follow-up
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Defining exposure (confounding)	Low risk	24-hour urinary sodium excretion
Other confounding	Low risk	Models controlled for other common risk factors

Table 3.25 Tunstall-Pedoe 1997

Methods	Cohort study conducted in United Kingdom of Great Britain and Northern Ireland (Scotland)
Participants	11 629 men and women 40–59 years of age randomly selected from 25 districts of Scotland
Interventions	Baseline measurement of sodium intake and population divided into quintiles and outcomes compared between quintiles; potassium also measured • Quintile 1 – 1.8 g sodium/day • Quintile 2 – 2.1 g sodium/day • Quintile 3 – 2.7 g sodium/day • Quintile 4 – 3.5 g sodium/day • Quintile 5 – 3.9 g sodium/day
Outcomes	Myocardial infarction (non-fatal) Coronary artery surgery Death from coronary disease (the sum of which was considered all CHD) All-cause mortality
Notes	Follow-up: 7.6 years Sodium intake measured through 24-hour urinary sodium excretion Outcomes measured through death certificates and hospital/clinician records Fully adjusted models adjusted for age Models did not adjust for blood pressure

CHD, coronary heart disease Reference: (*25*)

Table 3.26 Risk of bias table Tunstall-Pedoe 1997

Bias	Authors' judgement	Support for judgement
Selection of participants (selection bias)	Low risk	Random selection of clinics, then patients from clinics; selection from the Scottish Heart Health Study
Blinding of participants and personnel (performance bias)	Low risk	Personnel not aware of urinary sodium 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 of loss to follow-up unclear
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Defining exposure (confounding)	Low risk	24-hour urinary sodium excretion
Other confounding	High risk	Models only controlled for age

Table 3.27 Tuomilehto 2001

Methods	Cohort study conducted in Finland
Participants	1173 men and 1263 women 25–64 years of age; excluded from CHD analysis if had an acute coronary event (n = 34) before baseline and excluded from stroke analysis if had an acute cerebrovascular event (n = 16) before baseline, but each type of patient could be included in the analysis for the other event Men: • Quartile 1 – 3.7 sodium g/day • Quartile 2 – 4.2 sodium g/day • Quartile 3 – 5.4 sodium g/day • Quartile 4 – 6.0 sodium g/day Women: • Quartile 1 – 2.7 sodium g/day • Quartile 2 – 3.1 sodium g/day • Quartile 3 – 4.0 sodium g/day • Quartile 4 – 4.5 sodium g/day
Interventions	Measured sodium and other dietary exposures and other CVD risk factors at baseline
Outcomes	Incident coronary event Incident stroke event Death from CHD Death from CVD All-cause mortality
Notes	Follow-up: 8–13 years Sodium intake measured via 24-hour urinary sodium excretion End-points were measured through Statistics Finland (mortality) and national hospital discharge registers (morbidity) Fully adjusted models adjusted for age, study year, smoking, serum total, HDL cholesterol, systolic blood pressure, body mass index Models adjusted for blood pressure Less adjusted models adjusted for age, study year

CHD, coronary heart disease; CVD, cardiovascular disease; HDL, high-density lipoprotein
Reference: (*34*)

Table 3.28 Risk of bias table Tuomilehto 2001

Bias	Authors' judgement	Support for judgement
Selection of participants (selection bias)	Low risk	Randomly selected sample of men and women from two eastern provinces of Finland
Blinding of participants and personnel (performance bias)	High risk	No blinding
Blinding of outcome assessment (detection bias)	Low risk	Mortality and morbidity measured through national registry systems
Incomplete outcome data (attrition bias)	Low risk	Participants followed through health registry system
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Defining exposure (confounding)	Low risk	24-hour urinary sodium
Other confounding	Low risk	Models controlled for other common risk factors

Table 3.29 Umesawa 2008

Methods	Cohort study conducted in Japan; sample derived from 45 communities across Japan
Participants	58 730 adult men (23 119) and women (35 611), age range 40–79 years, blood pressure status not specified, not specified whether taking blood pressure medication
Interventions	Sodium and potassium intake in diet measured and quintiles compared on outcomes: • Quintile 1 35 mmol potassium – 1.15 g sodium • Quintile 2 44 mmol potassium – 1.68 g sodium • Quintile 3 51 mmol potassium – 2.07 g sodium • Quintile 4 58 mmol potassium – 2.51 g sodium • Quintile 5 68 mmol potassium – 3.11 g sodium
Outcomes	Mortality from stroke Mortality from CHD Mortality total CVD
Notes	Follow-up: 12.7 years (average) Sodium intake measured through food frequency questionnaire End-points measured by death certificate Fully adjusted models adjusted for age, sex, body mass index, smoking, alcohol, history of hypertension, diabetes, menopause and hormone replacement therapy (women), sports activities, walking time, education, perceived mental stress, calcium intake Models did not control for blood pressure but did control for history of hypertension

CHD, coronary heart disease; CVD, cardiovascular disease
Reference: (*36*)

Table 3.30 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 other common risk factors

3.6.2 Excluded studies and reasons for exclusion

The excluded studies, and the reasons for their exclusions, are as shown in **Table 3.30**, below.

Table 3.31 Excluded studies and reasons for exclusion

Study ID	Reason for exclusion
Chang 2006 (*22*)	Intervention manipulated sodium and potassium intake
Hu 1992 (*24*)	No quantitative measure of exposure
Paterna 2008 (*21*)	Study population not healthy (patients with heart failure)
Thomas 2011 (*23*)	Study population not healthy (individuals with type I diabetes)

3.6.3 Effect estimate tables

Table 3.32 Effect estimate of reduced sodium intake on cardiovascular disease, stroke, coronary heart disease and all-cause mortality from randomized controlled trials

Outcome or subgroup	Studies/comparisons	Effect estimate[a]
Cardiovascular disease	2/2	0.84 [0.57, 1.23]
Stroke	Insufficient number of events to generate effect estimate	
Coronary heart disease	Insufficient number of events to generate effect estimate	
All-cause mortality	4/4	0.70 [0.44, 1.13]

[a] An effect estimate of < 1 indicates a decreased risk of outcome with decreased sodium intake.

Table 3.33 Effect estimate of sodium intake and cardiovascular disease: cohort studies

Outcome or subgroup	Studies/comparisons	Effect estimate[b]
1. Cardiovascular disease[a]	9/13	1.12 [0.93, 1.34]
1.1 Cardiovascular disease (subgroup: outcome type)		Subtotals only
Combined fatal and non-fatal events	4/6	1.08 [0.78, 1.47]
Fatal events only	7/9	1.08 [0.87, 1.33]
Non-fatal events only	0/0	Not estimable
1.2 Cardiovascular disease (subgroup: intake in reference group)		Subtotals only
< 2 g sodium/day	4/6	1.17 [0.91, 1.50]
> 2 g sodium/day	4/6	1.16 [0.86, 1.57]
< 1.2 g sodium/day	1/1	1.42 [1.19, 1.69]
1.3 Cardiovascular disease (subgroup: difference in intake)		Subtotals only
< 50 mmol (1.15 g) sodium/day	3/4	1.15 [0.86, 1.55]
50–100 mmol (1.15–2.3 g) sodium/day	6/9	1.06 [0.81, 1.39]
> 100 mmol (> 2.3 g) sodium/day	2/2	1.06 [0.84, 1.34]
2. Cardiovascular disease[c]	11/15	1.04 [0.87, 1.25]

[a] Relative risk or hazard ratio from each original study calculated from models that adjusted for the most number of covariates **not** including systolic or diastolic blood pressure.
[b] An effect estimate of > 1 indicates an association between increased risk of outcome and higher sodium intake.
[c] Relative risk or 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.

Table 3.34 Effect estimate of sodium intake and stroke: cohort studies

Outcome or subgroup	Studies/comparisons	Effect estimate[b]
1. Stroke[a]	10/14	1.24 [1.08, 1.43]
1.1 Stroke (subgroup: outcome type)		Subtotals only
Combined fatal and non-fatal events	8/11	1.13 [1.01, 1.26]
Fatal events only	3/5	1.63 [1.27, 2.10]
Non-fatal events only	0/0	Not estimable
1.2 Stroke (subgroup: reference intake)		Subtotals only
< 2 g sodium/day	5/6	1.30 [1.03, 1.64]
> 2 g sodium/day	5/7	1.24 [1.00, 1.53]
< 1.2 g sodium/day	1/1	1.55 [1.20, 2.00]
1.3 Stroke (subgroup: difference in intake)		Subtotals only
< 50 mmol (1.15 g) sodium/day	6/8	1.15 [0.96, 1.38]
50–100 mmol (1.15–2.3 g) sodium/day	8/11	1.21 [1.05, 1.40]
>100 mmol (> 2.3 g) sodium/day	3/3	1.44 [0.99, 2.12]
2. Stroke[c]	11/15	1.18 [1.03, 1.36]

[a] Relative risk or hazard ratio from each original study calculated from models that adjusted for the most number of covariates **not** including systolic or diastolic blood pressure.
[b] An effect estimate of > 1 indicates an association between increased risk of outcome and higher sodium intake.
.
[c] Relative risk or 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.

Table 3.35 Effect estimate of sodium intake and coronary heart disease: cohort studies

Outcome or subgroup	Studies/comparisons	Effect estimate[b]
1. Coronary heart disease[a]	6/9	1.04 [0.86, 1.24]
1.1 Coronary heart disease (subgroup: outcome type)		Subtotals only
Combined fatal and non-fatal events	5/8	1.02 [0.83, 1.24]
Fatal events only	3/5	1.32 [1.13, 1.53]
Non-fatal events only	0/0	Not estimable
1.2 Coronary heart disease (subgroup: reference intake)		Subtotals only
< 2 g sodium/day	3/4	1.07 [0.94, 1.22]
> 2 g sodium/day	3/4	0.86 [0.52, 1.42]
< 1.2 g sodium/day	1/1	1.19 [0.82, 1.72]
1.3 Coronary heart disease (subgroup: difference in intake)		Subtotals only
< 50 mmol (1.15 g) sodium/day	3/4	1.02 [0.87, 1.18]
50–100 mmol (1.15–2.3 g) sodium/day	5/8	1.09 [0.91, 1.30]
> 100 mmol (> 2.3 g) sodium/day	1/1	1.35 [0.99, 1.85]
2. Coronary heart disease[c]	7/10	1.01 [0.86, 1.20]

[a] Relative risk or hazard ratio from each original study calculated from models that adjusted for the most number of covariates **not** including systolic or diastolic blood pressure.
[b] An effect estimate of > 1 indicates an association between increased risk of outcome and higher sodium intake.
.
[c] Relative risk or 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.

Table 3.36 Effect estimate of sodium intake and all-cause mortality: cohort studies

Outcome or subgroup	Studies/comparisons	Effect estimate[b]
1. All-cause mortality[a]	7/10	1.06 [0.94, 1.20]
1.1 All-cause mortality (subgroup: reference intake)		Subtotals only
< 2 g sodium/day	3/4	1.15 [0.95, 1.40]
> 2 g sodium/day	4/6	1.03 [0.82, 1.29]
< 1.2 g sodium/day	0/0	Not estimable
1.2 All-cause mortality (subgroup: difference in intake)		Subtotals only
< 50 mmol (1.15 g) sodium/day	2/3	0.96 [0.69, 1.33]
50–100 mmol (1.15–2.3 g) sodium/day	4/6	1.08 [0.91, 1.27]
> 100 mmol (> 2.3 g) sodium/day	2/2	0.98 [0.76, 1.25]
2. All-cause mortality[c]	9/12	0.99 [0.87, 1.14]

[a] Relative risk or hazard ratio from each original study calculated from models that adjusted for the most number of covariates **not** including systolic or diastolic blood pressure.
[b] An effect estimate of > 1 indicates an association between increased risk of outcome and higher sodium intake.
.
[c] Relative risk or 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.

3.7 Figures

Figure 3.1 Flow through screening, inclusion and exclusion (randomized controlled trials)

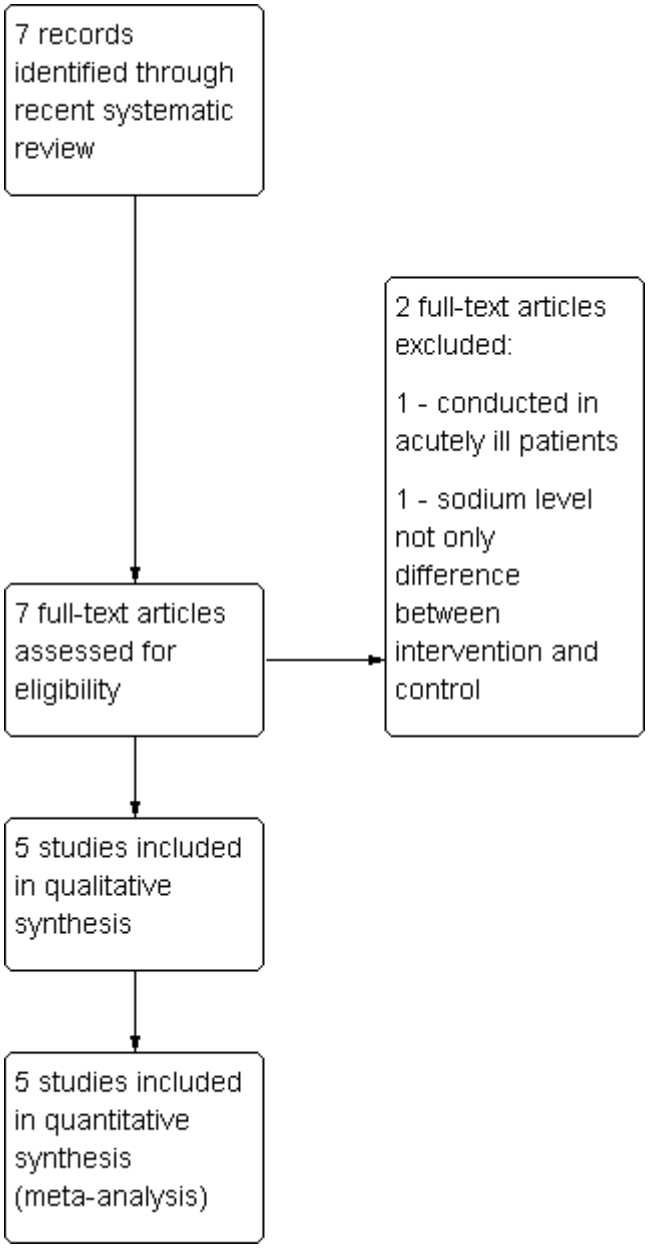


Figure 3.2 Flow through screening, inclusion and exclusion (cohort studies)

