Altered dietary salt intake for people with chronic kidney disease

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Altered dietary salt intake for people with chronic kidney disease (Review)

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[Intervention Review]

Altered dietary salt intake for people with chronic kidney disease

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ABSTRACT

Background

Salt intake shows great promise as a modifiable risk factor for reducing heart disease incidence and delaying kidney function decline in people with chronic kidney disease (CKD). However, a clear consensus of the benefits of reducing salt in people with CKD is lacking.

Objectives

This review evaluated the benefits and harms of altering dietary salt intake in people with CKD.

Search methods

We searched the Cochrane Renal Group's Specialised Register to 13 January 2015 through contact with the Trials' Search Co-ordinator using search terms relevant to this review.

Selection criteria

We included randomised controlled trials (RCTs) that compared two or more levels of salt intake in people with any stage of CKD.

Data collection and analysis

Two authors independently assessed studies for eligibility and conducted risk of bias evaluation. Results were expressed as risk ratios (RR) and their 95% confidence intervals (CI) for dichotomous outcomes, and mean difference (MD) and 95% CI for continuous outcomes. Mean effect sizes were calculated using the random-effects models.

Main results

We included eight studies (24 reports, 258 participants). Because duration of the included studies was too short (1 to 26 weeks) to test the effect of salt restriction on endpoints such as mortality, cardiovascular events or CKD progression, changes in salt intake on blood pressure and other secondary risk factors were applied. Three studies were parallel RCTs and five were cross-over studies. Selection bias was low in five studies and unclear in three. Performance and detection biases were low in two studies and unclear in six. Attrition and reporting biases were low in four studies and unclear in four. One study had the potential for high carryover effect; three had high risk of bias from baseline characteristics (change of medication or diet) and two studies were industry funded.

There was a significant reduction in 24 hour sodium excretion associated with low salt interventions (range 52 to 141 mmol) (8 studies, 258 participants: MD -105.86 mmol/d, 95% CI -119.20 to -92.51; I^2 = 51%). Reducing salt intake significantly reduced systolic blood pressure (8 studies, 258 participants: MD -8.75 mm Hg, 95% CI -11.33 to -6.16; I^2 = 0%) and diastolic blood pressure (8 studies, 258 participants: MD -3.70 mm Hg, 95% CI -5.09 to -2.30; I^2 = 0%). One study reported restricting salt intake reduced the risk of oedema by 56%. Salt restriction significantly increased plasma renin activity (2 studies, 71 participants: MD 1.08 ng/mL/h, 95% CI 0.51 to 1.65; I^2 = 0%) and serum aldosterone (2 studies, 71 participants: 6.20 ng/dL (95% CI 3.82 to 8.58; I^2 = 0%). Antihypertensive medication dosage was significantly reduced with a low salt diet (2 studies, 52 participants): RR 5.48, 95% CI 1.27 to 23.66; I^2 = 0%). There was no significant difference in eGFR (2 studies, 68 participants: MD -1.14 mL/min/1.73 m^2, 95% CI -4.38 to 2.11; I^2 = 0%), creatinine clearance (3 studies, 85 participants): MD -4.60 mL/min, 95% CI -11.78 to 2.57; I^2 = 0%), serum creatinine (5 studies, 151 participants: MD 5.14 µmol/L, 95% CI -8.98 to 19.26; I^2 = 59%) or body weight (5 studies, 139 participants: MD -1.46 kg; 95% CI -4.55 to 1.64; I^2 = 0%). There was no significant change in total cholesterol in relation to salt restriction (3 studies, 105 participants: MD -0.23 mmol/L, 95% CI -0.57 to 0.10; I^2 = 0%) or symptomatic hypotension (2 studies, 72 participants: RR 6.60, 95% CI 0.77 to 56.55; I^2 = 0%). Salt restriction significantly reduced urinary protein excretion in all studies that reported proteinuria as an outcome, however data could not be meta-analysed.

Authors' conclusions

We found a critical evidence gap in long-term effects of salt restriction in people with CKD that meant we were unable to determine the direct effects of sodium restriction on primary endpoints such as mortality and progression to end-stage kidney disease (ESKD). We found that salt reduction in people with CKD reduced blood pressure considerably and consistently reduced proteinuria. If such reductions could be maintained long-term, this effect may translate to clinically significant reductions in ESKD incidence and cardiovascular events. Research into the long-term effects of sodium-restricted diet for people with CKD is warranted, as is investigation into adherence to a low salt diet.

PLAIN LANGUAGE SUMMARY

Altered dietary salt intake for people with chronic kidney disease

People with CKD are at increased risk of heart disease and deteriorating kidney health which can lead to need for dialysis or kidney transplantation to survive. Reducing risk of heart disease and preserving kidney function are important treatment goals.

High salt intake is linked to risk factors for both heart disease and worsening kidney function, including high blood pressure, excess protein in the urine (proteinuria) and fluid overload. It is thought to be particularly important for people with CKD to have a low salt intake due to kidneys' role in salt balance. We aimed to find out if altering salt in the diet was beneficial for people with CKD.

We searched the literature for studies that looked at the effects of restricting salt in the diets of people with CKD up to January 2015. We found eight studies that involved 258 people which met our inclusion criteria. Study participants included people in the early stages of CKD (six studies), who were on peritoneal dialysis (one study), or were kidney transplant recipients (one study). The average study duration was six weeks, and ranged from one to 26 weeks. We did not find any studies that measured the effect of salt intake on the incidence of death, heart disease, or need to begin dialysis.

We found that reducing salt intake reduced 24 hour sodium excretion, blood pressure. One study reported restricting salt intake reduced the risk of oedema (swelling). Antihypertensive medication dosage was significantly reduced with a low salt diet. There was no significant difference in kidney function measures or body weight. There was no significant change in total cholesterol or hypotension.

Long-term effects of salt restriction in people with CKD is lacking that meant we were unable to determine the direct effects of sodium restriction on primary endpoints such as mortality and progression to end-stage kidney disease (ESKD). Research into the long-term effects of sodium-restricted diet for people with CKD is warranted, as is investigation into adherence to low salt diet.

BACKGROUND

Description of the condition

Chronic kidney disease (CKD) is a major global public health problem; data from Australia, the United States, Japan and Europe indicate that CKD occurs in 6% to 13% of people (Chadban 2003; Coresh 2007; Meguid El Nahas 2005; Hamer 2006). CKD prevalence is increasing rapidly and is thought to be related in part to dramatic increases in rates of diabetes and hypertension - two of the most common causes of CKD (Coresh 2007).

CKD is a progressive condition. People with end-stage kidney disease (ESKD) require renal replacement therapy as dialysis or kidney transplantation to survive. Mortality risk is 40 times higher among people with ESKD compared with the general population (Collins 2003). Annual healthcare costs of treating people with ESKD have been estimated at about 10 times greater than the cost of CKD management (Hunsicker 2004).

CKD is an independent risk factor for cardiovascular disease; people with CKD are up to 10 times more likely to die of cardiovascular disease than progress to ESKD (Go 2004). Because both cardiovascular disease and progression to ESKD may be delayed, or possibly prevented, effective strategies to reduce these outcomes are needed to improve patients' prognoses and reduce healthcare costs.

Description of the intervention

Excessive salt (sodium) intake is related to many risk factors for cardiovascular disease and CKD progression. These include increased blood pressure, fluid retention, proteinuria, inflammation, oxidative stress and endothelial dysfunction (Al-Solaiman 2009; Ritz 2009). Salt restriction has beneficial effects against risk factors such as hypertension and proteinuria over and above those provided by antihypertensive medications (Vogt 2008). Despite this, evidence suggests salt restriction is not adequately emphasised for people with CKD (Thijssen 2008). A possible reason may be that there is no clear consensus on the benefits of reducing salt intake in people with CKD. Evidence-based practice guidelines show inconsistencies in the ideal target for salt intake in people with CKD, with salt targets ranging from less than 3.8 g of salt (65 mmol sodium) per day to 6.5 g (110 mmol sodium) per day (Ash 2006; USDA 2010).

How the intervention might work

Studies in the general population have consistently demonstrated a link between dietary salt intake and blood pressure, particularly among those who are salt sensitive (He 2013; Svetkey 1999). A Cochrane review on reducing salt intake in people with diabetic kidney disease showed considerable blood pressure reductions; systolic/diastolic blood pressure was lowered by 7/3 mm Hg (Suckling 2010).

It has also been suggested that salt has adverse effects independent of blood pressure. Todd 2010 found arterial stiffness measured by pulse wave velocity was significantly decreased independently of blood pressure changes in hypertensive people on a low salt diet. (Increased pulse wave velocity is a predictor of all-cause and cardiovascular mortality (Guerin 2001)). Proteinuria, a risk factor for both CKD progression and cardiovascular disease in people with CKD, has also shown to be reduced by salt restriction independent of blood pressure (Verhave 2004).

Why it is important to do this review

Salt intake shows great promise as a modifiable risk factor for reducing cardiovascular risk and CKD progression even among people in the very early stages of the disease. However, clear consensus of the benefits of reducing salt for people with CKD, and the optimal target salt intake for this population, has yet to be established.

OBJECTIVES

This review evaluated the benefits and harms of altering dietary salt intake in people with CKD.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) measuring the effect of low versus high salt intake in people with CKD.

Types of participants

Inclusion criteria

- Adults ($\geq$ 18 years) with CKD (as defined by Kidney Disease Outcomes Quality Initiative (K/DOQI) Clinical Practice Guidelines) at all disease stages (NKF 2002)

Exclusion criteria

- Pregnant women
- Children (aged up to 18 years).

Types of interventions

We planned to evaluate the following interventions.

- Comparing two or more differing levels of sodium intake
- Of at least one week duration
- Evaluated sodium intake estimated by 24 hour urinary sodium excretion (24 h UNa) with a minimum difference in 24 h UNa of 34 mmol (2 g salt/d) achieved between allocated interventions. Reduction in 24 h UNa was calculated as the difference between UNa at the end of each intervention for cross-over studies, and the difference in change between groups from baseline to the end of intervention for parallel studies
- Where concomitant interventions such as antihypertensive medication or other dietary modifications were used during the study period, providing that these interventions were constant throughout the low and high salt interventions.

Types of outcome measures

Primary outcomes

1. Cardiovascular mortality
2. All-cause mortality.

Secondary outcomes

1. Cardiovascular disease (coronary artery disease, heart failure, cerebrovascular disease and peripheral vascular disease)
2. Progression to ESKD requiring dialysis or transplantation
3. 24 h UNa
4. Change in blood pressure (clinic and 24 hour measurement)
5. Change in arterial stiffness (pulse wave velocity and augmentation index)
6. Change in kidney function measures (creatinine clearance (CrCl), serum creatinine (SCr), proteinuria, glomerular filtration rate (GFR))
7. Change in markers of fluid overload (brain natriuretic peptide, weight, bio-impedance analysis)
8. Change in markers of oxidative stress or inflammation (C-reactive protein, adipokines)
9. Adverse events: hypotensive episodes, undesirable change in blood lipids (low density lipoprotein, high-density lipoprotein).

Search methods for identification of studies

Electronic searches

We searched the Cochrane Renal Group's Specialised Register to 13 January 2015 through contact with the Trials' Search Co-ordinator using search terms relevant to this review. The Cochrane Renal Group's Specialised Register contains studies identified from the following sources.

- Monthly searches of the Cochrane Central Register of Controlled Trials CENTRAL
- Weekly searches of MEDLINE OVID SP
- Hand-searching of renal-related journals and the proceedings of major renal conferences
- Searching of the current year of EMBASE OVID SP
- Weekly current awareness alerts for selected renal journals
- Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the Specialised Register were identified through search strategies for CENTRAL, MEDLINE, and EMBASE based on the scope of the Cochrane Renal Group. Details of these strategies, as well as a list of handsearched journals, conference proceedings and current awareness alerts, are available in the Specialised Register section of information about the Cochrane Renal Group.
See Appendix 1 for search terms used in strategies for this review.

Searching other resources

1. Reference lists of review articles, relevant studies and clinical practice guidelines
2. Letters seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies.

Data collection and analysis

Selection of studies

The search strategy described was used to obtain titles and abstracts of studies that may be relevant to the review. The titles and abstracts were screened independently by two authors, who discarded studies that were not applicable; however, studies and reviews that might have included relevant data or information on studies were retained initially. Two authors independently assessed the retrieved abstracts, and if necessary, the full text of these studies to determine which studies satisfied the inclusion criteria.

Data extraction and management

Data extraction was carried out independently by two authors using standard data extraction forms. Studies reported in non-English language journals were translated before assessment. Where more than one publication of one study exists, reports were grouped together and the publication with the most complete data

was used in the analyses. Where relevant outcomes were only published in earlier versions these data were used. Any discrepancies between published versions were to be highlighted.

Assessment of risk of bias in included studies

The following items were independently assessed by two authors using the risk of bias assessment tool (Higgins 2011) (see Appendix 2).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study (detection bias)?
    - Participants and personnel
    - Outcome assessors
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at a risk of bias? Two additional domains were addressed:
    - Risk of carry over effect
    - Potential bias from influence of confounding factors.

Measures of treatment effect

For dichotomous outcomes (cardiovascular mortality, all-cause mortality, progression to ESKD, cardiovascular disease) results were expressed as risk ratios (RR) with 95% confidence intervals (CI). Where continuous scales of measurement were used to assess the effects of treatment (blood pressure, pulse wave velocity, augmentation index, CrCl, SCr, proteinuria, GFR, brain natriuretic peptide, weight, bio-impedance analysis, C-reactive protein, adipokines) the mean difference (MD) was used, or the standardised mean difference (SMD) if different scales were used. Studies analysing change scores were included in meta-analysis along with studies including endpoint data only.

Where change from baseline values were absent, these were calculated by subtracting mean value at the end of the intervention to baseline values (parallel studies) or subtracting the value from the end of the higher sodium phase from the lower sodium phase (cross-over studies) (Higgins 2011).

Unit of analysis issues

In cross-over studies, we determined the mean difference in outcomes as the difference between the end of low salt and high salt periods. We calculated the treatment effect as the difference between treatment groups' change in outcomes from baseline for parallel studies.

Dealing with missing data

Any further information required from the original author was requested by written correspondence (e.g. emailing corresponding author) and any relevant information obtained in this manner was included in the review. Evaluation of important numerical data such as screened, randomised subjects as well as intention-to-treat, as-treated and per-protocol population were performed. Attrition rates, for example drop-outs, losses to follow-up and withdrawals were investigated. Issues of missing data and imputation methods (for example, last-observation-carried-forward) were critically appraised (Higgins 2011).

Assessment of heterogeneity

Heterogeneity was analysed using a Chi² test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I² test (Higgins 2003). I² values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity (Higgins 2011).

Assessment of reporting biases

If possible, funnel plots were to be constructed to assess for the potential existence of small study bias (Higgins 2011). There were insufficient data to enable construction of funnel plots for this review.

Data synthesis

Data were pooled using the random-effects model but the fixed-effect model was also used to ensure robustness of the model chosen and susceptibility to outliers.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis was used to explore possible sources of heterogeneity (such as intervention duration, levels of sodium intake). Heterogeneity among participants could be related to age, stage of CKD, presence of comorbidities (hypertension and diabetes) and renal pathology (e.g. dialysed versus non-dialysed patients with CKD).

Sensitivity analysis

Where necessary, we performed sensitivity analyses in order to explore the influence of the following factors on effect size:

- repeating the analysis excluding unpublished studies
- repeating the analysis taking account of risk of bias, as specified
- repeating the analysis excluding any very long or large studies to establish how much they dominate the results
- repeating the analysis excluding studies using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), and country.

RESULTS

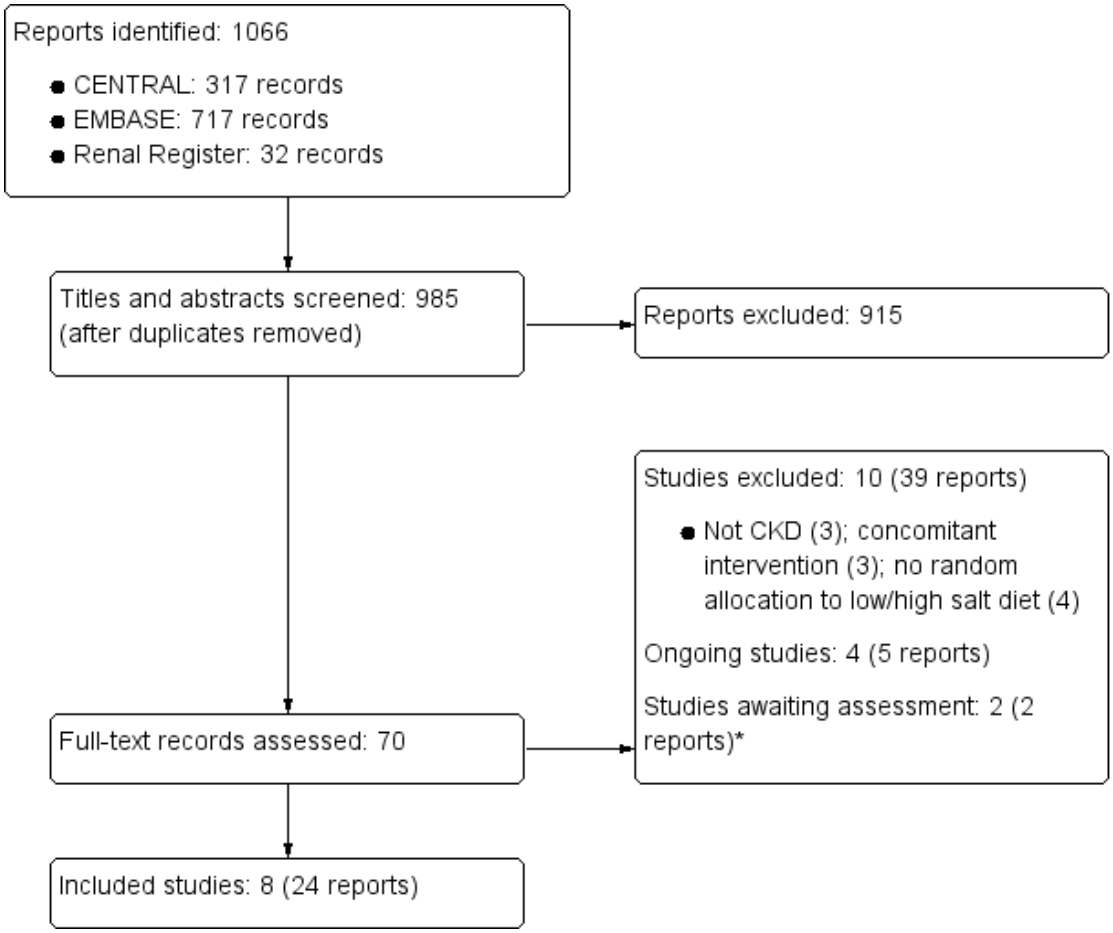
Description of studies

See Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; Characteristics of ongoing studies.

