Cochrane
Library

Cochrane Database of Systematic Reviews

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

McMahon EJ, Campbell KL, Bauer JD, Mudge DW, Kelly JT

McMahon EJ, Campbell KL, Bauer JD, Mudge DW, Kelly JT.
Altered dietary salt intake for people with chronic kidney disease.
Cochrane Database of Systematic Reviews 2021, Issue 6. Art. No.: CD010070.
DOI: [10.1002/14651858.CD010070.pub3](https://doi.org/10.1002/14651858.CD010070.pub3).

www.cochranelibrary.com

TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS	3
BACKGROUND	5
OBJECTIVES	5
METHODS	5
RESULTS	8
Figure 1.	8
Figure 2.	11
Figure 3.	12
Figure 4.	16
Figure 5.	17
Figure 6.	18
DISCUSSION	18
AUTHORS' CONCLUSIONS	21
ACKNOWLEDGEMENTS	22
REFERENCES	23
CHARACTERISTICS OF STUDIES	31
DATA AND ANALYSES	74
Analysis 1.1. Comparison 1: CKD stage, Outcome 1: Sodium intake/excretion	77
Analysis 1.2. Comparison 1: CKD stage, Outcome 2: Systolic blood pressure	78
Analysis 1.3. Comparison 1: CKD stage, Outcome 3: Diastolic blood pressure	79
Analysis 1.4. Comparison 1: CKD stage, Outcome 4: Proteinuria [ln mg/d]	79
Analysis 1.5. Comparison 1: CKD stage, Outcome 5: Albuminuria [ln mg/d]	80
Analysis 1.6. Comparison 1: CKD stage, Outcome 6: eGFR [mL/min/1.73 m ²]	80
Analysis 1.7. Comparison 1: CKD stage, Outcome 7: Creatinine clearance	81
Analysis 1.8. Comparison 1: CKD stage, Outcome 8: Serum creatinine	81
Analysis 1.9. Comparison 1: CKD stage, Outcome 9: Filtration fraction	81
Analysis 1.10. Comparison 1: CKD stage, Outcome 10: Weight	82
Analysis 1.11. Comparison 1: CKD stage, Outcome 11: Inter-dialytic weight gain	82
Analysis 1.12. Comparison 1: CKD stage, Outcome 12: Extracellular fluid volume	83
Analysis 1.13. Comparison 1: CKD stage, Outcome 13: Presence of oedema	83
Analysis 1.14. Comparison 1: CKD stage, Outcome 14: Plasma renin activity	83
Analysis 1.15. Comparison 1: CKD stage, Outcome 15: Aldosterone (plasma or serum)	84
Analysis 1.16. Comparison 1: CKD stage, Outcome 16: Reduction in antihypertensive dose	84
Analysis 1.17. Comparison 1: CKD stage, Outcome 17: Symptomatic hypotension	85
Analysis 1.18. Comparison 1: CKD stage, Outcome 18: Total cholesterol	85
Analysis 2.1. Comparison 2: Duration, Outcome 1: Sodium intake/excretion	87
Analysis 2.2. Comparison 2: Duration, Outcome 2: Systolic blood pressure	87
Analysis 2.3. Comparison 2: Duration, Outcome 3: Diastolic blood pressure	88
Analysis 2.4. Comparison 2: Duration, Outcome 4: Creatinine clearance	88
Analysis 2.5. Comparison 2: Duration, Outcome 5: Serum creatinine	89
Analysis 2.6. Comparison 2: Duration, Outcome 6: Weight	89
APPENDICES	89
WHAT'S NEW	93
HISTORY	93
CONTRIBUTIONS OF AUTHORS	93
DECLARATIONS OF INTEREST	94
SOURCES OF SUPPORT	94
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	94

INDEX TERMS	94
-------------------	----

[Intervention Review]

Altered dietary salt intake for people with chronic kidney disease

Emma J McMahon¹, Katrina L Campbell^{2,3}, Judith D Bauer⁴, David W Mudge⁵, Jaimon T Kelly²

¹Wellbeing and Preventable Chronic Diseases Division, Menzies School of Health Research, Charles Darwin University, Brisbane, Australia. ²Centre for Applied Health Economics, Menzies Health Institute Queensland, Griffith University, Nathan, Australia. ³Healthcare Excellence and Innovation, Metro North Hospital and Health Service, Herston, Australia. ⁴School of Human Movement and Nutrition Sciences, The University of Queensland, St Lucia, Australia. ⁵Department of Nephrology, University of Queensland at Princess Alexandra Hospital, Woolloongabba, Australia

Contact address: Emma J McMahon, e.j.mcmahon@outlook.com.

Editorial group: Cochrane Kidney and Transplant Group.

Publication status and date: New search for studies and content updated (conclusions changed), published in Issue 6, 2021.

Citation: McMahon EJ, Campbell KL, Bauer JD, Mudge DW, Kelly JT. Altered dietary salt intake for people with chronic kidney disease. *Cochrane Database of Systematic Reviews* 2021, Issue 6. Art. No.: CD010070. DOI: [10.1002/14651858.CD010070.pub3](https://doi.org/10.1002/14651858.CD010070.pub3).

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

Evidence indicates that reducing dietary salt may reduce the incidence of heart disease and delay decline in kidney function in people with chronic kidney disease (CKD). This is an update of a review first published in 2015.

Objectives

To evaluate the benefits and harms of altering dietary salt for adults with CKD.

Search methods

We searched the Cochrane Kidney and Transplant Register of Studies up to 6 October 2020 through contact with the Information Specialist using search terms relevant to this review. Studies in the Register are identified through searches of CENTRAL, MEDLINE, and EMBASE, conference proceedings, the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Selection criteria

Randomised controlled trials comparing two or more levels of salt intake in adults with any stage of CKD.

Data collection and analysis

Two authors independently assessed studies for eligibility, conducted risk of bias evaluation and evaluated confidence in the evidence using GRADE. Results were summarised using random effects models as risk ratios (RR) for dichotomous outcomes or mean differences (MD) for continuous outcomes, with 95% confidence intervals (CI).

Main results

We included 21 studies (1197 randomised participants), 12 in the earlier stages of CKD (779 randomised participants), seven in dialysis (363 randomised participants) and two in post-transplant (55 randomised participants). Selection bias was low in seven studies, high in one and unclear in 13. Performance and detection biases were low in four studies, high in two, and unclear in 15. Attrition and reporting biases were low in 10 studies, high in three and unclear in eight.

Because duration of the included studies was too short (1 to 36 weeks) to test the effect of salt restriction on endpoints such as death, cardiovascular events or CKD progression, changes in salt intake on blood pressure and other secondary risk factors were examined.

Reducing salt by mean -73.51 mmol/day (95% CI -92.76 to -54.27), equivalent to 4.2 g or 1690 mg sodium/day, reduced systolic/diastolic blood pressure by -6.91/-3.91 mm Hg (95% CI -8.82 to -4.99/-4.80 to -3.02; 19 studies, 1405 participants; high certainty evidence). Albuminuria was reduced by 36% (95% CI 26 to 44) in six studies, five of which were carried out in people in the earlier stages of CKD (MD -0.44, 95% CI -0.58 to -0.30; 501 participants; high certainty evidence). The evidence is very uncertain about the effect of lower salt intake on weight, as the weight change observed (-1.32 kg, 95% CI -1.94 to -0.70; 12 studies, 759 participants) may have been due to fluid volume, lean tissue, or body fat. Lower salt intake may reduce extracellular fluid volume in the earlier stages of CKD (-0.87 L, 95% CI -1.17 to -0.58; 3 studies; 187 participants; low certainty evidence). The evidence is very uncertain about the effect of lower salt intake on reduction in antihypertensive dose (RR 2.45, 95% CI 0.98 to 6.08; 8 studies; 754 participants). Lower salt intake may lead to symptomatic hypotension (RR 6.70, 95% CI 2.40 to 18.69; 6 studies; 678 participants; moderate certainty evidence). Data were sparse for other types of adverse events.

Authors' conclusions

We found high certainty evidence that salt reduction reduced blood pressure in people with CKD, and albuminuria in people with earlier stage CKD in the short-term. If such reductions could be maintained long-term, this effect may translate to clinically significant reductions in CKD progression and cardiovascular events. Research into the long-term effects of sodium-restricted diet for people with CKD is warranted.

PLAIN LANGUAGE SUMMARY

Altered dietary salt intake for adults with chronic kidney disease

What is the issue?

People with chronic kidney disease (CKD) have a reduced kidney function that persists over time. People with CKD are at increased risk of heart disease and worsening kidney function which can lead to the need for dialysis or kidney transplantation to survive. 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 and fluid overload. Therefore reducing salt intake may help reduce risk of heart disease and preserve kidney function. We aimed to assess the benefits and harms of reducing salt intake for people with CKD.

What did we do?

We searched the evidence up to October 2020 to find randomised controlled trials comparing two or more levels of salt intake in adults with CKD, including those in the earlier stages of CKD, those treated with dialysis, and those who had received a kidney transplant.

What did we find?

We found 21 studies that included 1197 adults with CKD (725 in low salt and 725 people in high salt group). Study participants included adults who were in the early stages of CKD (779 people in 12 studies), adults who were on dialysis (363 people in seven studies), and adult kidney transplant recipients (55 people in two studies). The average study duration was seven weeks, ranging from one to 36 weeks. We did not find any studies that measured the effect on the incidence of death, heart disease, or need for dialysis or kidney transplantation. Instead, we found studies that measured risk factors for these outcomes.

We found that lowering salt intake reduced blood pressure and protein in the urine in people with CKD. Lowering salt intake may reduce extracellular fluid volume in the earlier stages of CKD. The evidence is very uncertain about the effects on body weight and reductions in blood pressure medications. The effect on kidney function measures was mixed. Lower salt intake may increase dizziness due to low blood pressure.

Conclusions

We found that reducing salt intake reduced risk factors for heart disease and worsening kidney function in people with CKD in the short term. We could not find evidence of the longer term effects of reducing salt intake, which meant we were unable to determine the direct effects of salt intake on death, heart disease, or need for dialysis or kidney transplantation. We need more high quality research in these areas.

SUMMARY OF FINDINGS

Summary of findings 1. Lower salt intake versus higher salt intake for participants with chronic kidney disease

Lower salt intake versus higher salt intake for participants with CKD

Patient or population: participants with CKD

Setting: any

Intervention: lower salt intake

Comparison: higher salt intake

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with higher salt intake	Risk with lower salt intake			
Systolic blood pressure	The mean SBP in the lower salt intake group was 6.91 mm Hg lower (8.82 lower to 4.99 lower) than the higher salt intake group		-	1261 (19)	⊕⊕⊕⊕ HIGH
Diastolic blood pressure	The mean DBP in the lower salt intake group was 3.91 mm Hg lower (4.8 lower to 3.02 lower) than the higher salt intake group		-	1257 (19)	⊕⊕⊕⊕ HIGH
Albuminuria	The mean albuminuria in the lower salt intake group was 36% ¹ lower (44% lower to 26% lower) than the higher salt intake group		-	501 (6)	⊕⊕⊕⊕ HIGH
Extracellular fluid volume	The mean extracellular fluid volume in the lower salt intake group was 0.87 L lower (1.17 lower to 0.58 lower) than the higher salt intake group		-	187 (3)	⊕⊕⊕⊖ LOW ^{2 3}
Weight	The mean weight in the lower salt intake group was 1.32 kg lower (1.94 lower to 0.7 lower) than the higher salt intake group		-	759 (12)	⊕⊕⊕⊖ VERY LOW ^{2 4 5}
Reduction in anti-hypertensive dose	24 per 1,000	58 per 1,000 (23 to 144)	RR 2.45 (0.98 to 6.08)	664 (7)	⊕⊕⊕⊖ VERY LOW ^{6 7}
Symptomatic hypotension	8 per 1,000	56 per 1,000 (20 to 156)	RR 6.70 (2.40 to 18.69)	478 (6)	⊕⊕⊕⊖ MODERATE ³

***The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CKD: chronic kidney disease; **CI:** confidence interval; **SBP:** systolic blood pressure; **DBP:** diastolic blood pressure; **RR:** risk ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

- 1 Albuminuria was analysed as log-transformed (mg/day) and expressed as a percentage reduction
- 2 Evidence certainty downgraded one level for uncertain or high risk of bias
- 3 Evidence certainty downgraded one level for few events and/or participants across all studies
- 4 Evidence certainty downgraded one level for moderate heterogeneity
- 5 Evidence certainty downgraded one levels for indirectness of outcome
- 6 Evidence certainty downgraded two levels for a high risk of bias
- 7 Evidence certainty downgraded one level for wide confidence interval range that include benefit or harm

BACKGROUND

Description of the condition

Chronic kidney disease (CKD) is a major global public health problem, affecting an estimated 10% of the global population (GBD 2019). According to the Global Burden of Disease, CKD was the 12th most common cause of death in 2017, accounting for 1.2 million deaths worldwide (GBD 2019). Overall CKD death increased by 34% from 2007 to 2017, making it one of the fastest rising major causes of death, alongside diabetes and dementia (GBD 2019). Diabetes and high blood pressure (BP) remain the two biggest risks for developing CKD, with 28% of CKD deaths being due to diabetes, and 28% due to high BP (GBD 2019).

CKD is a progressive condition, and risk of cardiovascular disease and death increases with declining glomerular filtration rate (GFR) (Go 2004). Healthcare costs of treating people with end-stage kidney disease (ESKD), where dialysis or kidney transplantation is required to survive, have been estimated at about 10 times greater than the cost of CKD management (Hunsicker 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 (Jones-Burton 2006; Suckling 2010; Malta 2018). These include increased BP, fluid retention, proteinuria, inflammation, oxidative stress, and endothelial dysfunction (Al-Solaiman 2009; Ritz 2009). The World Health Organisation recommends adults consume less than 5 g of salt (2 g or 87 mmol sodium) per day (WHO 2012). Data from populations around the world show that salt intakes far exceed this (Mozaffarian 2014; Trieu 2015). Estimates in people with CKD are commonly between 9 to 12 g (150 to 200 mmol sodium) (McMahon 2012a). National salt reduction strategies have been established in 75 countries; most of these aim to reduce population salt intake through reducing salt content of food and/or consumer education to shift dietary behaviour (Trieu 2015). Intervention trials comparing two or more levels of salt intake usually achieve a difference in salt intake by dietary education (e.g., individual or group counselling, online support), providing meals to participants and/or using salt supplements (McMahon 2012a).

How the intervention might work

Sodium is an essential nutrient, and has vital roles in regulating fluid homeostasis, blood volume and osmotic pressure (Elliot 2006). Excess sodium increases serum osmolality, triggering the release of vasopressin (arginine vasopressin (AVP), also known as antidiuretic hormone) which initiates a cascade of metabolic actions including activation of the renin-angiotensin-aldosterone system (RAAS) causing blood vessels to constrict and increasing water reabsorption from the urine (Qian 2018). Chronic high-salt intake (> 7 days) leads to excessive AVP production and vasoconstriction. This can lead to kidney and cardiovascular damage through dysregulation of fluid volume homeostasis and BP. Non-osmotic storage of salt in the skin and the muscle is thought to be linked to increased risk of cardiovascular and kidney disease (Garofalo 2018; Qian 2018).

High BP is common in CKD, and sustained elevations in BP hasten CKD progression (Bakris 2000). Studies in the general population have consistently demonstrated a link between dietary salt intake and BP (He 2013; Svetkey 1999). A 2017 Cochrane review found that reducing salt from 11.5 g/day to 3.8 g/day reduced systolic BP/diastolic BP in people with normotension by 1/0 mm Hg, and in people with hypertension about approximately 5.5/3 mm Hg (Graudal 2020). High salt intake may have a greater impact on BP in people with CKD than in those without CKD since CKD may reduce the ability to excrete the excess salt. A 2010 Cochrane review on reducing salt intake in people with diabetic kidney disease showed considerable BP reductions; systolic/diastolic BP was lowered by 7/3 mm Hg (Suckling 2010).

It has also been suggested that salt has adverse effects independent of BP. Todd 2010 found arterial stiffness measured by pulse wave velocity was significantly decreased independently of BP changes in hypertensive people on a low salt diet. Increased pulse wave velocity is a predictor of all-cause and cardiovascular death (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 BP (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 have yet to be established. This review updates a 2015 Cochrane review of altered dietary salt intake in people with CKD (McMahon 2015). Updating the review will ensure that best evidence is available for the benefits (and potential adverse effects) of reducing salt for people with CKD.

OBJECTIVES

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

Types of participants

Inclusion criteria

Adults (≥ 18 years) with CKD were included. For this review update, we defined CKD as those who are receiving any form of kidney replacement therapy, have a functioning kidney transplant, have impaired kidney function defined as a reduced GFR (< 60 mL/min/1.73 m²) or the presence of other markers of kidney damage such as proteinuria (KDOQI stages 1-5) or an elevated serum creatinine (SCr > 120 mmol/L) (KDIGO 2013), or as defined by study authors. This definition of CKD has been updated from that used in the initial review (McMahon 2015), where we defined CKD using

the Kidney Disease Outcomes Quality Initiative (KDOQI) 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
- 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.

In the initial review (2015), we included studies that evaluated sodium intake using 24-hour urinary sodium excretion (24-hour UNa) with a minimum difference in 24-hour UNa of 34 mmol/day (2 g salt/day) achieved between allocated interventions. No studies were excluded based on this criterion in the initial review. This eligibility criterion has been removed in this update, allowing the inclusion of studies measuring sodium intake using other methods (such as food records or 24-hour recalls) and allowing any magnitude of difference in sodium intake between the allocated interventions.

Types of outcome measures

Primary outcomes

1. Cardiovascular death
2. Death (any cause)

Secondary outcomes

1. Cardiovascular disease (coronary artery disease, heart failure, cerebrovascular disease, peripheral vascular disease)
2. Progression to ESKD requiring dialysis or transplantation
3. 24-hour UNa
4. Change in BP: 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), SCr, proteinuria, GFR
7. Change in markers of fluid overload: brain natriuretic peptide (NT-proBNP), 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 Kidney and Transplant Register of Studies up to 6 October 2020 through contact with the Information Specialist using search terms relevant to this review. The Register contains studies identified from the following sources:

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)
2. Weekly searches of MEDLINE OVID SP
3. Searches of kidney and transplant journals, and the proceedings and abstracts from major kidney and transplant conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected kidney and transplant journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the Register are identified through searches of CENTRAL, MEDLINE, and EMBASE based on the scope of Cochrane Kidney and Transplant. Details of search strategies, as well as a list of handsearched journals, conference proceedings and current awareness alerts, are available on the [Cochrane Kidney and Transplant website](#).

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. Contacting relevant individuals/organisations seeking information about unpublished or incomplete studies.

Data collection and analysis

Selection of studies

2021 update

The search results were screened and studies included or excluded based on the selection criteria listed above. Excluded studies from the 2015 review were reassessed based on the updated eligibility criteria. Screening was done independently by two authors.

2015 review

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 for studies new to this 2021 update was done using standard data extraction forms. In the 2015 review, data extraction was carried out independently by two authors. 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 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?
 - * Participants and personnel (performance bias)
 - * Outcome assessors (detection bias)
- 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:
 - * Carry-over effect
 - * Confounding factors (bias due to differences between groups other than sodium intake that are likely to impact the effect estimate (in either direction) including differential changes in diet/medication (potassium intake, body weight changes, anti-hypertensive medication dosage) and baseline differences in the outcome, where likely to impact the effect estimate)

Measures of treatment effect

For dichotomous outcomes (cardiovascular death, death (any cause), progression to ESKD, cardiovascular disease, symptomatic hypotension, reduction in anti-hypertensive dose) 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 (BP, pulse wave velocity, augmentation index, CrCl, SCr, proteinuria, GFR, brain natriuretic peptide (NT-proBNP), 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.

Unit of analysis issues

For cross-over studies, we determined the mean difference in outcomes as the difference between the end of low salt and high salt periods. Standard deviations for cross-over studies were imputed from paired analysis CIs or P values. Where these were not reported, SD of the values at the end of each period was used.

For parallel studies, we calculated the treatment effect as the difference between treatment groups' change in outcomes from baseline. Where these were not reported, or could not be imputed from reported values, values at the end of the intervention were used.

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 (e.g. last-observation-carried-forward) were critically appraised (Higgins 2011).

Assessment of heterogeneity

We first assessed the heterogeneity by visual inspection of the forest plot. We then quantified statistical heterogeneity using the I^2 statistic, which describes the percentage of total variation across studies that is due to heterogeneity rather than sampling error (Higgins 2003). A guide to the interpretation of I^2 values was as follows.

- 0% to 40%: might not be important
- 30% to 60%: may represent moderate heterogeneity
- 50% to 90%: may represent substantial heterogeneity
- 75% to 100%: considerable heterogeneity.

The importance of the observed value of I^2 depends on the magnitude and direction of treatment effects and the strength of evidence for heterogeneity (e.g. P value from the χ^2 test, or a CI for I^2) (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. Heterogeneity among participants could be related to age, ethnicity, stage of CKD and presence of comorbidities (e.g. hypertension and diabetes).

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.

Summary of findings and assessment of the certainty of the evidence

We presented the main results of the review in 'Summary of findings' tables. These tables present key information concerning the quality of the evidence, the magnitude of the effects of the interventions examined, and the sum of the available data

for the main outcomes ([Schunemann 2011a](#)). The 'Summary of findings' tables also include an overall grading of the evidence related to each of the main outcomes using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach ([GRADE 2008](#); [GRADE 2011](#)). The GRADE approach defines the quality of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the true quantity of specific interest. The quality of a body of evidence involves consideration of within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias ([Schunemann 2011b](#)). We presented the following outcomes in the 'Summary of findings' tables.

- Systolic BP
- Diastolic BP
- Albuminuria
- Extracellular fluid volume
- Weight

- Reduction in antihypertensive dose
- Symptomatic hypotension.

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

[Figure 1](#) details the study search results. The initial version of this review ([McMahon 2015](#)) included eight studies (24 reports) with 224 participants in the low salt group and 218 participants in the high salt group (442 combined; 261 unique). Nine studies were excluded, four were ongoing, and two studies were awaiting assessment. None of the previously excluded studies were eligible when reassessed against the updated eligibility criteria.

Figure 1. Study flow diagram

For this update (2021), we identified 67 new reports. We included 13 new included studies (45 reports) ([BalanceWise-HD 2013](#); [BalanceWise-PD 2011](#); [Catto 1973](#); [de Vries 2016](#); [Doulton 2007](#);

[ESMO 2017](#); [ESPECIAL 2014](#); [Kwakernaak 2014](#); [Mulhauser 1996](#); [Power 2010](#); [Rodrigues Telini 2014](#); [Saran 2017](#); [ViRTUE-CKD 2016](#)); three of these were previously ongoing studies ([BalanceWise-HD](#)

2013; Doulton 2007; Saran 2017). We also identified six new reports of five previously included studies; seven new excluded studies (14 reports); four new reports of two existing excluded studies; and six reports for five new ongoing studies. One study previously listed as ongoing was withdrawn in late 2015 and has been moved to excluded studies (Reyes 2013). All non-randomised studies and RCTs in non-CKD patients have been removed from this update.

A total of 21 studies (72 reports) have been included and 11 studies (26 reports) have been excluded from this review update. There are five ongoing studies (6 reports) which will be assessed in a future update of this review.

Included studies

See [Characteristics of included studies](#).

We included 21 studies (1197 randomised participants), 12 in the earlier stages of CKD (779 randomised participants), seven in dialysis (363 randomised participants) and two in post-transplant (55 randomised participants). These studies reported the results of 725 participants in the low salt arm and 725 participants in the high salt arm. Power 2010 (31 participants) did not report the sample size for each group and therefore the results could not be included in the quantitative synthesis.

Six studies were conducted in the Netherlands (de Vries 2016; DUAAL 2011; ESMO 2017; Kwakernaak 2014; ViRTUE-CKD 2016; Vogt 2008), four in the USA (BalanceWise-HD 2013; BalanceWise-PD 2011; Fine 1997; Saran 2017), four in the UK (de Brito-Ashurst 2013; Catto 1973; Doulton 2007; Power 2010), and one study in Australia (LowSALT CKD 2012), Brazil (Rodrigues Telini 2014), Germany (Mulhauser 1996), Japan (Konishi 2001), Korea (ESPECIAL 2014), Spain (Ruilopec 1992a), and Turkey (Keven 2006).

Of the 21 included studies, 12 were cross-over studies (Catto 1973; de Vries 2016; Doulton 2007; DUAAL 2011; Fine 1997; Konishi 2001; Kwakernaak 2014; LowSALT CKD 2012; Ruilopec 1992a; Saran 2017; ViRTUE-CKD 2016; Vogt 2008) and nine were parallel design studies (BalanceWise-HD 2013; BalanceWise-PD 2011; de Brito-Ashurst 2013; ESMO 2017; ESPECIAL 2014; Keven 2006; Mulhauser 1996; Power 2010; Rodrigues Telini 2014). Values from paired analyses were reported for most cross-over studies, although not always for all outcomes. Konishi 2001 and Ruilopec 1992a did not report paired analyses and values from the end of the intervention were used. Four of the parallel studies (BalanceWise-HD 2013; BalanceWise-PD 2011; de Brito-Ashurst 2013; ESPECIAL 2014) reported change from baseline for each group, and these data were used for analysis. Mulhauser 1996 reported change from baseline for BP but not for other outcomes. Four of the parallel studies (ESMO 2017; Keven 2006; Power 2010; Rodrigues Telini 2014) did not present data on change from baseline, and because there were no appropriate data available to impute values, values at the end of the intervention were used.

Nine studies enrolled participants with ESKD, seven in dialysis (haemodialysis (HD): BalanceWise-HD 2013; Catto 1973; Doulton 2007; Power 2010; Rodrigues Telini 2014; peritoneal dialysis (PD): BalanceWise-PD 2011; Fine 1997) and two post-transplant (Keven 2006; de Vries 2016). Twelve studies enrolled participants in earlier stages of CKD (de Brito-Ashurst 2013; DUAAL 2011; ESMO 2017; ESPECIAL 2014; Konishi 2001; Kwakernaak 2014; LowSALT CKD

2012; Mulhauser 1996; Ruilopec 1992a; Saran 2017; ViRTUE-CKD 2016; Vogt 2008).

Median study duration was seven weeks, ranging from one to 36 weeks. A cut-off of four weeks was used to classify studies according to intervention duration (short-term: fewer than four weeks; longer-term: four weeks or more). Three studies were classified as short-term, all of which were cross-over studies with two arms and enrolled participants in the earlier stages of CKD: Konishi 2001 and Ruilopec 1992a had one-week interventions and LowSALT CKD 2012 had two-week interventions. We classified 15 studies as longer-term (range: four to 36 weeks); these included all ESKD studies (BalanceWise-HD 2013; BalanceWise-PD 2011; Catto 1973; de Vries 2016; Doulton 2007; Fine 1997; Keven 2006; Power 2010; Rodrigues Telini 2014) and nine studies in earlier CKD (de Brito-Ashurst 2013; DUAAL 2011; ESMO 2017; ESPECIAL 2014; Kwakernaak 2014; Mulhauser 1996; Saran 2017; ViRTUE-CKD 2016; Vogt 2008).