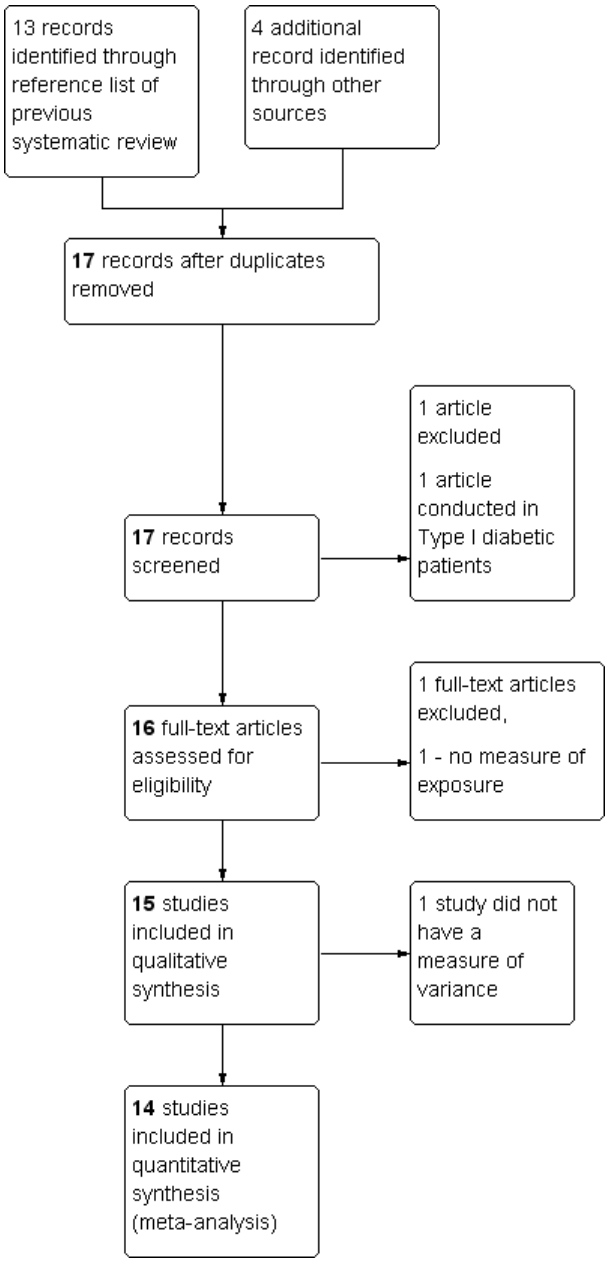
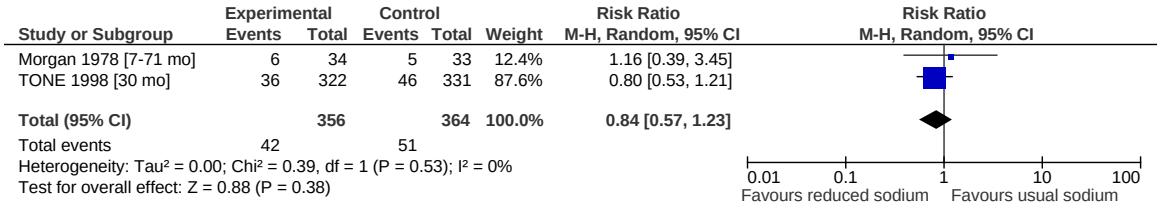
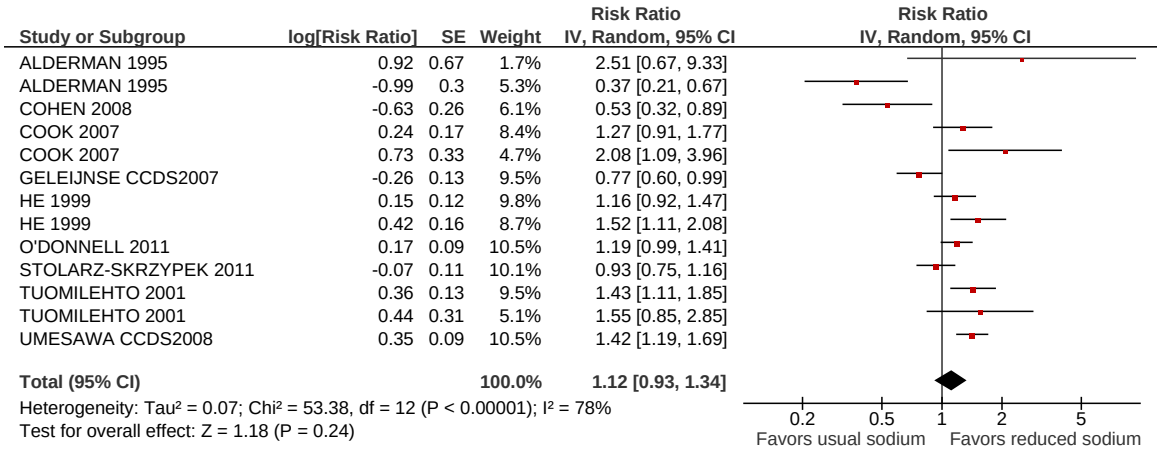


Figure 3.3 Cardiovascular disease: randomized controlled trials[a]



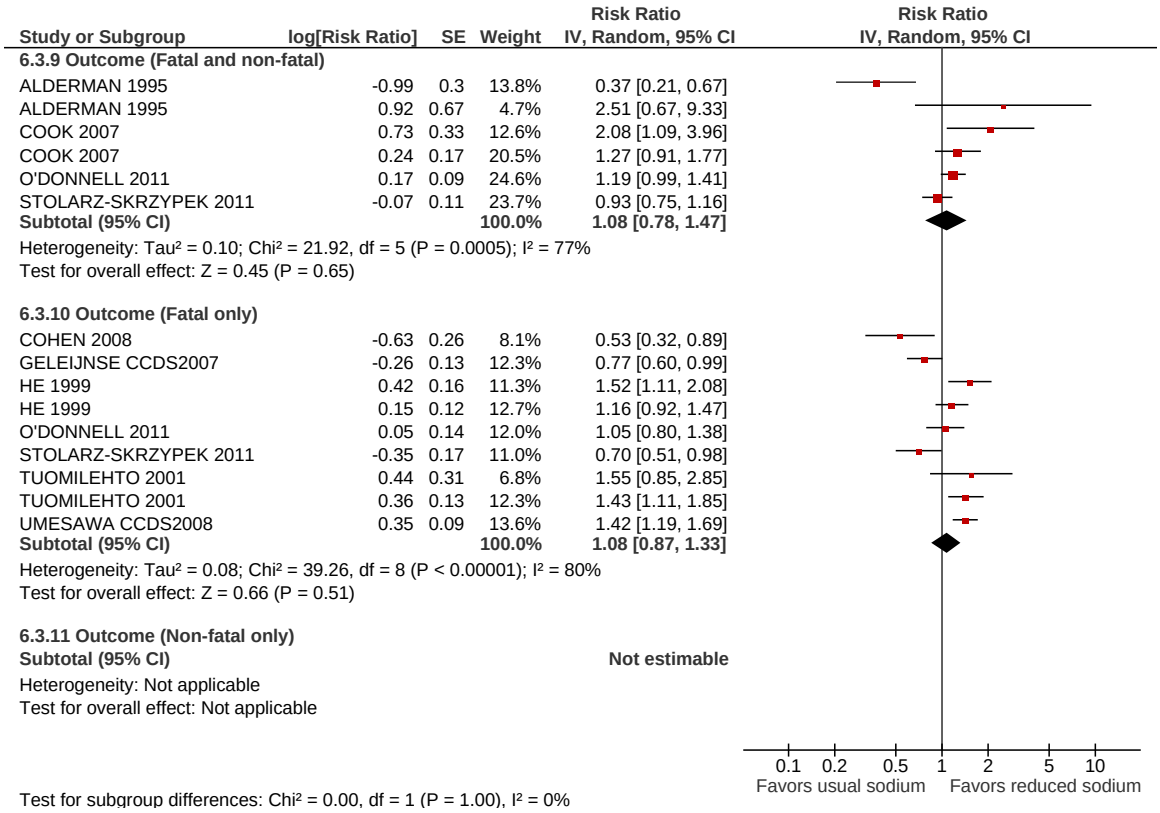
[a] Relative risk < 1 indicates decreased risk in cardiovascular disease with reduced sodium intake.

Figure 3.4 Cardiovascular disease: cohort studies using relative risk and hazard ratio from less adjusted model[ab]



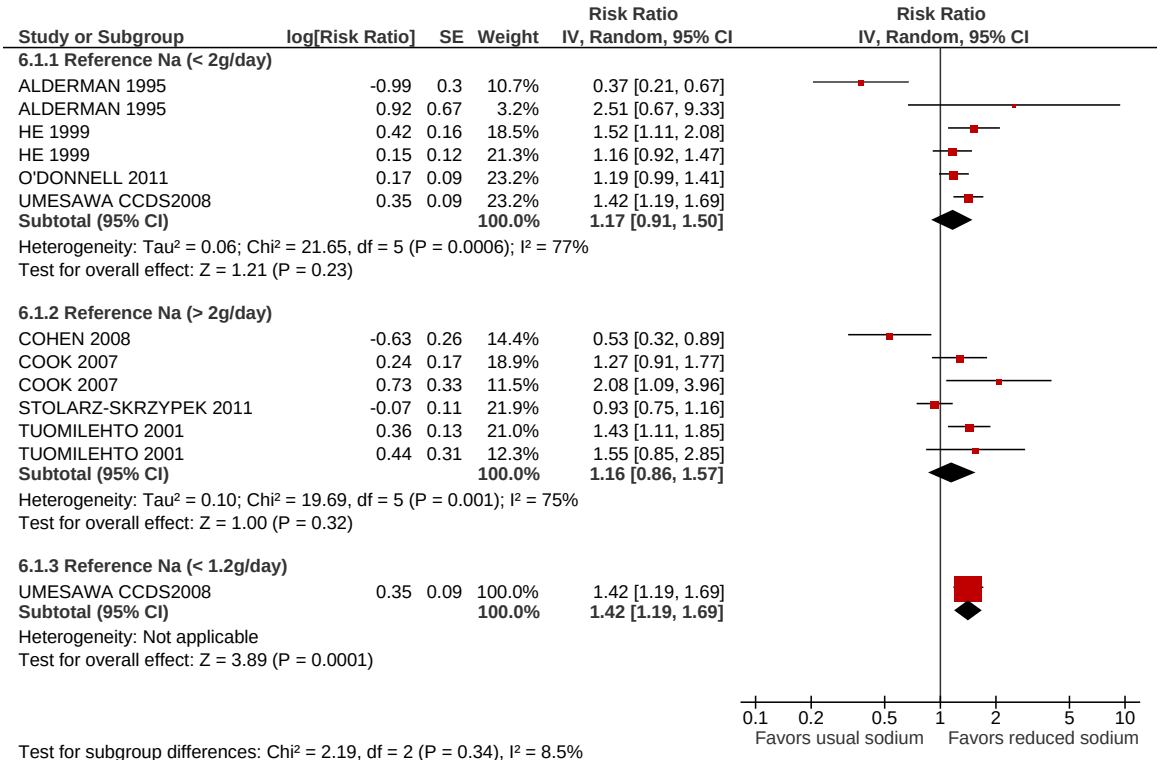
[a] Relative risk > 1 indicates an association between increased risk of outcome and higher sodium intake.
[b] Relative risk or hazard ratio from each original study calculated from models that adjusted for the most number of covariates **not** including systolic or diastolic blood pressure.

Figure 3.5 Cardiovascular disease by outcome type: cohort studies[ab]



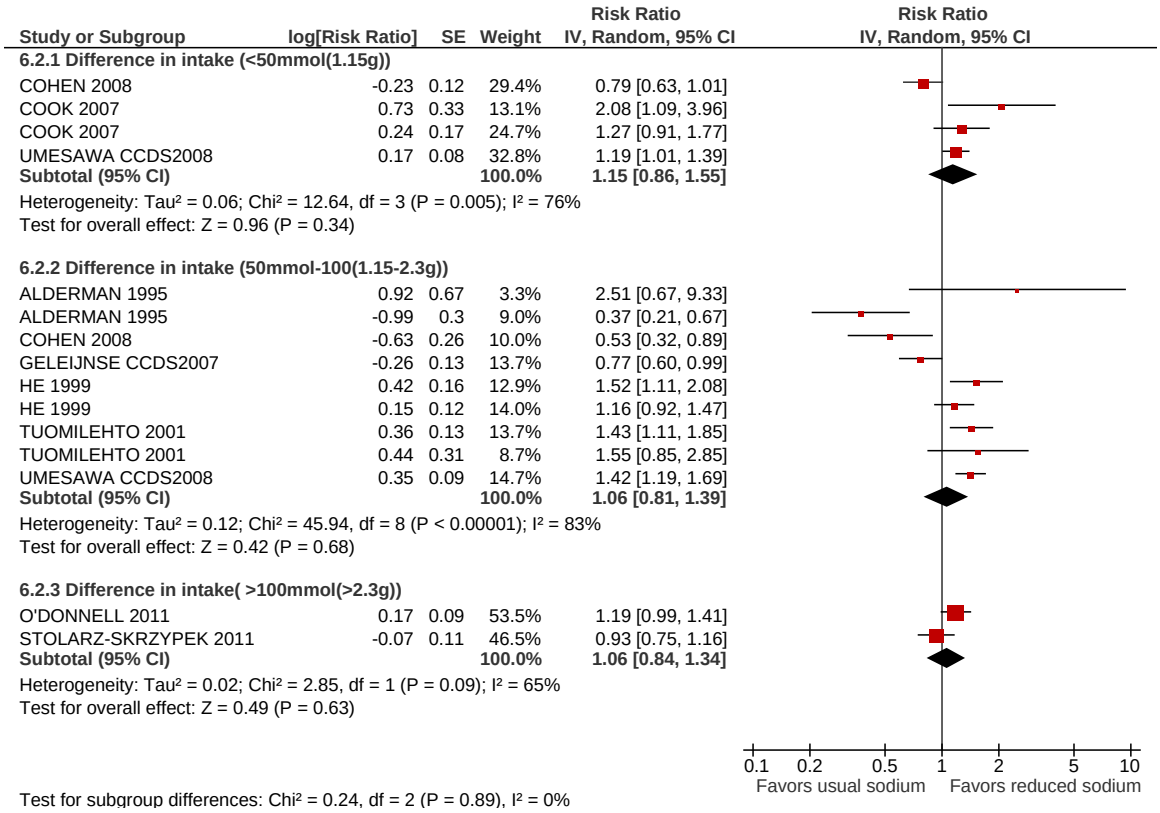
[a] Relative risk > 1 an association between increased risk of outcome and higher sodium intake.
[b] Relative risk or hazard ratio from each original study calculated from models that adjusted for the most number of covariates **not** including systolic or diastolic blood pressure.