Results of the search

The search identified 1066 records. After removal of duplicates we assessed 985 records; of these, 915 were excluded based on the title and abstract. We assessed the full text of the remaining 70 articles. We identified eight studies (24 reports; 261 participants) that met our inclusion criteria (Figure 1).

Figure 1. Study flow diagram* 2 records were identified in a prepublication search and will be assessed in a future update of this review



Included studies

See Characteristics of included studies.

Of the eight included studies, six were cross-over (DUAAAL Study 2011; Fine 1997; Konishi 2001; LowSALT CKD Study 2012; Ruilope 1992a; Vogt 2008) and two were parallel design studies (de Brito-Ashurst 2013; Keven 2006). Because the cross-over studies did not repeat outcome measurement at the beginning of each intervention (baseline for each intervention), the difference between values at the end of each intervention were used. de Brito-Ashurst 2013 reported change from baseline for each group, and these data were used for analysis. Keven 2006 did not present data on change from baseline, and because there were no appropriate data available to impute standard deviations for change, differences between values at the end of the intervention were used for this review.

Two studies enrolled participants with ESKD (peritoneal dialysis Fine 1997; post-transplant Keven 2006), and six enrolled participants in earlier stages of CKD (de Brito-Ashurst 2013; DUAAAL Study 2011; Konishi 2001; LowSALT CKD Study 2012; Ruilope 1992a; Vogt 2008).

Median study duration was six weeks, ranging from one to 26 weeks.

A cut-off of four weeks was used to classify studies according to intervention duration (short-term: fewer than four weeks; long-term: four weeks or more). Three studies, two with one-week interventions (Konishi 2001; Ruilope 1992a), and one with two-week interventions (LowSALT CKD Study 2012), were classified as short-term. We classified four studies as long-term (range: six to 26 weeks) (de Brito-Ashurst 2013; Fine 1997; DUAAAL Study 2011; Keven 2006; Vogt 2008).

Three studies used sodium supplements to achieve difference in sodium intake (Fine 1997; LowSALT CKD Study 2012; Ruilope 1992a); Konishi 2001 provided all food for participants; three compared sodium restriction achieved through dietary counselling with usual diet (de Brito-Ashurst 2013; DUAAAL Study 2011; Keven 2006) and Vogt 2008 compared sodium restriction through dietary counselling to a high salt version of the diet (aiming to keep intake of other nutrients stable).

LowSALT CKD Study 2012 applied dietary education techniques to reduce sodium intake among participants by using sodium supplements in the high salt intervention (120 mmol sodium) and placebo in the low salt intervention. Ruilope 1992a used unspecified means to achieve a very low sodium intake (17 mmol) with 170 mmol of supplemental sodium in the high salt intervention versus 51 mmol of supplemental sodium in the low salt intervention. Fine 1997 investigated usual diet with 60 mmol of supplemental sodium in the high salt intervention versus placebo in the low salt intervention.

Two studies used concomitant interventions that remained stable throughout the high and low salt phases. DUAAAL Study 2011 started all participants on lisinopril 40 mg/d and Ruilope 1992a used verapamil 240 mg/d. The protocol for Konishi 2001 included cessation of all medications one week before the study.

Outcome reporting in included studies

All studies measured 24 hour urinary sodium excretion as a marker of sodium intake. Fine 1997, whose participants were receiving peritoneal dialysis, added 24 hour urinary sodium to 24 hour dialysate sodium to achieve a total value for urinary sodium excretion, and this value was used for analysis. Fine 1997 and LowSALT CKD Study 2012 included additional self-reported measures of sodium intake, but to enhance comparability, we used sodium excretion as an intake marker.

All studies reported blood pressure measurements. Four studies measured 24 hour ambulatory blood pressure (de Brito-Ashurst 2013; Konishi 2001; LowSALT CKD Study 2012; Ruilope 1992a) and four used clinic-assessed blood pressure. Two studies measured both clinic and 24 hour blood pressure (LowSALT CKD Study 2012; Ruilope 1992a); however 24 hour blood pressure was used for our analyses.

Proteinuria data could not be entered into pooled analysis, but is summarised in Table 1.

Excluded studies

We excluded 10 studies (39 reports) that did not meet our inclusion criteria. Reasons for exclusion were: non-CKD population (Forrester 2010; Suckling 2010b; Swift 2005); concomitant intervention that was not stable between interventions (Esnault 2005; Kauric-Klein 2012; Rupp 1978) or no randomised allocation to low or high salt diet (De Nicola 2000; IDNT 2001; Mahmoodi 2011; Osanai 2002). No studies were excluded on the basis of not reporting change in 24 hour urinary sodium excretion.

Studies awaiting classification

Two studies were identified during the final prepublication search and will be assessed in a future update of this review (Hwang 2014; Rodrigues Telini 2014).

Ongoing studies

Four studies (five reports) are ongoing and will be assessed once they have been completed (Clark-Cutaia 2013; NCT00141609; NCT00974636; NCT01015313).

Risk of bias in included studies

Figure 2 and Figure 3 summarise risk of bias assessment for the included studies.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

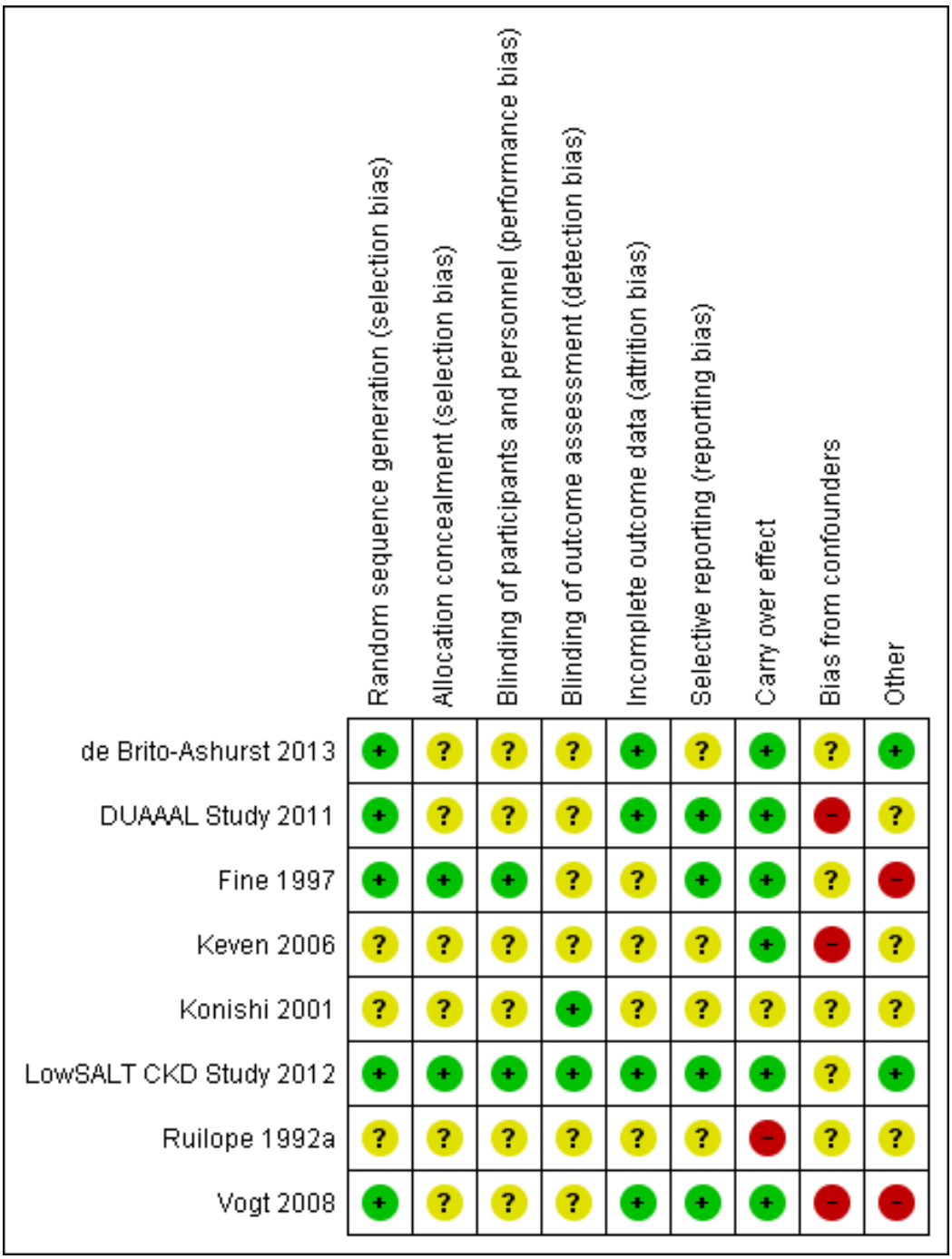
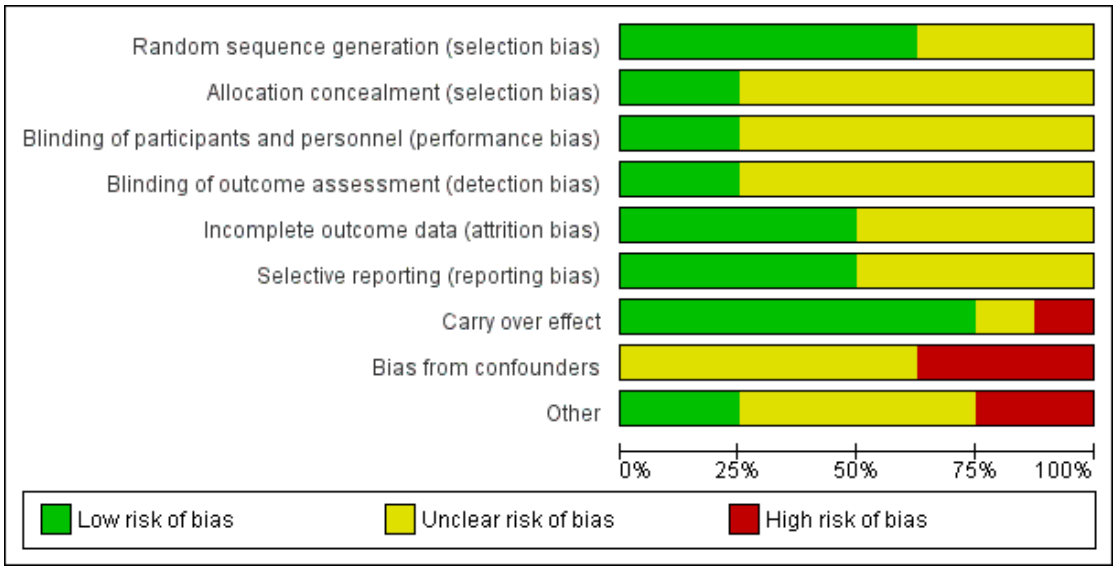


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.Studies were frequently assessed as having unclear or high risk of bias for the risk of bias study domains with selection bias, performance bias, detection bias, and confounding bias domains having the largest proportion of unclear/high risk of bias.



Allocation

All included studies were randomised. Investigators from five studies (de Brito-Ashurst 2013; Fine 1997; DUAAAL Study 2011; LowSALT CKD Study 2012; Vogt 2008) provided further information about the method of randomisation.

Blinding

Fine 1997 and LowSALT CKD Study 2012 were blinded, four studies were open-label (de Brito-Ashurst 2013; DUAAAL Study 2011; Keven 2006; Vogt 2008); Konishi 2001 and Ruilope 1992a did not describe blinding.

Incomplete outcome data

Konishi 2001 and Ruilope 1992a did not report participant attrition. Fine 1997 reported significant attrition (37%), but did not discuss if there were systematic differences between study completers and non-completers.

Selective reporting

Risk of reporting bias was unclear for three studies for which trial registration or study protocol could not be located (Keven 2006; Konishi 2001; Ruilope 1992a). We found that de Brito-Ashurst 2013 had incomplete data for some outcomes or evidence of incorrect data; body weight data could not be meta-analysed because data provided (MD -4 kg, 95% CI -4 to -1) were not statistically viable and corrected data were not available. Standard deviation or P values for change in total body water were unavailable in the publications for this study and were not provided by the authors; hence, this outcome could not be entered into the analysis.

Other potential sources of bias

Carry over effect may have introduced bias in Konishi 2001 and Ruilope 1992a; both were one week duration with no washout between interventions. Ruilope 1992a introduced a new antihypertensive medication at day 1 of the first intervention, increasing risk of treatment order effect. Bias from confounders was classified as unclear or high risk for all studies, mostly due to lack of measurement or failing to account for changes in dietary potas-

sium intake, protein intake and/or weight loss between interventions. We assessed that two studies were at high risk of bias in relation to funding sources (Fine 1997; Vogt 2008); unclear in four (DUAAAL Study 2011; Keven 2006; Konishi 2001; Ruilope 1992a); and low in two (de Brito-Ashurst 2013; LowSALT CKD Study 2012).

Effects of interventions

Duration of the included studies was too short to test the efficacy of salt restriction on endpoints such as mortality, cardiovascular events or progression to ESKD. Therefore, changes in salt intake on blood pressure and risk factors for cardiovascular disease and ESKD were considered in evaluating the evidence for this review.

Urinary sodium excretion

There was a significant reduction in 24 hour sodium excretion associated with low salt interventions (range 52 to 141 mmol) (Analysis 1.1 (8 studies, 258 participants): MD -105.86 mmol/d, 95% CI -119.20 to -92.51; I^2 = 51%).

Duration of studies

There was a significant reduction in 24 hour sodium excretion associated with low salt interventions in both the short-term (Analysis 1.1.1 (3 studies, 72 participants): MD -115.06 mmol/d, 95% CI -132.50 to -97.62; I^2 = 32%) and long-term studies (Analysis 1.1.2 (5 studies, 186 participants): MD -99.11 mol/d, 95% CI -117.31 to -80.92; I^2 = 47%). There was no significant difference between the short-term and long-term studies (test for subgroup differences: Chi^2 = 1.54, df = 1 (P = 0.21); I^2 = 35%).

Stage of chronic kidney disease

Six studies investigated people in early stages of CKD (de Brito-Ashurst 2013; DUAAAL Study 2011; Konishi 2001; LowSALT CKD Study 2012; Ruilope 1992a; Vogt 2008). There was a significant reduction in 24 hour sodium excretion associated with low salt interventions (Analysis 2.1.1 (6 studies, 206 participants): MD -107.21 mmol/d, 95% CI -120.24 to -94.18; I^2 = 51%).
Fine 1997 included 20 participants on peritoneal dialysis and reported a non-significant decrease in 24-hour sodium excretion with a low salt intervention (Analysis 2.1.2: MD -52.00 mmol/d, 95% CI -113.06 to 9.06).
Keven 2006 included 32 post-transplant participants and reported a significant decrease in 24-hour sodium excretion with a low salt intervention (Analysis 2.1.3: MD -131.00 mmol/d, 95% CI -194.21 to -67.79).

Blood pressure

All studies provided data on systolic and diastolic blood pressure for analysis. Reducing salt intake significantly reduced systolic blood pressure (Analysis 1.2 (8 studies, 258 participants): MD -8.75 mm Hg, 95% CI -11.33 to -6.16; I^2 = 0%) and diastolic blood pressure (Analysis 1.3 (8 studies, 258 participants): MD -3.70 mm Hg, 95% CI -5.09 to -2.30; I^2 = 0%).

Duration of studies

In short-term studies, low salt interventions significantly reduced systolic blood pressure (Analysis 1.2.1 (3 studies, 72 participants): MD -7.18 mm Hg, 95% CI -11.48 to -2.89; I^2 = 0%) and diastolic blood pressure (Analysis 1.3.1 (3 studies, 72 participants): MD -3.50 mm Hg, 95% CI -6.48 to -0.51; I^2 = 0%).
In long-term studies, low salt interventions significantly reduced systolic blood pressure (Analysis 1.2.2 (5 studies, 186 participants): MD -9.64 mm Hg, 95% CI -12.88 to -6.40; I^2 = 0%) and diastolic blood pressure (Analysis 1.3.2 (5 studies, 186 participants): MD -3.75 mm Hg, 95% CI -5.33 to -2.17; I^2 = 0%). There was no significant difference between the short-term and long-term studies (systolic blood pressure: test for subgroup differences: Chi^2 = 0.80, df = 1 (P = 0.37); I^2 = 0%) (diastolic blood pressure: test for subgroup differences: Chi^2 = 0.02, df = 1 (P = 0.88); I^2 = 0%).
A notable difference in blood pressure measurement techniques between the studies related to use of 24 hour blood pressure in the three short-term studies (Konishi 2001; LowSALT CKD Study 2012; Ruilope 1992a) and clinic blood pressure in four of the five long-term studies (DUAAAL Study 2011; Fine 1997; Keven 2006; Vogt 2008). This may limit comparison by study duration.