Thirteen studies used dietary counselling to achieve a difference in sodium intake. Of these, 11 studies compared sodium restriction achieved through dietary counselling in the low salt intervention to usual diet or usual care in the high salt intervention (BalanceWise-PD 2011; de Brito-Ashurst 2013; de Vries 2016; DUAAL 2011; ESMO 2017; Keven 2006; Kwakernaak 2014; Rodrigues Telini 2014; Saran 2017; ViRTUE-CKD 2016; Vogt 2008). Two studies compared against a less intensive education strategy to reduce dietary sodium: ESPECIAL 2014 compared intensive education to reduce sodium in the high salt intervention versus brief education in the low salt intervention, and BalanceWise-HD 2013 provided individualised dietary counselling paired with personal digital assistant-based self-monitoring and feedback on sodium intake to participants in the low salt intervention and six educational modules to both groups (attention control for the high salt group). Six studies used sodium supplements to achieve difference in sodium intake with sodium supplements in the high salt group compared against placebo (Catto 1973; Doulton 2007; Fine 1997; LowSALT CKD 2012; Mulhauser 1996) or a lower dose of sodium supplementation (Ruilopec 1992a) in the low salt group. Power 2010 did not specify means for achieving difference in sodium intake. Konishi 2001 provided all food for participants.

Five studies included concomitant interventions of medications that remained stable throughout the high and low salt phases. DUAAL 2011 and Kwakernaak 2014 started all participants on lisinopril 40 mg/day, ESPECIAL 2014 used olmesartan medoxomil 40 mg/day, Ruilopec 1992a used verapamil 240 mg/day, and ViRTUE-CKD 2016 used ramipril 10 mg/day. The protocol for Konishi 2001 included cessation of all medications one week before the study.

Outcome reporting in included studies

Where multiple markers of sodium intake were collected, 24-hour UNa excretion was used preferentially in analyses. Fifteen studies reported 24-hour UNa excretion as a marker of sodium intake (de Brito-Ashurst 2013; de Vries 2016; DUAAL 2011; ESMO 2017; ESPECIAL 2014; Fine 1997; Keven 2006; Konishi 2001; Kwakernaak 2014; LowSALT CKD 2012; Mulhauser 1996; Ruilopec 1992a; Saran 2017; ViRTUE-CKD 2016; Vogt 2008). Fine 1997, whose participants were receiving PD, added 24-hour UNa excretion to 24-hour dialysate sodium to achieve a total value for sodium excretion, and this value was used for analysis. Four studies collected self-reported dietary sodium intake measurements (values were converted to mmol/day prior to analysis); BalanceWise-HD 2013

and [BalanceWise-PD 2011](#) used three, 24-hour recalls, [Rodrigues Telini 2014](#) used three-day diet records, while [Catto 1973](#), [Doulton 2007](#) and [Power 2010](#) did not report sodium intake or excretion.

All studies except [BalanceWise-HD 2013](#) and [Power 2010](#) measured and reported BP. Where more than one BP measurement was reported, 24-hour ambulatory BP was used preferentially in analyses, and clinic-assessed BP was used preferentially over self-assessed BP measurements. Seven studies measured 24-hour ambulatory BP ([de Brito-Ashurst 2013](#); [Doulton 2007](#); [ESMO 2017](#); [Konishi 2001](#); [LowSALT CKD 2012](#); [Ruilope 1992a](#); [Saran 2017](#)), 10 used clinic-assessed BP ([Catto 1973](#); [de Vries 2016](#); [DUAAAL 2011](#); [ESPECIAL 2014](#); [Keven 2006](#); [Kwakernaak 2014](#); [Mulhauser 1996](#); [Rodrigues Telini 2014](#); [ViRTUE-CKD 2016](#); [Vogt 2008](#)); [BalanceWise-PD 2011](#) and [Fine 1997](#) used self-assessed BP. If more than one position was reported, standing BP was the first preference, except in [BalanceWise-PD 2011](#) where sitting BPs were used due to there being more missing data for the standing measurements.

Eleven studies reported changes in urinary protein or albumin ([de Vries 2016](#); [DUAAAL 2011](#); [ESMO 2017](#); [ESPECIAL 2014](#); [Konishi 2001](#); [Kwakernaak 2014](#); [LowSALT CKD 2012](#); [Mulhauser 1996](#); [Saran 2017](#); [ViRTUE-CKD 2016](#); [Vogt 2008](#)). Pooled analyses were performed on log-transformed values (mg/day) to give log mean (95% CI of log mean). The exponential of these values were also reported to indicate percentage change for ease of understanding ([Bland 1996](#)).

Nine studies reported 24-hour urinary protein excretion ([de Vries 2016](#); [DUAAAL 2011](#); [ESMO 2017](#); [Konishi 2001](#); [Kwakernaak 2014](#); [LowSALT CKD 2012](#); [Mulhauser 1996](#); [ViRTUE-CKD 2016](#); [Vogt 2008](#)). Three studies ([DUAAAL 2011](#); [Kwakernaak 2014](#); [ViRTUE-CKD 2016](#)) reported geometric mean (95% CI) which was transformed to log mean and SD using the methods specified in the Cochrane Handbook. Two studies ([ESMO 2017](#); [Vogt 2008](#)) reported values as mean and standard error which were converted to log mean and SD using the methods specified in [Higgins 2008](#). [LowSALT CKD 2012](#) provided raw data and these were log-transformed. Two studies ([de Vries 2016](#); [Konishi 2001](#)) reported data as median and inter-quartile range and could not be entered into pooled analysis. [Mulhauser 1996](#) reported values as mean and range and from these values it appeared that the data were not normally distributed therefore could not be entered into pooled analysis.

Six studies reported 24-hour urinary albumin excretion ([de Vries 2016](#); [ESPECIAL 2014](#); [Kwakernaak 2014](#); [LowSALT CKD 2012](#); [Saran](#)

[2017](#); [ViRTUE-CKD 2016](#)). [de Vries 2016](#) and [Saran 2017](#) reported values as change in log mean and 95% CI. Two studies ([Kwakernaak 2014](#); [ViRTUE-CKD 2016](#)) reported geometric mean (95% CI) which was transformed to log mean and SD using the methods specified in the Cochrane Handbook. Two studies ([LowSALT CKD 2012](#); [ESPECIAL 2014](#)) provided raw data which were log-transformed for analysis.

Thirteen studies reported change in body weight ([BalanceWise-HD 2013](#); [de Brito-Ashurst 2013](#); [de Vries 2016](#); [Doulton 2007](#); [DUAAAL 2011](#); [ESMO 2017](#); [Fine 1997](#); [Kwakernaak 2014](#); [LowSALT CKD 2012](#); [Ruilope 1992a](#); [Saran 2017](#); [ViRTUE-CKD 2016](#); [Vogt 2008](#)).

Objective markers of fluid status were reported by six studies; three studies reported extracellular fluid volume ([LowSALT CKD 2012](#); [Rodrigues Telini 2014](#); [Saran 2017](#)), [de Brito-Ashurst 2013](#) reported total body water, two studies reported presence of oedema ([DUAAAL 2011](#); [ViRTUE-CKD 2016](#)), and three reported intradialytic weight gain ([BalanceWise-HD 2013](#); [Doulton 2007](#); [Rodrigues Telini 2014](#)). [Doulton 2007](#) reported only mean values at the end of each intervention arm and the P value for the mean difference for body weight and inter-dialytic weight gain, therefore SDs were imputed from P values using the methods described in the Cochrane Handbook.

Excluded studies

We excluded 11 studies (26 reports) that did not meet our inclusion criteria. Reasons for exclusion were non-CKD population ([Li 2013f](#); [Suckling 2016](#)), concomitant intervention that was not stable between interventions ([DD 2017](#); [Esnault 2005](#); [Kauric-Klein 2012](#); [HHK 2018](#)) not comparing two or more levels of sodium intake ([Chanwikrai 2012](#); [Imanishi 1997](#)), or less than one week duration ([Clark-Cutaia 2016](#); [De Nicola 2000](#)).

Ongoing studies

Five studies are ongoing and will be assessed once they have been completed ([NCT03373500](#); [OxCKD1 2012](#); [STICK 2015](#); [SUBLIME 2020](#); [SUPER 2016](#)).

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

Random sequence generation

All included studies were randomised. Further details were provided about the method of randomisation for 12 studies and these studies were judged to be at low risk of bias (BalanceWise-HD 2013; BalanceWise-PD 2011; de Brito-Ashurst 2013; de Vries 2016; DUAAL 2011; ESMO 2017; ESPECIAL 2014; Fine 1997; Kwakernaak 2014; LowSALT CKD 2012; Vogt 2008; ViRTUE-CKD 2016). The remaining nine studies were judged to have unclear risk of bias.

Allocation concealment

Allocation concealment was not described for 11 studies and these were judged to be low risk of bias (Catto 1973; de Brito-Ashurst 2013; de Vries 2016; DUAAL 2011; Keven 2006; Konishi 2001; Kwakernaak 2014; Power 2010; Rodrigues Telini 2014; Ruilope 1992a; Vogt 2008). Saran 2017 was considered to be at high risk of bias due to allocation concealment. Randomisation was concealed using sealed envelopes but it was unclear how this process was monitored. This study had considerable violation of the protocol at one of the two study sites (6/21 given treatment in the reverse order for unknown reasons, 4/21 recommended to continue low salt instead of crossing over to high salt diet) (Saran 2017). The remaining nine studies were judged to have unclear risk of bias.

Blinding

Most outcomes were objective and therefore at lower risk of being influenced by performance bias. Five studies (Catto 1973; Doulton 2007; Fine 1997; LowSALT CKD 2012; Mulhauser 1996) were double blinded. Clinicians, but not participants, were blinded in ESPECIAL 2014. Investigators, but not participants or study coordinators, were blinded in Saran 2017, and the lack of blinding of study coordinators may have influenced the outcomes, as evidenced by the protocol deviations described previously.

Twelve studies had open-label dietary interventions (BalanceWise-HD 2013; BalanceWise-PD 2011; de Brito-Ashurst 2013; de Vries 2016; DUAAL 2011; ESMO 2017; Keven 2006; Kwakernaak 2014; Power 2010; Rodrigues Telini 2014; ViRTUE-CKD 2016; Vogt 2008).

Konishi 2001 and Ruilope 1992a did not describe blinding.

Incomplete outcome data

There was a high risk of attrition bias due to incomplete outcome data for three studies; BalanceWise-PD 2011 reported 19% attrition and data were missing for a large proportion of participants for BP, weight and urine outcomes; Power 2010 had 38% attrition and did not report reasons or attrition by allocation; Saran 2017 had a proportion of participants with missing data for some outcomes (e.g. only 10/21 participants at one of the sites included in urinary albumin data, but 21/21 included in urinary creatinine data), and reasons for this were not provided. The authors were contacted to provide further information, but none was provided.

Konishi 2001 and Ruilope 1992a did not report participant attrition. Doulton 2007 specified a target enrolment of 20 and reported 13 completers but did not report actual enrolment to determine attrition. Fine 1997 reported a large degree of attrition (12/32 participants; 37%) that was even among the two groups, however may have introduced bias as some participants withdrew due to concern about values when self-measuring BP. Rodrigues Telini 2014 reported 26% attrition which was higher in the high salt (9/30; 30%) than the low salt group (5/23; 21%).

Selective reporting

Risk of reporting bias was unclear for four studies for which trial registration or study protocol could not be located (Keven 2006; Konishi 2001; Ruilope 1992a) and for Saran 2017 with unexplained missing outcome data. Risk of reporting bias was high for two studies where most or all outcomes could not be meta-analysed due to the way that they were reported (Mulhauser 1996; Power 2010).

Other potential sources of bias

Carry-over effect in cross-over studies

Carry-over effect may have introduced bias in Konishi 2001 and Ruilope 1992a; both were of 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 cofounders

Bias from cofounders was classified as unclear or high risk for nearly all studies, mostly due to lack of measurement or failing to adequately report or account for the impact of changes in medications and/or dietary changes such as potassium intake, protein intake and/or weight loss between interventions. Dietary changes were considered more likely to introduce bias in studies comparing a sodium restricted to usual diet, and less so those using sodium supplements to achieve differences in salt intake. Mean systolic/diastolic BP was 6-7/3 mm Hg higher in low salt versus high salt group at baseline in both [Keven 2006](#) and [Rodrigues Telini 2014](#). While this difference may not have been statistically significant, this may have impacted the clinical significance of the results, as both studies did not report results as change from baseline. This information was sought from authors but was not provided.

We assessed that two studies were at high risk of bias in relation to funding sources ([Fine 1997](#); [Saran 2017](#)).

Effects of interventions

See: [Summary of findings 1 Lower salt intake versus higher salt intake for participants with chronic kidney disease](#)

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

Sodium intake/excretion

Low salt intake resulted in sodium intake/excretion being reduced in included studies ([Analysis 1.1](#) (18 studies, 1383 participants): MD -73.51 mmol/day, 95% CI -92.76 to -54.27; high certainty evidence) although heterogeneity was high ($I^2 = 93\%$).

CKD stage

In the earlier stages of CKD, reducing salt intake reduced sodium intake/excretion ([Analysis 1.1.1](#) (12 studies, 1048 participants): MD -83.81 mmol/day, 95% CI -104.54 to -63.08; $I^2 = 92\%$). In studies in dialysis patients, reducing salt intake reduced sodium intake/excretion ([Analysis 1.1.2](#) (4 studies, 259 participants): MD -27.17 mmol/day, 95% CI -48.59, -5.76; $I^2 = 70\%$). In studies in post-transplant recipients, reducing salt intake reduced sodium intake/excretion ([Analysis 1.1.3](#) (2 studies, 76 participants): MD -96.99 mmol/day, 95% CI -148.10 to -45.89; $I^2 = 55\%$).

The test for subgroup differences showed a difference between the earlier stages of CKD and dialysis patients ($\text{Chi}^2 = 13.87$, $\text{df} = 1$ ($P = 0.0002$), $I^2 = 92.8\%$) and dialysis patients and transplant recipients ($\text{Chi}^2 = 6.10$, $\text{df} = 1$ ($P = 0.01$), $I^2 = 83.6\%$) but not between the earlier stages of CKD and transplant recipients ($\text{Chi}^2 = 0.22$, $\text{df} = 1$ ($P = 0.64$), $I^2 = 0\%$).

Duration

In short-term studies (< 4 weeks), reducing salt intake reduced sodium intake/excretion ([Analysis 2.1.1](#) (3 studies, 142 participants): MD -111.29 mmol/day, 95% CI -134.25 to -88.32; $I^2 = 77\%$). In longer-term studies (≥ 4 weeks), reducing salt intake

reduced sodium intake/excretion ([Analysis 2.1.2](#) (15 studies, 1241 participants): MD -64.53 mmol/day, 95% CI -83.29, -45.78; $I^2 = 90\%$).

The test for subgroup differences showed a difference between short- and longer-term studies ($\text{Chi}^2 = 248.56$, $\text{df} = 1$ ($P = 0.00001$), $I^2 = 93\%$).

Blood pressure

Reducing salt intake reduced both systolic ([Analysis 1.2](#) (19 studies, 1261 participants): MD -6.91 mm Hg, 95% CI -8.82 to -4.99; $I^2 = 50\%$; high certainty evidence) and diastolic BP ([Analysis 1.3](#) (19 studies, 1257 participants): MD -3.91 mm Hg, 95% CI -4.80 to -3.02; $I^2 = 21\%$; high certainty evidence).

[Power 2010](#) reported intradialytic BP stability as being significantly improved when sodium restriction was combined with low dialysate ($P < 0.05$), but did not report results for sodium restriction alone.

CKD stage

In the earlier stages of CKD, reducing salt intake reduced both systolic ([Analysis 1.2.1](#) (12 studies, 1036 participants): MD -6.10 mm Hg, 95% CI -8.11 to -4.08; $I^2 = 48\%$) and diastolic BP ([Analysis 1.3.1](#) (12 studies, 1032 participants): MD -3.47 mm Hg, 95% CI -4.28 to -2.65; $I^2 = 0\%$).

In dialysis patients, reducing salt intake reduced both systolic ([Analysis 1.2.2](#) (5 studies, 149 participants): MD -6.32 mm Hg, 95% CI -11.04 to -1.60; $I^2 = 0\%$) and diastolic BP ([Analysis 1.3.2](#) (5 studies, 149 participants): MD -3.46 mm Hg, 95% CI -6.39 to -0.54; $I^2 = 0\%$).

In post-transplant recipients, reducing salt intake reduced both systolic ([Analysis 1.2.3](#) (2 studies, 76 participants): MD -11.94 mm Hg, 95% CI -15.77 to -8.11; $I^2 = 12\%$) and diastolic BP ([Analysis 1.3.2](#) (2 studies, 76 participants): MD -7.13 mm Hg, 95% CI -9.46 to -4.79; $I^2 = 0\%$).

For systolic BP, the test for subgroup differences showed a difference between the earlier stages of CKD and post-transplant recipients (Test for subgroup differences: $\text{Chi}^2 = 7.01$, $\text{df} = 1$ ($P = 0.008$), $I^2 = 85.7\%$) but not between the earlier stages of CKD and dialysis patients ($\text{Chi}^2 = 0.01$, $\text{df} = 1$ ($P = 0.93$), $I^2 = 0\%$) or dialysis patients and post-transplant recipients ($\text{Chi}^2 = 3.28$, $\text{df} = 1$ ($P = 0.07$), $I^2 = 69.6\%$).

For diastolic BP, the test for subgroup differences showed a difference between earlier stages of CKD and post-transplant recipient ($\text{Chi}^2 = 8.38$, $\text{df} = 1$ ($P = 0.004$), $I^2 = 88.1\%$), but not for earlier stages of CKD and dialysis patients ($\text{Chi}^2 = 0.00$, $\text{df} = 1$ ($P = 1.00$), $I^2 = 0\%$) or dialysis patients and post-transplant recipients ($\text{Chi}^2 = 3.68$, $\text{df} = 1$ ($P = 0.06$), $I^2 = 72.8\%$).

Duration

In short-term studies (< 4 weeks), reducing salt intake reduced both systolic ([Analysis 2.2.1](#) (3 studies, 144 participants): MD -7.91 mm Hg, 95% CI -11.53 to -4.28; $I^2 = 0\%$) and diastolic BP ([Analysis 2.3.1](#) (3 studies, 144 participants): MD -3.70 mm Hg, 95% CI -5.74 to -1.67; $I^2 = 0\%$). In longer-term studies (≥ 4 weeks), reducing salt intake reduced both systolic ([Analysis 2.2.2](#) (16 studies, 1117 participants): MD -6.82 mm Hg, 95% CI -9.00 to -4.64; $I^2 = 56\%$) and diastolic BP ([Analysis 2.3.2](#) (16 studies, 1113 participants): MD -3.99 mm Hg, 95% CI -5.03 to -2.94; $I^2 = 32\%$; .2).

The tests for subgroup differences showed no difference between short- and longer-term studies for both systolic ($\text{Chi}^2 = 0.25$, $\text{df} = 1$ ($P = 0.6155$), $I^2 = 0\%$) and diastolic BP ($\text{Chi}^2 = 0.06$, $\text{df} = 1$ ($P = 0.8073$), $I^2 = 0\%$).

Urinary protein excretion

Reducing salt intake reduced 24-hour urinary protein excretion in the earlier stages of CKD ([Analysis 1.4](#) (6 studies, 436 participants): MD -0.41 ln mg/day, 95% CI -0.58 to -0.25; $I^2 = 78\%$) corresponding to an average percentage difference of -33.9% (95% CI -44.1 to -21.9) from the high salt to the low salt intervention.

Three studies could not be entered into the pooled analysis ([de Vries 2016](#); [Konishi 2001](#); [Mulhauser 1996](#)). [Konishi 2001](#) reported a reduction in median protein excretion with salt restriction ($P = 0.004$, 38 CKD participants) equivalent to a 27% reduction. [de Vries 2016](#) found no effect on urinary protein excretion ($P = 0.9$, 22 post-transplant participants). [Mulhauser 1996](#) reported no significant difference in proteinuria between the low salt group and the high salt group ($P > 0.05$ using analysis of covariance adjusted for baseline values), although the analysis method may have been inappropriate as it is likely that data were not normally distributed (mean (range) values g/day end of run-in low salt: 1 (0.06 to 1.92) High salt: 0.71 (0.06 to 2.31); end of intervention: low salt 0.79 (0.1 to 1.39) high salt 1.14 (0.1 to 5.06)).

Reducing salt intake reduced 24-hour urinary albumin excretion ([Analysis 1.5](#) (6 studies, 501 participants): MD -0.44 ln mg/day, 95% CI -0.58 to -0.3; $I^2 = 29\%$; high certainty evidence) corresponding to an average percentage difference of -35.6 (95% CI -44.2 to -25.7) from the high salt to the low salt intervention.

All six studies reporting 24-hour urinary protein (520 participants) were in the earlier stages of CKD and all but one ([LowSALT CKD 2012](#)) were of longer-term duration.

Most studies reporting 24-hour urinary albumin were in the earlier stages of CKD (except [de Vries 2016](#) which is in post-transplant) and most were of longer-term duration (except [LowSALT CKD 2012](#)).

Measures of kidney function

Measures of kidney function reported by the included studies included eGFR, SCr, CrCl, effective renal plasma flow, and filtration fraction. [Mulhauser 1996](#) reported no significant effect on renal parameters including eGFR, CrCl, effective renal plasma flow, filtration fraction or renal vascular resistance ($P > 0.05$ using analysis of covariance adjusted for baseline values) but data could not be pooled as values were reported as mean and range.

Estimated glomerular filtration rate

Reducing salt intake made little or no difference to eGFR ([Analysis 1.6](#) (7 studies, 559 participants): MD -0.82 mL/min/1.73 m², 95% CI -2.31 to 0.66; $I^2 = 0\%$). Of the seven studies that reported eGFR, all but one ([de Vries 2016](#), post-transplant) were in the earlier stages of CKD and all but one ([LowSALT CKD 2012](#)) were of longer-term duration. Results were similar if including only earlier stages of CKD or in longer-term studies only. Results did not change when analysed using fixed effects.

Creatinine clearance

Reducing salt intake reduced CrCl ([Analysis 1.7](#) (7 studies, 529 participants): MD -4.70 mL/min, 95% CI -6.94 to -2.47; $I^2 = 0\%$). [DUAAAL 2011](#) (52 participants) analysed log-transformed CrCl and reported the results as geometric means with a significant reduction from 72 (62 to 84) mL/min in high salt to 66 (57 to 76) mL/min in low salt ($P = 0.002$).

The test for subgroup differences showed no difference between short- and longer-term studies in CrCl ($\text{Chi}^2 = 0.96$, $\text{df} = 1$ ($P = 0.33$), $I^2 = 0\%$). Results did not change when analysed using fixed versus random effects.

Serum creatinine

Reducing salt intake increased SCr ([Analysis 1.8](#) (7 studies, 519 participants): MD 4.46 $\mu\text{mol/L}$, 95% CI 0.08 to 8.83; $I^2 = 24\%$). [de Vries 2016](#) analysed log transformed SCr and found no effect with salt restriction (MD ln -0.02 mg/dL, 95% CI -0.03 to 0.07 $P = 0.4$). [LowSALT CKD 2012](#) reported a significant increase in SCr ($\mu\text{mol/L}$) from median 149 (IQR 135–230) with high salt intake to 172 (157–276) with low salt intake ($P < 0.05$).

Effective renal plasma flow

[Konishi 2001](#) (41 participants) reported no significant difference in effective renal plasma flow between low and high salt intake.

Filtration fraction

Reducing salt intake may make little or no difference to filtration fraction in the earlier stages of CKD ([Analysis 1.9](#) (2 studies, 160 participants): MD -0.40%, 95% CI -0.87 to 0.07; studies = 2; participants = 160; $I^2 = 0\%$).

Body weight

The evidence is very uncertain about the effect of reducing salt intake on body weight ([Analysis 1.10](#) (12 studies, 759 participants): MD -1.32 kg, 95% CI -1.94 to -0.70; $I^2 = 54\%$; very low certainty evidence).

CKD stage

In the earlier stages of CKD, reducing salt intake reduced body weight ([Analysis 1.10.1](#) (8 studies, 634 participants): MD -1.47 kg, 95% CI -2.42 to -0.53; $I^2 = 62\%$). In studies in dialysis patients, reducing salt intake may make little or no difference to body weight ([Analysis 1.10.2](#) (3 studies, 81 participants): MD -0.67 kg, 95% CI -1.37 to 0.04; $I^2 = 0\%$). In post-transplant recipients [de Vries 2016](#) reported reducing salt intake reduced body weight ([Analysis 1.10.3](#) (44 participants): MD -2.00 kg, 95% CI -3.00 to -1.00). The test for subgroup differences showed no differences between the stages of CKD ($\text{Chi}^2 = 5.01$, $\text{df} = 2$ ($P = 0.0819$), $I^2 = 60\%$).

Duration

In both short-term studies (< 4 weeks) ([Analysis 2.6.1](#) (2 studies, 68 participants): MD -0.41 kg, 95% CI -0.81 to -0.01; $I^2 = 0\%$) and longer-term studies (≥ 4 weeks) ([Analysis 2.6.2](#) (10 studies, 691 participants): MD -1.53 kg, 95% CI -2.02 to -1.04; $I^2 = 11\%$) reducing salt intake reduced body weight. The test for subgroup differences showed no difference between short- and longer-term studies for body weight ($\text{Chi}^2 = 12.09$, $\text{df} = 1$ ($P = 0.0005$), $I^2 = 91.7\%$).

Fluid status

Reducing salt intake may reduce extracellular fluid volume in the earlier stages of CKD ([Analysis 1.12](#) (3 studies, 187 participants): MD -0.87 L, 95% CI -1.17 to -0.58; $I^2 = 0\%$; low certainty evidence). [de Brito-Ashurst 2013](#) reported a significant reduction in mean total body water in the low salt group of 0.50 L ($P < 0.01$) and no change in the control group (0.26 L, not statistically significant).

Reducing salt intake did not change interdialytic weight gain ([Analysis 1.11](#) (2 studies, 187 participants): MD -0.11 kg, 95% CI -0.28 to 0.06; $I^2 = 0\%$). [Power 2010](#) reported intradialytic weight gain was significantly reduced when sodium restriction was combined with low dialysate but did not report results for sodium restriction alone. [Catto 1973](#) did not report intradialytic weight gain; however differences between mean pre- and post-dialysis weights taken over 15 dialysis sessions were similar in the low salt (2.17 kg) and the high salt (2.21 kg) arms.

Reducing salt intake reduced oedema in the earlier stages of CKD ([Analysis 1.13](#) (2 studies, 191 participants): RR 0.52, 95% CI 0.31 to 0.90; $I^2 = 0\%$).

Renin-angiotensin-aldosterone system and N-terminal pro-brain natriuretic peptide stimulation

RAAS stimulation was reported as plasma renin activity, plasma renin, plasma aldosterone and serum aldosterone.