Figure 3.6 Cardiovascular disease by reference group intake: cohort studies[ab]



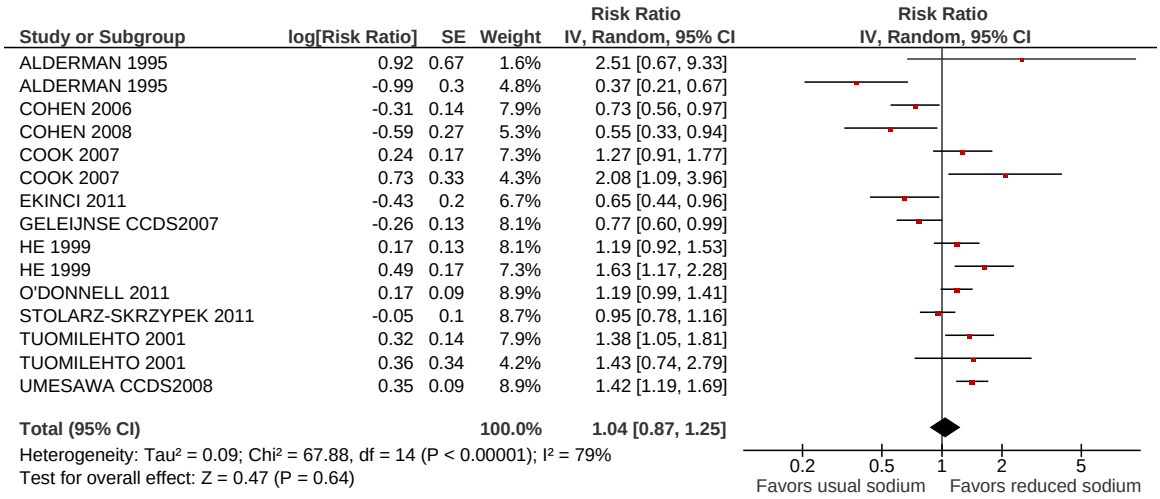
[a] Relative risk > 1 indicates an association between increased risk of outcome and higher sodium intake.
[b] Relative risk or hazard ratio from each original study calculated from models that adjusted for the most number of covariates **not** including systolic or diastolic blood pressure.

Figure 3.7 Cardiovascular disease by difference in intake: cohort studies[ab]



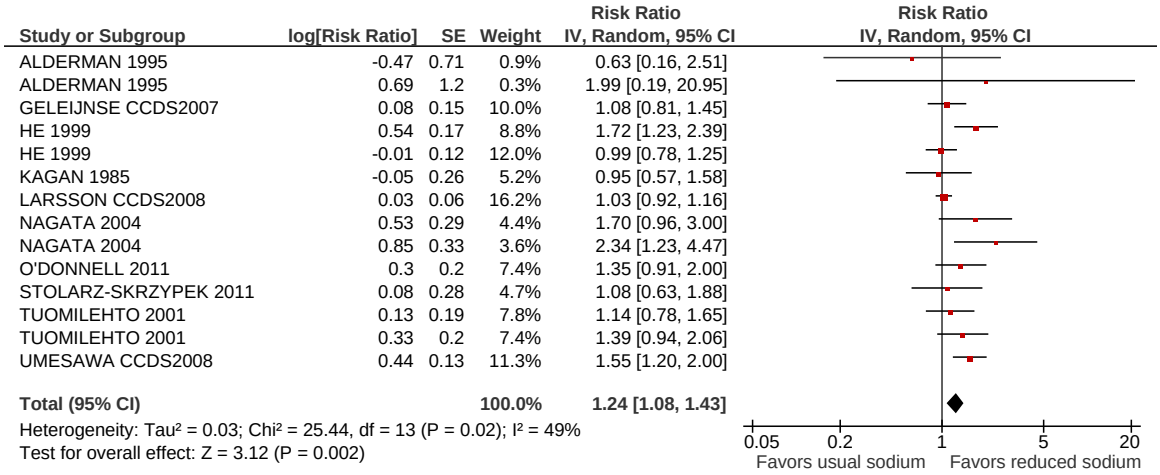
[a] Relative risk > 1 indicates an association between increased risk of outcome and higher sodium intake.
[b] Relative risk or hazard ratio from each original study calculated from models that adjusted for the most number of covariates **not** including systolic or diastolic blood pressure.

Figure 3.8 Cardiovascular disease: cohort studies relative risk and hazard ratio from fully adjusted model[ab]



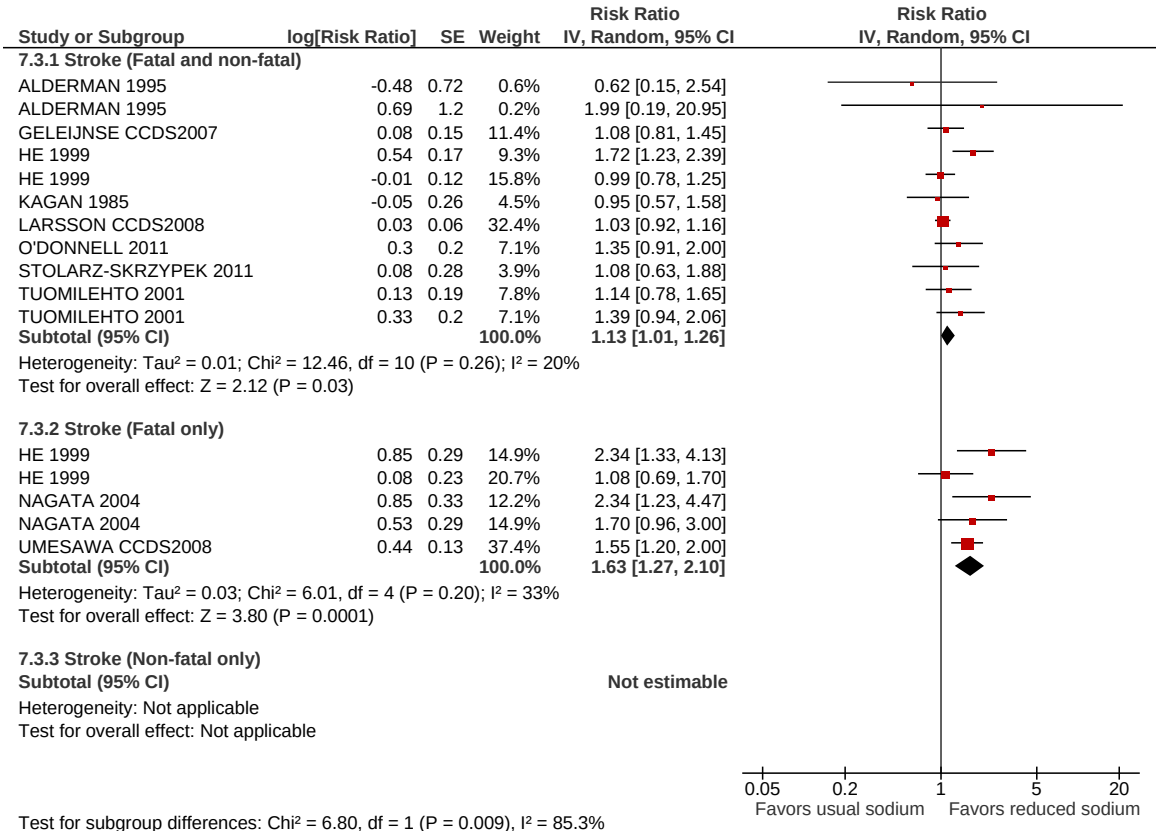
[a] Relative risk > 1 indicates an association between increased risk of outcome and higher sodium intake.
[b] Relative risk or hazard ratio from each original study calculated from models that adjusted for the most number of covariates including, in some cases, systolic or diastolic blood pressure.

Figure 3.9 Stroke: cohort studies using relative risk and hazard ratio from less adjusted model[ab]



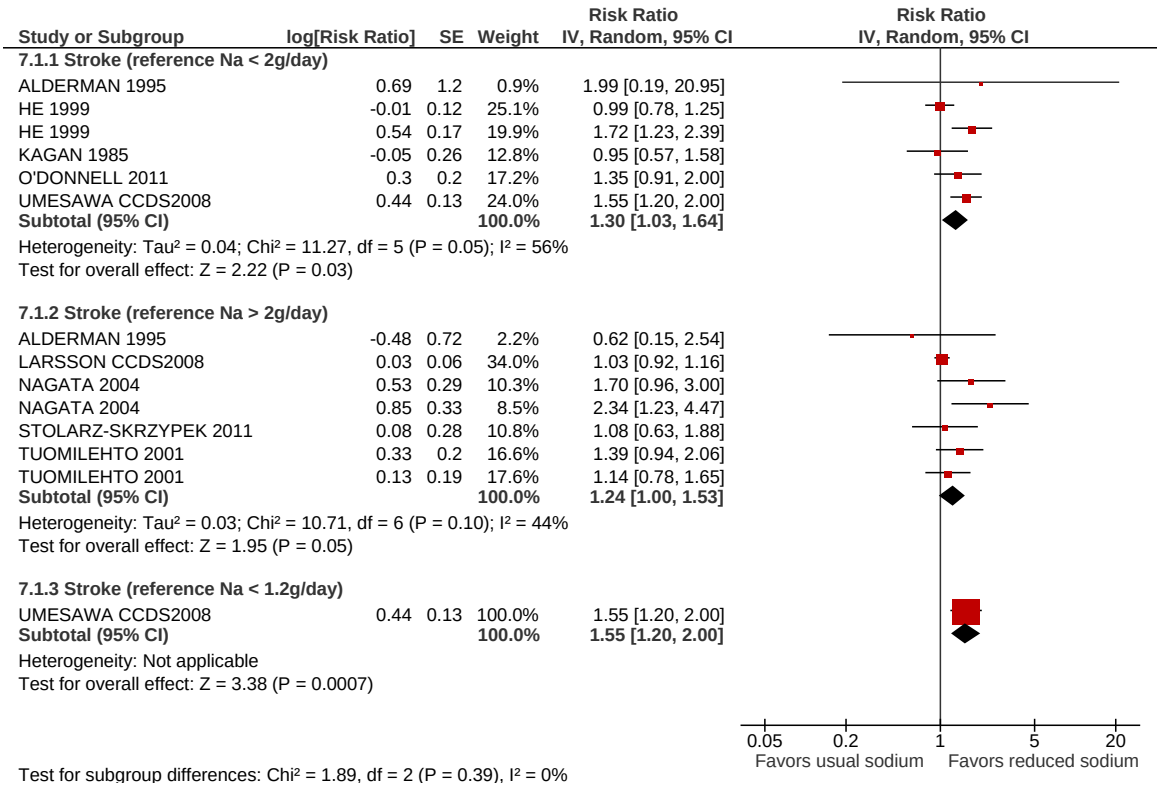
[a] Relative risk > 1 indicates an association between increased risk of outcome and higher sodium intake.
[b] Relative risk or hazard ratio from each original study calculated from models that adjusted for the most number of covariates **not** including systolic or diastolic blood pressure.

Figure 3.10 Stroke by outcome type: cohort studies[ab]



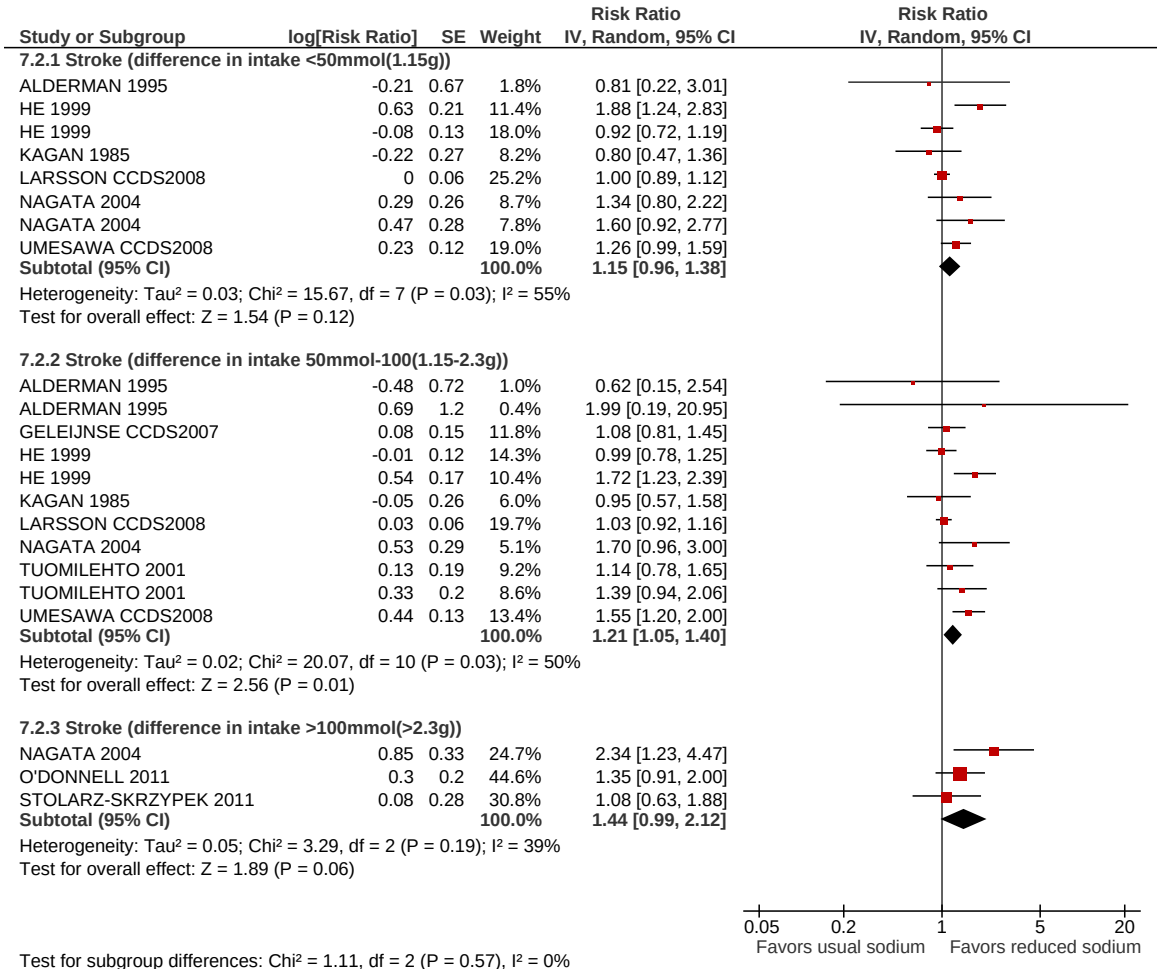
[a] Relative risk > 1 indicates an association between increased risk of outcome and higher sodium intake.
[b] Relative risk or hazard ratio from each original study calculated from models that adjusted for the most number of covariates **not** including systolic or diastolic blood pressure.