Stage of chronic kidney disease

In early stages of CKD salt restriction reduced systolic blood pressure (Analysis 2.2.1 (6 studies, 206 participants): MD -7.96 mm Hg, 95% CI -10.74 to -5.17; I^2 = 0%) and diastolic blood pressure (Analysis 2.3.1 (6 studies, 206 participants): MD -3.40 mm Hg, 95% CI -4.86 to -1.94; I^2 = 0%).
Fine 1997 included 20 peritoneal dialysis patients and reported that with a low salt intervention there was a non-significant decrease in systolic blood pressure (Analysis 2.2.2: MD -9.00 mm Hg, 95% CI -21.41 to 3.41) and diastolic blood pressure (Analysis 2.3.2: MD -5.00 mm Hg, 95% CI -11.32 to 1.32).
Keven 2006 included 32 post-transplant patients and reported that with a low salt intervention there was a significant decrease in systolic blood pressure Analysis 2.2.3: MD -16.00 mm Hg, 95% CI -24.50 to -7.50) and diastolic blood pressure (Analysis 2.3.3: MD -8.00 mm Hg, 95% CI -14.60 to -1.40).
Both fixed and random-effects models were used to ensure robustness of the analyses. Reductions in systolic and diastolic blood pressure did not change between these analyses.

Measures of kidney function

Analyses of eGFR, SCr, CrCl, effective renal plasma flow and filtration fraction were similar when analysed using the random-effect method. Due to the small number of studies that reported these outcomes, subgroup analyses were not possible.

Estimated glomerular filtration rate

There was no significant difference in eGFR between low and high salt intake (Analysis 1.4 (2 studies, 68 participants): MD -1.14 mL/min/1.73 m^2, 95% CI -4.38 to 2.11; I^2 = 0%)

Creatinine clearance

There was no significant difference in CrCl between the low and high salt intake groups (Analysis 1.5; 3 studies, 85 participants): MD -4.60 mL/min, 95% CI -11.78 to 2.57; I^2 = 0%).
DUAAAL Study 2011 (52 participants) reported CrCl as log-transformed; these data could not be pooled with studies that reported normally distributed CrCl. DUAAAL Study 2011 did not report a significant change in CrCl with salt restriction (Analysis 1.6: MD -6.00 mL/min, 95% CI -20.55 to 8.55).

Serum creatinine

There was no significant difference in SCr between the low and high salt intake groups (Analysis 1.7 (5 studies, 151 participants): MD 5.14 µmol/L, 95% CI -8.98 to 19.26; I^2 = 59%).

Effective renal plasma flow

Konishi 2001 (41 participants) reported no significant difference in effective renal plasma flow between low and high salt intake (Analysis 1.8: -33.00 mL/min, 95% CI -117.64 to 51.64)

Filtration fraction

Konishi 2001 (41 participants) reported no significant difference in filtration fraction between low and high salt intake (Analysis 1.9: MD -1.00%, 95% CI -3.16 to 1.16).

Urinary protein excretion

Four studies (DUAAAL Study 2011; Konishi 2001; LowSALT CKD Study 2012; Vogt 2008) presented changes in urinary protein; however, data could not be pooled for analysis. Available data are presented in Table 1.
Salt restriction significantly reduced urinary protein excretion in all studies that reported proteinuria as an outcome. Reductions in 24 hour proteinuria ranged from 21% to 49%. Konishi 2001 and LowSALT CKD Study 2012, which were short-term studies, reported reductions of 27% and 41% from the high salt to the low salt period. The DUAAAL Study 2011 and Vogt 2008 (long-term studies) reported reductions of 49% and 21%. LowSALT CKD Study 2012 reported urinary albumin excretion and found that 24-hour urinary albumin was reduced by 51% from the high to the low salt period.

Body weight and presence of oedema

Although body weight was decreased with salt restriction, this change was not significant (Analysis 1.10 (5 studies, 139 participants): MD -1.46 kg; 95% CI -4.55 to 1.64; I^2 = 0%).
Objective markers of fluid status were not routinely reported, making it difficult to determine if body weight changes were attributable to change in extracellular volume or body fat. LowSALT CKD Study 2012 (20 participants) reported no significant change in extracellular volume (Analysis 1.11: MD -0.80 L, 95% CI -3.09 to 1.49).
DUAAAL Study 2011 (52 participants) reported restricting salt intake reduced the risk of oedema by 56% (Analysis 1.12: RR 0.44, 95% CI 0.21 to 0.93).
Body weight, extracellular fluid volume and presence of oedema analyses did not change when analysis was performed with a fixed-effect model.

Renin-angiotensin-aldosterone system (RAAS) and N-terminal pro-brain natriuretic peptide stimulation (NT pro-BNP)

RAAS stimulation was reported as plasma renin activity, plasma renin, plasma aldosterone and serum aldosterone. Salt restriction significantly increased plasma renin activity (Analysis 1.13 (2 studies, 71 participants): MD 1.08 ng/mL/h, 95% CI 0.51 to 1.65; I^2 = 0%) and serum aldosterone (Analysis 1.14 (2 studies, 71 participants): 6.20 ng/dL (95% CI 3.82 to 8.58; I^2 = 0%).
LowSALT CKD Study 2012 (20 participants) reported plasma renin and plasma aldosterone as non-normally distributed data; therefore, these data were not pooled. Plasma renin was increased by median 48 pmol/L (interquartile range (IQR) 23.5 to 70.5) and plasma aldosterone by 53.8 mU/L (IQR 4.8 to 74.7) with salt restriction ($P < 0.001$ for both analyses).
Vogt 2008 (32 participants) reported salt restriction significantly decreased NT pro-BNP (Analysis 1.15: -29.00 pg/mL, 95% CI -54.18 to -3.82). LowSALT CKD Study 2012 reported NT pro-BNP as non-normally distributed data, and therefore, these data were not pooled. The LowSALT CKD Study 2012 reported that salt restriction reduced NT pro-BNP by 125 pg/mL ($P < 0.05$).
Results of these analyses did not change when performed using a fixed-effect model.

Change in antihypertensive regimen

Antihypertensive medication dosage was significantly reduced with low salt diet (Analysis 1.16 (2 studies, 52 participants): RR

5.48, 95% CI 1.27 to 23.66; I^2 = 0%). This may also reduce the effect size of sodium restriction on blood pressure in these studies.

Adverse effects

Potential adverse effects reported included symptomatic hypotension and serum cholesterol. There was no significant change in total cholesterol in relation to salt restriction (Analysis 1.17 (3 studies, 105 participants): MD -0.23 mmol/L, 95% CI -0.57 to 0.10; I^2 = 0%).

There was a non-significant increase in symptomatic hypotension with sodium restriction (Analysis 1.18 (2 studies, 72 participants): RR 6.60, 95% CI 0.77 to 56.55; I^2 = 0%). This is a potential adverse effect associated with salt restriction, although one that could be rectified by reducing the antihypertensive dose.

DISCUSSION

Summary of main results

We found that reducing salt intake by approximately 6 g/d (100 mmol or 2300 mg sodium/d) lowered blood pressure by 9/4 mm Hg in people with CKD. This is a clinically significant reduction in blood pressure, comparable to expectations of administering a single antihypertensive drug.

Studies of four weeks or longer showed greater reduction in blood pressure than short-term studies: reductions of 10/4 mm Hg and 7/4 mm Hg respectively. This may however be partially attributable to methodological differences. In non-dialysed, non-transplanted people with CKD, reducing salt intake reduced blood pressure by 8/3 mm Hg. We found only one study conducted in people on dialysis (Fine 1997) and one in people who had undergone transplantation (Keven 2006), making comparisons according to CKD severity difficult. These studies reported reductions of 9/5 mm Hg with 3 g reduction in salt intake (50 mmol or 1150 mg sodium) and 16/8 mm Hg with 8 g reduction in salt intake (130 mmol or 2990 mg sodium), respectively. It was found that eGFR, SCr and CrCl were not significantly changed by salt restriction. Changes in proteinuria data could not be entered into pooled analysis; however, studies consistently reported significant reductions with salt restriction: 24 hour proteinuria or albuminuria reduction ranged from 20% to 50%.

Overall completeness and applicability of evidence

We aimed to evaluate the benefits and harms of altering dietary salt intake for people with CKD. This review included a small number of studies of relatively short duration. We could not assess the effect of restricting salt intake on endpoints such as mortality or cardiovascular events in people with CKD because there were no RCTs of adequate size or duration to examine these outcomes. This limitation has been noted in previous reviews in non-CKD populations (Hooper 2002; Suckling 2010), and is likely due to the practical aspects of achieving adherence to a sodium-restricted diet in a long-term study (McMahon 2012a). Evidence for the longer-term effects of sodium restriction on patient-level outcomes and secondary risk markers (such as blood pressure and proteinuria) is required.

Exploration of the differential effects of salt restriction by CKD stage was limited due to the small number of included studies, particularly in the more advanced stages of CKD. Only one study included post-transplant participants, and one was conducting with people receiving peritoneal dialysis, and none in people receiving haemodialysis. Salt restriction studies have been conducted in people undergoing haemodialysis, but these are either observational (Kayikcioglu 2009), non-randomised (Ang 1999; Osanai 2002) or used a concomitant intervention in the sodium restricted group (Rupp 1978) and were not eligible for inclusion in this review.

Subgroup analyses were not viable for outcomes other than blood pressure due to the small number of studies measuring these outcomes.

There was limited evidence for effects on albuminuria, fluid volume and arterial stiffness.

Controversy has arisen regarding the safety of long-term sustained low sodium intake; studies have suggested an increased risk of hospitalisation and mortality associated with very low sodium diet (Kotchen 2013). Studies included in this review were not sufficiently long to examine this effect.

Quality of the evidence

There was a considerable degree of heterogeneity among study results. The small number of included studies limited exploration of sources of heterogeneity, although a potential contributor was the range of people with CKD who were represented - early stage CKD (non-dialysis), dialysis, and transplant populations. Sodium handling in people with mild CKD is likely to differ considerably from those with severe kidney dysfunction, people on dialysis, and kidney transplant recipients.

It is likely that differing magnitude and duration of salt restriction and study methodology differences also impacted heterogeneity. A previous analysis showed a dose-response relationship between salt reduction and blood pressure reduction (He 2003); again, there were too few included studies to explore this possibility for our review.

An important difference was in relation to methods applied to achieve salt-restricted diets. Studies that provided meals (Konishi 2001) or supplementary sodium (Fine 1997; LowSALT CKD Study 2012; Ruilope 1992a) to manage sodium intake were at lower risk of bias from dietary confounders because other di-

etary factors were likely to remain stable over the study period (McMahon 2012a). Previous research has found that when dietary advice is given about reducing sodium intake, other factors such as energy and potassium intake can also change (Korhonen 2000). This means that studies relying on dietary advice to manage sodium intake (de Brito-Ashurst 2013; DUAAAL Study 2011; Keven 2006; Vogt 2008) may be at a higher risk of bias from dietary confounders.

Measurement of potential dietary confounders was poor overall. Although it is widely accepted that potassium intake affects blood pressure (Whelton 1997), only four of the six studies that investigated blood pressure as an outcome measured potassium intake either directly or indirectly. Both LowSALT CKD Study 2012 and de Brito-Ashurst 2013 reported data showing no change in urinary potassium excretion with sodium restriction; however, de Brito-Ashurst 2013 did not present specific data. DUAAAL Study 2011 and Ruilope 1992a reported small, but significant, reductions in urinary potassium excretion in the sodium-restricted groups (3 to 4 mmol/d), which is likely to reflect reduction in urinary volume. DUAAAL Study 2011 and LowSALT CKD Study 2012 reported modest, but significant increases, in serum potassium with sodium restriction (increases of 0.1 and 0.3 mmol/L).

Body weight has also been reported to affect blood pressure (Siebenhofer 2011). Change in body weight was reported by five studies, and was reduced by mean -1.46 kg, although this was not statistically significant (95% CI -4.55 to 1.64 kg). Given that most studies did not report change in fluid status or energy intake, we could not determine the degree to which body weight change was due to reduction in fluid volume or body fat. The latter could introduce bias by overestimating the effect of salt restriction on blood pressure. Body weight is also related to proteinuria; two of the four studies that reported proteinuria found that reduced body weight with salt restriction did not measure fluid status. It is therefore unknown if body weight reflected reduction in fluid, body fat or other tissues (DUAAAL Study 2011; Vogt 2008). Konishi 2001 did not measure body weight change. LowSALT CKD Study 2012 reported reduction in body weight and fluid volume - the reduction in body weight reflected reduction in fluid volume.

A further confounder to proteinuria is change in protein intake. Three of the four studies that reported proteinuria as an outcome also measured a surrogate for protein intake. LowSALT CKD Study 2012 reported no change in protein intake as assessed by self-reported dietary history. DUAAAL Study 2011 and Vogt 2008 reported urinary urea as a marker of protein intake and found significantly reduced urinary urea in the sodium-restricted group (40 to 50 mmol/24 h). This potentially reflected reduced protein intake which may have overestimated the effect of salt restriction. Although Konishi 2001 reported proteinuria as an outcome there was no measurement of any protein intake marker.

Reduction in markers of dietary intake such as body weight could indicate that consumption of other dietary nutrients may have decreased with salt restriction. Overall, quality of the included studies would have been greatly improved by measuring and accounting for change in potassium and protein intake, fluid volume or both.

Other potential sources of bias in the included studies were unclear method of random sequence generation or allocation concealment, lack of blinding or not disclosing if participants, investigators and/or outcome assessors were blinded introducing potential for risk of performance or detection bias. It was difficult to assess risk of bias for selective outcome reporting, because protocols or trial registrations were unavailable for most studies. Where these were available, most did not report all outcomes measured.

There were important differences in methodology between short- (fewer than four weeks) and long-term studies (four weeks and more) that limited subgroup analysis according to study duration. All shorter-term studies used 24 hour blood pressure, but four of the five long-term studies used clinic blood pressure. Furthermore, short-term studies used either supplemental sodium (Konishi 2001; LowSALT CKD Study 2012) or full meal provision (Ruilope 1992a). Hence, it was likely that dietary confounders were more tightly controlled than in long-term studies which mostly used dietary education methods. A limitation in two of the three short-term studies was that neither employed a washout period. Considering that these studies had intervention durations of only one week, carry-over effect may have influenced study results. Ruilope 1992a, a short-term study, began a new antihypertensive medication on day one of the study, further increasing risk of carry-over effect.

Potential biases in the review process

All efforts were made to minimise bias inherent in the review process. Study inclusion and risk of bias assessment were carried out by two authors working independently.

We contacted all study authors for additional information to inform our risk of bias assessment and received data for five of the eight included studies (de Brito-Ashurst 2013; LowSALT CKD Study 2012; Vogt 2008; Konishi 2001; DUAAAL Study 2011).

We obtained corrected data for some outcomes reported by de Brito-Ashurst 2013 (systolic and diastolic blood pressure); however, incomplete data mean that standard deviation or P values for change in total body water could not be provided. Body weight data could not be meta-analysed because these were not statistically viable (MD -4 kg, 95% CI -4 to -1) and corrected data could not be obtained (de Brito-Ashurst 2013).

Change from baseline data was not available for Keven 2006; neither were other data from which we could impute values for standard deviation of change.

Despite applying a search strategy to include both published and unpublished studies, we were unable to include any unpublished studies.

Agreements and disagreements with other studies or reviews

We found no previous published reviews of salt restriction in people with CKD. Previous reviews investigating salt-restriction have been conducted in people with normal kidney function, and these consistently show that reducing dietary sodium intake reduces blood pressure, although magnitudes vary (Graudal 2011; He 2013; Hooper 2002; Suckling 2010). Generally, dietary salt reduction had a greater effect on people who are hypertensive (Graudal 2011; He 2013; Hooper 2002). In this review, most participants in the included studies were hypertensive; therefore, subgroup analysis could not be conducted. Graudal 1998 identified that increased serum cholesterol level was an adverse effect in a meta-analysis of sodium restriction. We found no significant change in total cholesterol in relation to salt restriction in people with CKD.

We found a reduction in blood pressure of 9/4 mm Hg with salt reduction of approximately 100 mmol in people with CKD. This is a larger benefit than reported elsewhere when a similar magnitude of salt reduction was investigated in the general population (Graudal 2011) or people with diabetes (Suckling 2010) which reported reductions of 5/3 mm Hg and 6/2 mm Hg in hypertensive Caucasian and black people, and 5/3 mm Hg in hypertensive people with diabetes, respectively.

This comparison must be interpreted cautiously because it is difficult to make direct comparisons due to systematic differences among populations (e.g. medication usage, baseline blood pressure) and differences in quality and methodologies of included studies. Nonetheless, we found that people with CKD may be particularly salt-sensitive.