In the earlier stages of CKD reducing salt intake increased plasma renin activity ([Analysis 1.14](#) (2 studies, 142 participants): MD 1.08 ng/mL/h, 95% CI 0.51 to 1.65; studies = 2; participants = 142; $I^2 = 0\%$) and increased aldosterone (plasma or serum) ([Analysis 1.15](#) (2 studies, 142 participants): MD 6.20 ng/dL, 95% CI 3.82 to 8.58; $I^2 = 0\%$). Some data on renin and aldosterone could not be pooled; [de Vries 2016](#) reported a significant increase in log transformed plasma aldosterone (MD 0.5 ln pmol/L; 95% CI 0.3 to 0.8; $P < 0.001$), corresponding to a percentage difference in geometric mean of 65% (35% to 123%) and no significant effect on plasma renin (MD 0.2 ln IU/mL; 95% CI -0.1 to 0.5; $P = 0.1$) in post-transplant recipients. [LowSALT CKD 2012](#) reported an increase in plasma renin of 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) in the earlier stages of CKD.

NT-proBNP results could not be pooled. Two studies in earlier stages of CKD reported a significant reduction in NT-proBNP with salt restriction; [LowSALT CKD 2012](#) reported that salt restriction reduced NT-proBNP by 125 pg/mL from median 330 (IQR 167–793) to 205 (124–528) pg/mL ($P < 0.05$); [Vogt 2008](#) reported salt restriction significantly decreased NT-proBNP from geometric mean 91 pg/mL (IQR 60 – 137) 62 (IQR 41 – 93) to ($P = 0.005$). [de Vries 2016](#) reported no significant effect of salt restriction on log-transformed NT-proBNP (-0.1 ln ng/L, 95% CI -0.4 to 0.1; $P = 0.3$) in post-transplant participants.

Change in antihypertensive regimen

Seven studies (664 participants) reported incidence of reduction in antihypertensives with salt restriction ([de Vries 2016](#); [DUAAL 2011](#); [ESPECIAL 2014](#); [Keven 2006](#); [LowSALT CKD 2012](#); [Saran 2017](#); [VIRTUE-CKD 2016](#)). Three of these reported no changes in either low

salt or high salt groups ([DUAAL 2011](#); [ESPECIAL 2014](#); [VIRTUE-CKD 2016](#)).

The evidence is very uncertain about the effect of reducing salt intake on antihypertensive medication dosage ([Analysis 1.16](#) (7 studies, 664 participants): RR 2.45, 95% CI 0.98 to 6.08; $I^2 = 12\%$; very low certainty evidence). Antihypertensive medication dosage were reported by four studies (228 participants; [de Vries 2016](#); [Keven 2006](#); [LowSALT CKD 2012](#); [Saran 2017](#)). This may have reduced the effect size of sodium restriction on BP in these studies. There were 20 instances of reduction in antihypertensive dosage in low salt group versus eight in the high salt group. Six of the eight instances in the high salt arm occurred in [Saran 2017](#), and these were mostly in the second arm of the cross-over study. [Saran 2017](#) also experienced protocol violations with respect to treatment order; 10 of the 56 patients were not receiving the correct treatment in the second arm (six in the first arm), therefore this may have impacted anti-hypertensive dose. If [Saran 2017](#) is excluded from the analysis, the effect size is larger (RR 5.38, 95% CI 1.45 to 20.01 12 events in low salt and two in high salt arms).

[ESMO 2017](#) reported the number of antihypertensive medications was not significantly changed with salt restriction (MD 0.0 95% -0.3 to 0.2) but did not report change in dosage. [Rodrigues Telini 2014](#) reported there was no significant difference in the number of antihypertensive medications between the groups at follow-up.

Some studies did not report change in antihypertensive medications but it is reasonable to assume medication changes did not occur due to their study protocols; the study protocols for [Kwakernaak 2014](#) and [Vogt 2008](#) specified keeping medications stable; [Konishi 2001](#) refrained from the use of antihypertensive medications during the study; [Ruilopec 1992a](#) specified that no medications were given during run-in and it is likely that this continued (besides the co-intervention of 240 mg verapamil); [Mulhauser 1996](#) excluded participants taking antihypertensive medications.

[Fine 1997](#) reported that there were no increases to medication in the 10 hypertensive patients during the high salt intervention, but it is unclear whether changes occurred in the low salt intervention or in the other 10 participants. [de Brito-Ashurst 2013](#) study protocol included salt restriction “in addition to standard hypertension medication management” therefore there may have been changes to medications but measurement of this was not specified. [Power 2010](#) measured antihypertensive dosage but did not report results.

Adverse effects

Potential adverse effects reported included symptomatic hypotension, cramps, and serum cholesterol.

Reducing salt intake may increase symptomatic hypotension ([Analysis 1.17](#) (4 studies, 478 participants): RR 6.70, 95% CI 2.40 to 18.69; $I^2 = 0\%$; moderate certainty evidence). These were mostly considered mild ([VIRTUE-CKD 2016](#)) or were resolved by lowering the dose of antihypertensive medication ([de Vries 2016](#); [LowSALT CKD 2012](#)). This is a potential adverse effect associated with salt restriction, although one that could be rectified by reducing the antihypertensive dose.

[Power 2010](#) reported that sodium restriction increased frequency, but not severity, of cramps by 21% ($P = 0.04$). [Catto 1973](#) reported that administration of slow sodium during dialysis (versus placebo)

resulted in a 26% reduction in the frequency ($P < 0.05$) and 30% in the severity ($P < 0.02$) of muscle cramps recorded over 15 dialysis sessions.

Reducing salt intake did not change total cholesterol (Analysis 1.18 (7 studies, 473 participants): MD -0.11 mmol/L, 95% CI -0.31 to 0.10; $I^2 = 0\%$)

Sensitivity analysis

The funnel plots of analyses for sodium intake/excretion (Figure 4), systolic BP (Figure 5) and diastolic BP (Figure 6) were investigated. Studies giving rise to asymmetry for systolic BP (BalanceWise-PD 2011) and diastolic BP (BalanceWise-PD 2011; Rodrigues Telini 2014) were removed with no change in direction or effect size.

Figure 4. Funnel plot of comparison: 1 CKD stage, outcome: 1.1 Sodium intake/excretion [mmol/d].

Figure 5. Funnel plot of comparison: 1 CKD stage, outcome: 1.2 Systolic blood pressure [mm Hg].

Figure 6. Funnel plot of comparison: 1 CKD stage, outcome: 1.3 Diastolic blood pressure [mm Hg].

Studies with high risk of bias in more than one domain ([BalanceWise-PD 2011](#); [Saran 2017](#)) were removed. The differences in analyses were mostly minimal except when [Saran 2017](#) was eliminated from antihypertensive dosage reduction analysis as discussed previously (analyses not shown).

DISCUSSION

Summary of main results

We included 21 studies (1197 randomised participants), 12 in the earlier stages of CKD (779 randomised participants), seven in dialysis (363 randomised participants) and two in post-transplant (55 randomised participants). Included studies had a median study duration of seven weeks (range 1 to 36 weeks) and compared two levels of sodium intake achieved via dietary counselling to reduce salt (13 studies); sodium supplements (six studies) providing food (one study) or unspecified methods (one study).

Reducing salt reduced BP in all stages of CKD. We found that reducing salt intake by approximately 4.2 g/day (73.52 mmol or 1690 mg sodium) lowered BP by 7/4 mm Hg in people with CKD and proteinuria/albuminuria by 34% to 36% in people in the earlier stages of CKD. This is a clinically significant reduction in BP, comparable to expectations of administering a single antihypertensive drug ([Law 2009](#)).

In non-dialysed, non-transplanted people with CKD, reducing salt intake by 4.8 g/day (84 mmol or 1930 mg sodium) for a median of six weeks duration reduced BP by 6.1/3.5 mm Hg. In dialysed people with CKD reducing salt by 1.6 g/day (27 mmol or 620 mg sodium) for a median of 16 weeks duration reduced BP by 6.3/3.5 mm Hg. In people who had undergone transplantation (two studies 6 and 12 week duration), reducing salt by 5.6 g/day (97 mmol or 2230 mg sodium) reduced BP by 11.9/7.1 mm Hg.

In studies of less than four weeks duration, reducing salt by 6.4 g/day (111 mmol or 2550 mg sodium) reduced BP by 7.9/3.7 mm Hg. In studies of four weeks or more duration, reducing salt by 3.7 g/day (64.53 mmol or 1480 mg sodium) reduced BP by 6.8/4.0 mm Hg.

The evidence is very uncertain about the effect of lower salt intake on weight. We found body weight was reduced by 1.3 kg with salt reduction, with a larger reduction in studies over 4 weeks (1.5 kg) than studies under 4 weeks duration (0.4 kg). However, it was not possible to determine the extent to which this weight loss was due to fluid volume, lean tissue, or body fat. Salt restriction resulted in reduced extracellular fluid volume by 0.87 L and a 48% reduced risk of oedema in non-transplanted people with CKD. Reducing salt intake did not significantly change inter-dialytic weight gain. Evidence for effects on fluid status was not available for transplanted people with CKD. Reductions in body weight were seen in all stages of CKD with 1.5 kg weight loss in non-

dialysed, non-transplanted CKD, 0.7 kg in dialysed CKD and 2 kg in transplanted CKD.

Reducing salt intake reduced 24-hour urinary protein excretion in the earlier stages of CKD by -0.41 ln mg/day (95% CI -0.58 to -0.25) which corresponded to an average percentage difference of -33.9% (95% CI -44.1 to -21.9). Reducing salt intake may reduce extracellular fluid volume and oedema in the earlier stages of CKD but did not alter interdialytic weight gain.

It was found that eGFR was not significantly changed by salt restriction, but salt restriction decreased CrCl by 4.7 ml/min and increased SCr by 4.5 μ mol/L. These effects were more pronounced in studies under four weeks duration than those four or more weeks duration, but the difference by duration was not statistically significant.

While reduced salt intake may increase symptomatic hypotension, the evidence is very uncertain about the effect of reducing salt intake on antihypertensive medication dosage.

Overall completeness and applicability of evidence

We aimed to evaluate the benefits and harms of altering dietary salt intake for people with CKD. We could not assess the effect of restricting salt intake on endpoints such as death, cardiovascular events of progression to ESKD 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 may be also in part due to the resources and practical aspects of providing the ongoing and regular support that is needed to achieve long-term adherence to a sodium-restricted diet (McMahon 2012a). In practice, supporting patients to achieve this requires an individualised approach tailored to support patients to improve their motivation, knowledge and develop personal coping skills to prevent behaviour change decay over time. More research on these elements are needed. In this review, we identified some ongoing studies with longer intervention durations meaning that we may be able to assess the longer-term effects on salt restriction in people with CKD in future updates of this review.

While nearly all included studies reported effects of salt restriction on dietary salt intake/excretion and BP, there were limited evidence for effects on kidney function, proteinuria/albuminuria, and fluid status. Subgroup analyses were not possible for many outcomes due to the small number of studies reporting these outcomes. We examined results by stage of CKD and study duration; we were unable to explore other potential sources of heterogeneity such as presence of diabetes mellitus or albuminuria/proteinuria, primary kidney disease, or antihypertensive regimen.

There was a substantial degree of heterogeneity among study results for some outcomes, including sodium intake/excretion, systolic BP, and weight, although this was reduced in subgroup analyses in most cases. A contributor to heterogeneity was inclusion of people across the stages of CKD, including 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. We analysed outcomes by CKD stage where possible, however this subgroup analysis was limited due to the small number of included studies, particularly in the

more advanced stages of CKD. Only two studies included post-transplant participants and seven in dialysis (two with people receiving PD, four with people receiving HD, one dialysis modality not specified). Other salt restriction studies have been conducted in people undergoing dialysis, 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.

There were important differences in methodology between short- (fewer than four weeks) and longer-term studies (four weeks and more) that limited subgroup analysis according to study duration. Short-term studies achieved a larger reduction in salt (6.4 g/day; 111 mmol or 2550 mg sodium) than studies of four weeks or longer reducing salt by (3.7 g/day; 64.53 mmol or 1480 mg sodium) but achieved similar reductions in BP (8/4 and 7/4 mm Hg respectively). However short-term studies used either supplemental sodium (Konishi 2001; LowSALT CKD 2012) or full meal provision (Ruilopec 1992a), therefore dietary confounders may have been more tightly controlled than in longer-term studies which most commonly compared dietary education to reduce salt versus usual diet. A limitation in two of the three short-term studies was that neither employed a washout period (Konishi 2001; Ruilopec 1992a). Considering that these studies had intervention durations of only one week, carry-over effect may have influenced study results. Ruilopec 1992a, a short-term study, began a new antihypertensive medication on day one of the study, further increasing risk of carry-over effect.

It is likely that differing magnitude of salt restriction impacted heterogeneity. A previous analysis showed a dose-response relationship between salt reduction and BP reduction (He 2003). We could not examine differential effects by magnitude of sodium reduction achieved as studies did not report results separately by level of sodium reduction achieved.

Quality of the evidence

We assessed the quality of study evidence using standard risks of bias domains within the Cochrane tool together with GRADE methodology. Confidence in evidence was high for systolic and diastolic BP and albuminuria. Confidence in evidence was low for sodium intake/excretion (substantial heterogeneity), extracellular fluid volume (uncertain or high risk of bias; few participants across all studies) and symptomatic hypotension (few participants across all studies; wide confidence interval range that include benefit or harm). Confidence in evidence was very low for weight (uncertain or high risk of bias; moderate heterogeneity; indirectness of outcome) and reduction in antihypertensive dose (high risk of bias; wide confidence interval range that include benefit or harm).

Potential bias from confounders were mostly due to lack of measurement or failing to adequately report or account for the impact of changes in medications and/or dietary changes such as potassium intake, protein intake and/or weight loss between interventions. Reduction in anti-hypertensive medications may have led to underestimations of the effect of salt restriction on BP and proteinuria. Studies that provided supplementary sodium (Catto 1973; Doulton 2007; Fine 1997; LowSALT CKD 2012; Mulhauser 1996; Ruilopec 1992a) to manage sodium intake were at lower risk of bias from dietary confounders because other dietary 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 (BalanceWise-HD 2013; BalanceWise-PD 2011; de Brito-Ashurst 2013; de Vries 2016; DUAAL 2011; ESMO 2017; ESPECIAL 2014; Keven 2006; Kwakernaak 2014; Rodrigues Telini 2014; Saran 2017; VIRTUE-CKD 2016; Vogt 2008) may be at a higher risk of bias from dietary confounders.

It is widely accepted that potassium intake affects BP. Nine of the 19 studies that reported BP as an outcome measured change in potassium intake either directly or indirectly and reported the findings. Seven studies (de Brito-Ashurst 2013; de Vries 2016; ESMO 2017; Kwakernaak 2014; LowSALT CKD 2012; Mulhauser 1996; VIRTUE-CKD 2016) reported potassium intake/excretion as unchanged with sodium restriction. DUAAL 2011 and Ruilope 1992a reported small, but significant, reductions in urinary potassium excretion in the sodium-restricted groups (3 to 4 mmol/day), which is likely to reflect reduction in urinary volume.

Body weight has also been reported to affect BP and proteinuria (Siebenhofer 2016). Given that most studies did not report change in fluid status, we could not determine the degree to which body weight change observed in included studies was due to reduction in fluid volume or body fat. The latter could introduce bias by overestimating the effect of salt restriction on BP and proteinuria.

Saran 2017 had high risk of bias across several domains due to protocol violation meaning that a large proportion of participants did not receive treatments in the allocated order or did not receive both treatments, incomplete outcome data and potential conflict of interest (due to two study authors holding stock in a company that makes the tool used for primary outcome measurement). Results for were similar when Saran 2017 was excluded for all outcomes anti-hypertensive dosage reduction; the magnitude of effect was increased when Saran 2017 was excluded.

Potential biases in the review process

This review was conducted according to a pre-specified protocol and used a highly sensitive search strategy. Inclusion/exclusion and risk of bias was conducted by two independent review authors and we considered evidence certainty in interpretation of the results. 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.

In the 2015 review, we contacted all study authors for additional information to inform our risk of bias assessment and received further information for five of the eight included studies (de Brito-Ashurst 2013; DUAAL 2011; Konishi 2001; LowSALT CKD 2012; Vogt 2008). Of the 13 additional studies included in this review update, we did not require further information for one study (Kwakernaak 2014); we could not find current contact details to request further information for three studies (Catto 1973; Doulton 2007; Mulhauser 1996); and we contacted study authors of the remaining nine studies and received further information for five studies (BalanceWise-HD 2013; BalanceWise-PD 2011; ESMO 2017; ESPECIAL 2014; VIRTUE-CKD 2016).

We applied a search strategy to include both published and unpublished studies, and were able to include one study where main findings were unpublished (BalanceWise-PD 2011) and

two studies where main findings were published as conference abstracts only (Doulton 2007; Power 2010).

Agreements and disagreements with other studies or reviews

Previous version of this review

This review update included 21 studies with 725 participants in the low salt group and 725 in the high salt group. This is a considerable increase compared with our 2015 review which included eight studies with 224 participants in the low salt group and 218 in the high salt group (McMahon 2015), and we were able to include additional outcomes in this update (proteinuria, albuminuria, inter-dialytic weight gain). A further difference from the 2015 review is that we included results from paired analyses where available which in most instances led to narrower confidence intervals than when results from unpaired analyses were included. Some key differences in the results of this update compared to the 2015 review are discussed below.

Our 2015 review included six studies in the earlier stages of CKD, one in dialysis, and one post-transplant. This update includes an additional six studies in the earlier stages of CKD (12 studies total), six in dialysis (seven studies total) and one post-transplant (two studies total). The additional studies in ESKD in this update improves generalisability of the findings to participants at this stage of kidney disease.

We found a smaller reduction on sodium intake/excretion in included studies in this update (mean 74 mmol/day) compared with the 2015 review (mean 106 mmol/day). This is likely due to an increase in the number of studies examining effectiveness of behavioural and education-based approaches to reducing salt intake, rather than the efficacy of salt reduction in a controlled setting. Included studies also had a longer intervention duration in this update compared with the 2015 review. Four of the eight included studies in the 2015 review used education to reduce sodium intake compared to 13 of the 21 studies in this update. Of these studies, those in the 2015 review tended to have higher baseline sodium intakes (mean values ranging from 177 to 261 mmol/day) than those added in this update (mean values ranging from 98 to 175 mmol/day), however target sodium intakes for the low salt group were similar, ranging between 50 to 100 mmol/day. This likely contributed to the smaller reduction in sodium seen in this review update versus the 2015 review. The inclusion of studies with lower sodium reduction also likely explains the slightly lower effect on systolic BP. We originally demonstrated that reducing salt intake by approximately 6 g/day (100 mmol or 2300 mg sodium/day) lowered BP by 9/4 mm Hg in people with CKD. In this update, we found that reducing salt intake by approximately 4.2 g/day (73.52 mmol or 1690 mg sodium) lowered BP by 7/4 mm Hg.

In the 2015 review, we did not meta-analyse the effects on proteinuria and albuminuria due to heterogeneity in outcome reporting. Instead we reported the range of effect in the four studies reporting proteinuria and one reporting albuminuria. In this update, we meta-analysed the effect of salt restriction on proteinuria (six studies) and albuminuria (six studies) mostly in the earlier stages of CKD, and our findings were consistent with those we reported in the 2015 review.

This update included three additional studies (four total) reporting on extracellular fluid, one (two total) reporting on presence of oedema and four (four total) reporting on intra-dialytic weight gain. We found significant reductions on extracellular fluid volume and presence of oedema which is an important finding as fluid overload is a strong predictor of cardiovascular events and kidney function decline in CKD (Essig 2008). We also found significant changes in CrCl and body weight in this update, while these were not significantly altered in the 2015 review, although these changes are likely due to changes in BP, proteinuria/albuminuria and fluid status and are unlikely to be clinically significant.

Other reviews in CKD

There have been three reviews of trials of salt restriction in people with CKD published since the 2015 review, including: 1) a narrative review of seven RCTs in non-dialysed, non-transplanted CKD participants (Nerbass 2018); 2) a systematic review of 12 randomised and non-randomised trials achieving at least one gram salt reduction in dialysis participants, and meta-analysis of the four RCTs (Cole 2019); and 3) a systematic review and meta-analysis of 11 RCTs in non-dialysed CKD patients (Garofalo 2018). Agreements and disagreements with the findings of the meta-analyses are discussed below.

Cole 2019 reported that salt restriction in four RCTs in dialysis reduced systolic/diastolic BP by 8/4. mm Hg. This is slightly higher than the difference in BP in our meta-analysis of five RCTs in dialysis (8/3 mm Hg), likely due to our inclusion of the BalanceWise-PD 2011 Study which did not achieve a significant reduction in sodium intake or BP.

Garofalo 2018 reported that a mean 80 mmol/day reduction in sodium excretion reduced ambulatory BP by 6/2 mm Hg and clinic-assessed BP by 5/3 in 11 RCTs in non-dialysed CKD patients, similar to our findings of a 6/3 reduction in 12 RCTs in the earlier stages of CKD, and resulted in a 29% mean reduction in proteinuria, similar to our results (34% reduction), and 14% reduction in albuminuria, whereas we found a 37% reduction in our analysis of the same five studies. These are likely due to differences in meta-analysis methods. We analysed albuminuria as log-transformed values (which in some cases was made possible only by provision of raw data by study authors), because these data are usually not normally distributed and effect is highly dependent on their baseline values. Garofalo 2018 converted medians and inter-quartile ranges to means and SD and pooled log-transformed with untransformed data. Three studies were weighted very low due to wide CI suggesting no effect on albuminuria (Kwakernaak 2014; LowSALT CKD 2012; VIRTUE-CKD 2016); however these studies all reported clinically and statistically significant effects on albuminuria ($P < 0.001$). It is likely that the study by Saran 2017 was weighted heavily because log-transformed values were used, leading to narrower confidence intervals.

Other reviews in non-CKD

Previous reviews investigating the effect of salt restriction have been conducted in people with normal kidney function, and these consistently show that reducing dietary sodium intake reduces BP, although magnitudes vary (Graudal 2020; He 2013; Hernandez 2018; Hooper 2002). Across these reviews, dietary salt reduction generally has a greater effect on people who are hypertensive (Graudal 2020; He 2013; Hooper 2002). We could not conduct subgroup analyses by hypertensive status as most participants

in the included studies were hypertensive and it was rare to report findings separately for hypertensive and normotensive participants. We found a reduction in BP of approximately 7/4 mm Hg with salt reduction of approximately 74 mmol. This is a similar to that found in hypertensive people without CKD; Graudal 2020 reported mean reduction of 6/3 mm Hg with median salt reduction of 145 mmol; Hernandez 2018 found that low-sodium salt substitutes decreased systolic BP by 8/4 mm Hg, with a 27 mmol decrease in urinary sodium and 13 mmol increase in urinary potassium.

Graudal 2020 also 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.

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). Our update found similar, with CrCl significantly reducing by 4.46 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).

Suckling 2010 found mixed results for the effects of salt restriction on proteinuria in people with diabetes. Aburto 2013 reported urinary protein excretion and albuminuria was reduced with lower sodium intake in a systematic review including two studies in the general population. Our review demonstrated proteinuria to significantly reduce by 34% following salt restriction; this difference was expected as people with CKD are more susceptible to proteinuria.

AUTHORS' CONCLUSIONS

Implications for practice

We found a strong case for the benefits of salt restriction in people with CKD. We found that reducing dietary salt considerably reduced BP in people with CKD. We found consistent evidence that dietary salt restriction reduced proteinuria in people with earlier stage (non-dialysed, non-transplanted) CKD by 34% to 36%. If such reductions were maintained long-term, this may translate to clinically significant reductions in ESKD and cardiovascular events.

Reduced salt intake may increase symptomatic hypotension. Data were sparse for other types of adverse events.

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 longer-term adherence to this target can be challenging for patients without regular and ongoing support to improve their motivation, knowledge and prevent behaviour change decay. These findings were based on studies with intervention durations up to 6 months. There are ongoing studies with longer intervention durations which will strengthen the evidence for longer-term effects.

Implications for research

We found that salt reduction in people with CKD reduced BP considerably and consistently reduced proteinuria over a time-

frame of up to 6 months. 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 critical outcomes such as death and progression to ESKD. If the reductions we found in short-term studies could be maintained long-term, these benefits may translate to clinically significant reductions in ESKD incidence and cardiovascular events. Research into longer-term effects of dietary sodium restriction for people with CKD is warranted, along with investigation of adherence to a low salt diet.

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 of salt restriction 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.

ACKNOWLEDGEMENTS

We would like to acknowledge the Cochrane Kidney and Transplant for providing administrative and support for the conduct of this review, and Brydee Johnston and Rabia Khalid for providing support with data extraction. We would also like to acknowledge the ongoing support from Menzies School of Health Research, University of Queensland, the Princess Alexandra Hospital and the Queensland Government. Emma McMahon is currently supported by a cofunded NHMRC/Australian Heart Foundation Early Career Fellowship (100085) and previously received support from the Australian Government through an Australian Postgraduate Award scholarship. The information and opinions contained in this paper are solely the responsibility of the authors and do not necessarily reflect the views or policy of NHMRC, Australian Heart Foundation, Menzies School of Health Research, University of Queensland, Griffith University, the Princess Alexandra Hospital and the Queensland Government.

The authors are grateful to the following peer reviewers for their time and comments: Ronald L. Koretz, M.D. Emeritus Professor of Clinical Medicine, David Geffen-UCLA School of Medicine, Los Angeles, California, USA; Retired Chief, Division of Gastroenterology, Olive View-UCLA Medical Center, Sylmar, California, USA; Colin H Jones, Consultant Physician and Nephrologist, York Teaching Hospital NHS Foundation Trust.

REFERENCES

References to studies included in this review

BalanceWise-HD 2013 {published and unpublished data}

Clark-Cutaia MN, Ren D, Hoffman LA, Burke LE, Sevvick MA. Adherence to hemodialysis dietary sodium recommendations: influence of patient characteristics, self-efficacy, and perceived barriers. *Journal of Renal Nutrition* 2014;**24**(2):92-9. [MEDLINE: 24462498]

Clark-Cutaia MN, Ren D, Hoffman LA, Snetselaar L, Sevvick MA. Psychometric validation of the self-efficacy for restricting dietary salt in hemodialysis scale. *Topics in Clinical Nutrition* 2013;**28**(4):384-91. [EMBASE: 2013726385]

Clark-Cutaia MN, Sevvick MA, Thurheimer-Cacciotti J, Hoffman LA, Snetselaar L, Burke LE, et al. Perceived barriers to adherence to hemodialysis dietary recommendations. *Clinical Nursing Research* 2019;**28**(8):1009-29. [MEDLINE: 29732932]

Hu L, St-Jules DE, Popp CJ, Sevvick MA. Determinants and the role of self-efficacy in a sodium-reduction trial in hemodialysis patients. *Journal of Renal Nutrition* 2019;**29**(4):328-32. [MEDLINE: 30579673]

Sevvick MA, Piraino BM, St-Jules DE, Hough LJ, Hanlon JT, Marcum ZA, et al. No difference in average interdialytic weight gain observed in a randomized trial with a technology-supported behavioral intervention to reduce dietary sodium intake in adults undergoing maintenance hemodialysis in the United States: primary outcomes of the BalanceWise study. *Journal of Renal Nutrition* 2016;**26**(3):149-58. [MEDLINE: 26868602]

Stark S, Snetselaar L, Piraino B, Stone RA, Kim S, Hall B, et al. Personal digital assistant-based self-monitoring adherence rates in 2 dialysis dietary intervention pilot studies: BalanceWise-HD and BalanceWise-PD. *Journal of Renal Nutrition* 2011;**21**(6):492-8. [MEDLINE: 21420316]

St-Jules DE, Woolf K, Pompeii ML, Sevvick MA. Exploring problems in following the hemodialysis diet and their relation to energy and nutrient intakes: the BalanceWise study. *Journal of Renal Nutrition* 2016;**26**(2):118-24. [MEDLINE: 26586249]

BalanceWise-PD 2011 {published and unpublished data}

Koprucki M, Piraino B, Bender F, Snetselaar L, Hall B, Stark S, et al. RCT of Personal Digital Assistant (PDA) supported dietary intervention to reduce sodium intake in PD [abstract no: 162]. *American Journal of Kidney Diseases* 2010;**55**(4):A72. [EMBASE: 70124819]

* Sevvick MA. BalanceWise-PD final progress report redacted (as supplied 14 June 2019). Data on file.