Figure 3.11 Stroke by reference group intake: cohort studies[ab]



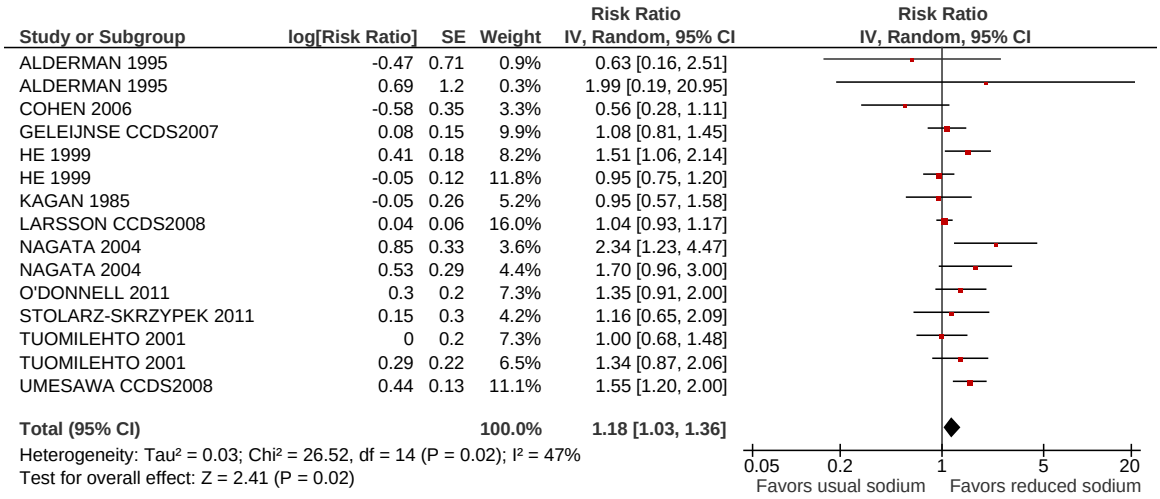
[a] Relative risk > 1 indicates an association between increased risk of outcome and higher sodium intake.
[b] Relative risk or hazard ratio from each original study calculated from models that adjusted for the most number of covariates **not** including systolic or diastolic blood pressure.

Figure 3.12 Stroke by difference in intake: cohort studies[ab]



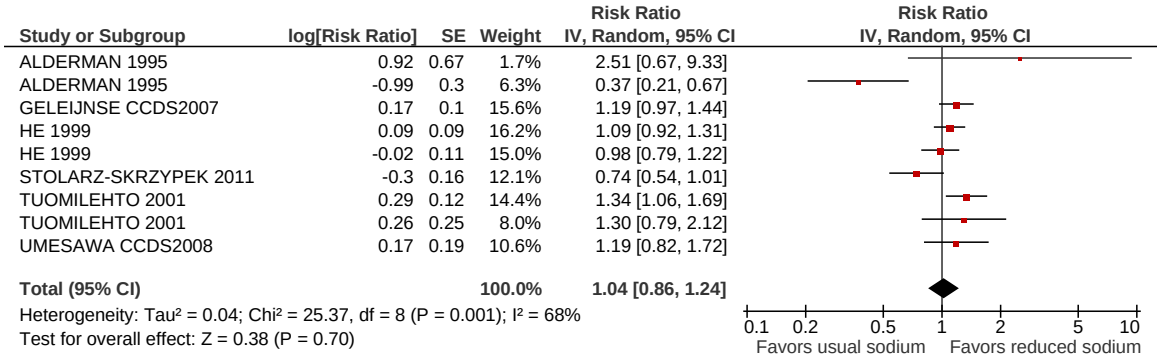
[a] Relative risk > 1 indicates an association between increased risk of outcome and higher sodium intake.
[b] Relative risk or hazard ratio from each original study calculated from models that adjusted for the most number of covariates **not** including systolic or diastolic blood pressure.

Figure 3.13 Stroke: cohort studies using relative risk and hazard ratio from fully adjusted model[ab]



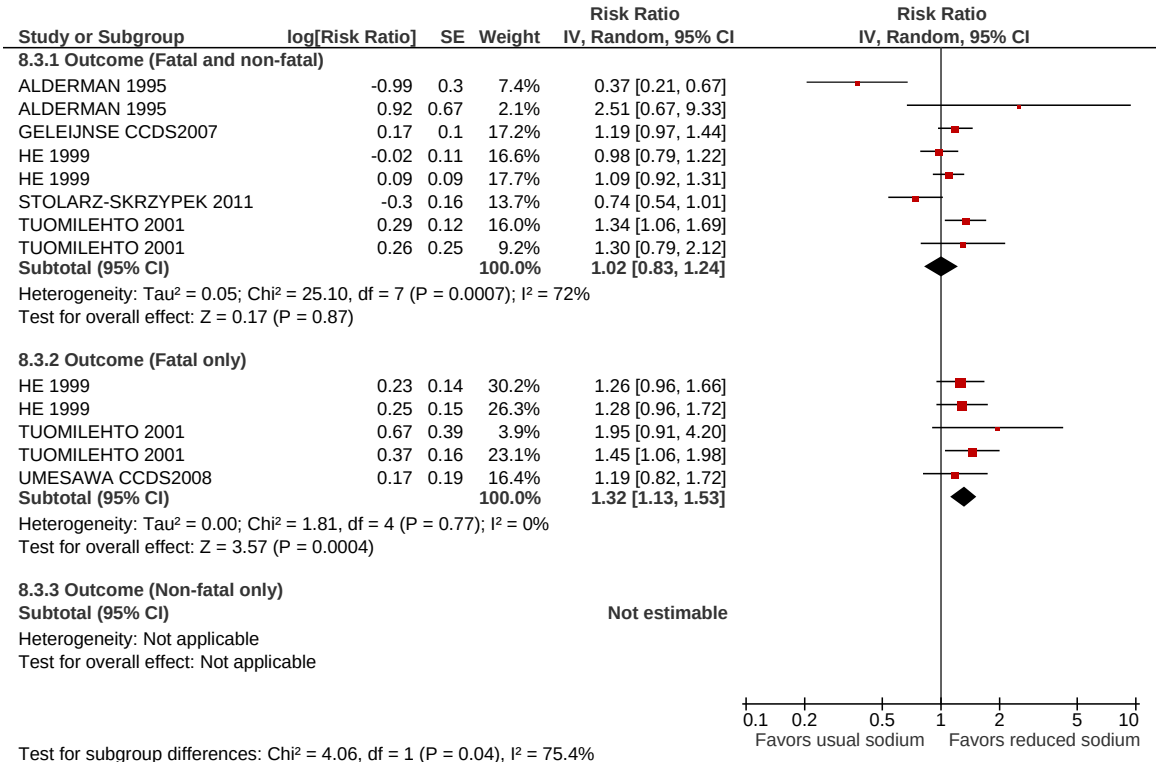
[a] Relative risk > 1 > 1 indicates an association between increased risk of outcome and higher sodium intake.
[b] Relative risk or hazard ratio from each original study calculated from models that adjusted for the most number of covariates including, in some cases, systolic or diastolic blood pressure.

Figure 3.14 Coronary heart disease: cohort studies using relative risk and hazard ratio from less adjusted model[ab]



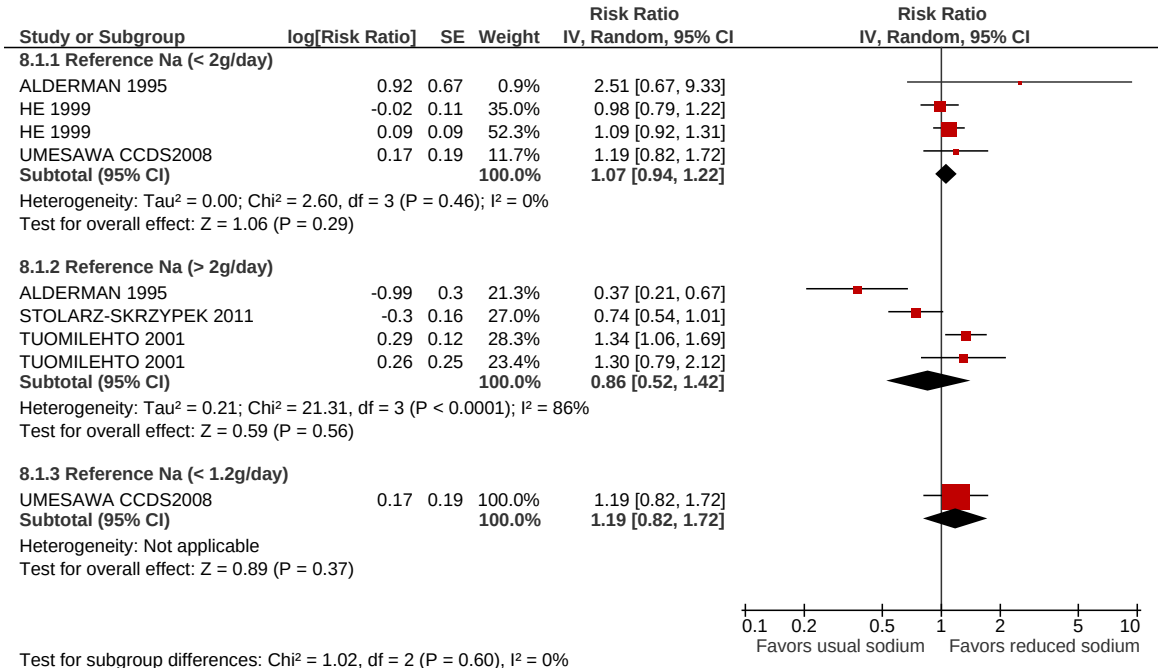
[a] Relative risk > 1 indicates an association between increased risk of outcome and higher sodium intake.
[b] Relative risk or hazard ratio from each original study calculated from models that adjusted for the most number of covariates **not** including systolic or diastolic blood pressure.

Figure 3.15 Coronary heart disease by outcome type: cohort studies[ab]



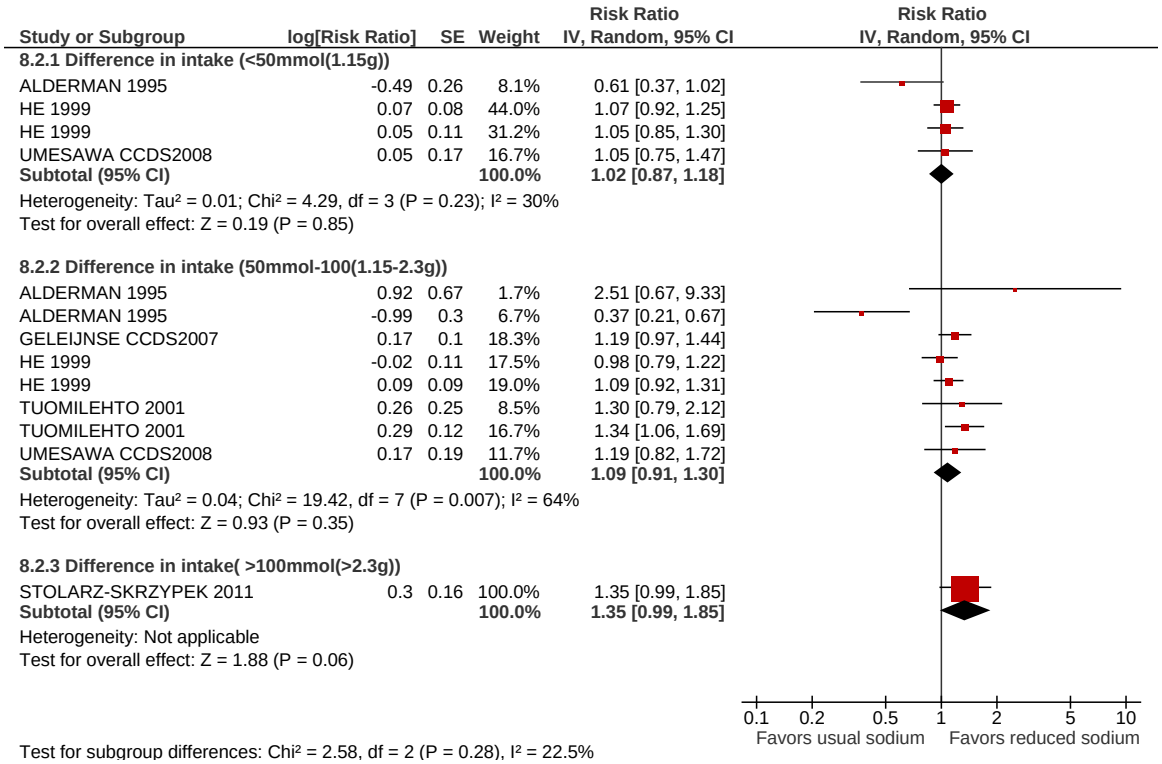
[a] Relative risk > 1 indicates an association between increased risk of outcome and higher sodium intake.
[b] Relative risk or hazard ratio from each original study calculated from models that adjusted for the most number of covariates **not** including systolic or diastolic blood pressure.

Figure 3.16 Coronary heart disease by reference group intake: cohort studies[ab]



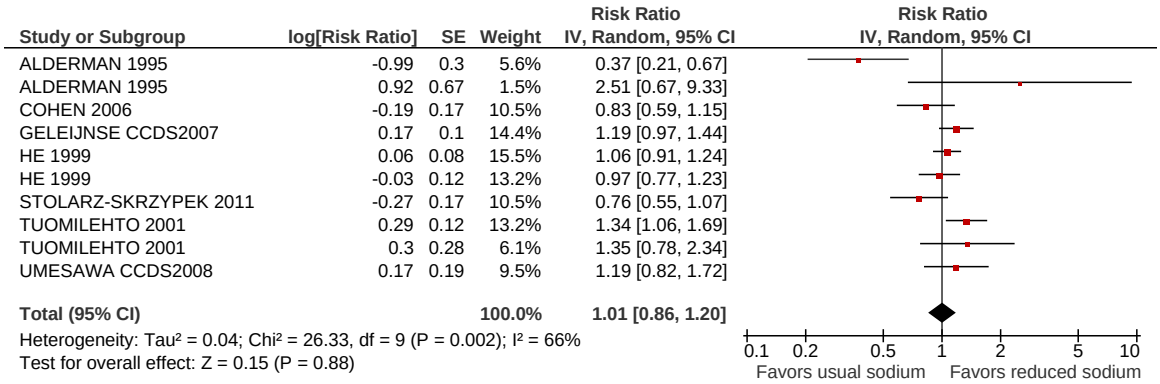
[a] Relative risk > 1 indicates an association between increased risk of outcome and higher sodium intake.
[b] Relative risk or hazard ratio from each original study calculated from models that adjusted for the most number of covariates **not** including systolic or diastolic blood pressure.