In a pooled meta-analysis of people with diabetes Suckling 2010 reported that CrCl was significantly reduced (-6.33 mL/min, 95% CI -10.47 to -2.19) with salt restriction; eGFR was not significantly changed (MD -1.92; 95% CI -4.49 to 0.64). We found occurrence of CrCl, and did not reach statistical significance (MD -4.60 mL/min, 95% CI -11.78 to 2.57) and that eGFR did not change significantly with salt restriction. It is thought that reductions in CrCl with salt restriction occur as a result of hyperfiltration paradoxically decreasing risk of kidney disease (Allen 1997). However, longer-term studies are needed to ascertain effects of salt restriction on kidney function.

Salt restriction was found to consistently reduce proteinuria. This was less consistent in the review by Suckling 2010 in people with diabetes, with some studies reporting a significant reduction and others finding no change. This difference was expected because people with CKD are more susceptible to proteinuria. Albuminuria, a risk factor for kidney function decline and cardiovascular disease (Suckling 2010; Jones-Burton 2006), was also reduced in only included study that reported this outcome (LowSALT CKD Study 2012).

AUTHORS' CONCLUSIONS

Implications for practice

We found that reducing dietary salt considerably reduced blood pressure in people with CKD. Despite widespread antihypertensive use, hypertension is prevalent among people with CKD. Salt reduction represents a cost-effective and low risk strategy to reduce blood pressure for people with CKD.

We found consistent evidence that dietary salt restriction reduced proteinuria in people with CKD; reductions ranged from 20% to 50%. If such reductions were maintained long term, this may translate to clinically significant reductions in ESKD and cardiovascular events. We found a strong case for the benefits of salt restriction in people with CKD. Current evidence-based clinical guidelines recommend a sodium intake target of less than 6 g of salt (100 mmol; 2300 mg sodium) per day for people with CKD, although achieving long-term adherence to this target can be problematic. Referral to an accredited dietician who can provide individualised strategies to reduce sodium intake should be considered.

Implications for research

Most included studies were of short duration. Further research to assess longer-term effects of salt restriction is warranted. High-quality data on the effect of salt restriction on primary endpoints such as mortality, progression to ESKD and cardiovascular events would be ideal, but difficult to implement. Despite consistent data from observational and non-randomised studies showing that salt restriction reduced fluid volume in people with CKD, high quality RCTs are lacking. Further research on the effect on other cardiac and vascular abnormalities such as arterial stiffness, left ventricular hypertrophy, inflammation and oxidative stress is warranted.

Future studies investigating salt restriction should employ methods that limit risk of bias due to dietary confounders where possible, and should take care to adequately measure dietary intake of not only sodium, but other nutrients that may confound study results. Research into long-term adherence to a sodium-restricted diet may assist in translating these results into a practical setting.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

de Brito-Ashurst 2013

Methods	• Study design: parallel RCT • Time frame: June 2008 to July 2009 • Duration: 6 month intervention
Participants	• Country: UK • Setting: tertiary renal unit based in acute care hospital in East London • Inclusion criteria: eGFR < 60 mL/min; mean BP > 130/80 mm Hg on at least two clinic visits or taking antihypertensive medication; Bangladeshi origin; Attending predialysis clinic • Baseline characteristics ○ CKD eGFR: low salt (41 ± 17 mL/min/1.73 m^2); high salt (42 ± 15 mL/min/1.73 m^2) ○ BP (systolic/diastolic): low salt (149 ± 15/85 ± 6 mm Hg); high salt (156 ± 11/85 ± 6 mm Hg) ○ Sodium intake: low salt: (263 ± 54 mmol); high salt (259 ± 47 mmol) • Number: low salt (25); high salt (23) • Mean age ± SD (years): low salt (56 ± 11); high salt (61 ± 9) • Sex (M/F): 28/20 • Exclusion criteria: on dialysis; BMI < 20 or > 35 kg/m^{2-} urinary incontinence; cognitive impairment or mental problems impairing ability to participate
Interventions	Low salt group • Reduced sodium intake by ongoing individualised dietary education (in person and phone calls) and cooking lessons • Duration: 26 weeks High salt group • Sodium intake: usual care (general low salt advice sent with doctor's letter) • Duration: 26 week Co-interventions: nil
Outcomes	• 24 h BP • Total body water by body composition monitor • Measurement of sodium intake: 24 h urine • Measurement of confounders ○ 24 h urinary potassium and creatinine ○ Body weight change ○ Physical activity levels measured using a pedometer
Notes	• Funding: this study was funded by a PhD fellowship grant from the trustees of Barts and The London Charitable Foundation. The analysis, interpretation of data, generation of the manuscript and decision to submit for publication were carried out independently of the funding body • Additional data: provided by authors

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomisation to treatment was conducted by the study statistician using computer-generated random blocks with block sizes between four and eight"
Allocation concealment (selection bias)	Unclear risk	"Group assignment given to the researcher". Further information not provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unblinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Neither participants nor the dietitian administering the intervention could be blinded to treatment allocation. Data analysis was conducted by the study statistician who was blinded to treatment allocation." Blinding of participants: No Blinding of investigators: No Blinding of outcomes assessors: No Blinding of data assessors: Yes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for attrition unlikely to be related to allocation • 56 participants enrolled • Unwilling to complete: 24 hour urine collection (3), BP monitoring (2), attend dietary education (1) • Lost to follow-up: death (1); emigration (1) • Attrition by allocation: low salt group (3); high salt group (5)
Selective reporting (reporting bias)	Unclear risk	No evidence of outcomes missing from report; however, some data missing for certain outcomes (e.g. change for total body water, P values for differences among baseline data)
Carry over effect	Low risk	N/A
Bias from confounders	Unclear risk	Major confounders (potassium intake, body weight change, physical activity) mea-

de Brito-Ashurst 2013 (*Continued*)

		sured and reported as 'unchanged'
Other	Low risk	Funding: PhD scholarship from charitable trust

DUAAAL Study 2011

Methods	• Study design: Double blind, cross-over RCT • Time frame: April 2006 to October 2009 • Study duration (weeks): total (30); run in (6); interventions (6); no washout
Participants	• Country: The Netherlands • Setting: multicentre; outpatient clinics (3) • Inclusion criteria: consecutive patients with kidney disease who visited the nephrology outpatient clinic with non-diabetic nephropathy (confirmed by analysis of blood and urine or kidney biopsy); CrCl ≥ 30 mL/min; BP > 125/75 mm Hg; residual proteinuria > 1.0 g/d during ACE inhibition at maximal dose (lisinopril 40 mg/d); aged > 18 years • Baseline characteristics ○ BP (systolic/diastolic): 131 ± 18/71 ± 12.5 mm Hg • Number: randomised (54); analysed (52) • Mean age ± SD: 51 ± 13 years • Sex (M/F): 43/9 male (83%) • Exclusion criteria: systolic BP > 180 mm Hg or diastolic BP > 110 mm Hg; diabetes; renovascular hypertension; decrease in CrCl by ≥ 6 mL/min in previous year; cardiovascular event in the previous 6 months; immunosuppressive treatment; regular use (> 1 d/wk) of NSAIDs; pregnancy or breastfeeding

Interventions	Low salt group
	• Target sodium intake 50 mmol/d (individualised counselling by dietician)
	• Duration: 12 weeks
	High salt group
	• Sodium intake: usual diet
	• Duration: 12 weeks
	Co-interventions
	• Each participant was on lisinopril 40 mg/d for entire study and went through four interventions for six weeks each in random order
	  ○ Usual salt, placebo*
	  ○ Usual salt valsartan 320 mg/d
	  ○ High salt, placebo*
	  ○ High salt valsartan 320 mg/d
	  ○ * *used for analysis*
	Other information
	• No other RAAS blockers. Additional antihypertensive drugs such as beta-blockers, alpha-blockers, calcium channel blockers, and diuretics were allowed and kept stable during the study

Outcomes	• 24 hour proteinuria
	• Clinic BP
	• Clinical evaluation of oedema
	• Weight
	• Serum markers (electrolytes, lipids, proteins, creatinine)
	• Urinary electrolytes and CrCl
	• Measurement of sodium intake: 24 hour urine
	• Measurement of confounders
	  ○ Medication intake measured by pill counts
	  ○ Protein intake measured from urea excretion (Maroni formula)

Notes	• Funding: Unrestricted grant from Novartis. No role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript • Additional data: provided by authors

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"An independent pharmacist randomised these sequences, using a computer program"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Dietary interventions were open label
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Additionally, we analysed the data for all 54 patients who were included (intention to treat). As the effect estimates and confidence intervals were very similar and the statistical and clinical conclusions did not change, we have not shown these data" 54 randomised, 2 withdrew after randomisation; 52 included in analysis
Selective reporting (reporting bias)	Low risk	No evidence of reporting bias
Carry over effect	Low risk	Adequate intervention duration to reduce risk of carry over effect

DUAAAL Study 2011 (*Continued*)

Bias from confounders	High risk	Comparison of usual intake versus low sodium intervention increases risk of dietary confounders - reduction in body weight, potassium excretion and urinary urea in low salt phase suggests potential confounding
Other	Unclear risk	Funding: study supported by Novartis; declaration of non-involvement by funder

Fine 1997

Methods	• Study design: double blind, cross-over RCT • Time frame: NS • Study duration (weeks): total (18); run in/washout (3); intervention (6)

Participants	• Country: Canada
	• Setting: renal outpatients clinic
	• Inclusion criteria: CAPD > 4 months
	• Baseline data
	  ○ GFR: NS
	  ○ Baseline BP: NS
	  ○ Mean duration of dialysis: 15 ± 15 months
	• Number: 20
	• Mean age ± SD: 61 ± 13 years
	• Sex (M/F): 14/6
	• Exclusion criteria: diastolic BP > 100 mm Hg; difficulty staying oedema-free; medication noncompliance; considered by researchers to be unable to keep an accurate dietary history or record own BP; use of 4.25% dialysate in 75% on more of their usual cycles; large geographical distance between unit and the patient's home

Interventions	Low salt diet • Usual diet plus placebo • Duration: 6 weeks High salt diet • Sodium intake: usual diet plus 60 mmol sodium capsule • Duration: 6 weeks Other information • Co-interventions: none • Dialysate sodium 132 mmol/L in all participants

Outcomes	• Clinic BP (self-recorded)
	• Weight (self-recorded)
	• Measurement of sodium intake
	  ○ 24 hour urine + dialysate collection
	  ○ 3 day food record
	  ○ Change in dialysate regimen self-recorded
	• Measurement of confounders

Fine 1997 (*Continued*)

	○ Medication changes discussed but measurement not described ○ Measurement of other dietary confounders not described ○ Adherence to study medication not described
Notes	• Funding: Baxter Healthcare Corporation and Kidney Foundation of Canada, Manitoba Branch

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"By pharmacy". Further information not provided; however, low risk of bias due to study design
Allocation concealment (selection bias)	Low risk	"Double blind" and medications packaged by pharmacy. Probably concealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Physician, patient, and study nurse were blinded"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Weight/BP: "Patients recorded own weights and BP" Objective outcome; however, introduced attrition and could have unblinded allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Large degree of attrition but even in both groups and well-explained 32 participants enrolled, 12 withdrew (6 in each intervention), 20 completed and were included for analysis
Selective reporting (reporting bias)	Low risk	No evidence of reporting bias
Carry over effect	Low risk	Sufficient washout
Bias from confounders	Unclear risk	Measurement of dietary confounders not described
Other	High risk	Funding: Baxter Healthcare Corporation

Keven 2006

Methods	• Study design: parallel RCT • Time frame: January 2004 to December 2004 • Study duration (weeks): total (12); intervention (12)

Participants	• Country: Turkey
	• Setting: NS
	• Inclusion criteria: underwent kidney transplant between 1993 and 2002 and continuing care at time of screening; stable allograft function at the time of evaluation (SCr < 2.5 mg/dL); on antihypertensive treatment; residing in geographic proximity to the institution
	• Baseline characteristics
	  ○ Duration of transplant (years): Low salt (5.3 ± 3.1); high salt (7.2 ± 3.9)
	  ○ Baseline BP (systolic/diastolic): low salt (146 ± 21/89 ± 8 mm Hg); high salt (140 ± 16/86 ± 8 mm Hg)
	  ○ Baseline sodium intake: 190 mmol
	• Number: low salt (18); high salt (14)
	• Mean age ± SD (years): low salt (40 ± 14); high salt (43 ± 9)
	• Sex (M/F): 25/7
	• Exclusion criteria: evidence of renal artery stenosis on Doppler ultrasonography

Interventions	Low salt group • Target sodium intake 80 to 100 mmol/d (counselling by dietician) • Duration: 12 weeks High salt group • Sodium intake: assumed usual diet (information not provided) • Duration: 12 weeks Co-interventions • Antihypertensive treatment (including dose/number of drugs) adjusted if systolic BP > 140 or < 100 mm Hg, and/or diastolic BP > 90 mm Hg or < 70 mm Hg as assessed by a blinded physician
Outcomes	• Clinic BP • Serum markers (electrolytes, creatinine) • Measurement of sodium intake: 24 hour urine • Measurement of confounders: medication changes recorded
Notes	• Funding: NS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomised". Further information not provided. Considerable difference in baseline BP likely to underestimate effect of intervention with parallel design
Allocation concealment (selection bias)	Unclear risk	Not described

Keven 2006 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Open-label dietary intervention
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors not specified
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition reasons explained; however, attrition for each group not provided 35 participants began study, 3 withdrew (noncompliance with study visits (1), long-term hospitalisation secondary to chronic diarrhoea (1), development of chronic allograft nephropathy (1))
Selective reporting (reporting bias)	Unclear risk	No evidence of reporting bias; however, study registration could not be located
Carry over effect	Low risk	Not applicable
Bias from confounders	High risk	Confounding factors not measured/described (body weight, potassium, insufficient information provided about antihypertensive medication changes). Highly likely that other dietary factors may have confounded results with unblinded, usual intake versus low sodium, study design
Other	Unclear risk	Funding: NS

Konishi 2001

Methods	• Study design: cross-over RCT • Time frame: NS • Duration of study (weeks): total (3); run in (1); interventions (1); no washout

Participants	• Country: Japan
	• Setting: NS
	• Inclusion criteria: IgA nephropathy as diagnosed by percutaneous kidney biopsy
	• Baseline characteristics
	  ○ GFR: NS
	  ○ BP: NS
	• Number: 38
	• Mean age ± SD: 45 ± 15 years
	• Sex: 14/27
	• Exclusion criteria: other kidney or heart disease; taking any medication

Konishi 2001 (*Continued*)

Interventions	Low salt group • Sodium intake 87 mmol/d (meals provided) • Duration: 1 week High salt group • Sodium intake 209 mmol/d (meals provided) • Duration: 1 week Other information • Study diets contained the same amount of protein (1.2 g/kg body weight/d) and calories (35 kcal/kg/d) • Participants were asked to maintain usual levels of physical activity and to refrain from drugs for 1 week before and during the study • Co-interventions: none
Outcomes	• 24 hour BP (hourly measurements) • 24 hour proteinuria • Serum markers (electrolytes, renin, aldosterone) • Renal plasma flow, CrCl • Measurement of sodium intake: 24 hour urine (3 days) • Measurement of confounders: assumed medications recorded from medical charts
Notes	• Funding: not reported • Additional data: provided by authors

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Information not provided
Allocation concealment (selection bias)	Unclear risk	Information not provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information not provided
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Information not provided. However, given nature of outcomes (objective and results not available immediately)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition not provided
Selective reporting (reporting bias)	Unclear risk	No evidence of reporting bias; however, study registration could not be located
Carry over effect	Unclear risk	Short interventions with no washout - carry over effect may be present

Konishi 2001 (*Continued*)

Bias from confounders	Unclear risk	Standardised meals were provided reducing risk of dietary confounders, but as confounders (e.g. potassium intake, weight loss) were not discussed, risk of bias is unclear
Other	Unclear risk	Funding not reported

LowSALT CKD Study 2012

Methods	• Study design: cross-over, double blind RCT • Time frame: NS • Duration of study (weeks): total (6); run in/washout (1); interventions (2)

Participants	• Setting: single centre
	• Country: Australia
	• Inclusion criteria: systolic BP 130 to 169 mm Hg; diastolic BP > 70 mm Hg; aged at least 18 years
	• Baseline characteristics
	  ○ CKD: Stage 3 to 4 non-dialysed, non-transplanted
	  ○ Baseline BP (systolic/diastolic): low salt (149 ± 15/85 ± 6 mm Hg); high salt (156 ± 11/85 ± 6 mm Hg)
	  ○ Baseline sodium intake (mmol): low salt (263 ± 54); high salt (259 ± 47)
	• Number: 20
	• Mean age ± SD: 68.5 ± 11.0 years
	• Sex (M/F): 15/5
	• Exclusion criteria: receiving RRT (dialysis or transplant) or likely to within study period; salt-wasting CKD (as diagnosed by nephrologist); prescribed > 1680 mg sodium bicarbonate and unable to cease therapy for 6 weeks; pregnant or breastfeeding; life expectancy < 6 months; current involvement in other intervention; unable to comprehend study protocol

Interventions	Low salt group • 60 to 80 mmol sodium intake - achieved by dietary education from trained dietician (goal 60 to 80 mmol/d), plus placebo tablets • Duration: 2 weeks High salt group • 180 to 200 mmol sodium intake - low salt diet (goal 60 to 80 mmol/d) achieved by dietary education plus 120 mmol of sodium capsules • Duration: 2 weeks Other details • Aimed to keep intake of other nutrients stable • Co-interventions: none
Outcomes	• 24 hour BP (every 20 min during day at 30 min at night) • 24 hour proteinuria and albuminuria • Pulse wave velocity • Augmentation index (pulse wave analysis)