Stark S, Snetselaar L, Piraino B, Stone RA, Kim S, Hall B, et al. Personal digital assistant-based self-monitoring adherence rates in 2 dialysis dietary intervention pilot studies: BalanceWise-HD and BalanceWise-PD. *Journal of Renal Nutrition* 2011;**21**(6):492-8. [MEDLINE: 21420316]

Catto 1973 {published data only}

Catto GR, Smith FW, MacLeod M. Treatment of muscle cramps during maintenance haemodialysis. *BMJ* 1973;**3**(5876):389-90. [MEDLINE: 4581080]

de Brito-Ashurst 2013 {published and unpublished data}

De Brito-Ashurst I, Dobbie H, Raftery MJ, Yaqoob MM. Are hypertensive chronic kidney disease patients salt-sensitive? A randomised controlled study [abstract no: PUB722]. *Journal of the American Society of Nephrology* 2009;**20**(Abstract Suppl):990A.

* de Brito-Ashurst I, Perry L, Sanders TA, Thomas JE, Dobbie H, Varagunam M, et al. The role of salt intake and salt sensitivity in the management of hypertension in South Asian people with chronic kidney disease: a randomised controlled trial. *Heart* 2013;**99**(17):1256-60. [MEDLINE: 23766446]

de Brito-Ashurst I, Perry L, Sanders TA, Thomas JE, Dobbie H, Yaqoob MM. A dietitian's role in the management of blood pressure: results of a randomised controlled trial in British Bangladeshi chronic kidney disease patients [abstract no: PP077-MON]. *Clinical Nutrition Supplements* 2012;**7**(1):168-9. [EMBASE: 70903810]

de Vries 2016 {published data only (unpublished sought but not used)}

de Vries LV, Dobrowolski LC, Krediet CTP, Bemelman FJ, Bakker SJ, Navis G. Effect of dietary sodium restriction on blood pressure and urinary protein excretion in renal transplant recipients on RAAS-blockade [abstract no: FR-PO1030]. *Journal of the American Society of Nephrology* 2015;**26**(Abstract Suppl):605a.

* de Vries LV, Dobrowolski LC, van den Bosch JJ, Riphagen IJ, Krediet CT, Bemelman FJ, et al. Effects of dietary sodium restriction in kidney transplant recipients treated with renin-angiotensin-aldosterone system blockade: a randomized clinical trial. *American Journal of Kidney Diseases* 2016;**67**(6):936-44. [MEDLINE: 26803690]

Doulton 2007 {published data only}

* Doulton TW, Cassidy A, Wood M, Markandu ND, MacGregor GA. Reducing salt intake by 5 grams a day decreases thirst, interdialytic weight gain and blood pressure in haemodialysis patients [abstract]. In: Renal Association Annual Conference; 2007; Brighton, UK. 2007:152.

DUAAL 2011 {published and unpublished data}50137410

Humalda JK, Lambers Heerspink HJ, Kwakernaak AJ, Slagman MC, Waanders F, Vervloet MG, et al. Fibroblast growth factor 23 and the antiproteinuric response to dietary sodium restriction during renin-angiotensin-aldosterone system blockade. *American Journal of Kidney Diseases* 2015;**65**(2):259-66. [MEDLINE: 25278093]

Kwakernaak AJ, Lambert G, Slagman MC, Waanders F, Laverman GD, Petrides F, et al. Proprotein convertase subtilisin-kexin type 9 is elevated in proteinuric subjects: relationship

with lipoprotein response to antiproteinuric treatment. *Atherosclerosis* 2013;**226**(2):459-65. [MEDLINE: 23261172]

Kwakernaak AJ, Waanders F, Slagman MC, Dokter MM, Laverman GD, de Boer RA, et al. Sodium restriction on top of renin-angiotensin-aldosterone system blockade increases circulating levels of N-acetyl-seryl-aspartyl-lysyl-proline in chronic kidney disease patients. *Journal of Hypertension* 2013;**31**(12):2425-32. [MEDLINE: 24029871]

* Slagman MC, Waanders F, Hemmelder MH, Woittiez AJ, Janssen WM, Lambers Heerspink HJ, et al. Moderate dietary sodium restriction added to angiotensin converting enzyme inhibition compared with dual blockade in lowering proteinuria and blood pressure: randomised controlled trial. *BMJ* 2011;**343**:d4366. [MEDLINE: 21791491]

ESMO 2017 {published and unpublished data}

* Meuleman Y, Hoekstra T, Dekker FW, Navis G, Vogt L, van der Boog PJ, et al. Sodium restriction in patients with CKD: a randomized controlled trial of self-management support. *American Journal of Kidney Diseases* 2017;**69**(5):576-86. [MEDLINE: 27993433]

ESPECIAL 2014 {published and unpublished data}

Ahn SY, Kim DK, Han SS, Park JH, Choi B, Lim CS, et al. Weight loss has an additive effect on the anti-proteinuric effects of angiotensin II receptor blockers in hypertensive patients with CKD [abstract no: FR-PO502]. *Journal of the American Society of Nephrology* 2017;**28**(Abstract Suppl):531. [EMBASE: 633703439]

Ahn SY, Kim DK, Han SS, Park JH, Shin SJ, Lee SH, et al. Weight loss has an additive effect on the proteinuria reduction of angiotensin II receptor blockers in hypertensive patients with chronic kidney disease. *Kidney Research & Clinical Practice* 2018;**37**(1):49-58. [MEDLINE: 29629277]

Ahn SY, Kim DK, Park JH, Shin SJ, Lee SH, Choi BS, et al. Long-term effects of intensive low-salt diet education on deterioration of glomerular filtration rate among non-diabetic hypertensive patients with chronic kidney disease. *Kidney & Blood Pressure Research* 2019;**44**(5):1101-14. [MEDLINE: 31533093]

Am JN, Hwang JH, Lee JP, Chin HJ, Kim S, Kim DK, et al. The decrement of hemoglobin concentration with angiotensin II receptor blocker treatment is correlated with the reduction of albuminuria in non-diabetic hypertensive patients: post-hoc analysis of ESPECIAL trial. *PLoS ONE [Electronic Resource]* 2015;**10**(6):e0128632. [MEDLINE: 26098847]

Baek SH, Kim S, Kim DK, Park JH, Shin SJ, Lee SH, et al. A low-salt diet increases the estimated net endogenous acid production in nondiabetic chronic kidney disease patients treated with angiotensin receptor blockade. *Nephron* 2014;**128**(3-4):407-13. [MEDLINE: 25531146]

ESPECIAL study investigators. Individual participant data urinary albumin (as supplied 30 May 2019). Data on file.

Han SS, Bae E, Ahn SY, Kim S, Park JH, Shin SJ, et al. Urinary adiponectin and albuminuria in non-diabetic hypertensive

patients: an analysis of the ESPECIAL trial. *BMC Nephrology* 2015;**16**:123. [MEDLINE: 26232133]

* Hwang JH, Chin HJ, Kim S, Kim DK, Kim S, Park JH, et al. Effects of intensive low-salt diet education on albuminuria among nondiabetic patients with hypertension treated with olmesartan: a single-blinded randomized, controlled trial. *Clinical Journal of the American Society of Nephrology: CJASN* 2014;**9**(12):2059-69. [MEDLINE: 25332317]

Lee A, Chin HJ. Long term effects of intensive low salt diet education on deterioration of glomerular filtration rate among non-diabetic hypertensive patients with CKD [abstract no: FR-PO389]. *Journal of the American Society of Nephrology* 2017;**28**(Abstract Suppl):501. [EMBASE: 633700111]

Lim CS, Hwang JH, Chin HJ, Kim DK, Kim S, Park JH, et al. Effects of low sodium intake on the antiproteinuric efficacy of olmesartan in hypertensive patients with albuminuria (ESPECIAL): a randomized clinical trial [abstract no: MP146]. *Nephrology Dialysis Transplantation* 2014;**29**(Suppl 3):iii376. [EMBASE: 71492549]

Lim CS, Hwang JH, Chin HJ, Kim S, Choi BS. Effects of low sodium intake on the anti-proteinuric efficacy of olmesartan in hypertensive patients with albuminuria [abstract no: SA-PO155]. *Journal of the American Society of Nephrology* 2013;**24**(Abstract Suppl):659A.

Yu MY, Kim DK, Park JH, Shin SJ, Lee SH, Choi BS, et al. Albuminuria during treatment with angiotensin type II receptor blocker is a predictor for GFR decline among non-diabetic hypertensive CKD patients. *PLoS ONE [Electronic Resource]* 2018;**13**(8):e0202676. [MEDLINE: 30148871]

Fine 1997 {published data only}

* Fine A, Fontaine B, Ma M. Commonly prescribed salt intake in continuous ambulatory peritoneal dialysis patients is too restrictive: results of a double-blind crossover study. *Journal of the American Society of Nephrology* 1997;**8**(8):1311-4. [MEDLINE: 9259359]

Fine A. CAPD patients can take more salt in diet than usually prescribed [abstract]. *Nephrology Dialysis Transplantation* 1997;**12**(9):A183. [CENTRAL: CN-00261430]

Keven 2006 {published and unpublished data}

* Keven K, Yalcin S, Canbakan B, Kutlay S, Sengul S, Erturk S, et al. The impact of daily sodium intake on posttransplant hypertension in kidney allograft recipients. *Transplantation Proceedings* 2006;**38**(5):1323-6. [MEDLINE: 16797292]

Konishi 2001 {published and unpublished data}

Konishi Y, Imanishi M, Morikawa T, Teramoto K, Okada N, Okumura M, et al. Relationship of impairment of the renin-angiotensin system and sodium sensitivity of blood pressure in immunoglobulin A (IgA) nephropathy [abstract no: FC2-04]. *Nephrology* 2003;**8**(Suppl 1):A16. [CENTRAL: CN-01657789]

Konishi Y, Morikawa T, Yasu T, Teramoto K, Okada N, Yoshioka K, et al. Blunted response of the renin-angiotensin system and nitric oxide synthesis related to sodium sensitivity in

immunoglobulin A nephropathy. *Hypertension Research - Clinical & Experimental* 2004;**27**(1):7-13. [MEDLINE: 15055250]

Konishi Y, Nishiyama A, Morikawa T, Kitabayashi C, Shibata M, Hamada M, et al. Relationship between urinary angiotensinogen and salt sensitivity of blood pressure in patients with IgA nephropathy. *Hypertension* 2011;**58**(2):205-11. [MEDLINE: 21670416]

* Konishi Y, Okada N, Okamura M, Morikawa T, Okumura M, Yoshioka K, et al. Sodium sensitivity of blood pressure appearing before hypertension and related to histological damage in immunoglobulin A nephropathy. *Hypertension* 2001;**38**(1):81-5. [MEDLINE: 11463764]

Kwakernaak 2014 {published data only}

Binnenmars SH, Corpeleijn E, Kwakernaak AJ, Touw DJ, Kema IP, Laverman GD, et al. Impact of moderate sodium restriction and hydrochlorothiazide on iodine excretion in diabetic kidney disease: data from a randomized cross-over trial. *Nutrients* 2019;**11**(9):2204. [MEDLINE: 31547438]

Humalda JK, Keyzer CA, Binnenmars SH, Kwakernaak AJ, Slagman MC, Laverman GD, et al. Concordance of dietary sodium intake and concomitant phosphate load: Implications for sodium interventions. *Nutrition Metabolism & Cardiovascular Diseases* 2016;**26**(8):689-96. [MEDLINE: 27266988]

Humalda JK, Seiler-Muler S, Kwakernaak AJ, Vervloet MG, Navis G, Fliser D, et al. Response of fibroblast growth factor 23 to volume interventions in arterial hypertension and diabetic nephropathy. *Medicine* 2016;**95**(46):e5003. [MEDLINE: 27861335]

Humalda JK, Seiler S, Kwakernaak AJ, Vervloet MG, Navis G, Heine GH, et al. Response of fibroblast growth factor 23 to sodium interventions in diabetic nephropathy and arterial hypertension [abstract no: PUB535]. *Journal of the American Society of Nephrology* 2015;**26**(Abstract Suppl):1012A.

* Kwakernaak AJ, Krikken JA, Binnenmars SH, Visser FW, Hemmelder MH, Woittiez AJ, et al. Effects of sodium restriction and hydrochlorothiazide on RAAS blockade efficacy in diabetic nephropathy: a randomised clinical trial. *Lancet Diabetes & Endocrinology* 2014;**2**(5):385-95. [MEDLINE: 24795252]

LowSALT CKD 2012 {published and unpublished data}

Campbell KL, Johnson DW, Bauer JD, Hawley CM, Isbel NM, Stowasser M, et al. A randomized trial of sodium-restriction on kidney function, fluid volume and adipokines in CKD patients. *BMC Nephrology* 2014;**15**(1):57. [MEDLINE: 24708818]

LowSALT CKD study Investigators. Individual patient data (as supplied 24 May 2019). Data on file.

McMahon E, Bauer J, Hawley C, Isbel N, Stowasser M, Johnson D, et al. Effect of sodium restriction on blood pressure, fluid status and proteinuria in CKD patients: results of a randomised crossover trial and 6-month follow-up [abstract no: 004]. *Nephrology* 2013;**18**(Suppl 1):15-6. [CENTRAL: CN-01062204] [EMBASE: 71356987]

* McMahon EJ, Bauer JD, Hawley CM, Isbel NM, Stowasser M, Johnson DW, et al. A randomized trial of dietary sodium

restriction in CKD. *Journal of the American Society of Nephrology* 2013;**24**(12):2096-103. [MEDLINE: 24204003]

McMahon EJ, Bauer JD, Hawley CM, Isbel NM, Stowasser M, Johnson DW, et al. The effect of lowering salt intake on ambulatory blood pressure to reduce cardiovascular risk in chronic kidney disease (LowSALT CKD study): protocol of a randomized trial. *BMC Nephrology* 2012;**13**(1):137. [MEDLINE: 23082956]

Mulhauser 1996 {published data only}

* Mulhauser I, Prange K, Sawicki PT, Bender R, Dworschak A, Schaden W, et al. Effects of dietary sodium on blood pressure in IDDM patients with nephropathy. *Diabetologia* 1996;**39**(2):212-9. [MEDLINE: 8635674]

Power 2010 {published data only (unpublished sought but not used)}

Power AJ, Singh S, Edwards C, Tandari D, Taube D, Duncan ND. A randomized controlled trial of low dialysate and dietary sodium on blood pressure in hemodialysis [abstract no: F-FC320]. *Journal of the American Society of Nephrology* 2010;**21**(Abstract Suppl):73A.

Rodrigues Telini 2014 {published data only (unpublished sought but not used)}

Rodrigues Telini LS, de Carvalho BG, Caramori JC, Castro JH, Martin LC, Barretti P. Effect of dietary sodium restriction on body water, blood pressure, and inflammation in hemodialysis patients: a prospective randomized controlled study. *International Urology & Nephrology* 2014;**46**(1):91-7. [MEDLINE: 23340794]

Ruilope 1992a {published data only}

Ruilope LM, Casal MC, Guerrero L, Alcázar JM, Fernández ML, Lahera V, et al. Sodium intake does not influence the effect of verapamil in hypertensive patients with mild renal insufficiency. *Drugs* 1992;**44** Suppl 1:94-8. [MEDLINE: 1283591]

Saran 2017 {published data only (unpublished sought but not used)}

* Saran R, Padilla RL, Gillespie BW, Heung M, Hummel SL, Derebail VK, et al. A randomized crossover trial of dietary sodium restriction in stage 3-4 CKD. *Clinical Journal of the American Society of Nephrology: CJASN* 2017;**12**(3):399-407. [MEDLINE: 28209636]

Saran R, Sands RL, Gillespie BW, Heung M, Hummel SL, Derebail VK, et al. A crossover trial of lowering dietary sodium (Na) in chronic kidney disease (CKD) [abstract no: FR-OR118]. *Journal of the American Society of Nephrology* 2012;**23**(Abstract Suppl):56A.

Saran R, Sands RL, Gillespie BW, Heung M, Hummel SL, Derebail VK, et al. Baseline observations from a randomized crossover trial of lowering sodium intake in chronic kidney disease (CKD)-LOSALT study [abstract no: TH-PO357]. *Journal of the American Society of Nephrology* 2011;**22**(Abstract Suppl):195A.

ViRTUE-CKD 2016 {published and unpublished data}

De Borst MH, Keyzer CA, van Breda F, Vervloet MG, Laverman GD, Hemmelder MH, et al. Vitamin D receptor activation and dietary sodium restriction to reduce residual albuminuria in chronic kidney disease [abstract no: SA-PO1106]. *Journal of the American Society of Nephrology* 2015;**26**(Abstract Suppl):B7.

de Jong MA, Keyzer CA, van Breda F, Vervloet MG, Laverman GD, Hemmelder MH, et al. Baseline 25-hydroxyvitamin D level and the anti-albuminuric response to vitamin D receptor activation in patients with chronic kidney disease [abstract no: TH-PO515]. *Journal of the American Society of Nephrology* 2016;**27**(Abstract Suppl):210A-1A.

de Jong MA, Keyzer CA, van Breda F, Vervloet MG, Navis G, Bakker SJ, et al. Effect of vitamin D receptor activation and sodium restriction on calcification propensity and fibroblast growth factor 23: the Virtue-CKD trial [abstract no: TH-PO516]. *Journal of the American Society of Nephrology* 2016;**27**(Abstract Suppl):211A.

Keyzer CA, de Jong MA, van Breda GF, Vervloet MG, Laverman GD, Hemmelder M, et al. Vitamin D receptor activator and dietary sodium restriction to reduce residual urinary albumin excretion in chronic kidney disease (ViRTUE study): rationale and study protocol. *Nephrology Dialysis Transplantation* 2016;**31**(7):1081-7. [MEDLINE: 25744274]

* Keyzer CA, van Breda GF, Vervloet MG, de Jong MA, Laverman GD, Hemmelder MH, et al. Effects of vitamin D receptor activation and dietary sodium restriction on residual albuminuria in CKD: the ViRTUE-CKD trial. *Journal of the American Society of Nephrology* 2016;**28**(4):1296-305. [MEDLINE: 27856633]

Vogt 2008 {published and unpublished data}

Gant CM, Laverman GD, Vogt L, Slagman MC, Heerspink HJ, Waanders F, et al. Renoprotective RAAS inhibition does not affect the association between worse renal function and higher plasma aldosterone levels. *BMC Nephrology* 2017;**18**(1):370. [MEDLINE: 29262813]

Krikken JA, Waanders F, Dallinga-Thie GM, Dikkeschei LD, Vogt L, Navis GJ, et al. Antiproteinuric therapy decreases LDL-cholesterol as well as HDL-cholesterol in non-diabetic proteinuric patients: relationships with cholesteryl ester transfer protein mass and adiponectin. *Expert Opinion on Therapeutic Targets* 2009;**13**(5):497-504. [MEDLINE: 19397474]

Mahmoodi BK, Mulder AB, Waanders F, Spronk HM, Mulder R, Slagman MC, et al. The impact of antiproteinuric therapy on the prothrombotic state in patients with overt proteinuria. *Journal of Thrombosis & Haemostasis* 2011;**9**(12):2416-23. [MEDLINE: 21972946]

Slagman MC, Kwakernaak AJ, Yazdani S, Laverman GD, van den Born J, Titze J, et al. Vascular endothelial growth factor C levels are modulated by dietary salt intake in proteinuric chronic kidney disease patients and in healthy subjects. *Nephrology Dialysis Transplantation* 2012;**27**(3):978-82. [MEDLINE: 21778278]

Slagman MC, Nguyen TQ, Waanders F, Vogt L, Hemmelder MH, Laverman GD, et al. Effects of antiproteinuric intervention on elevated connective tissue growth factor (CTGF/CCN-2) plasma and urine levels in nondiabetic nephropathy. *Clinical Journal of the American Society of Nephrology: CJASN* 2011;**6**(8):1845-50. [MEDLINE: 21784839]

Slagman MC, Sinkeler SJ, Hemmelder MH, Waanders F, Vogt L, Kluin-Nelemans HC, et al. Erythropoietin is reduced by combination of diuretic therapy and RAAS blockade in proteinuric renal patients with preserved renal function. *Nephrology Dialysis Transplantation* 2010;**25**(10):3256-60. [MEDLINE: 20339099]

Slagman MC, Waanders F, Vogt L, Damman K, Hemmelder M, Navis G, et al. Elevated N-terminal pro-brain natriuretic peptide levels predict an enhanced anti-hypertensive and anti-proteinuric benefit of dietary sodium restriction and diuretics, but not angiotensin receptor blockade, in proteinuric renal patients. *Nephrology Dialysis Transplantation* 2012;**27**(3):983-90. [MEDLINE: 21862455]

Vogt L, de Zeeuw D, Waanders F, Navis G. Independent and added effects of low sodium and diuretic on renoprotective effect of AII antagonist in non-diabetic proteinuric patients [abstract no: TH-FC171]. *Journal of the American Society of Nephrology* 2005;**16**:37A. [CENTRAL: CN-00644129]

* Vogt L, Waanders F, Boomsma F, de Zeeuw D, Navis G. Effects of dietary sodium and hydrochlorothiazide on the antiproteinuric efficacy of losartan. *Journal of the American Society of Nephrology* 2008;**19**(5):999-1007. [MEDLINE: 18272844]

Waanders F, Vaidya VS, van Goor H, Leuvenink H, Damman K, Hamming I, et al. Effect of renin-angiotensin-aldosterone system inhibition, dietary sodium restriction, and/or diuretics on urinary kidney injury molecule 1 excretion in nondiabetic proteinuric kidney disease: a post hoc analysis of a randomized controlled trial. *American Journal of Kidney Diseases* 2009;**53**(1):16-25. [MEDLINE: 18823687]

References to studies excluded from this review

Chanwikrai 2012 {published data only}

Chanwikrai Y, Satirapod B. A randomized controlled trial of dietary and lifestyle modification based on the empowerment approach among chronic kidney disease patients [abstract no: 311]. *Kidney Research & Clinical Practice* 2012;**31**(2):A95-6. [EMBASE: 70815020]

Clark-Cutaia 2016 {published data only}

Clark-Cutaia MN, Reisinger N, Anache MR, Ramos K, Sommers MS, Townsend RR, et al. Feasibility of assessing sodium-associated body fluid composition in end-stage renal disease. *Nursing Research* 2019;**68**(3):246-52. [MEDLINE: 31033867]

Clark-Cutaia MN, Sommers MS, Anderson E, Townsend RR. Design of a randomized controlled clinical trial assessing dietary sodium restriction and hemodialysis-related symptom

profiles. *Contemporary Clinical Trials Communications* 2016;**3**:70-3. [MEDLINE: 27822564]

DD 2017 {published data only}

Bovee DM, Danser AH, Zietse R, Hoorn EJ. Dietary sodium restriction versus diuretics for salt-sensitive hypertension in chronic kidney disease [abstract no: 053]. *Hypertension* 2018;**72**(Suppl 1). [EMBASE: 626089737]

Bovee DM, Danser AH, Zietse R, Hoorn EJ. Dietary sodium restriction versus diuretics for salt-sensitive hypertension in CKD [abstract no: TH-OR052]. *Journal of the American Society of Nephrology* 2017;**28**(Abstract Suppl):14. [EMBASE: 633699948]

Bovee DM, Visser WJ, Middel I, De Mik-van EA, Greupink R, Masereeuw R, et al. A randomized trial of distal diuretics versus dietary sodium restriction for hypertension in chronic kidney disease. *Journal of the American Society of Nephrology* 2020;**31**(3):650-62. [MEDLINE: 31996411]

De Nicola 2000 {published data only}

De Nicola L, Bellizzi V, Minutolo R, Cioffi M, Giannattasio P, Terracciano V, et al. Effect of dialysate sodium concentration on interdialytic increase of potassium. *Journal of the American Society of Nephrology* 2000;**11**(12):2337-43. [MEDLINE: 11095656]

Esnault 2005 {published data only}

Ekhlas Eid A, Nguyen J, Delcroix C, Moutel M, Esnault VL. Effect of diuretics after dual blockade of renin-angiotensin-aldosterone system on severe proteinuria [abstract]. In: 41st Congress. European Renal Association. European Dialysis and Transplantation Association; 2004 May 15-18; Lisbon, Portugal. 2004:434-5. [CENTRAL: CN-00509172]

Esnault VL, Ekhlas A, Delcroix C, Moutel MG, Nguyen JM. Diuretic and enhanced sodium restriction results in improved antiproteinuric response to RAS blocking agents. *Journal of the American Society of Nephrology* 2005;**16**(2):474-81. [MEDLINE: 15615822]

Esnault VL, Ekhlas A, Nguyen JM, Delcroix C, Moutel MG. Angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB) and diuretics for refractory proteinuria [abstract no: SU-PO1030]. *Journal of the American Society of Nephrology* 2003;**14**(Nov):762A. [CENTRAL: CN-00583888]

HHK 2018 {published data only}

Sevick MA, Woolf K, Mattoo A, Katz SD, Li H, St-Jules DE, et al. The Healthy Hearts and Kidneys (HHK) study: Design of a 2x2 RCT of technology-supported self-monitoring and social cognitive theory-based counseling to engage overweight people with diabetes and chronic kidney disease in multiple lifestyle changes. *Contemporary Clinical Trials* 2018;**64**:265-73. [MEDLINE: 28867396]

Imanishi 1997 {published data only}

Imanishi M, Yoshioka K, Okumura M, Konishi Y, Tanaka S, Fujii S, et al. Mechanism of decreased albuminuria caused by angiotensin converting enzyme inhibitor in early diabetic nephropathy. *Kidney International - Supplement* 1997;**51**(63):S198-200. [MEDLINE: 9407458]

Kauric-Klein 2012 {published data only}

Kauric-Klein Z, Peters RM, Yarandi HN. Self-efficacy and blood pressure self-care behaviors in patients on chronic hemodialysis. *Western Journal of Nursing Research* 2017;**39**(7):886-905. [MEDLINE: 27456461]

Kauric-Klein Z. Blood pressure knowledge in hypertensive hemodialysis patients. *Cannt Journal* 2012;**22**(4):18-25. [MEDLINE: 23413535]

Kauric-Klein Z. Improving blood pressure control in end stage renal disease through a supportive educative nursing intervention. *Nephrology Nursing Journal* 2012;**39**(3):217-28. [MEDLINE: 22866361]

Li 2013f {published data only}

Jardine A, Li NY, Ninomiya T, Feng X, Zhang J, Shi J, et al. A sustained dietary sodium reduction program reduces albuminuria: a large cluster randomised trial [abstract no: SA-OR079]. *Journal of the American Society of Nephrology* 2014;**25**(Abstract Suppl):99a.