Figure 3.17 Coronary heart disease by difference in intake: cohort studies[ab]



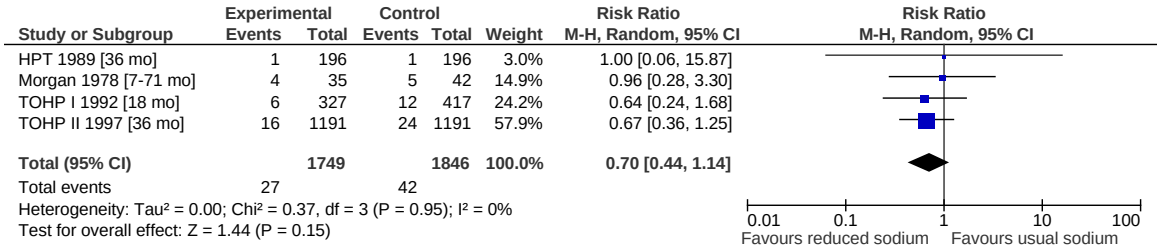
[a] Relative risk > 1 indicates an association between increased risk of outcome and higher sodium intake.
[b] Relative risk or hazard ratio from each original study calculated from models that adjusted for the most number of covariates **not** including systolic or diastolic blood pressure.

Figure 3.18 Coronary heart disease: cohort studies using relative risk and hazard ratio from fully adjusted model[ab]



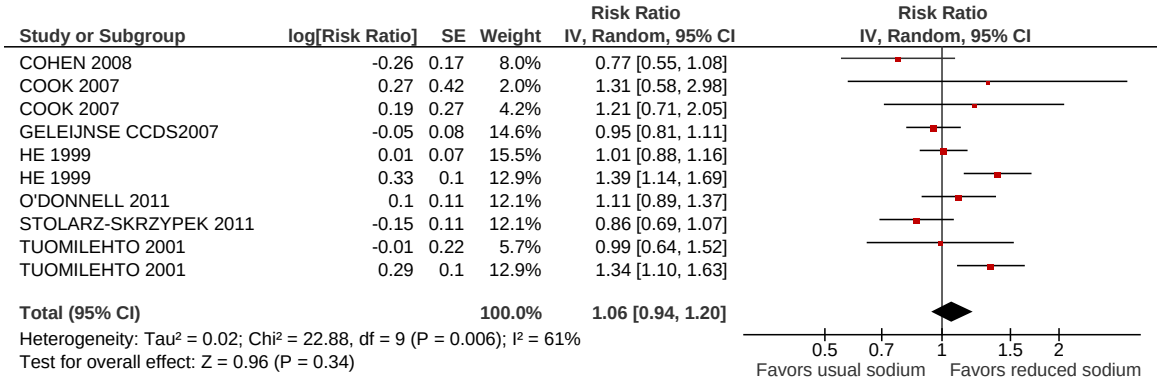
[a] Relative risk > 1 indicates an association between increased risk of outcome and higher sodium intake.
[b] Relative risk or hazard ratio from each original study calculated from models that adjusted for the most number of covariates including, in some cases, systolic or diastolic blood pressure.

Figure 3.19 All-cause mortality: randomized controlled trials[a]



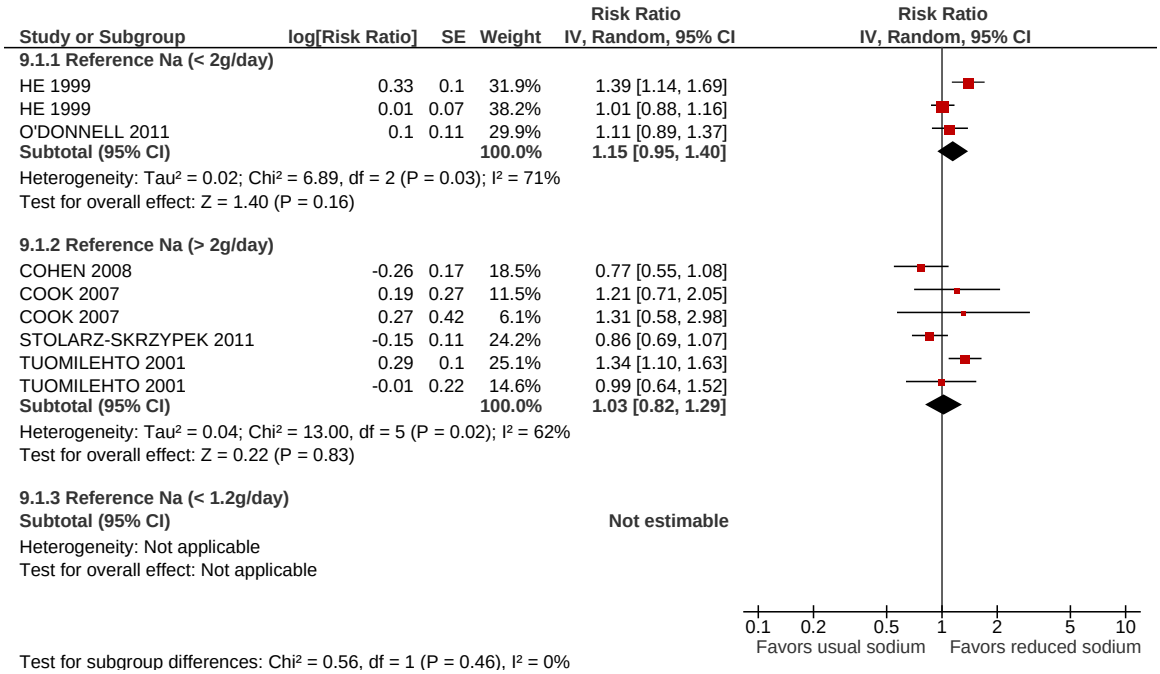
[a] Relative risk < 1 indicates decreased risk of all-cause mortality with decreased sodium intake.

Figure 3.20 All-cause mortality: cohort studies using relative risk and hazard ratio from less adjusted model[ab]



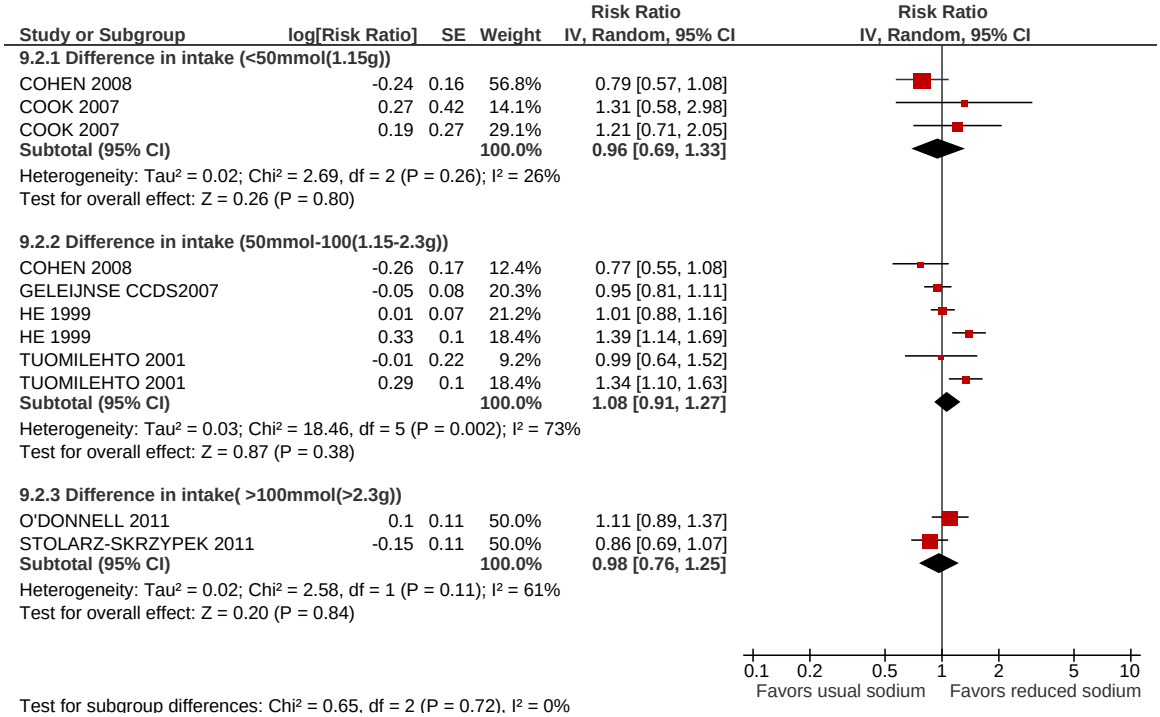
[a] Relative risk > 1 indicates an association between increased risk of outcome and higher sodium intake.
[b] Relative risk or hazard ratio from each original study calculated from models that adjusted for the most number of covariates **not** including systolic or diastolic blood pressure.

Figure 3.21 All-cause mortality by reference group intake: cohort studies[ab]



[a] Relative risk > 1 indicates an association between increased risk of outcome and higher sodium intake.
[b] Relative risk or hazard ratio from each original study calculated from models that adjusted for the most number of covariates **not** including systolic or diastolic blood pressure.

Figure 3.22 All-cause mortality by difference in intake: cohort studies[ab]

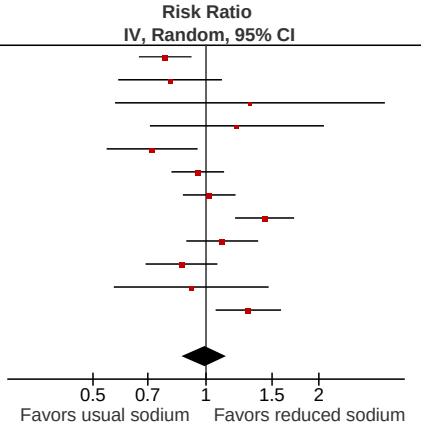


[a] Relative risk > 1 indicates an association between increased risk of outcome and higher sodium intake.
[b] Relative risk or hazard ratio from each original study calculated from models that adjusted for the most number of covariates **not** including systolic or diastolic blood pressure.

Figure 3.23 All-cause mortality: cohort studies using relative risk and hazard ratio from fully adjusted model[ab]

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
COHEN 2006	-0.25	0.08	10.9%	0.78 [0.67, 0.91]
COHEN 2008	-0.22	0.16	7.6%	0.80 [0.59, 1.10]
COOK 2007	0.27	0.42	2.3%	1.31 [0.58, 2.98]
COOK 2007	0.19	0.27	4.4%	1.21 [0.71, 2.05]
EKINCI 2011	-0.33	0.14	8.4%	0.72 [0.55, 0.95]
GELEIJNSE CCDS2007	-0.05	0.08	10.9%	0.95 [0.81, 1.11]
HE 1999	0.02	0.08	10.9%	1.02 [0.87, 1.19]
HE 1999	0.36	0.09	10.5%	1.43 [1.20, 1.71]
O'DONNELL 2011	0.1	0.11	9.6%	1.11 [0.89, 1.37]
STOLARZ-SKRZYPEK 2011	-0.15	0.11	9.6%	0.86 [0.69, 1.07]
TUOMILEHTO 2001	-0.09	0.24	5.1%	0.91 [0.57, 1.46]
TUOMILEHTO 2001	0.26	0.1	10.0%	1.30 [1.07, 1.58]
Total (95% CI)			**100.0%**	**0.99 [0.87, 1.14]**

Heterogeneity: Tau² = 0.04; Chi² = 44.16, df = 11 (P < 0.00001); I² = 75%
Test for overall effect: Z = 0.09 (P = 0.93)

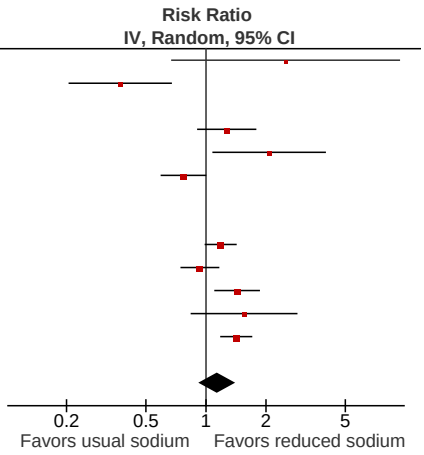


[a] Relative risk > 1 indicates an association between increased risk of outcome and higher sodium intake.
[b] Relative risk or hazard ratio from each original study calculated from models that adjusted for the most number of covariates including, in some cases, systolic or diastolic blood pressure.

Figure 3.24 Cardiovascular disease: sensitivity analysis in cohort studies (removal of studies at high risk of confounding due to exposure measure) [ab]

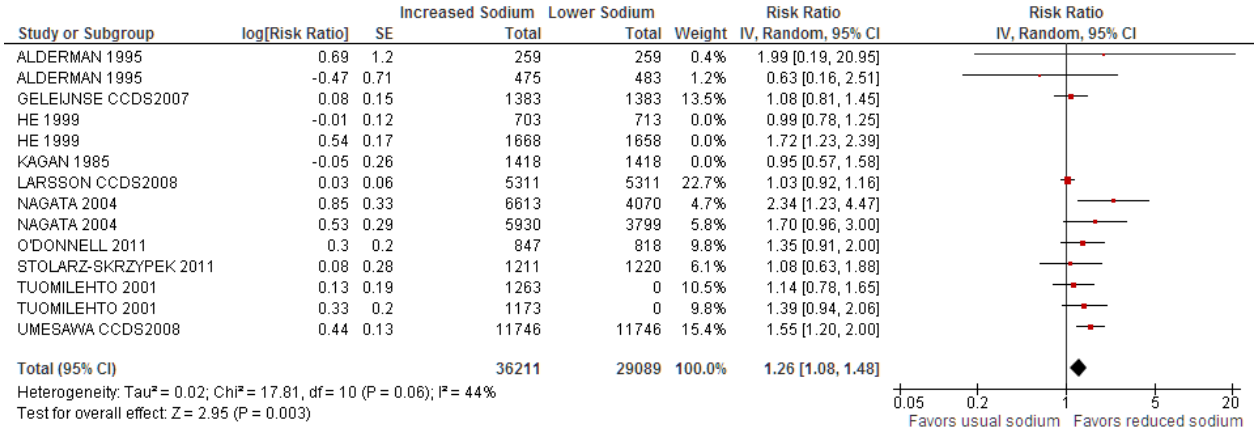
Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
ALDERMAN 1995	0.92	0.67	2.2%	2.51 [0.67, 9.33]
ALDERMAN 1995	-0.99	0.3	7.1%	0.37 [0.21, 0.67]
COHEN 2008	-0.63	0.26	0.0%	0.53 [0.32, 0.89]
COOK 2007	0.24	0.17	11.2%	1.27 [0.91, 1.77]
COOK 2007	0.73	0.33	6.3%	2.08 [1.09, 3.96]
GELEIJNSE CCDS2007	-0.26	0.13	12.6%	0.77 [0.60, 0.99]
HE 1999	0.15	0.12	0.0%	1.16 [0.92, 1.47]
HE 1999	0.42	0.16	0.0%	1.52 [1.11, 2.08]
O'DONNELL 2011	0.17	0.09	13.9%	1.19 [0.99, 1.41]
STOLARZ-SKRZYPEK 2011	-0.07	0.11	13.3%	0.93 [0.75, 1.16]
TUOMILEHTO 2001	0.36	0.13	12.6%	1.43 [1.11, 1.85]
TUOMILEHTO 2001	0.44	0.31	6.8%	1.55 [0.85, 2.85]
UMESAWA CCDS2008	0.35	0.09	13.9%	1.42 [1.19, 1.69]
Total (95% CI)			**100.0%**	**1.14 [0.92, 1.41]**