	• eGFR • Fluid status (bio-impedance spectroscopy using Body Composition Monitor) • 24 hour urine output • Weight • N-terminal pro-brain natriuretic peptide (via blood sample) • Thirst (via xerostomia Index) • C-reactive protein and adipokines • Stimulation of renin-angiotensin-aldosterone system (blood sample) • Taste test study • Barriers and enablers to adherence measured via beliefs about dietary compliance scale and attitudes to dietary recommendations questionnaires • Sodium intake measurement ○ 24 hour urine ○ Midstream urine sample ○ Semi-quantitative dietary history forms (verified by study dieticians) ○ Food-frequency questionnaire • Measurement of confounders ○ 24 hour urinary potassium and urea ○ Body weight change ○ Dietary history (verified by study dieticians) to assess protein, sodium and energy intake ○ Daily self-record of study medication intake
Notes	• Funding: research grants from the Princess Alexandra Hospital Private Practice Trust Fund and Kidney Health Australia. Study foods provided by Freedom Foods, Norco, Real Foods, Carman's Fine Foods, Sanitarium Health & Wellbeing Company, Rosella, and Diego's • Additional data: provided by authors

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation was performed by an external statistical consultant
Allocation concealment (selection bias)	Low risk	"Study medication was packaged offsite and labeled with the study numbers and intervention order"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Participants, investigators, and outcome assessors were blinded to the allocation"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Participants, investigators, and outcome assessors were blinded to the results of all outcomes." "Data analysis was initially performed blinded to treatment order and then was

		performed unblinded to confirm treatment order" Blinding of participants: All outcomes Blinding of investigators and outcome assessors: Serum and urinary markers, 24 hour BP and clinic BP blinded. Arterial stiffness (pulse wave velocity and analysis) unblinded Blinding of data assessors: Initial data analysis performed blinded to allocation and urinary sodium data
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition balanced between intervention periods and reasons for attrition well documented and unrelated to study results Those who withdrew from the study did not differ in age or sex, but had significantly higher weight and body mass index values compared with those who completed the study 25 participants randomised; 5 withdrew; visit schedule too demanding (3), hospital admission unrelated to study (1), symptoms related to pre-existing medical condition (1)
Selective reporting (reporting bias)	Low risk	Data for all outcomes available for inclusion in review
Carry over effect	Low risk	"To test for ... variation due to treatment order ... analysis of covariance was conducted" No relationship found significant difference. Data analysed for carry over effect
Bias from confounders	Unclear risk	Major confounding factors measured (potassium intake, energy intake, protein intake, body weight, medication changes) and assessed for potential impact on outcomes. Medication changes may have affected outcomes, although likely to underestimate effect size
Other	Low risk	Funding by hospital trust and not-for-profit organisation

Ruilope 1992a

Methods	• Study design: cross-over RCT • Time frame: NS • Duration of study (weeks): total (6); run in (4); interventions (1); no washout

Participants	• Country: NS
	• Setting: NS
	• Inclusion criteria: essential hypertension
	• Baseline characteristics
	  ○ BP (systolic/diastolic): 158.2 ± 29.1/99.9 ± 8.9 mm Hg
	  ○ GFR not reported
	  ○ "Mild renal insufficiency", diagnostic criteria (NS); nephrosclerosis (4); other clinical criteria (10)
	• Number: 14
	• Mean age ± SD: 63.5 ± 22.4 years
	• Sex: NS
	• Exclusion criteria: no other concurrent medical illness

Interventions	Low salt group • Sodium intake 68 mmol/d (17 mmol dietary intake plus 51 mmol supplement). Further information not provided • Duration: 1 week High salt group • Sodium intake 187 mmol/d (17 mmol dietary intake plus 170 mmol supplement) . Further information not provided) • Duration: 1 week Other details • Dietary intake target 60 mmol potassium/d • Co-interventions: 240 mg verapamil through both interventions
Outcomes	• 24 hour BP (every 20 to 30 min) • Clinic BP • 24 hour proteinuria • Weight • Measurement of sodium intake: 24 hour urine • Measurement of confounders: urinary potassium
Notes	• Funding: NS

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomised". Further information not provided
Allocation concealment (selection bias)	Unclear risk	Information not provided

Ruilope 1992a (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information not provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information not provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information not provided
Selective reporting (reporting bias)	Unclear risk	No evidence of reporting bias; however, study registration not available
Carry over effect	High risk	Addition of antihypertensive medication on study day 1; short study duration and lack of washout meant that carry over effect was likely
Bias from confounders	Unclear risk	Unable to assess using information provided; no indication of medication adherence; difference in sodium intake larger than intended suggesting some protocol deviation
Other	Unclear risk	Funding NS

Vogt 2008

Methods	• Study design: cross-over RCT • Time frame: March 2004 to June 2006 • Duration of study (weeks): total (36); interventions (6); no washout

Participants	• Country: The Netherlands
	• Setting: outpatient renal clinic
	• Inclusion criteria: stable proteinuria > 2 g/d and < 10 g/d; stable kidney function (< 6 mL/min/y decline); aged 18 to 70 years
	• Baseline characteristics
	  ○ CKD: CrCl ≥ 30 mL/min
	  ○ Systolic BP/diastolic BP: 131 ± 18/71 ± 12.5 mm Hg
	• Number: 34
	• Mean age ± SD: 50 ± 12 years
	• Sex (M/F): 25/9
	• Exclusion criteria: MAP > 100 mm Hg; serum K > 5.5 mmol/L; CVD (MI, unstable angina, percutaneous transluminal coronary angioplasty, CABG, or stroke within the last 6 months); contraindication for AT1-antagonist or diuretic use; diabetes; frequent users of NSAID (> 2 doses/wk)

Vogt 2008 (*Continued*)

Interventions	Low salt group • Target 50 mmol Na/d (individualised counselling by dietician) • Duration: 6 weeks High salt group • Target 200 mmol Na/d • Duration: 6 weeks Other details • Additional antihypertensive drugs except for RAAS-blocking agents or diuretics were allowed for BP control and kept stable during the study • Co-interventions: 6 weeks each with placebo, losartan, losartan plus hydrochlorothiazide on high-sodium diet or low-sodium diet in random order during 18 weeks. After 18 weeks, participants changed diet and the three 6 week periods were repeated. Placebo on high and low Na diet used for this review
Outcomes	• 24 hour proteinuria • Clinic BP • Serum markers (creatinine, urea, cholesterol, triglycerides, total protein, albumin) • N-terminal pro-brain natriuretic peptide • Renin, aldosterone • Uric acid • Plasma vascular endothelial growth factor C • Kidney Injury Molecule 1 • N-acetyl-beta-D-glucosaminidase • Measurement of sodium intake: 24 hour urine • Measurement of confounders: Urinary urea, weight
Notes	• Funding: supported by Merck Sharp & Dohme (grant MSGP NETH-15-01) • Additional data: provided by authors

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation was conducted by pharmacists using a computer generated model
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Dietary interventions were open label
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low attrition and unlikely to introduce bias 35 were randomised, one withdrew

Vogt 2008 (*Continued*)

Selective reporting (reporting bias)	Low risk	No evidence of reporting bias
Carry over effect	Low risk	Sufficient intervention duration to avoid carry over effect
Bias from confounders	High risk	Reduction in body weight (unable to determine if fluid change) and urinary urea in low salt phase may have confounded results
Other	High risk	Supported by Merck Sharp & Dohme

ACE - angiotensin-converting-enzyme; BMI - body mass index; BP - blood pressure; CABG - coronary artery bypass graft; CAPD - continuous ambulatory peritoneal dialysis; CKD - chronic kidney disease; CrCl - creatinine clearance; CVD - cardiovascular disease; eGFR - estimated glomerular filtration rate; ESKD - end-stage kidney disease; GFR - glomerular filtration rate; HD - haemodialysis; IgA - immunoglobulin A; MAP - mean arterial pressure; MI - myocardial infarction; Na - sodium; NS - not stated; NSAID - nonsteroidal anti-inflammatory drug; PD - peritoneal dialysis; RAAS - renin-angiotensin-aldosterone system; RCT - randomised controlled trial; RRT - renal replacement therapy; SCr - serum creatinine

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
De Nicola 2000	No random allocation to low or high salt diet
Esnault 2005	Concomitant intervention
Forrester 2010	Not CKD population
Kauric-Klein 2012	Concomitant intervention
Mahmoodi 2011	No random allocation to low or high salt diet
Osanai 2002	No random allocation to low or high salt diet
Rupp 1978	Concomitant intervention
Suckling 2010b	Not CKD population
Swift 2005	Not CKD population

CKD - chronic kidney disease

Characteristics of studies awaiting assessment *[ordered by study ID]*

Hwang 2014

Methods	• Study design: parallel, open label RCT • Time frame: March 2012 to March 2013 • Duration of study: 8 weeks
Participants	• Country: South Korea • Setting: multicentre, outpatient renal clinics (7) • Inclusion criteria: aged 19 to 75 years; systolic/diastolic BP ≥ 140/90 mm Hg and over, patients is newly diagnosed with hypertension or is prescribed antihypertensive medications; verified at least twice to have albumin: creatinine ratio of ≥ 30 mg/g in a spot urine sample with interval of 1 week or more in recent 6 months • CKD: eGFR by Modification of Diet in Renal Disease equation ≥ 30 mL/min/1.73 m^2 • Sample size: estimated 270 • Exclusion criteria: systolic/diastolic BP > 160/100 mm Hg; pregnant; serum potassium level > 5.5 mEq/L at screening period; malignancy; acute cerebral infarction; acute myocardial infarction; unstable angina; PCI or CABG in recent 6 months; diabetes mellitus; allergy to olmesartan; involved in other clinical study in recent 1 month or are participated in screening period; taking medications of corticosteroid or immunosuppressant in a screening period
Interventions	Low salt group • Low salt diet via dietary education from dietician (one 30 minute phone call every week) High salt group • Education for low salt diet will be conducted as in office with brief communication with a patient and a physician
Outcomes	• Spot urine albumin to creatinine ratio • Hb • 24 hour urinary sodium excretion • BP
Notes	• Registered at: NCT00702312

Rodrigues Telini 2014

Methods	• Study design: parallel, open-label RCT • Time frame: April 2007 to February 2009 • Duration of study: 16 weeks
Participants	• Country: Brazil • Setting: NS • Inclusion criteria: aged ≥ 18 y; haemodialysis for at least 90 days; CRP ≥ 0.7 mg/dL • Number: low salt (21); high salt (18) • Exclusion criteria: acute inflammatory processes confirmed by clinical criteria and/or complementary tests; acute inflammatory diseases; tuberculosis use of antibiotics within the past two months; chronic inflammatory diseases; neoplasia; chronic obstructive pulmonary disease; use of central venous catheter and positive HIV serology
Interventions	Low salt group • Reduction of 34 mmol sodium from usual intake High salt group

Rodrigues Telini 2014 (*Continued*)

	• No intervention
Outcomes	• C-reactive protein • Interleukin-6 • Alpha tumour necrosis serum concentrations
Notes	• Registered at: NCT01458808

BP - blood pressure; CRP - C-reactive protein; eGFR - estimated glomerular filtration rate; RCT - randomised controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

Clark-Cutaia 2013

Trial name or title	Intervention to reduce dietary sodium in hemodialysis (BalanceWise-HD)
Methods	• RCT testing a behavioral intervention to reduce dietary sodium intake
Participants	• Sample size: 200 adult HD patients • Inclusion criteria: aged ≥ 18 y; literacy; community-dwelling adults who have been receiving maintenance dialysis for at least 3 months • Exclusion criteria: illiteracy; non-English speakers; individuals who plan to move out of the area or change dialysis centres within the next six months; life expectancy < 12 months; scheduled for a living donor transplant; individuals who cannot see the PDA screen or use the stylus to make food selections from the PDA screen, or who live in an institutional setting in which they would have limited control over their dietary intake
Interventions	• Intervention participants continue to receive routine dialysis care, as well as a 16 week dietary counselling intervention based on Social Cognitive Theory. Dietary counselling is paired with Personal Digital Assistant-based dietary self-monitoring. • Behavioral: Social Cognitive Theory based dietary counselling paired with personal digital assistant based self-monitoring. • The intervention duration is 16 weeks. Intervention contacts are 2 x weekly for weeks 0 to 8, weekly for weeks 9 to 12, and every other week for weeks 13 to 16. • Personal digital assistant dietary records are used to provide targeted counselling and engaged the participant in problem solving around dietary issues. • Attention control participants continue to receive routine dialysis care. Attention control participants view 5 computerised educational programs PowerPoint slides) that summarise HD diet in 5 modules evenly over the 4-month study period. Attention control participants continue to receive routine dialysis care. Attention control participants view 5 computerised educational programs PowerPoint slides) that summarise the various elements of the HD diet. The 5 modules evenly over the 4 month study period
Outcomes	• Interdialytic weight gain • Dietary adherence (sodium intake) (3 x 24 hour diet recalls) • Clinic BP • Self-efficacy for restricting dietary sodium in HD

Clark-Cutaia 2013 (*Continued*)

	• Self-rated global health • Haemodialysis symptoms (10 point scale) • Barriers to dietary adherence (questionnaire) • Experience with the haemodialysis diet and intervention (qualitative interview)
Starting date	01/09/2009
Contact information	Linda J Hough, MPH, Susan Stark MS; University of Pittsburgh School of Medicine
Notes	

NCT00141609

Trial name or title	A study looking at the effects of a modest reduction in dietary salt intake on blood pressure control in haemodialysis patients (haemodialysis salt reduction study)
Methods	• Study design: double blind, cross over RCT. Single centre • Duration of study: 8 weeks
Participants	• Sample size: 20 (estimated) • CKD: HD • Inclusion criteria: haemodialysis/haemodiafiltration for ESKD > 3 months; clinically stable • Exclusion criteria: significant intercurrent illness; systolic BP > 240 mm Hg or diastolic BP > 120 mm Hg at enrolment; unstable BP whilst on haemodialysis; sodium profiled haemodialysis or haemodiafiltration
Interventions	Low salt group • Intervention: 100 mmol High salt group • Intervention: 170 to 200 mmol
Outcomes	• Pre-dialysis systolic BP • Post-dialysis ambulatory BP (24 hr) • Thirst score • Intradialytic weight gain • Systemic vascular resistance • Asymmetric dimethylarginine (ADMA)
Starting date	April 2004
Contact information	Principal investigator: Timothy WR Doulton St George's, University of London
Notes	

NCT00974636

Trial name or title	Lowering salt intake in chronic kidney disease: a pilot randomized crossover trial (BIA)
Methods	• Study design: open label, cross-over RCT. Single centre • Duration of study (weeks): total (12); interventions (4); washout (2)
Participants	• Number: 35 • CKD: Stages 3 and 4 • Inclusion criteria: aged ≥ 18 years and ≤ 85 years; willing and able to comply with all study procedures; eGFR 20 to 60 mL/min/1.73 m^2 and relatively stable clinical course; sitting systolic BP ≥ 100 mm Hg prior to study entry • Exclusion criteria: recent acute illness (≤ 1 month) (minor ailments left to the site principal investigator's discretion); recent hospitalisation (≤ 1 month) (unless clearly for a minor elective procedure unlikely to interfere with BIA measurements to the site principal investigator's discretion); any psychological condition (including alcoholism) that could interfere with the patient's ability to comply with the study protocol; baseline 24 hour urinary sodium excretion ≤ 100 mmol/d • Amputation of a limb other than fingers or toes; pacemaker, defibrillator, implantable pump, artificial joint, pins, plates or other types of metal objects in the body (other than dental fillings); coronary stents or metal suture material in the heart; use of any investigational product or investigational medical device within 30 days prior to screening, or requirement for any investigational agent prior to completion of all scheduled study assessments; weight over 300 pounds (limitation for examination table); pregnancy or lactation; salt wasting kidney disease; atrial fibrillation; any condition that in the view of the PI placed the subject at high risk of poor treatment compliance or of not completing the study
Interventions	Low salt group • ≤ 85 mmol/d for two weeks High salt group • Usual intake for two weeks
Outcomes	Change in volume status (intracellular, extracellular volume, and total body water) as measured by bioimpedance analysis using both whole body and segmental techniques
Starting date	May 2009
Contact information	Principal investigator: Rajiv Saran, MD; University of Michigan
Notes	

NCT01015313

Trial name or title	Effects of intensified sodium management in hemodialysis patients
Methods	• Study design: parallel, open label RCT. Multiple sites • Duration of study: total (12 months)
Participants	• Sample size: target (40) • CKD: Ambulatory, clinically stable maintenance haemodialysis patients on three times weekly HD regimen • Inclusion criteria: willing and able to provide written, signed informed consent after the nature of the study has been explained; willing and able to comply with all study procedures; aged ≥ 18 years

NCT01015313 (*Continued*)

	• Exclusion criteria: simultaneous participation in another clinical study except observational studies; any psychological condition that could interfere with the patient's ability to comply with the study protocol; pregnancy; amputation of a limb; pacemaker, implantable pump, artificial joint; expectation that native kidney function will recover; unable to verbally communicate in English or Spanish; scheduled for living donor kidney transplant, change to peritoneal dialysis, home HD or plans to relocate to another centre within the next 14 months; life expectancy < 15 months
Interventions	Low salt group • Dietary sodium restriction avoiding positive sodium balance during dialysis by ○ aligning dialysate sodium with plasma sodium, and ○ avoiding sodium profiling, and avoiding saline solutions to treat intradialytic symptoms High salt group • No intervention: standard care
Outcomes	• Feasibility of intensive sodium management • Hospitalisation
Starting date	November 2009
Contact information	Contact: Rebecca Apruzzese. rapruzzese@rriny.com
Notes	