Jardine MJ, Li N, Ninomiya T, Feng X, Zhang J, Shi J, et al. Dietary sodium reduction reduces albuminuria: a cluster randomized trial. *Journal of Renal Nutrition* 2019;**29**(4):276-84. [MEDLINE: 30591358]

Li N, Yan LL, Niu W, Labarthe D, Feng X, Shi J, et al. A large-scale cluster randomized trial to determine the effects of community-based dietary sodium reduction--the China Rural Health Initiative Sodium Reduction Study. *American Heart Journal* 2013;**166**(5):815-22. [MEDLINE: 24176436]

Reyes 2013 {published data only}

Cuff L, Padilla RL, Verma TP, Gillespie BW, Peterman D, Heung M, et al. Barriers to dietary sodium restrictions among patients on hemodialysis [abstract no: SA-PO961]. *Journal of the American Society of Nephrology* 2014;**25**(Abstract Suppl):862A.

Rao PS, Padilla RL, Cuff L, Verma TP, Peterman D, Heung M, et al. Salt taste sensitivity, sodium intake, and fluid status in hemodialysis [abstract no: TH-PO804]. *Journal of the American Society of Nephrology* 2015;**26**(Abstract Suppl):275a.

Reyes J, Williams CM, Raimann JG, Sheppard PF, Thijssen S, Levin NW, et al. Association of dietary sodium restriction and thirst in hemodialysis patients [abstract no: FR-PO447]. *Journal of the American Society of Nephrology* 2013;**24**(Abstract Suppl):468A.

Suckling 2016 {published data only}

Suckling R, He F, Markandu N, MacGregor G. Modest salt reduction in impaired glucose tolerance and type 2 diabetes lowers blood pressure and urinary albumin excretion [abstract no: Su139]. *NDT Plus* 2010;**3**(Suppl 3):iii349. [EMBASE: 70484357]

Suckling R, He F, Markandu N, MacGregor G. Modest salt reduction lowers blood pressure and urinary albumin excretion in impaired glucose tolerance and type 2 diabetes [abstract no: SA.01]. *Journal of Hypertension* 2010;**28**(Suppl A):e219. [EMBASE: 70214893]

Suckling RJ, He F, Markandu N, MacGregor G. Modest reduction in salt intake lowers blood pressure and urinary albumin excretion in individuals with impaired glucose tolerance and type II diabetes [abstract no: PE.02]. *Journal of Human Hypertension* 2010;**24**(10):708. [EMBASE: 70273931]

Suckling RJ, He FJ, Markandu ND, MacGregor GA. Modest salt reduction lowers blood pressure and albumin excretion in impaired glucose tolerance and type 2 diabetes mellitus: a randomized double-blind trial. *Hypertension* 2016;**67**(6):1189-95. [MEDLINE: 27160199]

References to ongoing studies

NCT03373500 {published data only}

Swift P. Effect of dietary salt reduction on blood pressure in kidney transplant recipients. [clinicaltrials.gov/show/nct03373500](https://clinicaltrials.gov/show/study/NCT03373500) (first received 14 December 2017).

OxCKD1 2012 {published data only}

O'Callaghan CA. OxCKD1 - Empowering healthy lifestyle choices in chronic kidney disease (OxCKD1). [clinicaltrials.gov/show/nct01552317](https://clinicaltrials.gov/show/study/NCT01552317) (first received 13 March 2012).

STICK 2015 {published data only}

O'Donnell MJ, Smyth A. Sodium Intake in Chronic Kidney Disease (STICK). [clinicaltrials.gov/ct2/show/NCT02458248](https://clinicaltrials.gov/ct2/show/study/NCT02458248) (first received 1 Jun 2015).

SUBLIME 2020 {published data only}

Humalda JK, Klaassen G, De Vries H, Meuleman Y, Laverman GD, Bos WJ, et al. The 'sublime' approach: Cost-efficacy of a novel self-management approach for dietary sodium restriction in CKD patients [abstract no: SP351]. *Nephrology Dialysis Transplantation* 2016;**31**(Suppl 1):i206-7. [EMBASE: 72326453]

Humalda JK, Klaassen G, de Vries H, Meuleman Y, Verschuur LC, Straathof EJ, et al. A self-management approach for dietary sodium restriction in patients with CKD: a randomized controlled trial. *American Journal of Kidney Diseases* 2020;**75**(6):847-56. [MEDLINE: 31955921]

SUPER 2016 {published data only}

Mills KT. Sodium Lowering and Urinary Protein Reduction Trial (SUPER) [Effect of dietary sodium reduction in kidney disease patients with albuminuria]. [clinicaltrials.gov/ct2/show/NCT02945969](https://clinicaltrials.gov/ct2/show/study/NCT02945969) (first received 26 October 2016).

Additional references

Aburto 2013

Aburto NJ, Ziolkovska A, Hooper L, Elliott P, Cappuccio FP, Meerpohl JJ. Effect of lower sodium intake on health: systematic review and meta-analyses. *BMJ* 2013;**346**:f1326. [MEDLINE: 23558163]

Allen 1997

Allen TJ, Waldron MJ, Casley D, Jerums G, Cooper ME. Salt restriction reduces hyperfiltration, renal enlargement, and albuminuria in experimental diabetes. *Diabetes* 1997;**46**(1):19-24. [MEDLINE: 8971091]

Al-Solaiman 2009

Al-Solaiman Y, Jesri A, Zhao Y, Morrow JD, Egan BM. Low-Sodium DASH reduces oxidative stress and improves vascular function in salt-sensitive humans. *Journal of Human Hypertension* 2009;**23**(12):826-35. [MEDLINE: 19404315]

Ang 1999

Ang KS, Benarbia S, Boulahrouz R, Stanescu C, Charasse C, Le Cacheux P, et al. Arterial hypertension in the hemodialysis patient. A model of salt-sensitive hypertension in man [L'hypertension arterielle du patient hemodialyse. Un modele d'hypertension sensible au sel chez l'homme]. *Archives des Maladies du Coeur et des Vaisseaux* 1999;**92**(8):1023-6. [MEDLINE: 10486658]

Bakris 2000

Bakris GL, Williams M, Dworkin L, Elliott WJ, Epstein M, Toto R, et al. Preserving renal function in adults with hypertension and diabetes: a consensus approach. National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. *American Journal of Kidney Diseases* 2000;**36**(3):646-61. [MEDLINE: 10977801]

Bland 1996

Bland JM, Altman DG. The use of transformation when comparing two means. *BMJ* 1996;**312**(7039):1153. [MEDLINE: 8620137]

Cole 2019

Cole NI, Swift PA, He FJ, MacGregor GA, Suckling RJ. The effect of dietary salt on blood pressure in individuals receiving chronic dialysis: a systematic review and meta-analysis of randomised controlled trials. *Journal of Human Hypertension* 2019;**33**(4):319-26. [MEDLINE: 30413764]

Elliot 2006

Elliot P, Brown I. Sodium intakes around the world: background document prepared for the forum and technical meeting on reducing salt intake in populations (Paris 5-7th October 2006). Geneva: WHO Press, 2006. [ISBN: 978 92 4 159593 5]

Essig 2008

Essig M, Escoubet B, de Zuttere D, Blanchet F, Arnoult F, Dupuis E, et al. Cardiovascular remodelling and extracellular fluid excess in early stages of chronic kidney disease. *Nephrology Dialysis Transplantation* 2008;**23**(1):239-48. [MEDLINE: 17704109]

Garofalo 2018

Garofalo C, Borrelli S, Provenzano M, De Stefano T, Vita C, Chiodini P, et al. Dietary salt restriction in chronic kidney disease: a meta-analysis of randomized clinical trials. *Nutrients* 2018;**10**(6):732. [MEDLINE: 29882800]

GBD 2019

Institute for Health Metrics and Evaluation (IHME). GBD Compare. Seattle, WA: IHME, University of Washington. 2019. www.vizhub.healthdata.org/gbd-compare (Accessed 8 May 2021).

Go 2004

Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization [Erratum in: *N Engl J Med*. 2008;18(4):4]. *New England Journal of Medicine* 2004;**351**(13):1296-305. [MEDLINE: 15385656]

GRADE 2008

Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;**336**(7650):924-6. [MEDLINE: 18436948]

GRADE 2011

Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *Journal of Clinical Epidemiology* 2011;**64**(4):383-94. [MEDLINE: 21195583]

Graudal 2020

Graudal NA, Hubeck-Graudal T, Jurgens G. Effects of low sodium diet versus high sodium diet on blood pressure, renin, aldosterone, catecholamines, cholesterol, and triglyceride. *Cochrane Database of Systematic Reviews* 2020, Issue 12. Art. No: CD004022. [DOI: [10.1002/14651858.CD004022.pub5](https://doi.org/10.1002/14651858.CD004022.pub5)]

Guerin 2001

Guerin AP, Blacher J, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness attenuation on survival of patients in end-stage renal failure. *Circulation* 2001;**103**(7):987-92. [MEDLINE: 11181474]

He 2003

He FJ, MacGregor GA. How far should salt intake be reduced? *Hypertension* 2003;**42**(6):1093-9. [MEDLINE: 14610100]

He 2013

He FJ, Li J, MacGregor GA. Effect of longer-term modest salt reduction on blood pressure. *Cochrane Database of Systematic Reviews* 2013, Issue 4. Art. No: CD004937. [DOI: [10.1002/14651858.CD004937.pub2](https://doi.org/10.1002/14651858.CD004937.pub2)]

Hernandez 2018

Hernandez AV, Emonds EE, Chen BA, Loayza JA, Pasupuleti V, Roman-Morillo YM, et al. Systematic review and meta-analysis of the effects of low sodium salt substitutes on cardiovascular outcomes [abstract]. *Journal of the American College of Cardiology* 2018;**71**(11):A1749. [EMBASE: 621787030]

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557-60. [MEDLINE: 12958120]

Higgins 2008

Higgins JP, White IR, Anzueto-Cabrera J. Meta-analysis of skewed data: combining results reported on log-transformed or raw scales. *Statistics in Medicine* 2008;**27**(29):6072-92. [MEDLINE: 18800342]

Higgins 2011

Higgins JP, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Hooper 2002

Hooper L, Bartlett C, Davey Smith G, Ebrahim S. Systematic review of long term effects of advice to reduce dietary salt in adults. *BMJ* 2002;**325**(7365):628. [MEDLINE: 12242173]

Hunsicker 2004

Hunsicker LG. The consequences and costs of chronic kidney disease before ESRD. *Journal of the American Society of Nephrology* 2004;**15**(5):1363-4. [MEDLINE: 15100382]

Jones-Burton 2006

Jones-Burton C, Mishra SI, Fink JC, Brown J, Gossa W, Bakris GK, et al. An in-depth review of the evidence linking dietary salt intake and progression of chronic kidney disease. *American Journal of Nephrology* 2006;**26**(3):268-75. [MEDLINE: 16763384]

Kayikcioglu 2009

Kayikcioglu M, Tumuklu M, Ozkahya M, Ozdogan O, Asci G, Duman S, et al. The benefit of salt restriction in the treatment of end-stage renal disease by haemodialysis. *Nephrology Dialysis Transplantation* 2009;**24**(3):956-62. [MEDLINE: 19004849]

KDIGO 2013

Levin A, Stevens PE, Bilous RW, Coresh J, De Francisco AL, De Jong PE, et al. Kidney disease: Improving global outcomes (KDIGO) CKD work group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney International Supplements* 2013;**3**(1):1-150. [EMBASE: 369856107]

Korhonen 2000

Korhonen MH, Jarvinen RM, Sarkkinen ES, Uusitupa MI. Effects of a salt-restricted diet on the intake of other nutrients. *American Journal of Clinical Nutrition* 2000;**72**(2):414-20. [MEDLINE: 10919936]

Law 2009

Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ* 2009;**338**:b1665. [MEDLINE: 19454737]

Malta 2018

Malta D, Petersen K S, Johnson C, Trieu K, Rae S, Jefferson K, et al. High sodium intake increases blood pressure and risk of kidney disease. From the Science of Salt: A regularly updated systematic review of salt and health outcomes (August 2016 to March 2017). *Journal of Clinical Hypertension* 2018;**20**(12):1654-65. [MEDLINE: 30402970]

McMahon 2012a

McMahon EJ, Campbell KL, Mudge D, Bauer JD. Achieving salt restriction in chronic kidney disease. *International Journal of Nephrology* 2012:720429. [MEDLINE: 23320173]

Mozaffarian 2014

Mozaffarian D, Fahimi S, Singh GM, Micha R, Khatibzadeh S, Engell RE, et al. Global sodium consumption and death from cardiovascular causes. *New England Journal of Medicine* 2014;**371**(7):624-34. [MEDLINE: 25119608]

Nerbass 2018

Nerbass FB, Calice-Silva V, Pecoits-Filho R. Sodium intake and blood pressure in patients with chronic kidney disease: a salty relationship. *Blood Purification* 2018;**45**(1-3):166-72. [MEDLINE: 29478050]

NKF 2002

National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *American Journal of Kidney Diseases* 2002;**39**(2 Suppl 1):S1-266. [MEDLINE: 11904577]

Osanai 2002

Osanai T, Fujiwara N, Saitoh M, Sasaki S, Tomita H, Nakamura M, et al. Relationship between salt intake, nitric oxide and asymmetric dimethylarginine and its relevance to patients with end-stage renal disease. *Blood Purification* 2002;**20**(5):466-8. [MEDLINE: 12207094]

Qian 2018

Qian Q. Salt, water and nephron: mechanisms of action and link to hypertension and chronic kidney disease. *Nephrology* 2018;**23** Suppl 4:44-9. [MEDLINE: 30298656]

Ritz 2009

Ritz E, Koleganova N, Piecha G. Role of sodium intake in the progression of chronic kidney disease. *Journal of Renal Nutrition* 2009;**19**(1):61-2. [MEDLINE: 19121773]

Rupp 1978

Rupp JW, Stone RA, Gunning BE. Sodium versus sodium fluid restriction in hemodialysis: control of weight gains and blood pressures. *American Journal of Clinical Nutrition* 1978;**31**(10):1952-5. [MEDLINE: 707354]

Schunemann 2011a

Schünemann HJ, Oxman AD, Higgins JP, Vist GE, Glasziou P, Guyatt GH. Chapter 11: Presenting results and 'Summary of findings' tables. In: Higgins JP, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Schunemann 2011b

Schünemann HJ, Oxman AD, Higgins JP, Deeks JJ, Glasziou P, Guyatt GH. Chapter 12: Interpreting results and drawing conclusions. In: Higgins JP, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Siebenhofer 2016

Siebenhofer A, Jeitler K, Berghold A, Horvath K, Posch N, Poggenberg S, et al. Long-term effects of weight-reducing

diets in people with hypertension. *Cochrane Database of Systematic Reviews* 2016, Issue 3. Art. No: CD008274. [DOI: [10.1002/14651858.CD008274.pub3](https://doi.org/10.1002/14651858.CD008274.pub3)]

Suckling 2010

Suckling RJ, He FJ, MacGregor GA. Altered dietary salt intake for preventing and treating diabetic kidney disease. *Cochrane Database of Systematic Reviews* 2010, Issue 12. Art. No: CD006763. [DOI: [10.1002/14651858.CD006763.pub2](https://doi.org/10.1002/14651858.CD006763.pub2)]

Svetkey 1999

Svetkey LP, Simons-Morton D, Vollmer WM, Appel LJ, Conlin PR, Ryan DH, et al. Effects of dietary patterns on blood pressure: subgroup analysis of the Dietary Approaches to Stop Hypertension (DASH) randomized clinical trial. *Archives of Internal Medicine* 1999;**159**(3):285-93. [MEDLINE: 9989541]

Todd 2010

Todd AS, Macginley RJ, Schollum JB, Johnson RJ, Williams SM, Sutherland WH, et al. Dietary salt loading impairs arterial vascular reactivity. *American Journal of Clinical Nutrition* 2010;**91**(3):557-64. [MEDLINE: 20107199]

Trieu 2015

Trieu K, Neal B, Hawkes C, Dunford E, Campbell N, Rodriguez-Fernandez R, et al. Salt reduction initiatives around the world - a systematic review of progress towards the global target. *PLoS ONE [Electronic Resource]* 2015;**10**(7):e0130247. [MEDLINE: 26201031]

Verhave 2004

Verhave JC, Hillege HL, Burgerhof JG, Janssen WM, Gansevoort RT, Navis GJ, et al. Sodium intake affects urinary albumin excretion especially in overweight subjects. *Journal of Internal Medicine* 2004;**256**(4):324-30. [MEDLINE: 15367175]

WHO 2012

World Health Organization. Guideline: sodium intake for adults and children. www.who.int/nutrition/publications/guidelines/sodium_intake_printversion.pdf 2012.

References to other published versions of this review

McMahon 2012b

McMahon EJ, Campbell KL, Bauer JD, Mudge DW. Altered dietary salt intake for chronic kidney disease. *Cochrane Database of Systematic Reviews* 2012, Issue 9. Art. No: CD010070. [DOI: [10.1002/14651858.CD010070](https://doi.org/10.1002/14651858.CD010070)]

McMahon 2015

McMahon EJ, Campbell KL, Bauer JD, Mudge DW. Altered dietary salt intake for people with chronic kidney disease. *Cochrane Database of Systematic Reviews* 2015, Issue 2. Art. No: CD010070. [DOI: [10.1002/14651858.CD010070.pub2](https://doi.org/10.1002/14651858.CD010070.pub2)]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

BalanceWise-HD 2013

Study characteristics

Methods	<ul style="list-style-type: none"> Study design: parallel, open-label RCT Time frame: September 2009 to September 2012 Duration (weeks): total (32); interventions (16)
Participants	<ul style="list-style-type: none"> Country: USA Setting: 17 dialysis units Inclusion criteria: community dwelling adults aged > 18 years who had been undergoing intermittent in-centre maintenance HD for > 3 months; willing to comply with study procedures Baseline characteristics <ul style="list-style-type: none"> * Median duration of ESKD: 33 months (IQR 16 to 68) * BP (SBP/SBP): not reported * Number of anti-hypertensive medications: not reported * Mean sodium intake $\pm$ SD (mmol/day): low salt: (111 $\pm$ 91); high salt (100 $\pm$ 42) Number <ul style="list-style-type: none"> * Randomised: total (179); low salt (93); high salt (86); 1 participant did not complete baseline measurements * Completed 8 weeks: total (165); low salt (82); high salt (83) * Completed 16 weeks: 89.4%; total (161); low salt (81); high salt (80) Median age (IQR): 60 years (51 to 70) Sex (M/F): 101/178 Exclusion criteria: could not read, write, or speak English (because the PDA software was available only in English); could not see the PDA or use a stylus to make selections from the PDA screen; had overt dementia; planned to move out of the area or change dialysis centres within the next 16 weeks; were scheduled for a living donor transplant within the study period; were deemed by dialysis centre staff to have a life expectancy < 12 months (to avoid overburdening such participants); or were institutionalised (e.g., in a nursing home - limited control over their dietary intake); those who were unwilling to speak 1 to 2 times/week with a study dietitian or record their food consumption during the 16-week study period
Interventions	<p>Low salt group</p> <ul style="list-style-type: none"> Individualised dietary education (by dietitian, twice/week for 8 weeks; weekly for weeks 9 to 12 and fortnightly for weeks 13 to 16) technology-based dietary self-monitoring (recorded meals); feedback on sodium intake; plus 6 dietary educational modules on different aspects of the standard HD dietary regimen Duration: 16 weeks <p>High salt group</p> <ul style="list-style-type: none"> Attention control: 6 dietary educational modules on different aspects of the standard HD dietary regimen Duration: 16 weeks <p>Co-interventions</p> <ul style="list-style-type: none"> Nil
Outcomes	<ul style="list-style-type: none"> Inter-dialytic weight gain Sodium intake: 24-hour recall (3 days)
Notes	<ul style="list-style-type: none"> Notes: 8-week follow-up data used for analysis

BalanceWise-HD 2013 (Continued)

- Funding: University of Pittsburgh
- Additional data: provided by authors
- Trial registration: <https://clinicaltrials.gov/ct2/show/NCT01125202>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Randomised. Change from baseline reported</p> <p>Quote: "Within each dialysis centre, participants were then randomised using a permuted block algorithm developed by the study statistician."</p> <p>Quote: "Median Kt/V differed somewhat between the groups with attention control group participants being better dialyzed. Otherwise, no significant differences were observed in baseline characteristics of the intervention and attention control group participants."</p>
Allocation concealment (selection bias)	Low risk	Randomisation occurred after participants were recruited and baseline measurements collected as above
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Outcomes were objective. Study staff performed measurements
Incomplete outcome data (attrition bias) All outcomes	Low risk	<p>16% attrition; 8-week sodium intake data used and this was mostly complete (a lot of missing data at week 16)</p> <p>Quote: "Of the 191 individuals enrolling, 31 (16.2%) did not complete the study. Three individuals withdrew before randomisation, and 3 were excluded post hoc (1 for confusion, 1 was a family relative of another participant, and 1 due to residence in an institutional setting). Of those who continued beyond the baseline assessment, 14 intervention participants and 11 attention control participants did not complete the study for the following reasons: 10 withdrew voluntarily (6 intervention, 4 control); 5 discontinued the study due to illness; 3 died; 3 relocated to a nonparticipating dialysis centre; 2 were admitted to an institutional setting; and 2 were transferred to home HD." "Some participants (16 intervention and 11 attention control) have missing sodium data due to missing dietary recalls, and some have missing IDGWA data due to missing haemodialysis sessions."</p>
Selective reporting (reporting bias)	Low risk	Study was registered online and the pre-specified outcomes were reported
Bias from confounders	Unclear risk	Confounding factors not measured/described. Baseline imbalances: Change from baseline reported
Other	Low risk	Funding: University of Pittsburgh

BalanceWise-PD 2011

Study characteristics

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

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

BalanceWise-PD 2011 (Continued)

Methods	<ul style="list-style-type: none"> Study design: open-label, parallel RCT Time frame: 2007 Duration: 16 weeks
Participants	<ul style="list-style-type: none"> Country: USA Setting: Dialysis clinic Inclusion criteria: ≥ 18 years; literate; community-dwelling adults; receiving maintenance PD for at least 3 months. Baseline characteristics <ul style="list-style-type: none"> * Mean dialysis duration $\pm$ SD: 3.4 ± 4.0 years * BP (SBP/DBP): not reported * Number of anti-hypertensive medications: not reported * Mean sodium intake $\pm$ SD (mmol/day): 98 ± 40 Number <ul style="list-style-type: none"> * Enrolled (26); target (60) * Randomised (26); low salt (13); high salt (13) * Attrition (7) low salt (3) high salt (4) * Completed 4 months: total (19); low salt (10); high salt (9) Mean age $\pm$ SD: 51.7 ± 16.4 years Sex (M/F): 101/178 Exclusion criteria: could not read, write, or speak English (because the PDA software was available only in English); could not see the PDA or use a stylus to make selections from the PDA screen; had overt dementia; planned to move out of the area or change dialysis centres within the next 16 weeks; were scheduled for a living donor transplant within the study period; were deemed by dialysis centre staff to have a life expectancy < 12 months (to avoid overburdening such participants); or were institutionalised (e.g., in a nursing home - limited control over their dietary intake); unwilling to speak 1 to 2 times/week with a study dietitian or record their food consumption during the 16-week study period; individuals on maintenance PD < 3 months are excluded to allow for patients to adjust to the PD regimen, and for stabilization of nutritional status in the early weeks of dialysis (i.e. they may be considered for the study after 3 months of dialysis)
Interventions	<p>Low salt group</p> <ul style="list-style-type: none"> Dietary counselling based on Social Cognitive Theory, paired with PDA-based dietary self-monitoring Duration: 16 weeks <p>High salt group</p> <ul style="list-style-type: none"> Attention control: standard PD education Duration: 16 weeks <p>Co-interventions</p> <ul style="list-style-type: none"> Nil
Outcomes	<ul style="list-style-type: none"> BP, sitting and standing (self-recorded); standing used for analysis as less missing data Fluid Weight (self-recorded) Sodium intake: 24-hour recall (3 days)
Notes	<ul style="list-style-type: none"> Additional data: provided by authors Trial registration: https://clinicaltrials.gov/ct2/show/NCT00447317
Risk of bias	
Bias	Authors' judgement Support for judgement

BalanceWise-PD 2011 (Continued)

Random sequence generation (selection bias)	Low risk	Quote: "In the BalanceWise-PD study, 2 dialysis units participated. Within dialysis centres, participants were stratified according to where they were dialyzed using CAPD versus CCPD, and then randomised within strata." (From email correspondence 23rd July 2019) Baseline values not provided, but change from baseline reported
Allocation concealment (selection bias)	Low risk	Randomisation on sequentially assigned participant identification numbers
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study; outcomes self-recorded
Incomplete outcome data (attrition bias) All outcomes	High risk	Considerable missing data; BP > 30%, weight 28%, urine ~50% missing. 19% attrition (5/26) but reasons well explained and unlikely to be due to allocation Quote: "Five participants were lost to follow-up, due to transfer to another dialysis facility (n = 2), transfer to haemodialysis (n = 1), prolonged hospitalisation (n = 1), or death (n = 1)."
Selective reporting (reporting bias)	Low risk	Study was registered online and the pre-specified outcomes were reported
Bias from confounders	Unclear risk	Confounding factors not measured/described. Baseline imbalances: Change from baseline reported
Other	Low risk	Funding: University of Pittsburgh; National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

Catto 1973

Study characteristics

Methods	<ul style="list-style-type: none"> Study design: double-blind cross-over RCT Time frame: not reported Duration: 4 months total; 2-month interventions
Participants	<ul style="list-style-type: none"> Country: UK Setting: dialysis unit Inclusion criteria: not reported Baseline characteristics <ul style="list-style-type: none"> * CKD: HD * BP (SBP/DBP): not reported * Number of anti-hypertensive medications: not reported * Sodium excretion (mmol/day): not measured/reported Number: randomised (19); analysed (17) Mean age $\pm$ SD (years): not reported Sex (M/F): randomised (12/7) completed (10/11; 6/7)

Catto 1973 (Continued)

- Exclusion criteria: not reported

Interventions	<p>Low salt group</p> <ul style="list-style-type: none"> • Usual salt intake plus placebo • Duration: 2 months <p>High salt group</p> <ul style="list-style-type: none"> • Usual salt intake and slow sodium twice/week (140 mmol) during dialysis (14 tablets over 7 hours; from 1 hour before to 6 hours after starting dialysis) • Duration: 2 months
Outcomes	<ul style="list-style-type: none"> • Muscle cramps frequency and severity: self-recorded during and 2 hours post-dialysis; averaged from 15 dialysis sessions • BP: pre- and post-dialysis erect and supine; averaged from 15 dialysis sessions (pre-dialysis erect used for analysis) • Weight: pre- and post-dialysis • Preferred therapy • Sodium intake: not measured
Notes	<ul style="list-style-type: none"> • Additional data: could not contact authors • Trial registration not available.