Heterogeneity: Tau² = 0.08; Chi² = 41.54, df = 9 (P < 0.00001); I² = 78%
Test for overall effect: Z = 1.19 (P = 0.23)



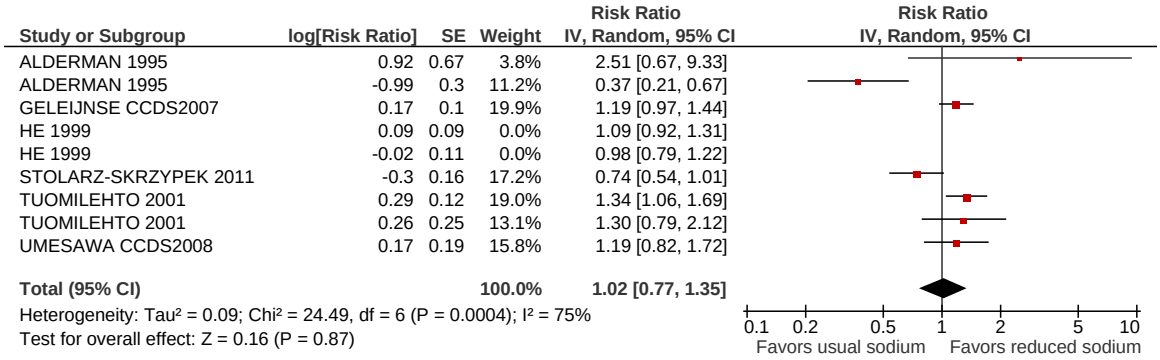
[a] Relative risk or hazard ratio from each original study calculated from models that adjusted for the most number of covariates **not** including systolic or diastolic blood pressure.
[b] Study considered at high risk of bias due to exposure measure if sodium intake estimated from one 24-hour dietary recall.

Figure 3.25 Stroke: sensitivity analysis in cohort studies (removal of studies at high risk of confounding due to exposure measure) [ab]



[a] Relative risk or HR from each original study calculated from models that adjusted for the most number of covariates **not** including systolic or diastolic blood pressure.
[b] Study considered at high risk of bias due to exposure measure if sodium intake estimated from one 24-hour dietary recall.

Figure 3.26 Coronary heart disease: sensitivity analysis in cohort studies (removal of studies at high risk of confounding due to exposure measure) [ab]

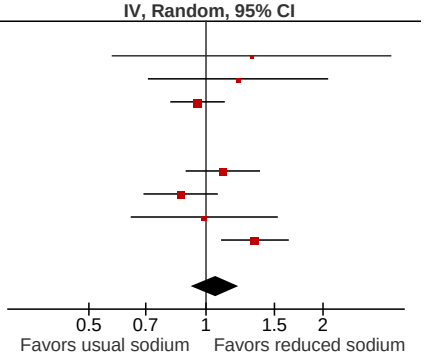


[a] Relative risk or hazard ratio from each original study calculated from models that adjusted for the most number of covariates **not** including systolic or diastolic blood pressure.
[b] Study considered at high risk of bias due to exposure measure if sodium intake estimated from one 24-hour dietary recall.

Figure 3.27 All-cause mortality: sensitivity analysis in cohort studies (removal of studies at high risk of confounding due to exposure measure) [ab]

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
COHEN 2008	-0.26	0.17	0.0%	0.77 [0.55, 1.08]
COOK 2007	0.27	0.42	2.7%	1.31 [0.58, 2.98]
COOK 2007	0.19	0.27	5.9%	1.21 [0.71, 2.05]
GELEIJNSE CCDS2007	-0.05	0.08	24.1%	0.95 [0.81, 1.11]
HE 1999	0.01	0.07	0.0%	1.01 [0.88, 1.16]
HE 1999	0.33	0.1	0.0%	1.39 [1.14, 1.69]
O'DONNELL 2011	0.1	0.11	19.1%	1.11 [0.89, 1.37]
STOLARZ-SKRZYPEK 2011	-0.15	0.11	19.1%	0.86 [0.69, 1.07]
TUOMILEHTO 2001	-0.01	0.22	8.2%	0.99 [0.64, 1.52]
TUOMILEHTO 2001	0.29	0.1	20.7%	1.34 [1.10, 1.63]
Total (95% CI)			**100.0%**	**1.06 [0.92, 1.22]**

Heterogeneity: Tau² = 0.02; Chi² = 11.44, df = 6 (P = 0.08); I² = 48%
Test for overall effect: Z = 0.78 (P = 0.44)



[a] Relative risk or HR from each original study calculated from models that adjusted for the most number of covariates **not** including systolic or diastolic blood pressure.
[b] Study considered at high risk of bias due to exposure measure if sodium intake estimated from one 24-hour dietary recall.

4 References

4.1 Included studies

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

Alderman 1995

Alderman MH, Madhavan S, Cohen H et al. Low urinary sodium is associated with greater risk of myocardial infarction among treated hypertensive men. *Hypertension,* 1995, 25(6):1144–1152.

Cohen 2006

Cohen HW, Hailpern SM, Fang J et al. Sodium intake and mortality in the NHANES II follow-up study. *American Journal of Medicine,* 2006, 119(3):275 e277–e214.

Cohen 2008

Cohen HW, Hailpern SM, Alderman MH. Sodium intake and mortality follow-up in the Third National Health and Nutrition Examination Survey (NHANES III). *Journal of General Internal Medicine,* 2008, 23(9):1297–1302.

Cook 2007

* Cook NR, Cutler JA, Obarzanek E et al. Long term effects of dietary sodium reduction on cardiovascular disease outcomes: observational follow-up of the trials of hypertension prevention (TOHP). *BMJ,* 2007, 334(7599):885–888.

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(1):32–40.

Ekinci 2011

Ekinci EI, Clarke S, Thomas MC et al. Dietary salt intake and mortality in patients with type 2 diabetes. *Diabetes Care,* 2011, 34(3):703–709.

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.

He 1999

He J, Ogden LG, Vupputuri S et al. Dietary sodium intake and subsequent risk of cardiovascular disease in overweight adults. *JAMA: Journal of the American Medical Association,* 1999, 282(21):2027–2034.

Kagan 1985

Kagan A, Popper JS, Rhoads GG et al. Dietary and other risk factors for stroke in Hawaiian Japanese men. *Stroke,* 1985, 16(3):390–396.

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.

Nagata 2004

Nagata C, Takatsuka N, Shimizu N et al. Sodium intake and risk of death from stroke in Japanese men and women. *Stroke,* 2004, 35(7):1543–1547.

O'Donnell 2011

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

Stolarz-Skrzypek 2011

Stolarz-Skrzypek K, Kuznetsova T, Thijs L et al. Fatal and nonfatal outcomes, incidence of hypertension, and blood pressure changes in relation to urinary sodium excretion. *JAMA: Journal of the American Medical Association,* 2011, 305(17):1777–1785.

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.

Tuomilehto 2001

Tuomilehto J, Jousilahti P, Rastenyte D et al. Urinary sodium excretion and cardiovascular mortality in Finland: a prospective study. *Lancet,* 2001, 357(9259):848–851.

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.

4.2 Excluded studies

Chang 2006

Chang HY, Hu YW, Yue CS et al. Effect of potassium-enriched salt on cardiovascular mortality and medical expenses of elderly men. *American Journal of Clinical Nutrition,* 2006, 83(6):1289–1296.

Hu 1992

Hu HH, Sheng WY, Chu FL et al. Incidence of stroke in Taiwan. *Stroke,* 1992, 23(9):1237–1241.

Paterna 2008

Paterna S, Gaspare P, Fasullo S et al. Normal-sodium diet compared with low-sodium diet in compensated congestive heart failure: is sodium an old enemy or a new friend? *Clinical Science (London),* 2008, 114(3):221–230.

Thomas 2011

Thomas MC, Moran J, Forsblom C et al. The association between dietary sodium intake, ESRD, and all-cause mortality in patients with type 1 diabetes. *Diabetes Care,* 2011, 34(4):861–866.

4.3 Other references

Cochrane handbook for systematic reviews of interventions version 5.1.0. The Cochrane Collaboration, 2011 (www.cochrane-handbook.org).

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

Graudal NA, Hubeck-Graudal T, Jurgens G. Effects of low sodium diet versus high sodium diet on blood pressure, renin, aldosterone, catecholamines, cholesterol, and triglyceride. *Cochrane Database of Systematic Reviews,* 2011, 11:CD004022.

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

He FJ, MacGregor GA. Effect of longer-term modest salt reduction on blood pressure. *Cochrane Database of Systematic Reviews,* 2004, 3:CD004937

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. *Statistics in Medicine,* 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:b270.

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

Morgan T, Adam W, Gillies A et al. Hypertension treated by salt restriction. *Lancet*, 1978, 1(8058):227-230.

Murray CJ, Lauer JA, Hutubessy RC et al. Effectiveness and costs of interventions to lower systolic blood pressure and cholesterol: a global and regional analysis on reduction of cardiovascular-disease risk. *Lancet,* 2003, 361(9359):717–725.

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.

Strazzullo P, D'Elia L, Kandala NB et al. Salt intake, stroke, and cardiovascular disease: meta-analysis of prospective studies. *BMJ,* 2009, 339:b4567.

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

Taylor RS, Ashton KE, Moxham T et al. Reduced dietary salt for the prevention of cardiovascular disease. *Cochrane Database of Systematic Reviews,* 2011, 7:CD009217.

TOHP. The Hypertension Prevention Trial: three-year effects of dietary changes on blood pressure. Hypertension Prevention Trial Research Group. *Archives of Internal Medicine*, 1990, 150(1):153–162.

TOHP. The effects of nonpharmacologic interventions on blood pressure of persons with high normal levels. Results of the Trials of Hypertension Prevention, Phase I. *JAMA: Journal of the American Medical Association*, 1992, 267:1213–1220.

TOHP. Effects of weight loss and sodium reduction intervention on blood pressure and hypertension incidence in overweight people with high-normal blood pressure. The Trials of Hypertension Prevention, Phase II. *Archives of Internal Medicine*, 1997, 157(6):657–667.

Whelton PK, Appel LJ, Espeland MA et al. Sodium reduction and weight loss in the treatment of hypertension in older persons: a randomized controlled trial of nonpharmacologic interventions in the elderly (TONE). TONE Collaborative Research Group. *JAMA: Journal of the American Medical Association*, 1998, 279(11):839–846.

WHO. Diet, nutrition and the prevention of chronic disease. Report of a Joint WHO/FAO Expert Consultation (WHO Technical report series 916). Geneva, World Health Organization (WHO), 2003

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

WHO. *Global status report on noncommunicable diseases.* Geneva, World Health Organization (WHO), 2010.

Annex 1: Funnel plots for primary outcomes

Figure A1 Funnel plot for studies reporting cardiovascular disease (cohort studies)

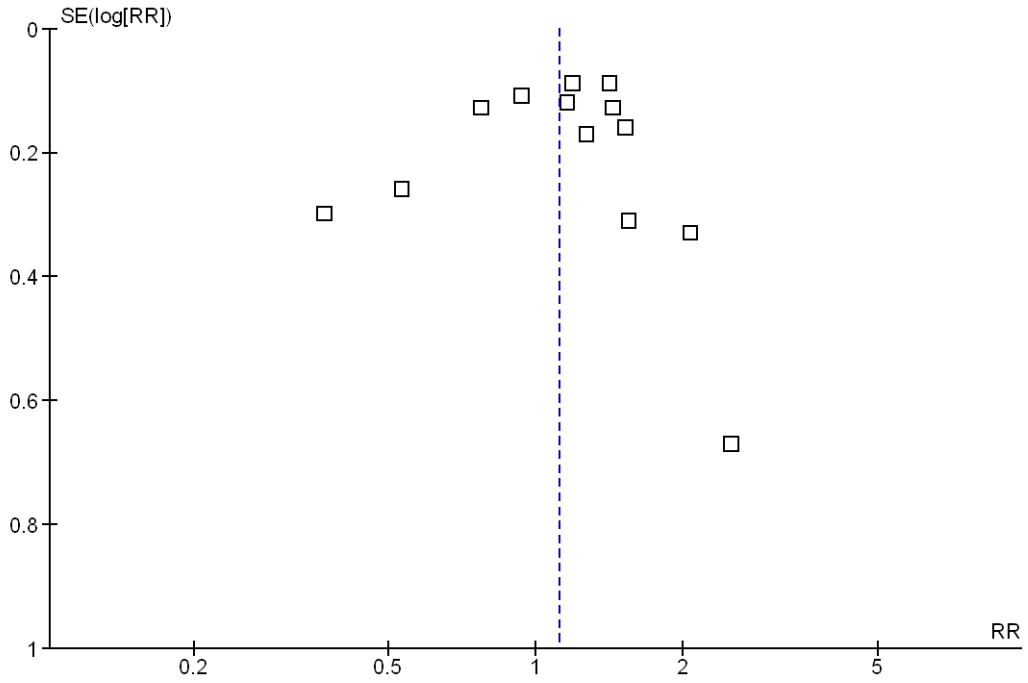


Figure A2 Funnel plot for studies reporting stroke (cohort studies)