BP - blood pressure; CABG - coronary artery bypass graft; CKD - chronic kidney disease; eGFR - estimated glomerular filtration rate; ESKD - end-stage kidney disease; Hb - haemoglobin; HD, haemodialysis; PCI - percutaneous coronary arterial intervention; RCT - randomised controlled trial

DATA AND ANALYSES

Comparison 1. Net change with altering salt and change by duration

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Sodium excretion	8	434	Mean Difference (IV, Random, 95% CI)	-105.86 [-119.20, -92.51]
1.1 Short-term (< 4 weeks)	3	144	Mean Difference (IV, Random, 95% CI)	-115.06 [-132.50, -97.62]
1.2 Long-term (≥ 4 weeks)	5	290	Mean Difference (IV, Random, 95% CI)	-99.11 [-117.31, -80.92]
2 Systolic blood pressure	8	434	Mean Difference (IV, Random, 95% CI)	-8.75 [-11.33, -6.16]
2.1 Short-term (< 4 weeks)	3	144	Mean Difference (IV, Random, 95% CI)	-7.18 [-11.48, -2.89]
2.2 Long-term (≥ 4 weeks)	5	290	Mean Difference (IV, Random, 95% CI)	-9.64 [-12.88, -6.40]
3 Diastolic blood pressure	8	434	Mean Difference (IV, Random, 95% CI)	-3.70 [-5.09, -2.30]
3.1 Short-term (< 4 weeks)	3	144	Mean Difference (IV, Random, 95% CI)	-3.50 [-6.48, -0.51]
3.2 Long-term (≥ 4 weeks)	5	290	Mean Difference (IV, Random, 95% CI)	-3.75 [-5.33, -2.17]
4 eGFR [mL/min/1.73 m^2]	2	88	Mean Difference (IV, Random, 95% CI)	-1.14 [-4.38, 2.11]
5 Creatinine clearance	3	170	Mean Difference (IV, Random, 95% CI)	-4.55 [-11.86, 2.75]
6 Log creatinine clearance	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
7 Serum creatinine	5	270	Mean Difference (IV, Random, 95% CI)	5.14 [-8.98, 19.26]
7.1 Short-term (< 4 weeks)	2	68	Mean Difference (IV, Random, 95% CI)	5.05 [-35.59, 45.70]
7.2 Long-term (≥ 4 weeks)	3	202	Mean Difference (IV, Random, 95% CI)	-0.05 [-12.73, 12.62]
8 Effective renal plasma flow	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
9 Filtration fraction (%)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
10 Weight	5	278	Mean Difference (IV, Random, 95% CI)	-1.46 [-4.55, 1.64]
10.1 Short-term (< 4 weeks)	2	68	Mean Difference (IV, Random, 95% CI)	-1.79 [-6.45, 2.87]
10.2 Long-term (≥ 4 weeks)	3	210	Mean Difference (IV, Random, 95% CI)	-1.19 [-5.34, 2.96]
11 Extracellular fluid volume	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
12 Presence of oedema	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
13 Plasma renin activity	2	142	Mean Difference (IV, Random, 95% CI)	1.08 [0.51, 1.65]
14 Serum aldosterone	2	142	Mean Difference (IV, Random, 95% CI)	6.20 [3.82, 8.58]
15 Brain natriuretic peptide (NT-Pro BNP)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
16 Reduction in antihypertensive dose	2	72	Risk Ratio (M-H, Random, 95% CI)	5.48 [1.27, 23.66]
17 Total cholesterol	3	210	Mean Difference (IV, Random, 95% CI)	-0.23 [-0.57, 0.10]
18 Symptomatic hypotension	2	144	Risk Ratio (M-H, Random, 95% CI)	5.95 [0.74, 48.11]

Comparison 2. CKD stage

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Sodium excretion	8	434	Mean Difference (IV, Random, 95% CI)	-105.86 [-119.20, -92.51]
1.1 CKD	6	362	Mean Difference (IV, Random, 95% CI)	-107.21 [-120.24, -94.18]
1.2 Dialysis	1	40	Mean Difference (IV, Random, 95% CI)	-52.0 [-113.06, 9.06]
1.3 Post-transplant	1	32	Mean Difference (IV, Random, 95% CI)	-131.0 [-194.21, -67.79]
2 Systolic blood pressure	8	434	Mean Difference (IV, Random, 95% CI)	-8.75 [-11.33, -6.16]
2.1 CKD	6	362	Mean Difference (IV, Random, 95% CI)	-7.96 [-10.74, -5.17]
2.2 Dialysis	1	40	Mean Difference (IV, Random, 95% CI)	-9.0 [-21.41, 3.41]
2.3 Post-transplant	1	32	Mean Difference (IV, Random, 95% CI)	-16.0 [-24.50, -7.50]
3 Diastolic blood pressure	8	434	Mean Difference (IV, Random, 95% CI)	-3.69 [-5.08, -2.29]
3.1 CKD	6	362	Mean Difference (IV, Random, 95% CI)	-3.40 [-4.86, -1.94]
3.2 Dialysis	1	40	Mean Difference (IV, Random, 95% CI)	-5.0 [-11.32, 1.32]
3.3 Post-transplant	1	32	Mean Difference (IV, Random, 95% CI)	-8.0 [-14.60, -1.40]

Analysis 1.1. Comparison 1 Net change with altering salt and change by duration, Outcome 1 Sodium excretion.

Review: Altered dietary salt intake for people with chronic kidney disease

Comparison: 1 Net change with altering salt and change by duration

Outcome: 1 Sodium excretion

Study or subgroup	Low salt N	Mean(SD)[mmol/d]	High salt N	Mean(SD)[mmol/d]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Short-term (< 4 weeks)							
Konishi 2001	38	48 (14)	38	166 (37)		23.2 %	-118.00 [-130.58, -105.42]
LowSALT CKD Study 2012	20	85 (35)	20	182 (54)		12.7 %	-97.00 [-125.20, -68.80]
Ruilope 1992a	14	72.6 (39.1)	14	214.4 (83.5)		6.1 %	-141.80 [-190.10, -93.50]
Subtotal (95% CI)	**72**		**72**			**41.9 %**	**-115.06 [-132.50, -97.62]**
Heterogeneity: Tau^2 = 87.21; Chi^2 = 2.94, df = 2 (P = 0.23); I^2 =32%							
Test for overall effect: Z = 12.93 (P < 0.00001)							
2 Long-term (≥ 4 weeks)							
de Brito-Ashurst 2013	25	-122.5 (40.4688)	23	-13 (12.113)		20.1 %	-109.50 [-126.12, -92.88]
DUAAAL Study 2011	52	106 (50.5)	52	189 (57.7)		17.1 %	-83.00 [-103.84, -62.16]
Fine 1997	20	155 (108)	20	207 (88)		4.1 %	-52.00 [-113.06, 9.06]
Keven 2006	18	106 (48)	14	237 (113)		3.9 %	-131.00 [-194.21, -67.79]
Vogt 2008	33	90 (57.4)	33	200 (57.4)		12.9 %	-110.00 [-137.70, -82.30]
Subtotal (95% CI)	**148**		**142**			**58.1 %**	**-99.11 [-117.31, -80.92]**
Heterogeneity: Tau^2 = 182.90; Chi^2 = 7.61, df = 4 (P = 0.11); I^2 =47%							
Test for overall effect: Z = 10.68 (P < 0.00001)							
Total (95% CI)	**220**		**214**			**100.0 %**	**-105.86 [-119.20, -92.51]**
Heterogeneity: Tau^2 = 158.74; Chi^2 = 14.21, df = 7 (P = 0.05); I^2 =51%							
Test for overall effect: Z = 15.55 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 1.54, df = 1 (P = 0.21), I^2 =35%							

Analysis 1.2. Comparison 1 Net change with altering salt and change by duration, Outcome 2 Systolic blood pressure.

Review: Altered dietary salt intake for people with chronic kidney disease

Comparison: 1 Net change with altering salt and change by duration

Outcome: 2 Systolic blood pressure

Study or subgroup	Low salt N	Mean(SD)[mm Hg]	High salt N	Mean(SD)[mm Hg]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Short-term (< 4 weeks)							
Konishi 2001	38	115 (11.2)	38	121.6 (13.1)		22.3 %	-6.60 [-12.08, -1.12]
LowSALT CKD Study 2012	20	144.9 (13.1)	20	154.6 (11.9)		11.1 %	-9.70 [-17.46, -1.94]
Ruilope 1992a	14	146.1 (20.2)	14	148 (21.2)		2.8 %	-1.90 [-17.24, 13.44]
Subtotal (95% CI)	**72**		**72**			**36.3 %**	**-7.18 [-11.48, -2.89]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.90$, df = 2 (P = 0.64); $I^2 = 0.0\%$							
Test for overall effect: Z = 3.28 (P = 0.0011)							
2 Long-term (≥ 4 weeks)							
de Brito-Ashurst 2013	25	-8.6 (6.9)	23	-0.6 (9.5)		29.9 %	-8.00 [-12.73, -3.27]
DUAAAL Study 2011	52	123 (16.6)	52	134 (20.2)		13.3 %	-11.00 [-18.11, -3.89]
Fine 1997	20	135 (19)	20	144 (21)		4.3 %	-9.00 [-21.41, 3.41]
Keven 2006	18	116 (11)	14	132 (13)		9.3 %	-16.00 [-24.50, -7.50]
Vogt 2008	33	137 (17.2)	33	143 (23)		7.0 %	-6.00 [-15.80, 3.80]
Subtotal (95% CI)	**148**		**142**			**63.7 %**	**-9.64 [-12.88, -6.40]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 3.29$, df = 4 (P = 0.51); $I^2 = 0.0\%$							
Test for overall effect: Z = 5.83 (P < 0.00001)							
Total (95% CI)	**220**		**214**			**100.0 %**	**-8.75 [-11.33, -6.16]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 5.00$, df = 7 (P = 0.66); $I^2 = 0.0\%$							
Test for overall effect: Z = 6.63 (P < 0.00001)							
Test for subgroup differences: $Chi^2 = 0.80$, df = 1 (P = 0.37), $I^2 = 0.0\%$							

Analysis 1.3. Comparison 1 Net change with altering salt and change by duration, Outcome 3 Diastolic blood pressure.

Review: Altered dietary salt intake for people with chronic kidney disease

Comparison: 1 Net change with altering salt and change by duration

Outcome: 3 Diastolic blood pressure

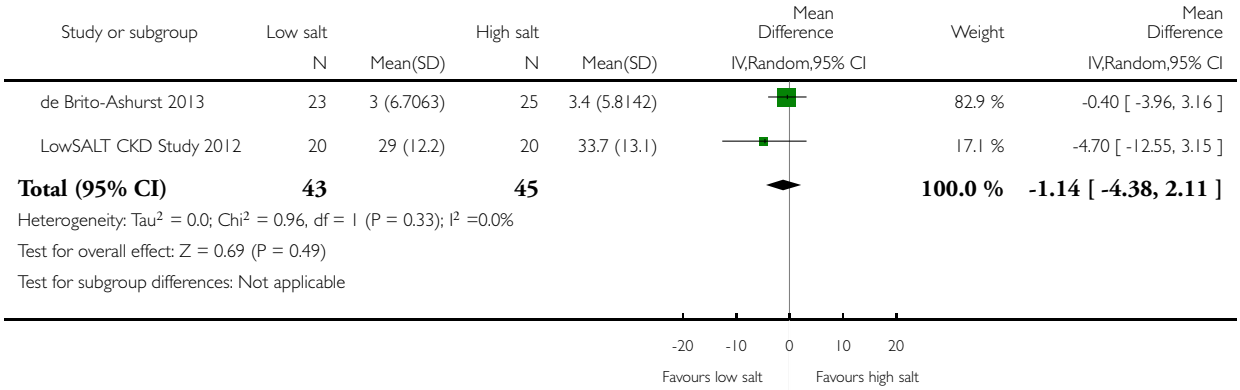
Study or subgroup	Low salt N	Low salt Mean(SD)[mm Hg]	High salt N	High salt Mean(SD)[mm Hg]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Short-term (< 4 weeks)							
Konishi 2001	38	75 (8)	38	79 (9)		13.2 %	-4.00 [-7.83, -0.17]
LowSALT CKD Study 2012	20	79.4 (9.4)	20	83.3 (9)		6.0 %	-3.90 [-9.60, 1.80]
Ruilope 1992a	14	90.3 (11.3)	14	90.3 (12.1)		2.6 %	0.0 [-8.67, 8.67]
Subtotal (95% CI)	**72**		**72**			**21.8 %**	**-3.50 [-6.48, -0.51]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.71$, df = 2 (P = 0.70); $I^2 = 0.0\%$							
Test for overall effect: Z = 2.30 (P = 0.022)							
2 Long-term (≥ 4 weeks)							
de Brito-Ashurst 2013	25	-4 (4.4)	23	-1 (2.1)		52.3 %	-3.00 [-4.93, -1.07]
DUAAAL Study 2011	52	73 (13)	52	80 (15)		6.7 %	-7.00 [-12.40, -1.60]
Fine 1997	20	77 (8)	20	82 (12)		4.9 %	-5.00 [-11.32, 1.32]
Keven 2006	18	72 (10)	14	80 (9)		4.5 %	-8.00 [-14.60, -1.40]
Vogt 2008	33	83 (6)	33	86 (11.5)		9.9 %	-3.00 [-7.43, 1.43]
Subtotal (95% CI)	**148**		**142**			**78.2 %**	**-3.75 [-5.33, -2.17]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 3.83$, df = 4 (P = 0.43); $I^2 = 0.0\%$							
Test for overall effect: Z = 4.67 (P < 0.00001)							
Total (95% CI)	**220**		**214**			**100.0 %**	**-3.70 [-5.09, -2.30]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 4.56$, df = 7 (P = 0.71); $I^2 = 0.0\%$							
Test for overall effect: Z = 5.20 (P < 0.00001)							
Test for subgroup differences: $Chi^2 = 0.02$, df = 1 (P = 0.88), $I^2 = 0.0\%$							

Analysis 1.4. Comparison 1 Net change with altering salt and change by duration, Outcome 4 eGFR [mL/min/1.73 m2].

Review: Altered dietary salt intake for people with chronic kidney disease

Comparison: 1 Net change with altering salt and change by duration

Outcome: 4 eGFR [mL/min/1.73 m^2]

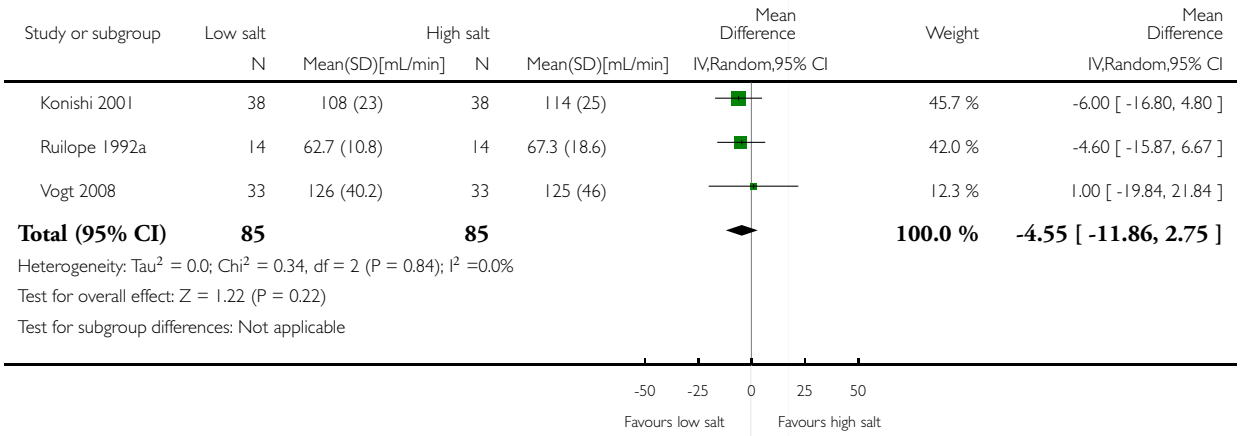


Analysis 1.5. Comparison 1 Net change with altering salt and change by duration, Outcome 5 Creatinine clearance.

Review: Altered dietary salt intake for people with chronic kidney disease

Comparison: 1 Net change with altering salt and change by duration

Outcome: 5 Creatinine clearance



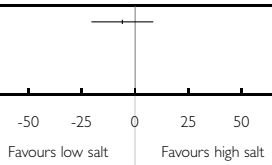
Analysis 1.6. Comparison 1 Net change with altering salt and change by duration, Outcome 6 Log creatinine clearance.