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	Double-blind, likely concealed, but not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Likely that outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	<p>12% attrition (2/17), reasons explained</p> <p>Quote: "One patient taking the placebo died from acute bacterial endocarditis and another was withdrawn from the trial while receiving the sodium chloride preparation." "The patient withdrawn from the trial, a 22-year-old bachelor, had a long history of erratic behaviour and hypertension that was difficult to control adequately; he was not able to keep to a standard diet or to control his fluid intake and his weight gain between dialyses was excessive. Though his blood pressure at the time was no higher than it had been on many previous occasions it was considered that the additional sodium intake was not justified."</p>
Selective reporting (reporting bias)	Unclear risk	Pre-specified study protocol not available. Inter-dialytic weight gain not reported (but mean pre- and post-dialysis weights reported). Two-month intervention meaning participants would have had 17-18 dialysis sessions, but only 15 analysed and further information not specified beyond

Catto 1973 (Continued)

Quote: "The results obtained from 15 dialyses on a particular treatment were analysed."

Carry-over effect	Low risk	Sufficient intervention duration to avoid carry-over effect (2 months)
Bias from confounders	Unclear risk	Dietary and medication confounders not described; actual sodium intake or excretion not described
Other	Low risk	No competing interests declared. Pharmaceutical company supplied tablets

de Brito-Ashurst 2013
Study characteristics

Methods	<ul style="list-style-type: none"> Study design: parallel, open-label RCT Time frame: June 2008 to July 2009 Duration: 6 month intervention
Participants	<ul style="list-style-type: none"> 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 2 clinic visits or taking antihypertensive medication; Bangladeshi origin; Attending predialysis clinic Baseline characteristics (mean ± SD) <ul style="list-style-type: none"> * CKD; mean eGFR ± SD (mL/min/1.73 m²): low salt (41 ± 17); high salt (42 ± 15) * Mean BP ± SD (SBP/DBP mm Hg): low salt (149 ± 15/85 ± 6); high salt (156 ± 11/85 ± 6) * Median number of anti-hypertensive medications: 3 (range 2 to 4) * Mean sodium excretion ± SD (mmol/day): total (261 ± 50); low salt: (263 ± 54); high salt (259 ± 47) 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/m²; urinary incontinence; cognitive impairment or mental problems impairing ability to participate
Interventions	<p>Low salt group</p> <ul style="list-style-type: none"> Reduced sodium intake by ongoing individualised dietary education (in person and phone calls) and cooking lessons Duration: 26 weeks <p>High salt group</p> <ul style="list-style-type: none"> Sodium intake: usual care (general low salt advice sent with doctor's letter) Duration: 26 week <p>Co-interventions</p> <ul style="list-style-type: none"> Nil
Outcomes	<ul style="list-style-type: none"> 24-hour BP Total body water by body composition monitor Measurement of sodium intake: 24-hour urine

de Brito-Ashurst 2013 (Continued)

- Measurement of confounders
 - * 24-hour urinary potassium and creatinine
 - * Body weight change
 - * Physical activity levels measured using a pedometer

Notes

- Additional data: provided by authors.
- Trial registration: <https://clinicaltrials.gov/ct2/show/NCT00702312>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "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	Quote: "Group assignment given to the researcher" Further information not provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unblinded; objective outcomes unlikely to be affected by performance bias; dietary behaviour may have differed due to lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were objective and not immediately available, analysis was performed blinded. Quote: "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; 8 withdrew (14% attrition); 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)	Low risk	No evidence of outcomes missing from report
Bias from confounders	Unclear risk	Intervention is described as salt restriction Quote: "in addition to standard hypertension medication management" but unclear whether changes to medication occurred (or were measured) during follow up. Major confounders (potassium intake, body weight change, physical activity) measured and reported as 'unchanged'. Baseline imbalances: Change from baseline reported
Other	Low risk	Funding: PhD scholarship from charitable trust Quote: "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"

de Vries 2016

Study characteristics

Methods	<ul style="list-style-type: none"> Study design: cross-over RCT Time frame: January 2012 to May 2014 Study duration (weeks): total (12); interventions (6); no run-in or washout
Participants	<ul style="list-style-type: none"> Country: the Netherlands Setting: multicentre; outpatient clinics (2) Inclusion criteria: transplant recipients who visited the outpatient clinics and had undergone kidney transplant at least a year before; aged ≥ 18 years; CrCl ≥ 30 mL/min; BP $\geq 120/80$ mm Hg; antihypertensive regimen include an ACEi or ARB Baseline characteristics <ul style="list-style-type: none"> * Median duration of transplant (IQR): 7.3 years (3.1 to 11.5) * CKD; mean eGFR $\pm$ SD: 51 ± 21 mL/min/1.73 m² * Mean BP $\pm$ SD (SBP/DBP): $138 \pm 15/85 \pm 9$ mm Hg * Median number of anti-hypertensive medications (range): 3 (1 to 4) * Sodium excretion (mmol/day): not reported Number: randomised (23); analysed (22) Mean age $\pm$ SD (years): 58 ± 8 Sex (M/F): 11/11 Exclusion criteria: SBP ≥ 180 mm Hg or DBP ≥ 100 mm Hg; use of a calcineurin inhibitor withdrawal regimen or corticosteroid withdrawal regimen or (suspected) rejection of the transplant; pregnancy or lactation; active malignancy; insufficient mastery of the Dutch language to participate in the study; participation in another intervention study during or within a month prior to this study
Interventions	<p>Low salt group</p> <ul style="list-style-type: none"> Target sodium intake: 50 mmol/day (individualised counselling by research physicians) Duration: 6 weeks <p>High salt group</p> <ul style="list-style-type: none"> Target sodium intake: 150 mmol/day (instructed to maintain usual diet) Duration: 6 weeks <p>Other information</p> <ul style="list-style-type: none"> Participants were instructed to maintain an isocaloric diet and stable protein intake; immunosuppressive regimen was kept stable throughout the study; antihypertensive medication kept stable unless patients experienced severe orthostatic complaints. Feedback on sodium intake given after each 24-hour urine collection
Outcomes	<ul style="list-style-type: none"> Clinic BP (1-minute intervals for 15 minutes with a semiautomatic device while the patient was left alone in a room in a semisupine position) 24-hour urinary albumin, urea, calcium, potassium, and creatinine excretion CrCl eGFR SCr, sodium, potassium, urea, total cholesterol, NT-proBNP, renin and aldosterone Measurement of sodium intake: 24-hour urine (at 3 and 6 weeks of each intervention)
Notes	<ul style="list-style-type: none"> Trial registration: https://www.trialregister.nl/trial/3785 Additional data: requested from authors

Risk of bias

de Vries 2016 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "For allocation, a computer-generated list of random numbers was used."
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
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	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Of the 23 who were randomly assigned, 1 patient withdrew halfway through the low-sodium period because of orthostatic hypotension (This participant was included in the orthostatic hypotension outcome). May have reduced the effect on BP, but only 1/23 participants
Selective reporting (reporting bias)	Low risk	No indication of selective reporting
Carry-over effect	Low risk	Adequate intervention duration to reduce risk of carry over effect (6 weeks follow-up)
Bias from confounders	Unclear risk	Antihypertensive dose reduction (5/23 in low salt group) likely to reduce effect on BP; Potassium not significantly changed
Other	Low risk	Quote: "Dr Krediet was supported by the innovation grant IP-11.40 of the Dutch Kidney Foundation." Quote: "Financial Disclosure: The other authors declare that they have no relevant financial interests."

Doulton 2007
Study characteristics

Methods	<ul style="list-style-type: none"> Study design: double-blind, cross-over RCT Time frame: not reported Duration of study (weeks): total (8); interventions (4); no run in or washout
Participants	<ul style="list-style-type: none"> Country: UK Setting: single centre Inclusion criteria: HD/HDF for ESKD > 3 months; clinically stable Baseline characteristics <ul style="list-style-type: none"> * CKD: HD * BP (SBP/DBP): 122 ± 5/69 ± 2 mm Hg * Sodium excretion (mmol/day): not reported Number: target enrolment (20); randomised (not reported); analysed (13) Mean age ± SD: 60 ± 5 years Sex (M/F): 10/3

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

Doulton 2007 (Continued)

- Exclusion criteria: significant intercurrent illness; SBP > 240 mm Hg or DBP > 120 mm Hg at enrolment; unstable BP whilst on HD; sodium profiled HD or HDF

Interventions	<p>Low salt group</p> <ul style="list-style-type: none"> • Target sodium intake: 100 mmol/day; dietary education (verbal and leaflet, administered by experienced renal dietitian) plus placebo • Duration: 4 weeks <p>High salt group</p> <ul style="list-style-type: none"> • Target sodium intake 170 to 200 mmol/day; slow sodium (90 mmol/day) • Duration: 4 weeks
Outcomes	<ul style="list-style-type: none"> • Pre-dialysis SBP • Post-dialysis ambulatory BP (24-hour) • Thirst score • Intradialytic weight gain • Systemic vascular resistance • Asymmetric dimethylarginine • Measurement of sodium intake: 3-day food diary
Notes	<ul style="list-style-type: none"> • Additional data: unable to contact study authors • Abstract only available. Mean values only reported (variation not reported) but P values used to impute confidence intervals • Trial registration: https://clinicaltrials.gov/ct2/show/study/NCT00141609 Study listed as completed October 2006; Last updated May 14 2007

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomised". Further information not provided. Baseline values not provided
Allocation concealment (selection bias)	Low risk	Double blind; allocation concealment not described; likely to have been concealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double blind". Slow sodium versus placebo. No details of placebo matching.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Double blind". Further information not provided. Some risk of unblinding with outcome measurement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition not provided. 13 completed; target 20 enrolled. Actual enrolment not provided 24-hour ambulatory BP outcome unavailable in 2 participants
Selective reporting (reporting bias)	Low risk	Study was pre-registered online and the pre-specified outcomes were reported. All outcomes reported in abstract
Carry-over effect	Low risk	Adequate intervention duration to reduce risk of carry over effect (4 weeks follow-up)

Doulton 2007 (Continued)

Bias from confounders	Unclear risk	Measurement of dietary or medication confounders not described; Target weight kept stable during the study; alterations to dialysis prescription not specified
Other	Low risk	Funding: British Heart Foundation

DUAAAL 2011
Study characteristics

Methods	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Country: the Netherlands Setting: multicentre; outpatient clinics (3) Inclusion criteria: consecutive patients with kidney disease who visited the nephrology outpatient clinic with non-diabetic kidney disease (confirmed by analysis of blood and urine or kidney biopsy); CrCl ≥ 30 mL/min; BP > 125/75 mm Hg; residual proteinuria > 1.0 g/day with ACEi at maximal dose (lisinopril 40 mg/day); aged > 18 years Baseline characteristics <ul style="list-style-type: none"> * CKD (eGFR): not reported * Mean BP $\pm$ SD (SBP/DBP): $131 \pm 18/71 \pm 12.5$ mm Hg * Mean sodium excretion $\pm$ SD: 177 ± 74 mmol/day Number: randomised (54); analysed (52) Mean age $\pm$ SD: 51 ± 13 years Sex (M/F): 43/9 (83% male) Exclusion criteria: SBP > 180 mm Hg or DBP > 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 day/week) of NSAIDs; pregnancy or breastfeeding
Interventions	<p>Low salt group</p> <ul style="list-style-type: none"> Target sodium intake: 50 mmol/day (individualised counselling by dietician) Duration: 12 weeks <p>High salt group</p> <ul style="list-style-type: none"> Sodium intake: usual diet Duration: 12 weeks <p>Co-interventions</p> <ul style="list-style-type: none"> Each participant was on lisinopril 40 mg/day for entire study and went through four interventions for six weeks each in random order (<i>*used for analysis</i>) <ul style="list-style-type: none"> * Usual salt, placebo* * Usual salt valsartan 320 mg/day * High salt, placebo* * High salt valsartan 320 mg/day <p>Other information</p> <ul style="list-style-type: none"> Run-in: 6 weeks; no dietary intervention 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

DUAAAL 2011 (Continued)

Outcomes	<ul style="list-style-type: none"> • 24-hour proteinuria • Clinic BP (supine) • 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 <ul style="list-style-type: none"> * Medication intake measured by pill counts (not relevant to dietary interventions) * Protein intake measured from urea excretion (Maroni formula)
----------	---

Notes	<ul style="list-style-type: none"> • Trial registration: http://www.isrctn.com/ISRCTN50137410 • Additional data: provided by authors
-------	---

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "An independent pharmacist randomised these sequences, using a computer program"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Dietary interventions were open label but outcomes were objective and unlikely to be influenced by performance bias
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	<p>Quote: "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"</p> <p>54 randomised, 2 withdrew after randomisation; 52 included in analysis</p>
Selective reporting (reporting bias)	Low risk	Study was pre-registered online and the pre-specified outcomes were reported
Carry-over effect	Low risk	Adequate intervention duration to reduce risk of carry-over effect
Bias from confounders	High risk	Medication changes reported and did not occur during placebo phases. 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	<p>Funding: study supported by Novartis; declaration of non-involvement by funder</p> <p>Quote: "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"</p>

ESMO 2017

Study characteristics

Methods	<ul style="list-style-type: none"> Study design: parallel, open-label RCT Time frame: June 2011 to August 2014 Duration of study: 6 months
Participants	<ul style="list-style-type: none"> Country: the Netherlands Setting: multicentre, hospitals (4) Inclusion criteria: eGFR ≥ 20 mL/min/1.73 m²; protein excretion > 0.2 g/L or 0.3 g/24-hour; 2 recent sodium excretion measurements ≥ 120 mmol/24-hour; BP $> 135/85$ mm Hg or controlled BP with the use of antihypertensive medication (including ≥ 1 RAAS blockade); Dutch speaking; ≥ 18 years; being treated by internist Baseline characteristics <ul style="list-style-type: none"> * Mean eGFR $\pm$ SD (mL/min/1.73 m²): total (49.7 $\pm$ 25.6); low salt (47.6 $\pm$ 25.0); high salt (51.8 $\pm$ 26.2) * Mean BP $\pm$ SD mm Hg (SBP/DBP): total (129 $\pm$ 15/76 $\pm$ 9); low salt (129 $\pm$ 15/77 $\pm$ 10); high salt (128 $\pm$ 15/75 $\pm$ 9) * Mean number of anti-hypertensive medications $\pm$ SD: total (2.4 $\pm$ 1.1); low salt (2.3 $\pm$ 1.2); high salt (2.4 $\pm$ 1.1) * Mean sodium intake $\pm$ SD (mmol/day): total (164.0 $\pm$ 75.2); low salt (151.1 $\pm$ 66.9); high salt (176.1 $\pm$ 60.9) Number (randomised/analysed): total (151/138); low salt (75/67); high salt (76/71) Mean age $\pm$ SD (years): low salt (55.6 $\pm$ 11.7) high salt (54.7 $\pm$ 16.0) Sex (M/F): 113/25 Exclusion criteria: BP $> 180/100$ mm Hg or $< 125/75$ mm Hg; received a kidney transplant < 1 year ago; type 1 DM; acute kidney failure; accelerated kidney function decrease > 6 mL/min/1.73 m² in previous year; cardiovascular event (i.e. MI or cerebrovascular event) < 6 months ago; diagnosed with malignancy < 5 years ago (other than basal cell or squamous cell carcinoma of skin); participating in other clinical trial that included medication
Interventions	<p>Low salt group</p> <ul style="list-style-type: none"> Education, motivational interviewing, coaching, self-monitoring of BP and sodium Duration: 3 months <p>High salt group</p> <ul style="list-style-type: none"> Usual care
Outcomes	<ul style="list-style-type: none"> BP(24-hour & clinic) 24-hour proteinuria eGFR & CrCl Measurement of sodium intake: 24-hour urine Measurement of confounders <ul style="list-style-type: none"> * Body weight change
Notes	<ul style="list-style-type: none"> Participants followed up at 3 months (t1) and 6 months (t2), 3 month follow up (t1) used for analysis Registered at: NTR2917 Values at end of 3 months (t1) used as change from baseline not available for each group; intention to treat analysis values adjusted for baseline values used Additional data: provided by authors

Risk of bias

Bias	Authors' judgement	Support for judgement
------	--------------------	-----------------------

ESMO 2017 (Continued)

Random sequence generation (selection bias)	Low risk	Quote: "A medical information specialist allocated patients to the intervention or control condition using a computer-based block randomisation procedure. The number of patients in each condition was predefined, and different sizes of blocks were used to prevent too many patients being consecutively assigned to the same condition."
Allocation concealment (selection bias)	Low risk	Quote: "Only the medical information specialist knew the block sizes. Thereafter, researchers and patients were notified of the allocation."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Outcomes were objective and unlikely to be influenced by performance bias Blinding of participants: no; Blinding of Investigators: no; Blinding of Outcomes assessors: not reported; Blinding of Data assessors: not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for attrition unlikely to be related to allocation. Both intention to treat and sensitivity analyses performed Details: between allocation to baseline, 13/151 withdrew (8 in intervention group & 5 in control; not included in intention-to-treat analysis). Between baseline to 3-month follow up, 21/138 withdrew: 8 from intervention group (health problems (4), too busy (1), too much burden (1), participation other study (1); 13 from control group (too much burden and no gain (6), health problems (2), too busy (2), negative experience phlebotomy (1), lost interest (1), no response (1))
Selective reporting (reporting bias)	Low risk	Study was pre-registered online and the pre-specified outcomes were reported
Bias from confounders	High risk	Body weight change: measured; significant reduction in intervention group (1.5 kg) but may be due to fluid (not measured) Quote: "An explanation for our intervention effect could be that the weight reduction was not sodium specific, but due to weight loss goals that 21 (31%) participants set in addition to sodium goals." Physical activity: not measured; antihypertensive dose: measured; reported not significantly changed; potassium excretion measured and not significantly changed Baseline imbalances: results not reported as change from baseline for each group but were adjusted for baseline values. Some differences between groups in baseline values (higher sodium excretion in control) Crude analyses and analyses performed adjusting for baseline values had similar results.
Other	Low risk	Funding: Grants from The Netherlands Organization for Health Research Development - Medical Sciences, the Dutch Kidney Foundation; Conflict of interest: nil

ESPECIAL 2014
Study characteristics
Altered dietary salt intake for people with chronic kidney disease (Review)

ESPECIAL 2014 (Continued)

Methods	<ul style="list-style-type: none"> Study design: parallel, open-label RCT Time frame: March 2012 to March 2013 Duration of study (weeks): total (16); run in (8); intervention (8)
Participants	<ul style="list-style-type: none"> Country: South Korea Setting: multicentre, outpatient renal clinics (7) Inclusion criteria: aged 19 to 75 years; diagnosis of hypertension or use of antihypertensive medication, MDRD study eGFR ≥ 30 mL/min/1.73 m², verified at least twice to have ACR ≥ 30 mg/g in a spot urine sample with interval of 1 week or more in recent 6 months Baseline characteristics <ul style="list-style-type: none"> * CKD: Stage 3 to 4 non-dialysed, non-transplanted * Mean eGFR $\pm$ SD (mL/min/1.73 m²): total (67.3 $\pm$ 24.6); low salt (68.4 $\pm$ 23.6); high salt (66.2 $\pm$ 25.6) * Mean baseline BP $\pm$ SD mm Hg (SBP/DBP): total (130.9 $\pm$ 11.8/79.4 $\pm$ 9.1); low salt (131.0 $\pm$ 11.0/79.7 $\pm$ 8.2); high salt (130.8 $\pm$ 12.4/79.2 $\pm$ 9.9) * Mean baseline sodium intake $\pm$ SD (mmol): total (155 $\pm$ 70); low salt (155 $\pm$ 70); high salt (156 $\pm$ 71) Number (randomised/analysed): total (256/245) low salt (125/119); high salt (131/126) Mean age $\pm$ SD: 49.5 $\pm$ 13.3 years Sex (M/F): 122/123 Exclusion criteria: SBP/DBP > 160/100 mm Hg; pregnant; serum potassium level > 5.5 mEq/L at screening period; malignancy; acute cerebral infarction; acute MI; unstable angina; PCI or CABG in recent 6 months; DM; 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	<p>Low salt group</p> <ul style="list-style-type: none"> Low salt diet: target 100 mmol/day via dietary education from dietician (one 30 minute phone call every week) Duration: 8 weeks <p>High salt group</p> <ul style="list-style-type: none"> Education for low salt diet will be conducted as in office with brief communication with a patient and a physician Duration: 8 weeks <p>Co-interventions</p> <ul style="list-style-type: none"> During run-in (8 weeks), all RAAS blocking agents and diuretic medications were ceased and switched to antihypertensive agents of different categories & all participants were prescribed olmesartan medoxomil (40mg/day)
Outcomes	<ul style="list-style-type: none"> BP (measured at clinics, number of measurements not recorded) 24-hour albuminuria 24-hour urinary creatinine Spot urine ACR Hb Sodium intake measurement <ul style="list-style-type: none"> * 24-hour UNa * Food frequency questionnaire Measurement of confounders <ul style="list-style-type: none"> * 24-hour urinary potassium * Body weight change

ESPECIAL 2014 (Continued)

Notes

- Other information
 - * Before randomisation, the participants who displayed poor medication adherence to olmesartan (used $\leq 60\%$ of the prescribed medication) were removed from the study
 - * $> 25\%$ reduction of salt intake was recommended in both groups
- Registered at: NCT00702312
- Values for change from week 8 (end of run-in) to week 16 (end of intervention) used for analysis
- Additional data: provided by authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomly assigned (1:1) to either conventional education or intensive education for LSD with computerized block randomisation (block size six) and balanced according to institution and sex."
Allocation concealment (selection bias)	Low risk	Quote: "It was not feasible to mask participants to allocation, but clinicians were masked to group assignment".
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Outcomes were objective and unlikely to be influenced by performance bias; blinding of participants: no; blinding of Investigators: yes; blinding of outcomes assessors: no; blinding of data assessors: unclear
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Most outcomes were objective and not immediately available (24-hour urinary markers)
Incomplete outcome data (attrition bias) All outcomes	Low risk	11/256 (4%) withdrew. Intervention group: 6 withdrawn (withdrew consent (1), adverse events (2), continuous user of steroids (1), missed education (1), follow-up loss (1)); control group: 5 withdrawn (withdrew consent (1), adverse events (1), diagnosed DM (1), education error (1), follow-up loss (1)); attrition balanced between groups and unlikely to introduce bias
Selective reporting (reporting bias)	Low risk	Study was pre-registered online and the pre-specified outcomes were reported
Bias from confounders	Unclear risk	<p>Potassium: measured but only reported at baseline; body weight: measured, not reported by group (total change calculated from Ahn 2018 = 0.1 ± 2.2); protein intake not significantly changed; Physical activity: measured at baseline but not follow up; No changes to medications</p> <p>Quote: "During the 16 weeks, no medications were changed, other than olmesartan medoxomil,"</p> <p>Quote: "During the study period, hyperkalaemia (range of 5.6–6.2 mEq/L) was detected in five participants (2.0%) after olmesartan treatment. However, all of the hyperkalaemic events were developed before randomisation and corrected with dietary potassium restriction and cation exchange resin"</p> <p>Baseline imbalances: some baseline differences, but unlikely to impact findings and change from baseline values was used for analysis. Details: significant difference at baseline in exercise minutes (intervention group median 0.0 (IQR 0.0; 180.0); control group 120.0 (0.0; 240.0), $P = 0.001$) and BUN</p>
Other	Unclear risk	Funding: This study was funded by Daiichi Sankyo Korea Co. Ltd. And Dae-wong Pharmaceutical Co. Ltd. Olmesartan medoxomil was provided by the

ESPECIAL 2014 (Continued)

same pharmaceutical companies for all participants. Conflict of interest: none reported

Quote: “the finding that the baseline 24-hour urinary sodium excretion amount was relatively low compared with the mean value of the Korean population on the basis of the 2011 Korea Health Statistics (18) can be explained by the possibility that somewhat routine LSD education was already applied and emphasized in study populations according to the guidelines for patients with hypertension and proteinuria.”

Fine 1997
Study characteristics

Methods	<ul style="list-style-type: none"> Study design: double-blind, cross-over RCT Time frame: not reported Study duration (weeks): total (18); run in/washout (3); intervention (6)
Participants	<ul style="list-style-type: none"> Country: Canada Setting: renal outpatient clinic Inclusion criteria: CAPD > 4 months Baseline data <ul style="list-style-type: none"> * GFR: not reported * Baseline BP: not reported, 10 were hypertensive * Mean duration of dialysis: 15 ± 15 months Number: 20 Mean age ± SD: 61 ± 13 years Sex (M/F): 14/6 Exclusion criteria: DBP > 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	<p>Low salt diet</p> <ul style="list-style-type: none"> Usual diet plus placebo Duration: 6 weeks <p>High salt diet</p> <ul style="list-style-type: none"> Sodium intake: usual diet plus 60 mmol sodium capsule Duration: 6 weeks <p>Other information</p> <ul style="list-style-type: none"> Co-interventions: none Dialysate sodium 132 mmol/L in all participants
Outcomes	<ul style="list-style-type: none"> Clinic BP (self-recorded, 3 weekly) Weight (self-recorded, twice weekly) Measurement of sodium intake <ul style="list-style-type: none"> * 24-hour urine + dialysate collection * 3-day food record * Change in dialysate regimen self-recorded

Fine 1997 (Continued)

- Measurement of confounders
 - * Medication changes discussed for hypertensive patients but not the CAPD group and measurement not described
 - * Measurement of other dietary confounders not described
 - * Adherence to study medication not described
- Values at the end of the intervention used

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	Quote: "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	Quote: "Physician, patient, and study nurse were blinded"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "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	<p>12/32 withdrew (37.5%). Large degree of attrition, even in both groups and well-explained, however self-measurement of BP led to some attrition. Details: 32 participants enrolled, 12 withdrew (6 in each intervention), 20 completed and were included for analysis. Reasons for attrition</p> <p>Quote: "Twelve patients. six on salt pills and six on placebo, could not complete both arms of the study for the following reasons: gastrointestinal symptoms (5), itch (1), depression (1), poor record keeping (1), patient decision for no identifiable reason (2), and patient concern about their BP based on single BP readings (2). In one of these two patients, the diastolic BP did not exceed 85, and in the second patient systolic BP did not exceed 160. Their data have been excluded. Twenty patients completed the entire study. The high dropout rate warrants further discussion. This protocol placed considerable demands on these patients. beyond the usual rigours of home dialysis, and in our view, five to six of the dropouts were related to a general apathy that developed during the study. The gastrointestinal symptoms may in part be related to the highly artificial manner in which the salt was given, but the strict design of the study mandated the procedure. To our surprise, two of the five patients whose gastrointestinal intolerance led to withdrawal from the study developed those symptoms when taking placebo."</p>
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. Medication changes not well reported. Quote: "None of the hypertensive patients had to adjust their medications during the salt period."