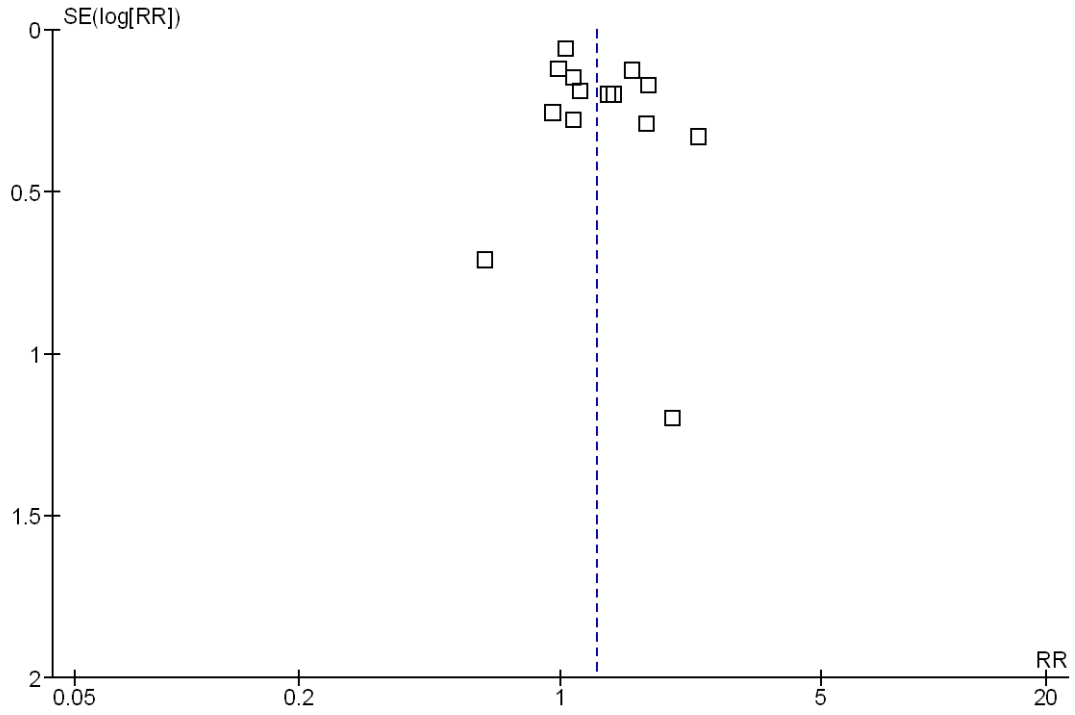


Figure A3 Funnel plot for studies reporting coronary heart disease (cohort studies)

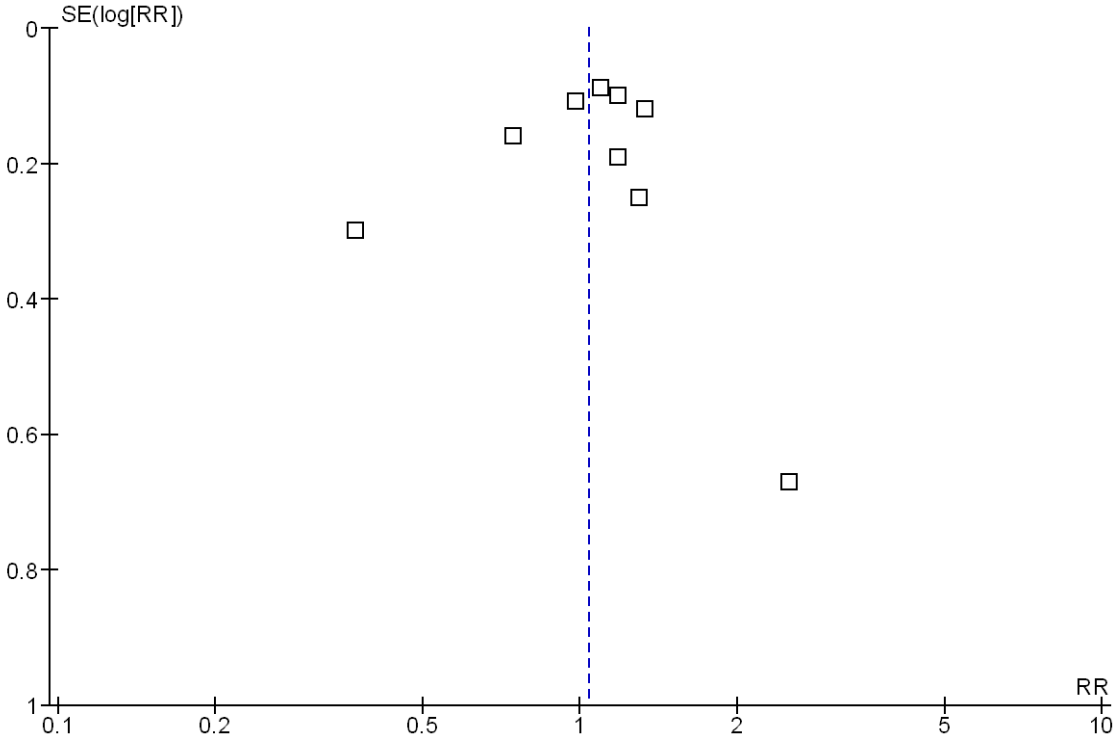
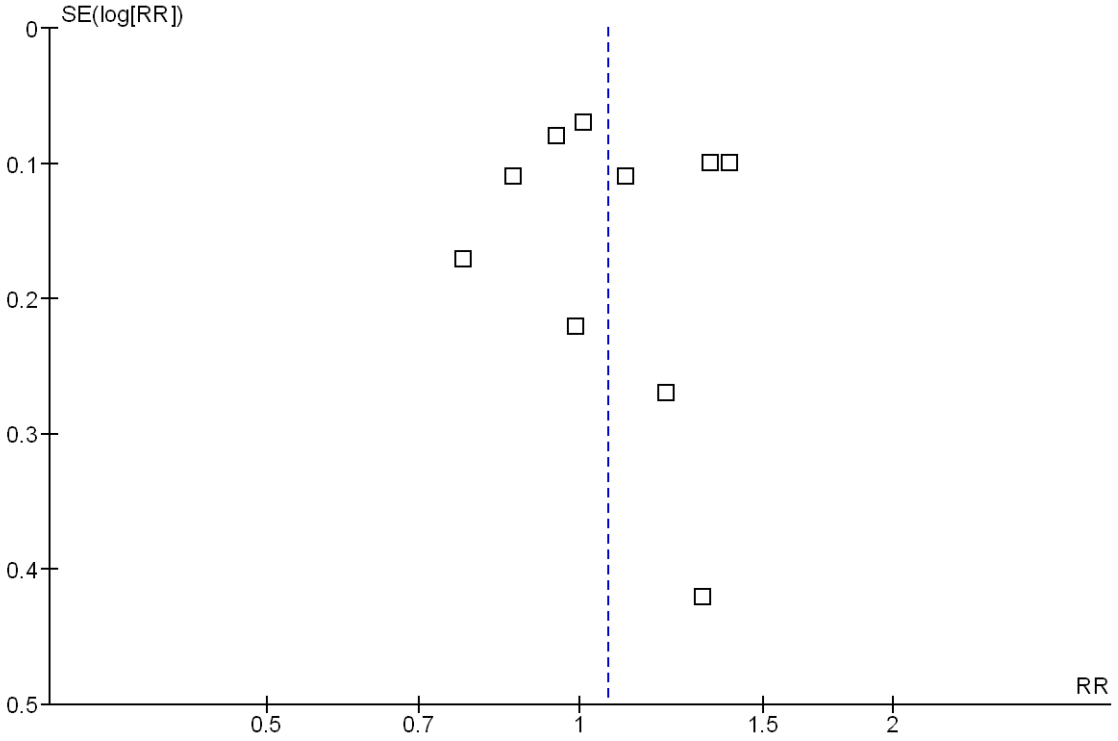
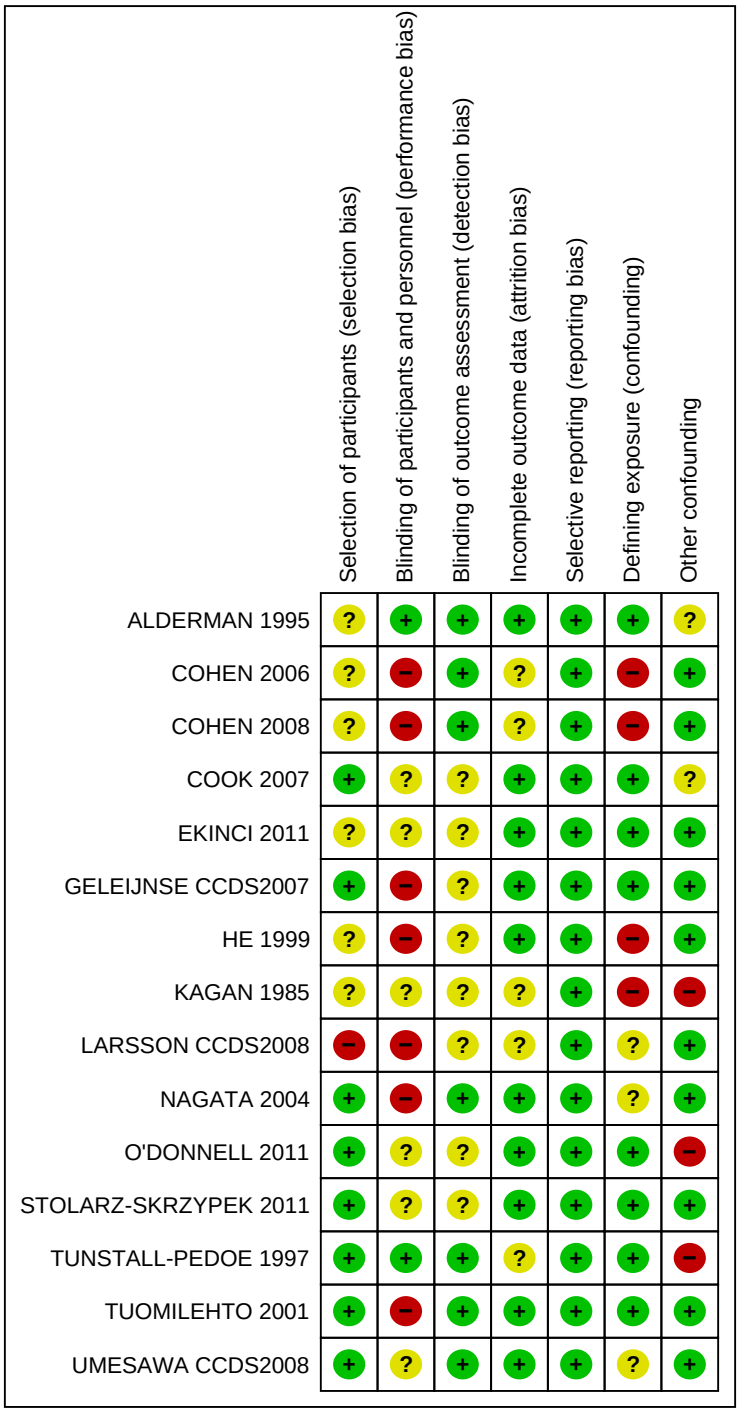


Figure A4 Funnel plot for studies reporting all-cause mortality (cohort studies)

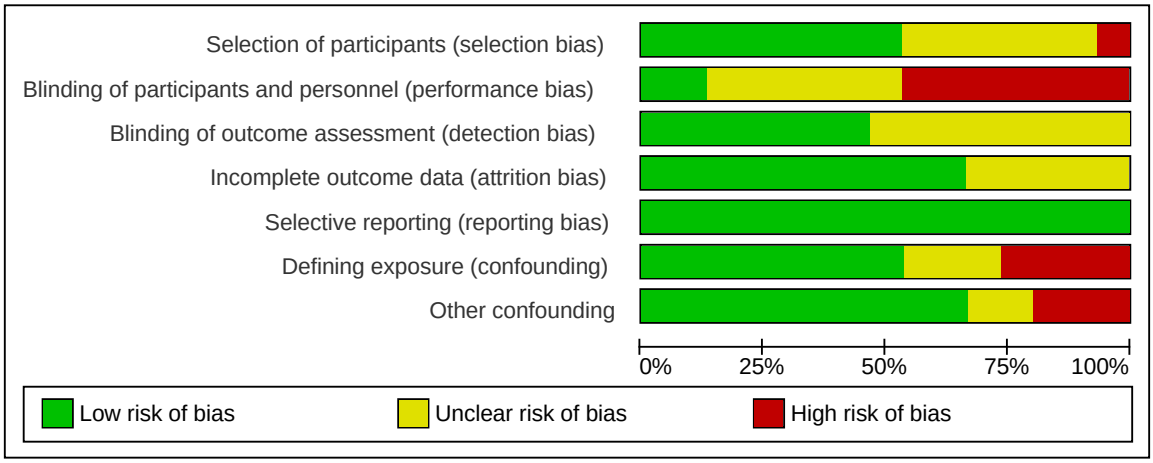


Annex 2: Risk of bias summary (cohort studies)[1]



[1] Risk of bias summary for RCTs found in Cochrane Library publication (*12*)

Annex 3: Risk of bias graph (cohort studies)[1]



[1] Risk of bias graph for RCTs found in Cochrane Library publication (12)

Annex 4: GRADE evidence profiles

Research question: What is the effect of reduced or lower sodium intake versus higher intake on cardiovascular disease risk?

Quality assessment						Effect	Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Relative risk (95%CI)**		
CVD ALL (follow-up 7–71 months; assessed with: RR and HR)[a]								
2/2	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[b]	RR 0.84 (0.57, 1.23)	⊕⊕⊕O Moderate[c]	Critical
CVD – combined fatal and non-fatal								
0/0	RCTs	No RCTs reported this outcome						Critical
CVD – fatal only								
1/1	RCTs	Insufficient number of events to generate a stable effect estimate or draw any conclusions						Critical
CVD ALL (follow-up 3.8–22 years; assessed with: RR and HR)[d]								
9/13	Observational studies	No serious risk of bias	Serious[e]	No serious indirectness	No serious imprecision[e]	RR 1.12 (0.93, 1.34)	⊕OOO Very low	Critical
CVD – combined fatal and non-fatal (follow-up 3.8–15 years; assessed with: RR and HR)[d]								
4/6	Observational studies	No serious risk of bias	Serious[e]	No serious indirectness	No serious imprecision[e]	RR 1.06 (0.75, 1.5)	⊕OOO Very low	Critical
CVD – fatal only (follow-up 4.5–22 years; assessed with: RR and HR)[d]								
7/10	Observational studies	No serious risk of bias	Serious[e]	No serious indirectness	No serious imprecision[e]	RR 1.18 (0.93, 1.49)	⊕OOO Very low	Critical

CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; RCT, randomized controlled trial; RR, relative risk

[a] Relative risk < 1 indicates reduced risk with reduced sodium intake.

[b] 95%CI of overall effect estimate crosses one.

[c] Data for generating effect estimate only from two studies.

[d] Relative risk > 1 indicates an association between increased risk of outcome and higher sodium intake.

[e] Downgraded for inconsistency because the 95%CIs of the individual studies fall on both sides of the value one. The inconsistency leads to the imprecision and therefore evidence not downgraded a second time for imprecision.

Research question: What is the effect of reduced or lower sodium intake versus higher intake on stroke risk?