Review: Altered dietary salt intake for people with chronic kidney disease

Comparison: 1 Net change with altering salt and change by duration

Outcome: 6 Log creatinine clearance

Study or subgroup	Low salt		High salt		Mean Difference	Mean Difference
	N	Mean(SD)[mL/min]	N	Mean(SD)[mL/min]	IV,Random,95% CI	IV,Random,95% CI
DUAAAL Study 2011	52	66 (35)	52	72 (40.5)		-6.00 [-20.55, 8.55]

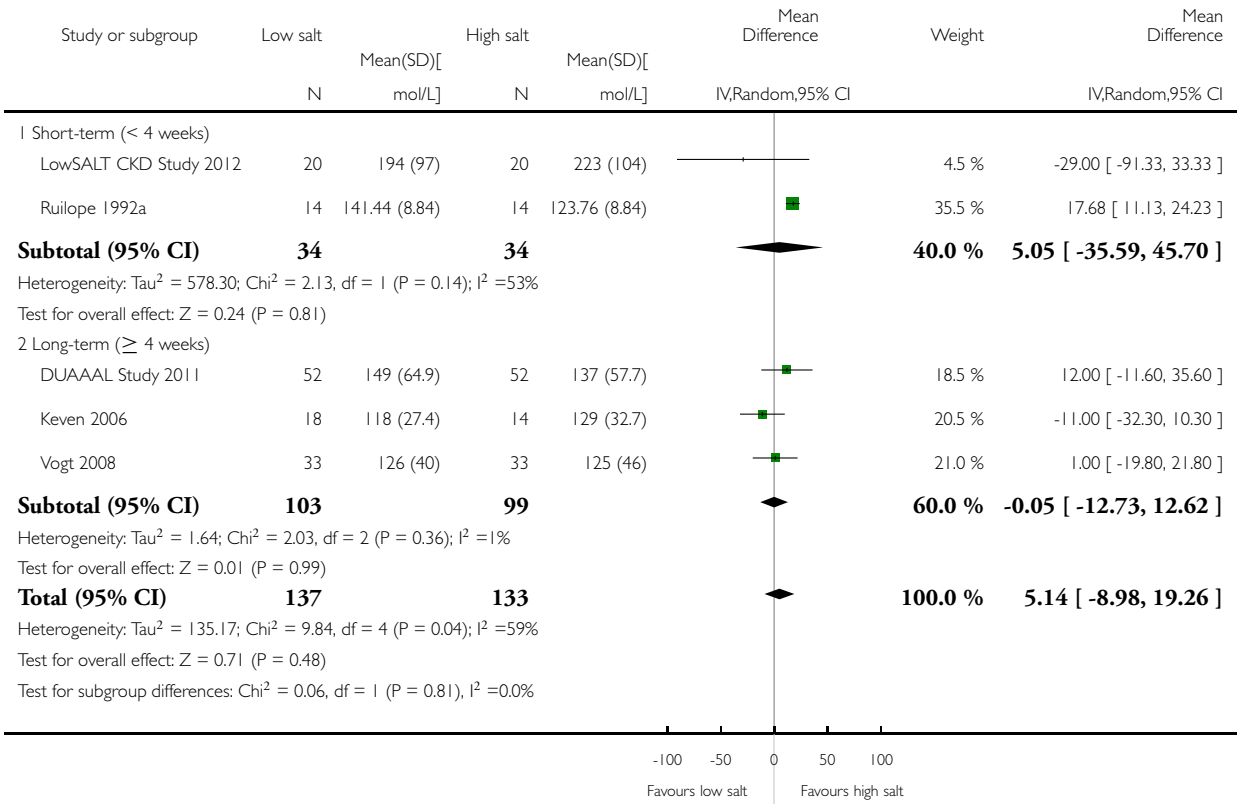


Analysis 1.7. Comparison 1 Net change with altering salt and change by duration, Outcome 7 Serum creatinine.

Review: Altered dietary salt intake for people with chronic kidney disease

Comparison: 1 Net change with altering salt and change by duration

Outcome: 7 Serum creatinine



Analysis 1.8. Comparison 1 Net change with altering salt and change by duration, Outcome 8 Effective renal plasma flow.

Review: Altered dietary salt intake for people with chronic kidney disease

Comparison: 1 Net change with altering salt and change by duration

Outcome: 8 Effective renal plasma flow

Study or subgroup	Low salt		High salt		Mean Difference	Mean Difference
	N	Mean(SD)[mL/min]	N	Mean(SD)[mL/min]	IV,Random,95% CI	IV,Random,95% CI
Konishi 2001	38	516 (199)	38	549 (192)		-33.00 [-120.92, 54.92]

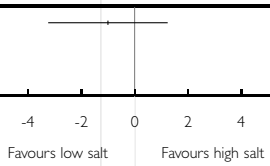
Analysis 1.9. Comparison 1 Net change with altering salt and change by duration, Outcome 9 Filtration fraction (%).

Review: Altered dietary salt intake for people with chronic kidney disease

Comparison: 1 Net change with altering salt and change by duration

Outcome: 9 Filtration fraction (%)

Study or subgroup	Low salt		High salt		Mean Difference	Mean Difference
	N	Mean(SD)[%]	N	Mean(SD)[%]	IV,Random,95% CI	IV,Random,95% CI
Konishi 2001	38	22 (5)	38	23 (5)		-1.00 [-3.25, 1.25]

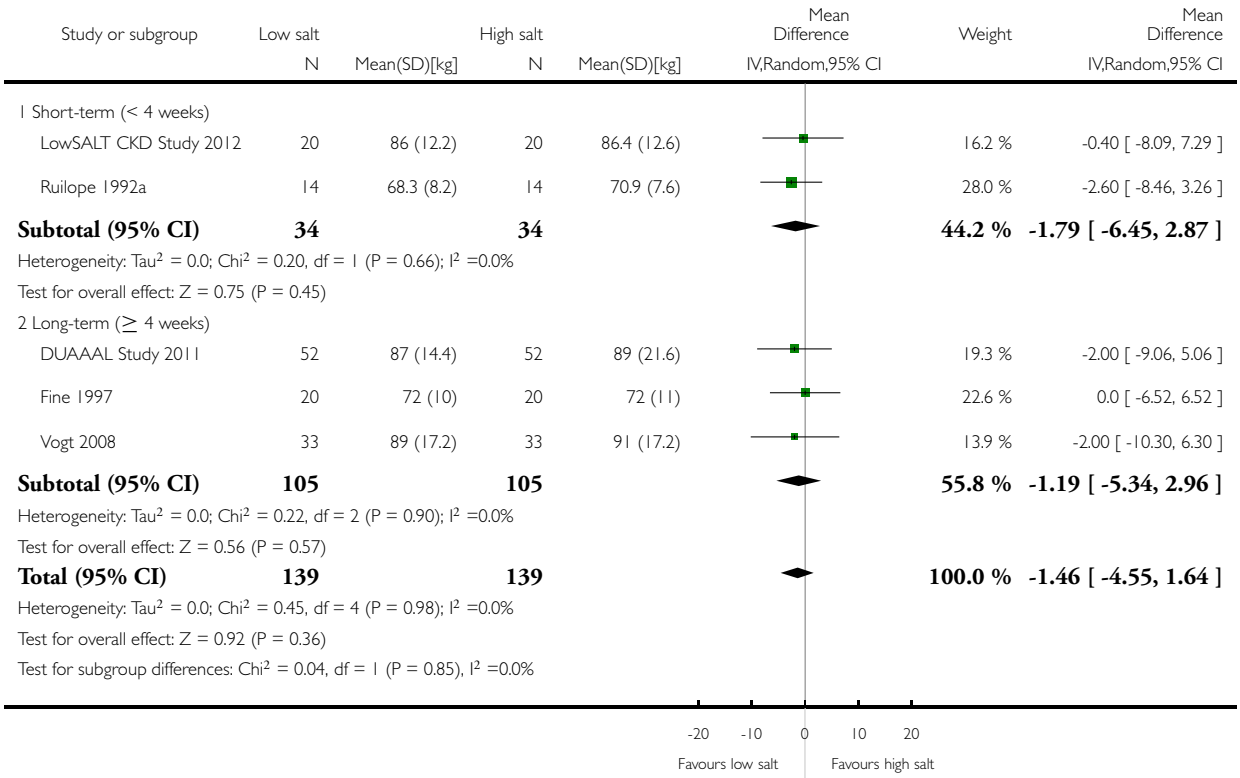


Analysis 1.10. Comparison 1 Net change with altering salt and change by duration, Outcome 10 Weight.

Review: Altered dietary salt intake for people with chronic kidney disease

Comparison: 1 Net change with altering salt and change by duration

Outcome: 10 Weight



Analysis 1.11. Comparison 1 Net change with altering salt and change by duration, Outcome 11 Extracellular fluid volume.

Review: Altered dietary salt intake for people with chronic kidney disease

Comparison: 1 Net change with altering salt and change by duration

Outcome: 11 Extracellular fluid volume

Study or subgroup	Low salt N	Mean(SD)[L]	High salt N	Mean(SD)[L]	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
LowSALT CKD Study 2012	20	19.2 (3.7)	20	20 (3.7)		-0.80 [-3.09, 1.49]

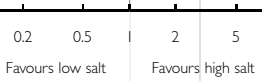
Analysis 1.12. Comparison 1 Net change with altering salt and change by duration, Outcome 12 Presence of oedema.

Review: Altered dietary salt intake for people with chronic kidney disease

Comparison: 1 Net change with altering salt and change by duration

Outcome: 12 Presence of oedema

Study or subgroup	Low salt n/N	High salt n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
DUAAAL Study 2011	8/52	18/52		0.44 [0.21, 0.93]

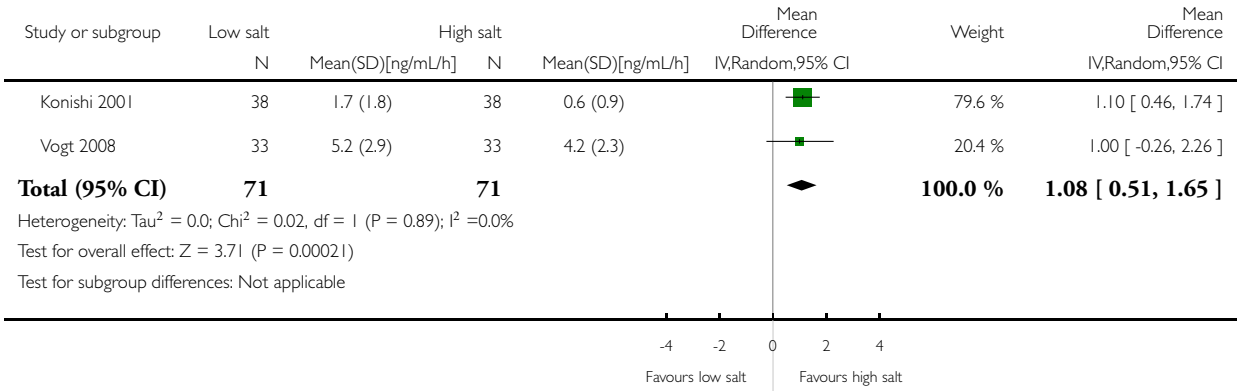


Analysis 1.13. Comparison 1 Net change with altering salt and change by duration, Outcome 13 Plasma renin activity.

Review: Altered dietary salt intake for people with chronic kidney disease

Comparison: 1 Net change with altering salt and change by duration

Outcome: 13 Plasma renin activity

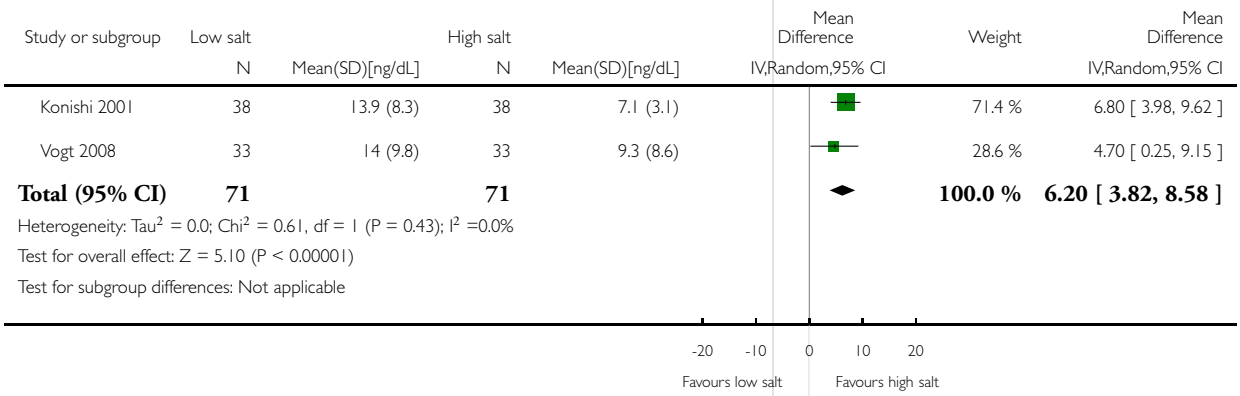


Analysis 1.14. Comparison 1 Net change with altering salt and change by duration, Outcome 14 Serum aldosterone.

Review: Altered dietary salt intake for people with chronic kidney disease

Comparison: 1 Net change with altering salt and change by duration

Outcome: 14 Serum aldosterone



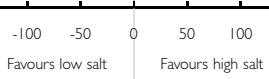
Analysis 1.15. Comparison 1 Net change with altering salt and change by duration, Outcome 15 Brain natriuretic peptide (NT-Pro BNP).

Review: Altered dietary salt intake for people with chronic kidney disease

Comparison: 1 Net change with altering salt and change by duration

Outcome: 15 Brain natriuretic peptide (NT-Pro BNP)

Study or subgroup	Low salt		High salt		Mean Difference	Mean Difference
	N	Mean(SD)[pg/mL]	N	Mean(SD)[pg/mL]	IV,Random,95% CI	IV,Random,95% CI
Vogt 2008	32	62 (41)	32	91 (60)		-29.00 [-54.18, -3.82]



Analysis 1.16. Comparison 1 Net change with altering salt and change by duration, Outcome 16 Reduction in antihypertensive dose.

Review: Altered dietary salt intake for people with chronic kidney disease

Comparison: 1 Net change with altering salt and change by duration

Outcome: 16 Reduction in antihypertensive dose

Study or subgroup	Low salt n/N	High salt n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Keven 2006	7/14	1/18		54.8 %	9.00 [1.25, 64.89]
LowSALT CKD Study 2012	3/20	1/20		45.2 %	3.00 [0.34, 26.45]
Total (95% CI)	**34**	**38**		**100.0 %**	**5.48 [1.27, 23.66]**

Total events: 10 (Low salt), 2 (High salt)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.54$, df = 1 (P = 0.46); $I^2 = 0.0\%$

Test for overall effect: Z = 2.28 (P = 0.023)

Test for subgroup differences: Not applicable

Analysis 1.17. Comparison 1 Net change with altering salt and change by duration, Outcome 17 Total cholesterol.

Review: Altered dietary salt intake for people with chronic kidney disease

Comparison: 1 Net change with altering salt and change by duration

Outcome: 17 Total cholesterol

Study or subgroup	Low salt N	Mean(SD)[mmol/L]	High salt N	Mean(SD)[mmol/L]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
DUAAAL Study 2011	52	4.8 (0.7)	52	5.1 (1.4)		61.0 %	-0.30 [-0.73, 0.13]
LowSALT CKD Study 2012	20	4.09 (1.43)	20	4.12 (1.26)		15.8 %	-0.03 [-0.87, 0.81]
Vogt 2008	33	5.9 (1.1)	33	6.1 (1.7)		23.1 %	-0.20 [-0.89, 0.49]
Total (95% CI)	**105**		**105**			**100.0 %**	**-0.23 [-0.57, 0.10]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.33$, df = 2 (P = 0.85); $I^2 = 0.0\%$

Test for overall effect: Z = 1.38 (P = 0.17)

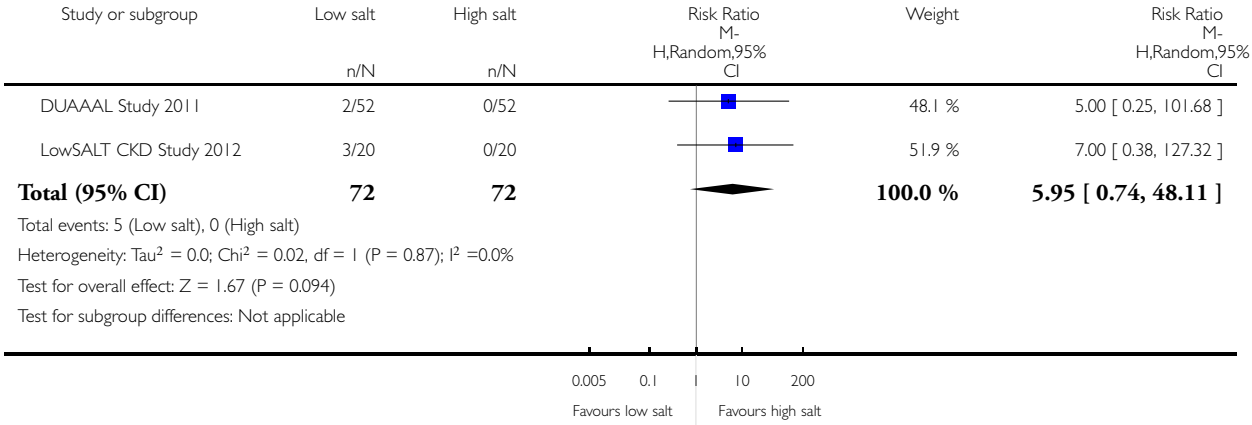
Test for subgroup differences: Not applicable

Analysis 1.18. Comparison 1 Net change with altering salt and change by duration, Outcome 18 Symptomatic hypotension.