Fine 1997 (Continued)

Other

High risk

Funding: Baxter Healthcare Corporation

Keven 2006

Study characteristics

Methods	<ul style="list-style-type: none"> Study design: parallel RCT Time frame: January 2004 to December 2004 Study duration (weeks): total (12); intervention (12)
Participants	<ul style="list-style-type: none"> Country: Turkey Setting: not reported 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 <ul style="list-style-type: none"> * Duration of transplant (years): low salt (5.3 ± 3.1); high salt (7.2 ± 3.9) * Mean baseline BP $\pm$ SD mm Hg (SBP/DBP): low salt ($146 \pm 21/89 \pm 8$); high salt ($140 \pm 16/86 \pm 8$) * Mean sodium excretion $\pm$ SD (mmol/day): total (190 ± 57); low salt (191 ± 17); high salt (190 ± 75) Number: low salt (18); high salt (14) Mean age $\pm$ 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	<p>Low salt group</p> <ul style="list-style-type: none"> Target sodium intake: 80 to 100 mmol/day (counselling by dietician) Duration: 12 weeks <p>High salt group</p> <ul style="list-style-type: none"> Sodium intake: assumed usual diet (information not provided) Duration: 12 weeks <p>Co-interventions</p> <ul style="list-style-type: none"> Antihypertensive treatment (including dose/number of drugs) adjusted if SBP > 140 or < 100 mm Hg, and/or DBP > 90 mm Hg or < 70 mm Hg as assessed by a blinded physician
Outcomes	<ul style="list-style-type: none"> Clinic BP (sitting, after 5 minutes rest) Serum markers (electrolytes, creatinine) Measurement of sodium intake: 24-hour urine Measurement of confounders: medication changes recorded
Notes	<ul style="list-style-type: none"> Funding: not reported Additional data: provided by authors

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

Keven 2006 (Continued)

Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Open-label dietary intervention however outcomes were objective and unlikely to be influenced by performance bias
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low 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
Bias from confounders	High risk	Confounding factors not measured/described (body weight, potassium, antihypertensive medication changes (7 in low salt group; 1 in high salt group). Highly likely that other dietary factors may have confounded results with unblinded, usual intake versus low sodium, study design. Baseline imbalances: SBP/DBP was 6/3 mm Hg higher in low salt versus high salt group at baseline which may have masked the effect on BP as change from baseline was not reported
Other	Unclear risk	Funding: not reported

Konishi 2001
Study characteristics

Methods	<ul style="list-style-type: none"> Study design: cross-over RCT Time frame: 1998 to 2002 Duration of study (weeks): total (3); run in (1); interventions (1); no washout
Participants	<ul style="list-style-type: none"> Country: Japan Setting: single centre, Osaka City General Hospital Inclusion criteria: IgA nephropathy as diagnosed by percutaneous kidney biopsy Baseline characteristics <ul style="list-style-type: none"> * GFR: not reported * BP: not reported Number: 38 Mean age $\pm$ SD: 45 $\pm$ 15 years Sex: 14/27 Exclusion criteria: other kidney or heart disease; taking any medication
Interventions	<p>Low salt group</p> <ul style="list-style-type: none"> Sodium intake: 87 mmol/day (meals provided) Duration: 1 week <p>High salt group</p>

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

Konishi 2001 (Continued)

- Sodium intake: 209 mmol/day (meals provided)
- Duration: 1 week

Other information

- Study diets contained the same amount of protein (1.2 g/kg body weight/day) and calories (35 kcal/kg/day)
- 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Funding: not reported • Additional data: provided by authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information not provided however outcomes were objective and unlikely to be influenced by performance bias
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	Insufficient information to permit judgement
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
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. Medications not reported but protocol was to refrain from medications
Other	Unclear risk	Funding not reported

Kwakernaak 2014

Study characteristics

Methods	<ul style="list-style-type: none"> Study design: cross-over RCT Time frame: October 2009 to December 2012 Study duration (weeks): total (30); run in (6); interventions (6); no washout
Participants	<ul style="list-style-type: none"> Country: the Netherlands Setting: multi-centre; outpatient clinics (3) Inclusion criteria: consecutive patients with type 2 DM and presence of diabetic kidney disease (as diagnosed by the patient's own nephrologist on the basis of medical history and analysis of blood and urine); presence of albuminuria (defined as albuminuria > 30 mg/day or urinary albumin concentration > 20 mg/L or urinary ACR > 2.5 mg/mmol for men and > 3.5 mg/mmol for women) at time of screening and after completion of the run-in period; aged ≥ 18 years; CrCl ≥ 30 mL/min with < 6 mL/min decline in the previous year Baseline characteristics <ul style="list-style-type: none"> * Mean GFR ± SD: 65 ± 25 mL/min/1.73 m² * BP (SBP/DBP): not reported * Mean BMI ± SD: 32 ± 5 kg/m² * Median time since DM diagnosis (IQR): 9 years (5 to 19) * Median number antihypertensives (range): 1 (0-3) Number: randomised (45); analysed (45) Mean age ± SD: 65 ± 9 years Sex (M/F): 38/7 Exclusion criteria: SBP of ≥180 mm Hg; DBP ≥110 mm Hg; overt nephrotic syndrome at baseline; second primary kidney disease in addition to diabetic kidney disease; type 1 DM; renovascular hypertension; a cardiovascular or cerebrovascular event within 3 months before inclusion; serum potassium ≥ 6.0 mmol/L; transplantation or immunosuppressive treatment; contraindication for the use of lisinopril or hydrochlorothiazide; pregnancy or lactation; noncompliance with medication; inability to provide informed consent
Interventions	<p>Low salt group</p> <ul style="list-style-type: none"> Target sodium intake: 50 mmol/day (individualised counselling by dietician) Duration: 12 weeks <p>High salt group</p> <ul style="list-style-type: none"> Sodium intake: usual diet (target 200 mmol/day) Duration: 12 weeks <p>Co-interventions</p> <ul style="list-style-type: none"> Each participant was on lisinopril 40 mg/day for entire study and went through four interventions for six weeks each in random order (* used for analysis) <ul style="list-style-type: none"> * Usual salt, placebo* * Usual salt, hydrochlorothiazide 50 mg/day * High salt, placebo* * High salt, hydrochlorothiazide 50 mg/day <p>Other information</p> <ul style="list-style-type: none"> During the 6 week run-in period, patients were titrated to maximum dose of ACEi (lisinopril 40 mg/day), whereas all other RAAS blockers and diuretics were discontinued No dietary intervention during the run-in period Additional antihypertensive drugs, such as alpha blockers, beta blockers, and calcium-channel blockers, were allowed when dosage was stable throughout the trial

Kwakernaak 2014 (Continued)

Outcomes	• 24-hour albuminuria and proteinuria • Clinic BP (semi-supine) • Weight • Serum markers (electrolytes, lipids, proteins, creatinine) • Urinary markers, CrCl • Measurement of sodium intake: 24-hour urine • Measurement of confounders * Medication intake measured by pill counts * Urea & potassium excretion

Notes	• Funding: Unfunded • Trial registration: http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=2366 • Additional data: additional data not requested

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Independent pharmacist used a computer program to randomise patients in blocks of two. No stratification was needed as the trial has a crossover design. An independent pharmacist randomised treatment sequences. Patients were sequentially enrolled according to moment of recruitment. The randomisation code remained secret during the entire trial"
Allocation concealment (selection bias)	Unclear risk	Quote "...drug intervention was double blind, whereas the dietary intervention was open label". "All patients, investigators, and health-care providers were masked, apart from the pharmacist who did the randomisation. On completion of the trial, the principal investigator (AJK) provided the pharmacist and the medical ethics committee with a written statement that the trial was completed, after which masking ended"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Dietary interventions were open label but outcomes were objective and unlikely to be influenced by performance bias Blinding of participants: yes for drug, no for diet; blinding of investigators: yes for drug, no for diet; blinding of outcomes assessors: yes for drug, no for diet; blinding of data assessors: yes for drug, no for diet
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The drug intervention was double blind, whereas the dietary intervention was open label
Incomplete outcome data (attrition bias) All outcomes	Low risk	45 randomised; 2 excluded after randomisation, due to onset of malignancy and 1 non-adherence to sodium restriction; all 45 included in intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	Study was pre-registered online and the pre-specified outcomes were reported
Carry-over effect	Low risk	Quote: "Use of 6-week treatment periods was based on previous studies from our department in patients with non-diabetic nephropathy, showing that changes in albuminuria generally stabilise 3–4 weeks after the change in therapy"
Bias from confounders	Unclear risk	Potassium: urinary excretion measured and reported unchanged; body weight change: measured and 2 kg significant reduction with low salt; physical activ-

Kwakernaak 2014 (Continued)

ity: not reported; antihypertensive dose: change not reported but protocol to keep stable; urinary urea excretion measured and reported unchanged

Other	Low risk	Quote: "No funding was received for this trial. The sponsor of this trial is the University Medical Centre Groningen, Netherlands." Conflict of interest: nil
-------	----------	--

LowSALT CKD 2012
Study characteristics

Methods	<ul style="list-style-type: none"> Study design: cross-over, double blind RCT Time frame: September 2011 to July 2012 Duration of study (weeks): total (6); run in/washout (1); interventions (2)
Participants	<ul style="list-style-type: none"> Setting: single centre Country: Australia Inclusion criteria: eGFR 15–59; SBP 130 to 169 mm Hg; DBP > 70 mm Hg; ≥ 18 years Baseline characteristics <ul style="list-style-type: none"> * CKD: Stage 3 to 4 non-dialysed, non-transplanted * Mean BP ± SD mm Hg (SBP/DBP): low salt (149 ± 15/85 ± 6); high salt (156 ± 11/85 ± 6) * Mean sodium excretion ± SD: 132 ± 57 mmol/day Number: 20 Mean age ± SD: 68.5 ± 11.0 years Sex (M/F): 15/5 Exclusion criteria: receiving KRT (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	<p>Low salt group</p> <ul style="list-style-type: none"> Sodium intake goal: 60 to 80 mmol/day achieved by dietary education from trained dietician, plus placebo tablets Duration: 2 weeks <p>High salt group</p> <ul style="list-style-type: none"> Sodium intake: low salt diet (goal 60 to 80 mmol/day) achieved by dietary education plus 120 mmol of sodium capsules Duration: 2 weeks <p>Other information</p> <ul style="list-style-type: none"> Aimed to keep intake of other nutrients stable Co-interventions: none Values and the end of the intervention used; for some outcomes standard deviations were imputed so that effect size matched actual effect size of paired data
Outcomes	<ul style="list-style-type: none"> 24-hour BP (every 20 min during the day and 30 min at night) 24-hour proteinuria and albuminuria Pulse wave velocity Augmentation index (pulse wave analysis) eGFR

LowSALT CKD 2012 (Continued)

- Fluid status (bio-impedance spectroscopy using Body Composition Monitor)
- 24-hour urine output
- Weight
- NT-proBNP (via blood sample)
- Thirst (via xerostomia Index)
- CRP and adipokines
- Stimulation of RAAS (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 dietitians)
 - * Food-frequency questionnaire
- Measurement of confounders
 - * 24-hour urinary potassium and urea
 - * Body weight change
 - * Dietary history (verified by study dietitians) to assess protein, sodium and energy intake
 - * Daily self-record of study medication intake

Notes

- Authors on this review (EM, KC) were investigators in the LowSALT CKD Study. The risk of bias was not assessed by these authors
- Additional data: provided by authors
- Trial registration: ACTRN12611001097932

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	Quote: "Study medication was packaged offsite and labelled with the study numbers and intervention order"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Participants, investigators, and outcome assessors were blinded to the allocation"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<p>Quote: "Participants, investigators, and outcome assessors were blinded to the results of all outcomes."</p> <p>Quote: "Data analysis was initially performed blinded to treatment order and then was performed unblinded to confirm treatment order"</p> <p>Blinding of participants: all outcomes</p> <p>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</p> <p>Blinding of data assessors: initial data analysis performed blinded to allocation and urinary sodium data</p>

LowSALT CKD 2012 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	25% attrition (5/25) 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). Some data missing for some outcomes but these are well justified Quote: "One patient had missing data for urinary measures (sample not collected, n = 1), and two for fluid measurement (presence of a pacemaker contraindicating measurement [n = 1]; data loss [n = 1])."
Selective reporting (reporting bias)	Low risk	Study was pre-registered online and the pre-specified outcomes were reported. 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	Low 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. 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

Mulhauser 1996

Study characteristics

Methods	<ul style="list-style-type: none"> Study design: double-blind, parallel RCT Time frame: 4 years Study duration (weeks): total (10); run-in (6) intervention (4)
Participants	<ul style="list-style-type: none"> Country: Germany Setting: two hospitals Inclusion criteria: insulin-dependent diabetic on intensified insulin therapy; aged 18 to 60 years; diabetes duration > 5 years, stable retinopathy; untreated SBP ≥ 140 and ≤ 160 mmHg and/or DBP ≥ 85 and ≤ 100 mm Hg Baseline characteristics (values at the end of run-in used) <ul style="list-style-type: none"> * CKD: increased proteinuria > 60 mg/24-hours in at least two of three 24-h urine samples * Mean baseline BP ± SD mm Hg (SBP/DBP): low salt (130 ± 7/86 ± 6); high salt (134 ± 7/86 ± 6) * Mean sodium excretion ± SD (mmol/day): low salt (94 ± 34); high salt (106 ± 16) Number: randomised (16) low salt (8); high salt (8) Mean age ± SD (years): low salt (35 ± 11); high salt (37 ± 9) Sex (M/F): Low salt (5/3) high salt (7/1) Exclusion criteria: UTI; prescribed any medications (including oral contraceptives) except insulin (one patient used thyroxine); pregnancy; history of short-term treatment with antihypertensive drugs was not an exclusion criteria, if the medication had been stopped for at least 4 weeks before recruitment

Mulhauser 1996 (Continued)

Interventions	<p>Low salt group</p> <ul style="list-style-type: none"> Sodium restriction and placebo (group 1) Duration: 4 weeks <p>High salt group</p> <ul style="list-style-type: none"> Sodium restriction and sodium tablets (group 2) Duration: 4 weeks <p>Other</p> <ul style="list-style-type: none"> Run-in: 4-week usual diet followed by 2-week sodium restriction (by dietitian and nutritionists; reduced sodium bread provided) Co-interventions: none
Outcomes	<ul style="list-style-type: none"> Clinic BP (mean of four sitting and four supine measurements, taken after 10 minutes rest) Home BP (as per clinic BP) Plasma markers (aldosterone, ACE, ANP, adrenaline, noradrenaline; renin, renin activity, angiotensin II) eGFR was assessed by the clearance of inulin and RPF by the clearance of PAH Renal vascular resistance (mean arterial BP x 100 x (1-haematocrit) divided by RPF filtration fraction (GFR divided by RPF) Total exchangeable body sodium (weeks 8 and 12) (whole body counter method in three patients, and modified isotope dilution method in 13 patients) Blood volume Plasma volume Erythrocyte volume Measurement of sodium intake: 24-hour urine; 3 day food diary Measurement of confounders: protein intake was calculated from 24-h urinary nitrogen excretion
Notes	<ul style="list-style-type: none"> Additional data: unable to contact authors Trial registration: none found

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described; some baseline differences but analyses adjusted for baseline values
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	Double blind Quote: "All relevant laboratory results of the blinded study period, including excretion of urinary electrolytes, were kept blinded to patients and investigators until the last patient had finished the study."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No attrition reported after randomisation; no missing data reported

Mulhauser 1996 (Continued)

Selective reporting (reporting bias)	High risk	Pre-specified study protocol not available. Many outcomes could not be included in meta-analyses as they were reported as mean and range and analysed using t-test (despite values indicating the data were not normally distributed), P values were not reported, adjustment for multiple comparisons occurred but not clear if this applied to all outcomes. Change (from end of run in to end of intervention) reported for BP only, unclear while other outcomes are reported only as values at the end of the intervention.
Bias from confounders	Unclear risk	Participants were not on anti-hypertensive medications; known dietary confounders measured and reported unchanged; weight stable Baseline imbalances: change from baseline not reported. Unable to determine if this would have impacted findings based on information given
Other	Unclear risk	Funding: The study has been supported by Cassella Riedel, Frankfurt, Germany, and by the E Klockner Stiftung, Duisburg, Germany. Unclear of role of funding bodies

Power 2010

Study characteristics

Methods	<ul style="list-style-type: none"> Study design: RCT, parallel Time frame: August 2008 to December 2009 Duration (weeks): run-in (12), intervention (36)
Participants	<ul style="list-style-type: none"> Country: UK Setting: hospital Inclusion criteria: not reported Baseline characteristics <ul style="list-style-type: none"> * CKD: HD * BP (SBP/DBP): not reported * Number of anti-hypertensive medications: not reported * Sodium excretion (mmol/day): not reported Number: randomised (50); analysed (31) Mean age $\pm$ SD (years): 65.1 $\pm$ 12.4 Sex (M/F): 84% male Exclusion criteria: not reported
Interventions	<p>Low salt group</p> <ul style="list-style-type: none"> Sodium intake: restriction to 2.3g/day with dietetic input Duration: 36 weeks <p>High salt group</p> <ul style="list-style-type: none"> Further information not provided Duration: not reported <p>Other information</p> <ul style="list-style-type: none"> Other groups <ul style="list-style-type: none"> * Low dialysate sodium alone: target 3 mM below patient's mean serum level by graded reduction: 1 mM/2 weeks * Low dialysate & sodium restriction

Power 2010 (Continued)

	<ul style="list-style-type: none"> Run-in period: dialysate sodium 140 mM, unrestricted diet
Outcomes	<ul style="list-style-type: none"> Ambulatory BP (every 6 weeks midpoint of dialysis week) Anti-hypertensive dose Dialysis symptom index (including cramps) Sodium gradient (NaG) (difference dialysate - serum Na)
Notes	<ul style="list-style-type: none"> Abstract-only publication Additional data: requested

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	38% attrition (50 entered, 31 analysed; reasons not described; attrition by allocation not stated); unclear if there are missing outcome data
Selective reporting (reporting bias)	High risk	Pre-specified study protocol not available. Results on ambulatory BP and anti-hypertensive dose for control versus sodium restriction groups not reported Note: abstract-only publication (requested additional results from study authors but have not received a response)
Bias from confounders	Unclear risk	Measurement of confounders not described Baseline imbalances: baseline values not reported
Other	Low risk	Disclosure of financial relationships "nothing to describe"

Rodrigues Telini 2014
Study characteristics

Methods	<ul style="list-style-type: none"> Study design: parallel, open-label RCT Time frame: April 2007 to February 2009 Duration of study: 16 weeks
Participants	<ul style="list-style-type: none"> Country: Brazil Setting: single centre, university hospital

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

Rodrigues Telini 2014 (Continued)

- Inclusion criteria: ≥ 18 years; HD for at least 90 days; diagnosed with inflammation (CRP levels ≥ 0.7 mg/dL, based on median of CRP levels in a sample of 119 HD patients in the dialysis unit)
- Baseline characteristics
 - * Median dialysis duration in months (IQR): low salt (30.90 (8.75, 105.5); high salt (49.50 (26.0; 58.0)
 - * Mean BP $\pm$ SD mm Hg (SBP/DBP): total ($146 \pm 17/85.89 \pm 11.92$); low salt ($149 \pm 13.70/87.24 \pm 10.99$); high salt ($142 \pm 19.30/84.31 \pm 13.06$)
 - * Mean sodium intake from 3 day record $\pm$ SD (converted to mmol/day): total (159 ± 26); low salt (157 ± 25); high salt (162 ± 27)
- Number
 - * Randomised: total (53); low salt (30); high salt (23)
 - * Completed/analysed: total (39); low salt (21); high salt (18)
- Mean age $\pm$ SD (years): total (57.95 ± 12.9); low salt (56.00 ± 11.91); high salt (60.22 ± 13.96)
- Sex (M/F): total (27/12); low salt (12/9); high salt (15/18)
- Exclusion criteria: acute inflammatory processes; chronic inflammatory diseases; antibiotic use within the past 2 months; malignancies; central venous catheter use

Interventions	<p>Low salt group</p> <ul style="list-style-type: none"> • Sodium intake: restriction aiming for a 2 g reduction; dietary counselling by nutritionist • Duration: 16 weeks <p>High salt group</p> <ul style="list-style-type: none"> • Usual sodium intake • Duration: 16 weeks <p>Other information:</p> <ul style="list-style-type: none"> • All patients were dialysed 3 times/week, for 3.5 to 4 hours/session using low-flux polysulfone dialysers and dialysate with bicarbonate buffer and a sodium concentration of 138 mEq/L • Prescribed dialysis doses (Kt/V) were at least 1.4
Outcomes	<ul style="list-style-type: none"> • BP: average of the last 10 routine predialysis measurements • Fluid status by bio-impedance analysis performed 30 minutes after dialysis sessions • Serum levels of albumin, sodium, creatinine, urea, glucose, cholesterol, HDL cholesterol, triglycerides, and bicarbonate, CRP, tumour necrosis factor-α, and interleukin-6 • HCT and Hb • Body weight change • Sodium intake: 3-day food record
Notes	<ul style="list-style-type: none"> • Registered at: CRSTSD: 2904970; https://clinicaltrials.gov/ct2/show/NCT01458808 • Change from baseline not reported, therefore values at end of intervention (week 16) used • Additional data: requested

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described. Imbalance in group numbers (30 randomised to high salt; 23 to low salt)
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias)	Unclear risk	Open-label study but outcomes were objective and unlikely to be influenced by performance bias

Rodrigues Telini 2014 (Continued)

All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	26% attrition (14/53) Quote: "During the follow-up, 9 of 30 subjects in group A and 5 of 23 in group B were excluded because of acute infections. Therefore, 39 patients (21 in group A and 18 in group B) completed the study period."
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Bias from confounders	High risk	Potassium: not measured; body weight change; physical activity: not measured; antihypertensive dose: reported not significantly different between groups. Reported energy and protein intake not changed Baseline imbalances: no significant differences at baseline, but there are clinically significant differences in the mean values. Change from baseline not reported, therefore baseline imbalances can bias estimated effect size when using values at the end of the intervention. SBP/DBP is 7/3 mm Hg higher at baseline in intervention than control. Using end of intervention mean change is 1.7/-3.78, using change from baseline 8.2/-0.8
Other	Low risk	Funding: São Paulo Research Foundation; Conflict of interest: None declared

Ruilope 1992a
Study characteristics

Methods	<ul style="list-style-type: none"> Study design: cross-over RCT Time frame: not reported Duration of study (weeks): total (6); run in (4); interventions (1); no washout
Participants	<ul style="list-style-type: none"> Country: Spain Setting: Hypertension unit Inclusion criteria: mild kidney insufficiency, essential hypertension Baseline characteristics <ul style="list-style-type: none"> * Mean BP $\pm$ SD (SBP/DBP): 158.2 $\pm$ 29.1/99.9 $\pm$ 8.9 mm Hg * GFR: not reported <ul style="list-style-type: none"> ☐ "Mild renal insufficiency", diagnostic criteria (not reported); nephrosclerosis (4); other clinical criteria (10) * Mean sodium excretion $\pm$ SD: 156.3 $\pm$ 101.4 mmol/day Number: 14 Mean age $\pm$ SD: 63.5 $\pm$ 22.4 years Sex: not reported Exclusion criteria: no other concurrent medical illness
Interventions	Low salt group <ul style="list-style-type: none"> Sodium intake: 68 mmol/day (17 mmol dietary intake + 51 mmol supplement). Further information not provided

Ruilope 1992a (Continued)

- Duration: 1 week

High salt group

- Sodium intake: 187 mmol/day (17 mmol dietary intake + 170 mmol supplement). Further information not provided
- Duration: 1 week

Other details

- Run in (4 weeks) "no patient received medication"
- Dietary intake target 60 mmol potassium/day
- Co-interventions: 240 mg verapamil through both interventions

Outcomes	<ul style="list-style-type: none"> • 24-hour BP (every 20 to 30 min) • Clinic BP • Weight • CrCl • SCr • Measurement of sodium intake: 24-hour urine • Measurement of confounders: urinary potassium
Notes	<ul style="list-style-type: none"> • Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomised", no further information provided
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information not provided, but outcomes were objective and unlikely to be influenced by performance bias
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
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	Insufficient information to permit judgement

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

Saran 2017

Study characteristics

Methods	<ul style="list-style-type: none"> Study design: open-label, cross-over RCT Time frame: May 2009 to May 2013 Duration of study (weeks): total (12); interventions (4); washout (2)
Participants	<ul style="list-style-type: none"> Country: USA Setting: multi-centre, universities (2) Inclusion criteria: aged ≥ 18 years and ≤ 85 years; willing and able to comply with all study procedures; CKD stages 3 and 4; eGFR 20 to 60 mL/min/1.73 m² and relatively stable clinical course; sitting SBP ≥ 100 mm Hg prior to study entry Baseline characteristics <ul style="list-style-type: none"> * Mean GFR $\pm$ SD: 37.9 $\pm$ 11.7 mL/min/1.73 m² * Mean BP $\pm$ SD (SBP/DBP): 138.2 $\pm$ 16.3/75.4 $\pm$ 9.9 mm Hg * Mean sodium excretion $\pm$ SD: 167 $\pm$ 46 mmol/day Number: randomised (58); analysed (56) Mean age $\pm$ SD: 62 $\pm$ 13 years Sex (M/F): 35/23 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 UNa ≤ 100 mmol/day; 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	<p>Low salt group</p> <ul style="list-style-type: none"> Sodium intake: restriction, goal 2000 mg sodium, dietary counselling by dietitian Duration: 4 weeks <p>High salt group</p> <ul style="list-style-type: none"> Salt intake: usual intake Duration: 4 weeks <p>Other information</p> <ul style="list-style-type: none"> Study participants were advised to maintain isocaloric diets and stable intake of total and saturated fat, potassium intake of 2 to 3 g/day, and phosphorus intake of < 1 g/day during both study phases. They were instructed to maintain their usual levels of alcohol, caffeine, and nicotine, and continue their usual level of physical activity
Outcomes	<ul style="list-style-type: none"> 24-hour albuminuria Ambulatory & clinic BP Fluid status (BIS; whole body and segmental techniques) Weight eGFR SCr, sodium & potassium Urinary creatinine & potassium

Saran 2017 (Continued)

- Sodium intake: 24-hour urinary sodium

Notes

- Funding: Renal Research Institute and grant from the National Center for Research Resources (NCRR)
- Additional data: requested
- Trial registration: <https://clinicaltrials.gov/ct2/show/record/NCT00974636>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	High risk	Quote: "Randomization was performed using sealed envelopes at each site." However allocation sequence not followed Quote: "Of the 21 patients enrolled at UNC, six were given treatment in the reverse sequence from the randomised assignment for unknown reasons."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Study investigators were blinded to assigned treatment, which was only known to study dieticians and coordinators" Blinding of participants: no; blinding of investigators: yes; blinding of outcomes assessors: unclear; blinding of data assessors: unclear Lack of blinding may have led to protocol deviation Quote: "Of the 21 patients enrolled at UNC, six were given treatment in the reverse sequence from the randomised assignment for unknown reasons. In addition, four patients who were initially randomised to the SRD in phase 1 had poor compliance and, in violation of the protocol, were encouraged to continue the SRD in phase 2."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	3 participants withdrew 2 illness unrelated to intervention; 1 for personal reasons (some data included for the latter). Incomplete outcome data as evidenced by supplementary table S3 (e.g. different in number for SBP & DBP, only 10/21 participants at one of the sites with urinary albumin), have contacted authors for further information
Selective reporting (reporting bias)	Unclear risk	No evidence of reporting bias in terms of outcomes not reported; incomplete outcome data evident for some outcomes and unexplained
Carry-over effect	Low risk	2-week washout; analysed both treatment orders & found no treatment order effect
Bias from confounders	Unclear risk	Potassium: measured, have requested data. Body weight change: measured, significant change & higher than body water loss, may have influenced outcomes Physical activity: not measured Antihypertensive dose: measured & change reported. Quote: "At enrolment, 48 patients were taking at least one antihypertensive medication, with 77% taking two or more and 48% taking three or more. During the study, 12 patients discontinued 27 medications; eight patients discontinued 15 medications during the SRD phase compared with six patients (and 12 medications) during

Saran 2017 (Continued)

the usual diet phase. The majority (75%) of the changes during the usual diet phase occurred during phase 2, after the SRD phase."