Quality assessment						Effect	Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Relative (95%CI)**		
Stroke ALL								
2/2	RCTs	Insufficient number of events to generate a stable effect estimate or draw any conclusions						Critical
Stroke – combined fatal and non-fatal								
0/0	RCTs	No RCTs reported this outcome						Critical
Stroke – fatal only								
0/0	RCTs	No RCTs reported this outcome						Critical
Stroke ALL (follow-up 3.8–22 years; assessed with: RR and HR)[a]								
10/14	Observational studies	No serious risk of bias	Serious inconsistency[b]	No serious indirectness	No serious imprecision	RR 1.24 (1.08, 1.43)	⊕OOO Very low	Critical
Stroke – combined fatal and non-fatal (follow-up 3.8–22 years; assessed with: RR and HR)[a]								
8/11	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	RR 1.13 (1.01, 1.26)	⊕⊕OO Low	Critical
Stroke – fatal only (follow-up 7–22 years; assessed with: RR and HR)[a]								
3/5	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	RR 1.63 (1.27, 2.10)	⊕⊕OO Low	Critical

CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; RCT, randomized controlled trial; RR, relative risk

[a] Relative risk > 1 indicates an association between increased risk of outcome and higher sodium intake

[b] 95%CI of individual studies do not always overlap and fall on both sides of the value one

Research question: What is the effect of reduced or lower sodium intake versus higher intake on coronary heart disease risk?

Quality assessment						Effect	Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Relative (95%CI)**		
CHD – ALL								
2/2	RCTs	Insufficient number of events to generate a stable effect estimate or draw any conclusions						Critical
CHD – combined fatal and non-fatal								
2/2	RCTs	Insufficient number of events to generate a stable effect estimate or draw any conclusions						Critical
CHD – fatal only								
0/0	RCTs	No RCTs reported this outcome						Critical
CHD – ALL (follow-up 3.8 – 22 years; assessed with: RR and HR)[a]								
6/9	Observational studies	No serious risk of bias	Serious[b]	No serious indirectness	No serious imprecision[b]	RR 1.04 (0.86, 1.24)	⊕OOO Very low	Critical
CHD – combined fatal and non-fatal (follow-up 3.8 – 22 years; assessed with: RR and HR)[a]								
3/5	Observational studies	No serious risk of bias	Serious[b]	No serious indirectness	No serious imprecision[b]	RR 1.02 (0.83, 1.24)	⊕OOO Very low	Critical
CHD – fatal only (follow-up 8 – 22 years; assessed with: RR and HR)[a]								
3/5	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	RR 1.32 (1.13, 1.53)	⊕⊕OO Low	Critical

CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; RCT, randomized controlled trial; RR, relative risk

[a] Relative risk > 1 indicates an association between increased risk of outcome and higher sodium intake.

[b] Downgraded for inconsistency because 95%CIs from individual studies fall on both sides of one. The inconsistency leads to the imprecision and therefore evidence not downgraded a second time for imprecision.

Research question: What is the effect of reduced or lower sodium intake versus higher intake on all-cause mortality risk?

Quality assessment						Effect	Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Relative (95%CI)**		
All-cause mortality (follow-up 7–71 months; assessed with: RR and HR)[a]								
4/4	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[b]	RR 0.70 (0.44, 1.13)	⊕⊕⊕O Moderate	Critical
All-cause mortality (follow-up 4.5–22 years; assessed with: RR and HR)[c]								
3/5	Observational studies	No serious risk of bias	Serious[d]	No serious indirectness	No serious imprecision[d]	RR 1.06 (0.94, 1.20)	⊕OOO Very low	Critical

CI, confidence interval; HR, hazard ratio; RCT, randomized controlled trial; RR, relative risk

[a] Relative risk < 1 indicates reduced risk with reduced sodium intake.

[b] 95%CI of effect estimate crosses one.

[c] Relative risk > 1 indicates an association between increased risk of outcome and higher sodium intake.

[d] Downgraded for inconsistency because 95%CIs fall on both sides of one. The inconsistency leads to the imprecision and therefore evidence not downgraded a second time for imprecision.

Research question: What is the effect of reduced or lower sodium intake of < 2 g/day versus ≥ 2 g/day?a

Quality assessment							Effect	Quality	Importance
No of studies/ comparisons	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative[b] (95%CI)**		
CVD – Reference Na < 2 g/day (follow-up 3.8–22 years; assessed with: RR and HR)									
4/6	Observational studies	No serious risk of bias	Serious[c]	No serious indirectness	No serious imprecision[c]	None	RR 1.17 (0.91, 1.50)	⊕OOO Very low	Critical
Stroke – reference Na < 2 g/day (follow-up 3.8– 22 years)									
5/6	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	RR 1.30 (1.03, 1.64)	⊕⊕OO Low	Critical
CHD – reference Na < 2 g/day (follow-up 3.8–22 years)									
3/4	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[d]	None	RR 1.07 (0.94, 1.22)	⊕OOO Very low	Critical
All-cause mortality – reference sodium intake < 2 g/day (follow-up 4.5–22 years)									
3/4	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[d]	None	RR 1.15 (0.95, 1.40)	⊕OOO Very low	Critical

CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; RCT, randomized controlled trial; RR, risk ratio

[a] No randomized controlled trials addressed this question.

[b] All effect estimates calculated using relative risk and hazard ratio from original studies that came from models that did not adjust for blood pressure (less adjusted models).

[c] Downgraded for inconsistency because 95%CIs of individual studies fall on both sides of one. The inconsistency leads to the imprecision and therefore evidence not downgraded a second time for imprecision.

[d] 95%CI of effect estimate crosses one.

Research question: What is the effect of reduced or lower sodium intake of < 1.2 g/day versus ≥ 1.2 g/day?a

Quality assessment							Effect	Quality	Importance
No of studies/ comparisons	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95%CI)**		
CVD – Reference sodium intake < 1.2 g/day (follow-up 12.7 years)									
1/1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	RR 1.42 (1.19, 1.69)	⊕⊕OO Low[b]	Critical
Stroke – Reference sodium intake < 1.2 g/day (follow-up 12.7 years)									
1/1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	RR 1.55 (1.20, 2.00)	⊕⊕OO Low[b]	Critical
CHD – Reference sodium intake < 1.2 g/day (follow-up 12.7 years)									
1/1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[c]	None	RR 1.19 (0.82, 1.72)	⊕OOO Very low[b]	Critical
All-cause mortality – Reference sodium intake < 1.2 g/day									
0/0	Observational studies	No studies reported this outcome							Critical

CI, confidence interval; HR, hazard ratio; RCT, randomized controlled trial; RR, relative risk

[a] No randomized controlled trials addressed this question.

[b] Data only drawn from one study.

[c] 95%CI of effect estimate crosses one.

List of tables and figures

Tables

Figures

Full list of references

1 Strazzullo P, D'Elia L, Kandala NB et al. Salt intake, stroke, and cardiovascular disease: meta-analysis of prospective studies. BMJ, 2009, 339:b4567 (http://www.ncbi.nlm.nih.gov/pubmed/19934192).

2 WHO. Preventing chronic disease: a vital investment. Geneva, World Health Organization (WHO), 2005 (http://www.who.int/chp/chronic_disease_report/full_report.pdf).

3 Strong K, Mathers C, Leeder S et al. Preventing chronic diseases: how many lives can we save? Lancet, 2005, 366(9496):1578–1582 (http://www.ncbi.nlm.nih.gov/pubmed/16257345).

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

5 WHO. Diet, nutrition and the prevention of chronic disease. Report of a Joint WHO/FAO Expert Consultation (WHO Technical report series 916). Geneva, World Health Organization (WHO), 2003 (http://www.fao.org/DOCREP/005/AC911E/AC911E00.HTM).

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

7 Murray CJ, Lauer JA, Hutubessy RC et al. Effectiveness and costs of interventions to lower systolic blood pressure and cholesterol: a global and regional analysis on reduction of cardiovascular-disease risk. Lancet, 2003, 361(9359):717–725 (http://www.ncbi.nlm.nih.gov/pubmed/12620735).

8 He FJ, MacGregor GA. Effect of longer-term modest salt reduction on blood pressure. Cochrane Database of Systematic Reviews, 2004, 3:CD004937 (http://www.ncbi.nlm.nih.gov/pubmed/15266549).

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

10 Stolarz-Skrzypek K, Kuznetsova T, Thijs L et al. Fatal and nonfatal outcomes, incidence of hypertension, and blood pressure changes in relation to urinary sodium excretion. JAMA: Journal of the American Medical Association, 2011, 305(17):1777–1785 (http://www.ncbi.nlm.nih.gov/pubmed/21540421).

11 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 (http://www.ncbi.nlm.nih.gov/pubmed/19622552).

12 Taylor RS, Ashton KE, Moxham T et al. Reduced dietary salt for the prevention of cardiovascular disease. Cochrane Database of Systematic Reviews, 2011, 7:CD009217 (http://www.ncbi.nlm.nih.gov/pubmed/21735439).

13 Cochrane handbook for systematic reviews of interventions version 5.1.0. The Cochrane Collaboration, 2011 (www.cochrane-handbook.org).

14 Deeks JJ, Dinnes J, D'Amico R et al. Evaluating non-randomised intervention studies. Health Technology Assessment, 2003, 7(27):iii–x, 1–173 (http://www.ncbi.nlm.nih.gov/pubmed/14499048).

15 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 (http://www.ncbi.nlm.nih.gov/pubmed/12493255).

16 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 (http://www.ncbi.nlm.nih.gov/pubmed/11822262).

17 Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Statistics in Medicine, 2002, 21(11):1539–1558 (http://www.ncbi.nlm.nih.gov/pubmed/12111919).

18 Lau J, Ioannidis JP, Terrin N et al. The case of the misleading funnel plot. BMJ, 2006, 333(7568):597–600 (http://www.ncbi.nlm.nih.gov/pubmed/16974018).

19 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 (http://www.ncbi.nlm.nih.gov/pubmed/11576817).

20 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 (http://www.ncbi.nlm.nih.gov/pubmed/18436948).

21 Paterna S, Gaspare P, Fasullo S et al. Normal-sodium diet compared with low-sodium diet in compensated congestive heart failure: is sodium an old enemy or a new friend? Clinical Science (London), 2008, 114(3):221–230 (http://www.ncbi.nlm.nih.gov/pubmed/17688420).

22 Chang HY, Hu YW, Yue CS et al. Effect of potassium-enriched salt on cardiovascular mortality and medical expenses of elderly men. American Journal of Clinical Nutrition, 2006, 83(6):1289–1296 (http://www.ncbi.nlm.nih.gov/pubmed/16762939).

23 Thomas MC, Moran J, Forsblom C et al. The association between dietary sodium intake, ESRD, and all-cause mortality in patients with type 1 diabetes. Diabetes Care, 2011, 34(4):861–866 (http://www.ncbi.nlm.nih.gov/pubmed/21307382).

24 Hu HH, Sheng WY, Chu FL et al. Incidence of stroke in Taiwan. Stroke, 1992, 23(9):1237–1241 (http://www.ncbi.nlm.nih.gov/pubmed/1519277).

25 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.

26 Alderman MH, Madhavan S, Cohen H et al. Low urinary sodium is associated with greater risk of myocardial infarction among treated hypertensive men. Hypertension, 1995, 25(6):1144–1152 (http://www.ncbi.nlm.nih.gov/pubmed/7768554).

27 Cohen HW, Hailpern SM, Fang J et al. Sodium intake and mortality in the NHANES II follow-up study. American Jounal of Medicine, 2006, 119(3):275 e277–e214 (http://www.ncbi.nlm.nih.gov/pubmed/16490476).

28 Cohen HW, Hailpern SM, Alderman MH. Sodium intake and mortality follow-up in the Third National Health and Nutrition Examination Survey (NHANES III). Journal of General Internal Medicine, 2008, 23(9):1297–1302 (http://www.ncbi.nlm.nih.gov/pubmed/18465175).

29 Cook NR, Cutler JA, Obarzanek E et al. Long term effects of dietary sodium reduction on cardiovascular disease outcomes: observational follow-up of the trials of hypertension prevention (TOHP). BMJ, 2007, 334(7599):885–888 (http://www.ncbi.nlm.nih.gov/pubmed/17449506).

30 He J, Ogden LG, Vupputuri S et al. Dietary sodium intake and subsequent risk of cardiovascular disease in overweight adults. JAMA: Journal of the American Medical Association, 1999, 282(21):2027–2034 (http://www.ncbi.nlm.nih.gov/pubmed/10591385).

31 Kagan A, Popper JS, Rhoads GG et al. Dietary and other risk factors for stroke in Hawaiian Japanese men. Stroke, 1985, 16(3):390–396 (http://www.ncbi.nlm.nih.gov/pubmed/4002255).

32 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.

33 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.

34 Tuomilehto J, Jousilahti P, Rastenyte D et al. Urinary sodium excretion and cardiovascular mortality in Finland: a prospective study. Lancet, 2001, 357(9259):848–851 (http://www.ncbi.nlm.nih.gov/pubmed/11265954).

35 Nagata C, Takatsuka N, Shimizu N et al. Sodium intake and risk of death from stroke in Japanese men and women. Stroke, 2004, 35(7):1543–1547 (http://www.ncbi.nlm.nih.gov/pubmed/15143292).

36 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(1):195–202 (http://www.ncbi.nlm.nih.gov/pubmed/18614741).

37 Ekinci EI, Clarke S, Thomas MC et al. Dietary salt intake and mortality in patients with type 2 diabetes. Diabetes Care, 2011, 34(3):703–709 (http://www.ncbi.nlm.nih.gov/pubmed/21289228).

38 Morgan T, Adam W, Gillies A et al. Hypertension treated by salt restriction. Lancet, 1978, 1(8058):227-230 (http://www.ncbi.nlm.nih.gov/pubmed/74660).

39 Whelton PK, Appel LJ, Espeland MA et al. Sodium reduction and weight loss in the treatment of hypertension in older persons: a randomized controlled trial of nonpharmacologic interventions in the elderly (TONE). TONE Collaborative Research Group. JAMA: Journal of the American Medical Association, 1998, 279(11):839–846 (http://www.ncbi.nlm.nih.gov/pubmed/9515998).

40 TOHP. The Hypertension Prevention Trial: three-year effects of dietary changes on blood pressure. Hypertension Prevention Trial Research Group. Archives of Internal Medicine, 1990, 150(1):153–162 (http://www.ncbi.nlm.nih.gov/pubmed/2404477).

41 TOHP. The effects of nonpharmacologic interventions on blood pressure of persons with high normal levels. Results of the Trials of Hypertension Prevention, Phase I. Journal of the American Medical Association, 1992, 267:1213–1220.

42 TOHP. Effects of weight loss and sodium reduction intervention on blood pressure and hypertension incidence in overweight people with high-normal blood pressure. The Trials of Hypertension Prevention, Phase II. Archives of Internal Medicine, 1997, 157(6):657–667 (http://www.ncbi.nlm.nih.gov/pubmed/9080920).

43 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.

For further information please contact:

Nutrition Policy and Scientific Advice Unit (NPU)
Department of Nutrition for Health and Development (NHD)
World Health Organization (WHO)
20, Avenue Appia
CH–1211 Geneva 27
Switzerland

Fax: +41.22.791.4156
E-mail: NPUinfo@who.int
NHD website: http://www.who.int//nutrition

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