Review: Altered dietary salt intake for people with chronic kidney disease

Comparison: 1 Net change with altering salt and change by duration

Outcome: 18 Symptomatic hypotension

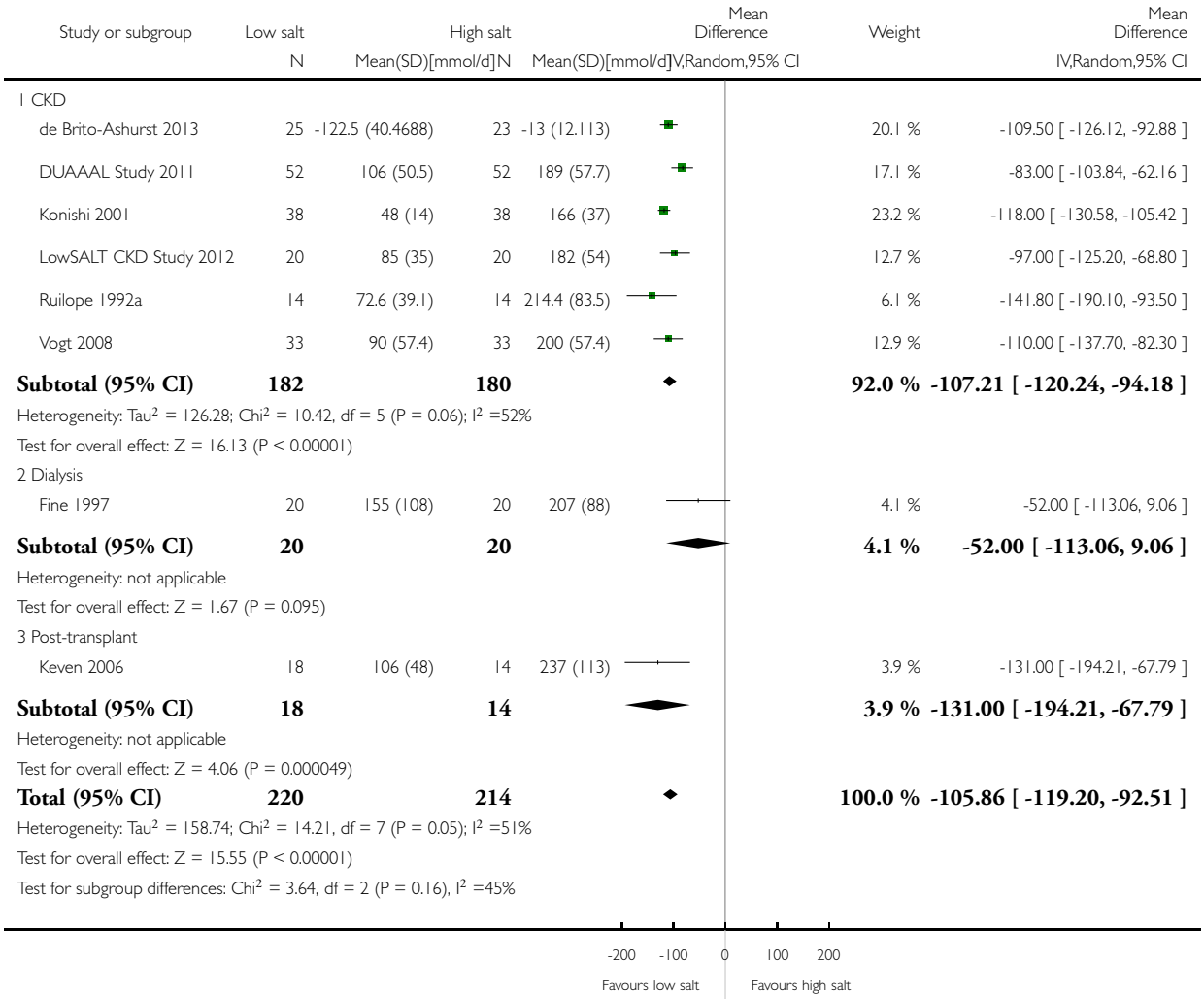


Analysis 2.1. Comparison 2 CKD stage, Outcome 1 Sodium excretion.

Review: Altered dietary salt intake for people with chronic kidney disease

Comparison: 2 CKD stage

Outcome: 1 Sodium excretion



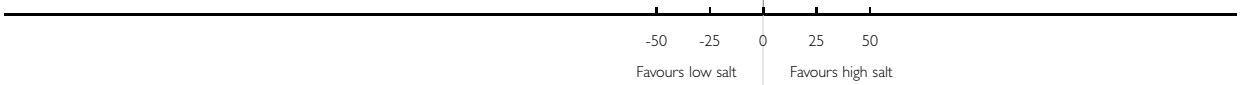
Analysis 2.2. Comparison 2 CKD stage, Outcome 2 Systolic blood pressure.

Review: Altered dietary salt intake for people with chronic kidney disease

Comparison: 2 CKD stage

Outcome: 2 Systolic blood pressure

Study or subgroup	Low salt N	Low salt Mean(SD)[mm Hg]	High salt N	High salt Mean(SD)[mm Hg]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 CKD							
Ruilope 1992a	14	146.1 (20.2)	14	148 (21.2)		2.8 %	-1.90 [-17.24, 13.44]
Vogt 2008	33	137 (17.2)	33	143 (23)		7.0 %	-6.00 [-15.80, 3.80]
LowSALT CKD Study 2012	20	144.9 (13.1)	20	154.6 (11.9)		11.1 %	-9.70 [-17.46, -1.94]
DUAAAL Study 2011	52	123 (16.6)	52	134 (20.2)		13.3 %	-11.00 [-18.11, -3.89]
Konishi 2001	38	115 (11.2)	38	121.6 (13.1)		22.3 %	-6.60 [-12.08, -1.12]
de Brito-Ashurst 2013	25	-8.6 (6.9)	23	-0.6 (9.5)		29.9 %	-8.00 [-12.73, -3.27]
Subtotal (95% CI)	**182**		**180**			**86.4 %**	**-7.96 [-10.74, -5.17]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.89$, df = 5 (P = 0.86); $I^2 = 0.0\%$							
Test for overall effect: Z = 5.60 (P < 0.00001)							
2 Dialysis							
Fine 1997	20	135 (19)	20	144 (21)		4.3 %	-9.00 [-21.41, 3.41]
Subtotal (95% CI)	**20**		**20**			**4.3 %**	**-9.00 [-21.41, 3.41]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.42 (P = 0.16)							
3 Post-transplant							
Keven 2006	18	116 (11)	14	132 (13)		9.3 %	-16.00 [-24.50, -7.50]
Subtotal (95% CI)	**18**		**14**			**9.3 %**	**-16.00 [-24.50, -7.50]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.69 (P = 0.00022)							
Total (95% CI)	**220**		**214**			**100.0 %**	**-8.75 [-11.33, -6.16]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 5.00$, df = 7 (P = 0.66); $I^2 = 0.0\%$							
Test for overall effect: Z = 6.63 (P < 0.00001)							
Test for subgroup differences: $Chi^2 = 3.11$, df = 2 (P = 0.21), $I^2 = 36\%$							

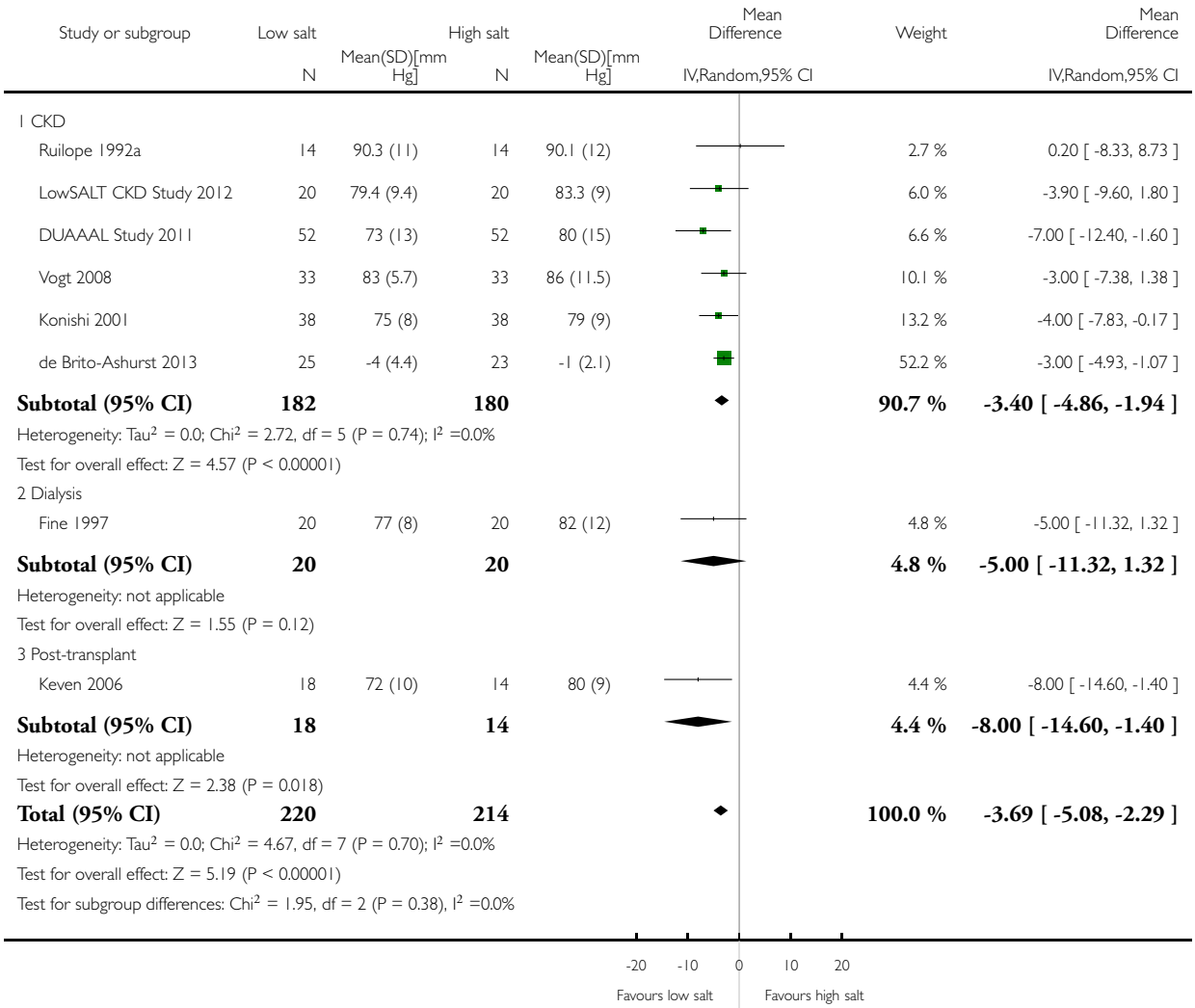


Analysis 2.3. Comparison 2 CKD stage, Outcome 3 Diastolic blood pressure.

Review: Altered dietary salt intake for people with chronic kidney disease

Comparison: 2 CKD stage

Outcome: 3 Diastolic blood pressure



ADDITIONAL TABLES

Table 1. Measurement of urinary protein in included studies

Study	Proteinuria measurement	High salt	Low salt	Reduction	Significance
DUAAAL Study 2011	Protein; geometric mean (95% CI) mg/d; 24 hour urine	1680 (1310 to 2140)	850 (660 to 1100)	49%	P < 0.001
	Protein to creatinine ratio; geometric mean (95% CI) mg/mg	1.2 (0.9 to 1.5)	0.6 (0.4 to 0.8)	51%	P < 0.01
Konishi 2001	Protein; median (IQR) mg/d; 24 hour urine	509 (207 to 1916)	372 (142 to 1134)	27%	P = 0.004
LowSALT CKD Study 2012	Protein; median (IQR) mg/d; 24 hour urine	835 (185 to 1600)	493 (123 to 1300)	40%	P < 0.01
	Albumin; median (IQR) mg/d; 24 hour urine	291 (40 to 1000)	143 (16 to 889)	51%	P < 0.001
	Protein: creatinine; median (IQR) g/mol creatinine; 24 hour urine	68 (23 to 164)	41 (17 to 126)	60%	P < 0.05
	Albumin:creatinine median (IQR) g/mol creatinine; 24 hour urine	27 (5 to 127)	9 (2 to 82)	67%	P < 0.05
Vogt 2008	Protein; mean (SE) mg/d; 24 hour urine	3800 (400)	3000 (300)	21%	P < 0.05
	Protein concentration; mean (SE) ng/mL	591 (78)	518 (85)	12%	P < 0.05
	Protein to creatinine ratio; mean (SE) mg/mg	2.45 (0.27)	2.10 (0.36)	14%	P < 0.05

CI - confidence interval; IQR - interquartile range; SE - standard error

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. sodium chloride:kw 2. ((sodium or salt) near/5 (low or high or alter* or reduce* or reducing or reduction or restrict* or intake* or diet* or increas* or decreas* or change* or changing)):ti,ab,kw 3. (#1 OR #2) 4. "renal replacement therapy":ti,ab,kw 5. (h*emodialysis or h*emofiltration or h*emodiafiltration):ti,ab,kw 6. dialysis:ti,ab,kw 7. (CAPD or CCPD or APD):ti,ab,kw 8. ("kidney disease" or "kidney diseases" or "renal disease" or "renal diseases"):ti,ab,kw 9. (chronic next kidney or chronic next renal):ti,ab,kw 10. ((kidney next failure) or (renal next failure)):ti,ab,kw 11. ("end-stage kidney" or "end-stage renal" or "endstage kidney" or "endstage renal"):ti,ab,kw 12. (ESRF or ESKF or ESRD or ESKD):ti,ab,kw 13. (CKF or CKD or CRF or CRD):ti,ab,kw 14. (predialysis or "pre-dialysis"):ti,ab,kw 15. (nephropath* or nephrit* or glomerulo*):ti,ab,kw 16. (glomerular next disease*):ti,ab,kw 17. (#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16) 18. (#3 AND #17)
MEDLINE	1. exp Sodium Chloride/ 2. Diet, Sodium Restricted/ 3. ((sodium or salt) adj5 (low or high or alter* or reduce* or reduction or restrict* or intake* or diet* or increas* or decreas* or change* or changing)).tw. 4. or/1-3 5. Renal Replacement Therapy/ 6. exp Renal Dialysis/ 7. (hemodialysis or haemodialysis).tw. 8. (hemofiltration or haemofiltration).tw. 9. (hemodiafiltration or haemodiafiltration).tw. 10. dialysis.tw. 11. (CAPD or CCPD or APD).tw. 12. exp Kidney Diseases/ 13. (kidney disease* or renal disease*).tw. 14. (nephropath* or nephrit* or glomerulo* or glomerular disease*).tw. 15. (end-stage renal or end-stage kidney or endstage renal or endstage kidney).tw. 16. (ESRF or ESKF or ESRD or ESKD).tw. 17. (chronic kidney or chronic renal).tw. 18. (CKF or CKD or CRF or CRD).tw. 19. (predialysis or pre-dialysis).tw. 20. or/5-19 21. and/4,20

(*Continued*)

EMBASE	1. Sodium Chloride/ 2. Salt Intake/ 3. Sodium Restriction/ 4. Sodium Intake/ 5. ((sodium or salt) adj5 (low or high or alter* or reduce* or reduction or restrict* or intake* or diet* or increas* or decreas* or change* or changing)).tw. 6. or/1-5 7. exp Renal Replacement Therapy/ 8. (hemodialysis or haemodialysis).tw. 9. (hemofiltration or haemofiltration).tw. 10. (hemodiafiltration or haemodiafiltration).tw. 11. dialysis.tw. 12. (CAPD or CCPD or APD).tw. 13. exp Kidney Disease/ 14. (kidney disease* or renal disease*).tw. 15. (nephrop* or nephrit* or glomerulo* or glomerular disease*).tw. 16. (chronic kidney or chronic renal).tw. 17. (CKF or CKD or CRF or CRD).tw. 18. (end-stage renal or end-stage kidney or endstage renal or endstage kidney).tw. 19. (ESRF or ESKF or ESRD or ESKD).tw. 20. (predialysis or pre-dialysis).tw. 21. or/7-20 22. and/6,21

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	*Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random)
	High risk of bias: Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention
	Unclear: Insufficient information about the sequence generation process to permit judgement
Allocation concealment Selection bias (biased allocation to interventions) due to inade-	*Low risk of bias:* Randomisation method described that would not allow investigator/participant to know or influence intervention

(*Continued*)

quate concealment of allocations prior to assignment	group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes)
	High risk of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure
	Unclear: Randomisation stated but no information on method used is available
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken
	High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding
	Unclear: Insufficient information to permit judgement
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors	*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken
	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding
	Unclear: Insufficient information to permit judgement
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data	*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome

(*Continued*)

	data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods
	High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation
	Unclear: Insufficient information to permit judgement
Selective reporting Reporting bias due to selective outcome reporting	*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon)
	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study
	Unclear: Insufficient information to permit judgement
Other bias Bias due to problems not covered elsewhere in the table	*Low risk of bias:* The study appears to be free of other sources of bias.

(*Continued*)

	High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem
	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias

CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: EM, KC, JB, DM
2. Study selection: EM, KC, JB
3. Extract data from studies: EM, KC
4. Enter data into RevMan: EM
5. Carry out the analysis: EM
6. Interpret the analysis: EM, KC, JB, DM
7. Draft the final review: EM, KC, JB, DM
8. Disagreement resolution: DM
9. Update the review: EM, KC

DECLARATIONS OF INTEREST

- Emma J McMahon: none known
- Katrina L Campbell: none known
- Judith D Bauer: none known
- David W Mudge: none known

SOURCES OF SUPPORT

Internal sources

- Princess Alexandra Hospital, Australia.

Salary (DM, KC)

- University of Queensland, Australia.

Salary (JB, EH)

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The outcome sodium excretion has been included.

INDEX TERMS

Medical Subject Headings (MeSH)

*Diet, Sodium-Restricted; Antihypertensive Agents [administration & dosage]; Blood Pressure [*drug effects; physiology]; Edema [prevention & control]; Hypertension [drug therapy]; Randomized Controlled Trials as Topic; Renal Insufficiency, Chronic [*diet therapy]; Selection Bias; Sodium Chloride, Dietary [*administration & dosage]

MeSH check words

Humans