Other	High risk	<p>Funding: Renal Research Institute and grant from the National Center for Research Resources (NCRR)</p> <p>Conflict of interest: Two study authors (N Levin and P Kotanko) hold stock in Fresenius Medical Care, which makes the machine used to assess the primary outcome. Protocol deviation: "Of the 21 patients enrolled at UNC, six were given treatment in the reverse sequence from the randomised assignment for unknown reasons. In addition, four patients who were initially randomised to the SRD in phase 1 had poor compliance and, in violation of the protocol, were encouraged to continue the SRD in phase 2."</p>
-------	-----------	---

ViRTUE-CKD 2016

Study characteristics

Methods	<ul style="list-style-type: none"> Study design: cross-over RCT (dietary intervention open-label) Time frame: January 2012 to March 2015 Study duration (weeks): total (38); run in (6); interventions (8); no washout
Participants	<ul style="list-style-type: none"> Country: the Netherlands Setting: multi-centre; hospitals (3) Inclusion criteria: nondiabetic patients with stages 1 to 3 CKD; residual albuminuria > 300 mg/day despite single-agent RAAS blockade; CrCl > 30 mL/min and < 6 mL/min decline in the previous year; parathyroid hormone values < 1.5 times the upper limit of normal; serum calcium (adjusted for serum albumin) 2.0 to 2.6 mmol/L; serum phosphate ≤ 1.5 mmol/L; age > 18 years Baseline characteristics <ul style="list-style-type: none"> * Mean GFR ± SD: 69.5 ± 23.5 mL/min/1.73 m² * BP (SBP/DBP): not reported * Mean sodium excretion ± SD: 175 ± 64 mmol/day Number: randomised (45); analysed (45) Mean age ± SD: 52 ± 13 years Sex (M/F): 33/12 Exclusion criteria: DM; uncontrolled hypertension; hyperkalaemia (potassium > 6.0 mmol/L); cardiovascular event in the previous 6 months; heart failure (NYHA class III–IV); epilepsy; liver disease; active malignancy; bowel disorder resulting in fat malabsorption; treatment with vitamin analogue in the previous 3 months; regular use (> 2 doses/week) of NSAID; use of immunosuppressive treatment; digoxin or psychiatric medication; drug or alcohol abuse; noncompliance with the study diet or study medication; pregnancy or breastfeeding; BP > 180/100 mm Hg after maximum 18 weeks run-in period
Interventions	<p>Low salt group</p> <ul style="list-style-type: none"> Target sodium intake: 50 mmol/day (individualised counselling by dietician) Duration: 16 weeks <p>High salt group</p> <ul style="list-style-type: none"> Target sodium intake: usual diet (200 mmol/day) Duration: 16 weeks <p>Co-interventions</p>

ViRTUE-CKD 2016 (Continued)

- Each participant was on ramipril at 10 mg/day for entire study and went through four interventions for eight weeks each in random order (* used for analysis)
 - * Usual salt, placebo*
 - * Usual salt, paricalcitol 2 mg/day
 - * High salt, placebo*
 - * High salt, paricalcitol 2 mg/day

Other information

- Anti-hypertensive regimen reduced where participants reported symptomatic hypotension & re-stored if BP > 140/90 mm Hg

Outcomes	<ul style="list-style-type: none"> 24-hour albuminuria Clinic BP (semi-supine) Weight Serum markers (electrolytes, lipids, proteins, creatinine) Urinary markers and CrCl Measurement of sodium intake: 24-hour urine Measurement of confounders <ul style="list-style-type: none"> * Urea & potassium excretion
Notes	<ul style="list-style-type: none"> Funding: unfunded Additional data: provided by authors Registered at: http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=2898

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "To prevent systematic errors resulting from the crossover design, the order of the treatment periods was randomised (1:1:1:1) for each patient. Four different treatment sequences were defined." "Randomization of these sequences was performed externally by the pharmaceutical company that delivered the study medication (AbbVie)".
Allocation concealment (selection bias)	Low risk	Quote: "Computer-generated randomisation was performed by AbbVie. The investigators (C.A.K. and G.F.v.B.) enrolled participants. Patients received study medication containers labelled with a unique number representing the randomly allocated sequence, whereby all participants and involved investigators and care providers remained blinded to the study medication type (paricalcitol or placebo) throughout the entire study. Assignment of the treatment order was not disclosed until the study database was locked. The dietary intervention was open label."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	<p>Dietary intervention was open label but outcomes were objective and unlikely to be influenced by performance bias</p> <p>Blinding of participants: yes for medication, no for diet; blinding of investigators: yes for medication, no for diet; blinding of outcomes assessors: yes for medication, no for diet; blinding of data assessors: yes for medication, no for diet</p>
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Lab personnel assessing proteinuria were not aware of allocation; study personnel that assessed BP, weight, oedema were aware of allocation.
Incomplete outcome data (attrition bias)	Low risk	3 patients excluded after randomisation, however all included in intention-to-treat analysis

ViRTUE-CKD 2016 (Continued)

All outcomes

Selective reporting (reporting bias)	Low risk	Study was pre-registered online and the pre-specified outcomes were reported
Carry-over effect	Low risk	Quote: “8-week period was long enough to minimize potential carryover”
Bias from confounders	Unclear risk	Potassium: measured and reported no change; body weight change: 2 kg weight loss with sodium restriction, difficult to determine if due to fluid; physical activity: not reported; antihypertensive medications: no changes to medication reported during placebo period
Other	Low risk	Funding: AbbVie (Chicago, IL) funded the study medication (paricalcitol and placebo) Quote: “This trial was supported by a consortium grant from the Dutch Kidney Foundation (NIGRAM Consortium grant CP10.11). H.J.L.H. is supported by a grant from The Netherlands Organization for Scientific Research (Veni and Vidi grants). M.H.d.B. is supported by personal grants from the Dutch Kidney Foundation (grant no. KJPB.08.07) and the Netherlands Organization for Scientific Research (Veni grant). The funding source had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript.”

Vogt 2008
Study characteristics

Methods	<ul style="list-style-type: none"> Study design: cross-over RCT Time frame: March 2004 to June 2006 Duration of study (weeks): total (36); interventions (6); no washout
Participants	<ul style="list-style-type: none"> Country: the Netherlands Setting: outpatient renal clinic Inclusion criteria: stable proteinuria > 2 g/day and < 10 g/day; stable kidney function (< 6 mL/min/year decline); aged 18 to 70 years Baseline characteristics <ul style="list-style-type: none"> * CKD: CrCl ≥ 30 mL/min * Mean BP ± SD (SBP/DBP): 131 ± 18/71 ± 12.5 mm Hg Number: 34 Mean age ± SD: 50 ± 12 years Sex (M/F): 25/9 Exclusion criteria: mean arterial BP > 100 mm Hg; serum potassium > 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/week)
Interventions	<p>Low salt group</p> <ul style="list-style-type: none"> Target salt intake: 50 mmol sodium/day (individualised counselling by dietician) Duration: 6 weeks <p>High salt group</p> <ul style="list-style-type: none"> Target salt intake: 200 mmol sodium/day Duration: 6 weeks

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

Vogt 2008 (Continued)

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	<ul style="list-style-type: none"> • 24-hour proteinuria • Clinic BP (semi-supine) • Serum markers (creatinine, urea, cholesterol, triglycerides, total protein, albumin) • NT-pro BNP • 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	<ul style="list-style-type: none"> • 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	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Dietary interventions were open label; outcomes were objective and unlikely to be affected by performance bias
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low (3%) attrition and unlikely to introduce bias. 35 were randomised, one withdrew
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. Change in medication not reported but protocol was to keep stable during the study

Vogt 2008 (Continued)

Other

Low risk

Quote: "The original RCT was supported by Merck Sharp & Dohme (grand MSGP NETH-15-01). The second study was supported by an unrestricted grant from Novartis (CVAL489ANL08). The funding bodies had no role in study design, data collection, data analysis or data interpretation." (From Gant 2017)

ACEi - angiotensin-converting-enzyme inhibitor; ACR - albumin:creatinine ratio; ANP - atrial natriuretic peptide; ARB - angiotensin receptor blocker; BMI - body mass index; BP - blood pressure; BUN - blood urea nitrogen; CABG - coronary artery bypass graft; CAPD - continuous ambulatory peritoneal dialysis; CKD - chronic kidney disease; CrCl - creatinine clearance; CRP - C-reactive protein; CVD - cardiovascular disease; DBP - diastolic BP; DM - diabetes mellitus; eGFR - estimated glomerular filtration rate; ESKD - end-stage kidney disease; Hb - haemoglobin; HCT - haematocrit; HD - haemodialysis; HDF - haemodiafiltration; IgA - immunoglobulin A; IQR - interquartile range; KRT - kidney replacement therapy; MAP - mean arterial pressure; MDRD - Modification of Diet in Renal Disease; MI - myocardial infarction; Na - sodium; NSAID - nonsteroidal anti-inflammatory drug; NT-proBNP - N-terminal pro-brain natriuretic peptide; NYHA - New York Heart Association; NSAID - non-steroidal anti-inflammatory drug/s; PAH - para-aminohippuric acid; PCI - percutaneous coronary arterial intervention; PD - peritoneal dialysis; PDA - personal digital assistant; RAAS - renin-angiotensin-aldosterone system; RCT - randomised controlled trial; RPF - renal plasma flow; SBP - systolic BP; SCr - serum creatinine; SD - standard deviation; UNa - urinary sodium excretion; UTI - urinary tract infection

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Chanwikrai 2012	Wrong intervention: not comparing two or more levels of salt intake; RCT where all groups are advised on low salt and low protein diet
Clark-Cutaia 2016	Wrong duration: < 1 week; RCT of sodium restriction in dialysis patients with 5-day follow up
DD 2017	Wrong intervention: concomitant intervention not stable between arms; RCT comparing diuretics versus sodium restriction in CKD
De Nicola 2000	Wrong duration: < 1 week; RCT of differing dialysate sodium concentrations with 68-hour follow up
Esnault 2005	Wrong intervention: concomitant intervention not stable between arms; cross-over RCT with 5 arms in proteinuric patients: ramipril at 5 mg/day with usual furosemide dosage and usual sodium intake; ramipril at 10 mg/day with usual furosemide dosage and usual sodium intake; valsartan at 160 mg/day with usual furosemide dosage and usual sodium intake; combined ramipril at 5 mg and valsartan at 80 mg/day with usual furosemide dosage and usual sodium intake; combined ramipril at 5 mg, valsartan at 80 mg/day with increased furosemide dosage & participants asked to avoid excess sodium
HHK 2018	Wrong intervention: concomitant intervention not stable between arms; RCT of multiple behaviour change (physical activity, weight loss, restriction of sodium and phosphate additives)
Imanishi 1997	Wrong intervention: not comparing two levels of salt intake; cross-over RCT of high versus low salt (1 week), then 2 weeks of ACEi. Comparisons are made only for ACEi versus high salt arms
Kauric-Klein 2012	Wrong intervention: concomitant intervention not stable between arms; RCT comparing supportive educative nursing intervention to reduce BP versus usual care in HD patients. Intervention goals included sodium restriction, fluid restriction/limiting weight gain between dialysis sessions and medication adherence
Li 2013f	Wrong population: cluster RCT comparing education program to reduce sodium plus provision of a salt substitute versus control in rural Chinese villages (not a CKD population); sodium excretion measured at follow up only
Reyes 2013	This study was stopped early and withdrawn 2015 (no reasons provided)

Study	Reason for exclusion
Suckling 2016	Wrong population: RCT of sodium restriction in participants with impaired glucose tolerance and type 2 diabetes mellitus; excludes those with impaired kidney function

ACEi - angiotensin-converting-enzyme inhibitor; BP - blood pressure; CKD - chronic kidney disease; eGFR - estimated glomerular filtration rate; HD - haemodialysis; RCT - randomised controlled trial

Characteristics of ongoing studies [ordered by study ID]

[NCT03373500](#)

Study name	Effect of dietary salt reduction on blood pressure in kidney transplant recipients
Methods	<ul style="list-style-type: none"> Study design: open-label, parallel RCT Duration of study: 9 months
Participants	<ul style="list-style-type: none"> Sample size: 66 CKD: transplant recipients Inclusion criteria: patients who have received a kidney transplant ≥ 6 months previously who have a SBP > 130 mm Hg and/or DBP > 80 mm Hg, or are receiving treatment for hypertension Exclusion criteria: BP $< 120/80$ on BP treatment; BP $> 160/100$; variation in creatinine $> 20\%$ over preceding 2 months; secondary hypertension due to a cause other than CKD; heart failure (left ventricular ejection fraction $< 30\%$ or NYHA class II - IV); MI within 6 months; stroke within 6 months; current diagnosis of cancer; liver disease; bilateral arterio-venous fistulae; evidence of significant active infection; pregnant or breastfeeding; hyponatraemia (Na < 130 mmol/L) or hypernatraemia (Na > 150 mmol/L); histologically confirmed episode of rejection within 6 months; steroids dose change in preceding 2 months; unable to give full informed consent; Initial 24-hour urinary Na < 80 mmol/24 hours
Interventions	<p>Low salt group</p> <ul style="list-style-type: none"> Intensive dietary advice to achieve a low salt diet, targeting a dietary salt intake of < 5 g/day (80 mmol/day) <p>High salt group</p> <ul style="list-style-type: none"> Usual care
Outcomes	<ul style="list-style-type: none"> Office SBP & DBP (9 months) (primary outcome) Ambulatory BP (9 months) Endothelial function, measured by digital pulse wave analysis (9 months) Arterial stiffness, measured by digital pulse wave analysis (9 months) Proteinuria (9 months) Biomarkers of fibrosis (9 months): TGF-$\beta 1$, 2 & 3; CTGF & EDA + Fibronectin 48 hr sodium excretion
Starting date	October 11, 2017
Contact information	Principal Investigator: Pauline Swift
Notes	Trial registration: https://clinicaltrials.gov/ct2/show/NCT03373500 Estimated completion date June 2019

OxCKD1 2012

Study name	OxCKD1 2012 - Empowering healthy lifestyle choices in chronic kidney disease (OxCKD1 2012)
Methods	<ul style="list-style-type: none"> Study design: open-label, parallel RCT Duration of study: 11 months
Participants	<ul style="list-style-type: none"> Sample size: 201 CKD: diagnosed with CKD and an eGFR ≥ 20 mL/min/1.73 m² Inclusion criteria: willing and able to give informed consent for participation in the study; aged ≥ 18 years; clinically acceptable laboratory data available to confirm the CKD diagnosis; able (in the opinion of the investigators) and willing to comply with all study requirements; willing to allow his or her General Practitioner and consultant, if appropriate, to be notified of participation in the study Exclusion criteria: pregnant, lactating or planning pregnancy during the course of the study; any other significant disease or disorder which, in the opinion of the investigator, may either put the participants at risk because of participation in the study, or may influence the result of the study, or the participant's ability to participate in the study; inability to understand English or special communication needs because the interventions will use English and is not funded to deal with special communication needs; known salt losing kidney disease
Interventions	<p>Low salt group</p> <ul style="list-style-type: none"> Practical advice on cutting down on salt using information booklets, text messages, emails, telephone calls, and a website <p>High salt group</p> <ul style="list-style-type: none"> Usual care
Outcomes	<ul style="list-style-type: none"> Salt intake as assessed by 24-hour urine Na excretion and dietary salt analysis (month 1) BP (month 1, 3 and 11) Urine protein (month 1, 3 and 11)
Starting date	April 2012
Contact information	Principal Investigator: Christopher A O'Callaghan
Notes	Trial registration: https://clinicaltrials.gov/ct2/show/NCT01552317 Listed as Completed November 2014. Emailed study authors on 11 July 2019 to ask if results are available.

STICK 2015

Study name	Sodium intake in chronic kidney disease (STICK)
Methods	<ul style="list-style-type: none"> Study design: open-label, parallel RCT Duration of study: 24 months
Participants	<ul style="list-style-type: none"> Sample size: 105 CKD: CKD (MDRD eGFR of 30 to 60 mL/min/1.73 m² on ≥ 2 occasions ≥ 3 months apart) Inclusion criteria: Aged ≥ 40 years; most recent eGFR measurement within 3 months; SBP < 160 mm Hg and DB < 95 mm Hg on 3 office BP readings at time of screening and confirmed by a study ambulatory BP before randomisation of < 150/90 mm Hg; no change in antihypertensive or diuretic medications (including dose) for 3 months before screening visit; consumption of moderate sodium intake at screening, defined as an estimated daily Na intake of > 2.3 g/day estimated from food frequency questionnaire completed during the screening visit; self-reported willingness to mod-

STICK 2015 (Continued)

ify dietary intake over sustained period, and adhere to directed recommendations over 2 years; signed written informed consent

- Exclusion criteria: AKI in the preceding 3 months, defined as doubling of baseline SCr or rapidly declining eGFR over the preceding 6 months, defined as a decline in eGFR of $\geq 10\text{ mL/min/1.73 m}^2$ in those with established CKD; any of the following renal conditions: glomerular disease due to post-infectious glomerulonephritis, IgA nephropathy, thin basement membrane disease, Henoch-Schonlein purpura, proliferative glomerulonephritis, membranous nephropathy (including lupus nephritis), rapidly progressive glomerulonephritis, minimal change disease, or focal segmental glomerulosclerosis; prior or planned kidney transplantation; prior, current or planned dialysis; medical diagnosis known to be associated with abnormal renal sodium excretion, including Bartter syndrome, SIADH, diabetes insipidus, or serum sodium $< 125\text{ mmol/L}$; severe heart failure (defined as left ventricular ejection fraction $\leq 30\%$ or NYHA class III/IV symptoms); high-dose loop or thiazide diuretic therapy, exceeding a total daily dose of frusemide 80 mg, bumetanide 2 mg, hydrochlorothiazide 50 mg, bendroflumethiazide 2.5 mg, indapamide 2.5 mg, metolazone 2.5 mg or the use of both a loop and thiazide diuretic; current use of NSAIDs for ≥ 3 days/week (low-dose aspirin $< 100\text{ mg/day}$ is not an exclusion); unable to follow educational advice of the research team; prescribed high-salt diet, low-salt diet or sodium bicarbonate; symptomatic postural hypotension or receiving treatment for postural hypotension; current or recent use (within 1 month) of immunosuppressive medications including tacrolimus, cyclosporin, azathioprine or mycophenolate mofetil; pregnancy or lactation; unable to comply with 24-hour urinary collections, or medical condition making collection of 24-hour urinary collection difficult (e.g. severe urinary incontinence); Participant unlikely to comply with study procedures or follow-up visits due to severe co-morbid illness or other factor (e.g. inability to travel for follow-up visits, drug or alcohol misuse) in opinion of research team; cognitive impairment defined as a known diagnosis of dementia, or inability to provide informed consent due to cognitive impairment in the opinion of the investigator; BMI $< 20\text{ kg/m}^2$ or BMI $> 40\text{ kg/m}^2$; participating in another clinical trial or previous allocation in this study

Interventions	<p>Low salt group</p> <ul style="list-style-type: none"> • In addition to usual care, those randomised to the intervention arm will receive specific counselling on behavioural and environmental factors that promote sodium reduction after randomisation and at all specified post-randomisation visits, targeting sodium intake of $< 100\text{ mmol/day}$ ($< 2.3\text{ g/day}$). A research dietitian will develop the specific components of the intervention, based on standardised approaches to education interventions <p>High salt group</p> <ul style="list-style-type: none"> • Usual care
Outcomes	<ul style="list-style-type: none"> • 24-hour urinary CrCl (change from baseline to final follow-up) • eGFR (MDRD formula) • eGFR (CKD-EPI formula) • Rates of requirement for RRT • 24-hour urinary protein • Increase in risk category for prognosis of CKD as measured by the KDIGO 2012 CKD classification table • 24-hour UNa • 24-hour ambulatory BP • Composite outcome of risk category for prognosis of CKD (increase in risk), requirement for renal replacement therapy or death as measured by the KDIGO 2012 CKD classification table • Functional status as measured by the assessment functional status questionnaire
Starting date	March 2016
Contact information	<p>Principal Investigator: Martin J O'Donnell, MB PhD MRCP National University of Ireland Galway</p> <p>Principal Investigator: Andrew Smyth, MB PhD National University of Ireland Galway</p>

STICK 2015 (Continued)

Notes

Trial registration: <https://clinicaltrials.gov/ct2/show/NCT02458248> Study listed as Active, not recruiting; Estimated Primary Completion Date: August 2020

SUBLIME 2020

Study name	SodiUm Burden Lowered by Lifestyle Intervention: Self-Management and E-health Technology (SUBLIME)
Methods	<ul style="list-style-type: none"> Study design: open-label, parallel RCT Duration of study: 9 months
Participants	<ul style="list-style-type: none"> Sample size: 99 CKD: stage 1 to 3, CKD 4 if eGFR ≥ 25 mL/min/1.73 m², (or a kidney transplant recipient) Inclusion criteria: ≥ 18 years; UNa during at least the last 2 subsequent visits > 130 mmol/day, or 1 last UNa > 150 mmol/day; SBP > 135 mm Hg, DBP > 85 mmHg or a well-controlled BP by treatment with antihypertensives including RAAS-blockade (ACEi or ARB); sufficient command of the Dutch language; access and ability to use the Internet Exclusion criteria: eGFR < 25 mL/min/1.73 m² or an anticipated need for predialysis work-up within the time frame of the study; unstable disease: defined as rapid, persistent, progressive kidney function loss (e.g. > 6 mL/min/1.73 m² per year), not from acute, intermittent origin; SBP > 170 mm Hg or DBP > 100 mm Hg during medical treatment; SBP < 95 mm Hg not responding to withdrawal of antihypertensives; cardiovascular event (MI, cerebrovascular accident) < 6 months ago; kidney transplantation < 1 year ago; medical conditions that are likely to interfere with completion of the study (such as progressive malignancy or other debilitating illness) at the discretion of the nephrologist; Every patient who has participated in the ESMO study (regardless whether intervention or control) cannot participate in the current study; current participation in any clinical trial that might interfere with SUBLIME trial
Interventions	<p>Low salt group</p> <ul style="list-style-type: none"> Behavioural; 2 group meetings with fellow-patients, motivational interviewing, e-coaching and ICT-based self-regulation as add-on to regular care for 9 months <p>High salt group</p> <ul style="list-style-type: none"> Usual care; 9 months
Outcomes	<ul style="list-style-type: none"> 24-hour UNa BP Psychological well-being Psychological well-being will be assessed with multiple choice questionnaires in all 150 participants. Cost-effectiveness (derived from questionnaires on health care use, contacts with health care professionals, change in medication in all participants). Cardiorenal biomarkers
Starting date	June 2014
Contact information	<p>Study Chair: Gerjan J Navis, MD PhD University Medical Center Groningen</p> <p>Principal Investigator: Paul JM Van der Boog, MD PhD Leiden University Medical Center</p> <p>Principal Investigator: Sandra Van Dijk, PhD Leiden University Medical Center</p>
Notes	<p>Trial registration: https://clinicaltrials.gov/ct2/show/study/NCT02132013 Study listed as completed December 2015 (last updated May 2016); Emailed on 12/6/19 re: availability of results</p>

SUPER 2016

Study name	Sodium lowering and Urinary ProtEin Reduction trial (SUPER)
Methods	<ul style="list-style-type: none"> Study design: open-label, parallel RCT. Duration of study: 8 weeks
Participants	<ul style="list-style-type: none"> Sample size: 150 (estimated) CKD: eGFR < 90 mL/min/1.73 m² but > 30 mL/min/1.73 m² Inclusion criteria: ≥ 21 years; ACR > 30 mg/g Exclusion criteria: albuminuria ≥ 1.5 g/g or kidney structural change; prior kidney transplant based on self-report; immunosuppression or other immunotherapy within the past 6 months prior to enrolment based on patient self-report; history of cancer other than non-melanoma skin cancer within two years prior to enrolment based on patient self-report; History of polycystic kidney disease; currently receiving dialysis treatment; history of HIV; current pregnancy, breastfeeding or plans to become pregnant during the study; consumption of ≥ 14 alcoholic drinks/week or consumption of ≥ 6 drinks/occasion; current participation in another lifestyle intervention trial; current residence or planned residence make it difficult to meet trial requirements; other concerns regarding ability to meet trial requirements, at the discretion of the principal investigator
Interventions	<p>Low salt group</p> <ul style="list-style-type: none"> Intensive behavioural modification program designed to reduce dietary sodium intake to 2,300 mg/day for 24 weeks <p>High salt group</p> <ul style="list-style-type: none"> Usual care
Outcomes	<ul style="list-style-type: none"> Urinary ACR Urinary albumin eGFR BP Number of antihypertensive medications
Starting date	June 2014
Contact information	Principal Investigator: Katherine T Mills, PhD, MSPH Tulane University School of Public Health and Tropical Medicine
Notes	Trial registration: https://clinicaltrials.gov/ct2/show/NCT02945969 Study not completed (Study completion date March 2020; last updated April 2019)

ACR - albumin-creatinine ratio; AKI - acute kidney injury; ACEi - angiotensin-converting enzyme inhibitors; ARB - angiotensin-receptor blockers; BMI - body mass index; BP - blood pressure; CKD - chronic kidney disease; CrCl - creatinine clearance; DBP - diastolic blood pressure; eGFR - estimated glomerular filtration rate; KRT - kidney replacement therapy; MDRD - Modification of Diet in Renal Disease; MI - myocardial infarction; Na - sodium; NSAID/s - nonsteroidal anti-inflammatory drug/s; NYHA - New York Heart Association; RAAS - renin-angiotensin-aldosterone system; RCT - randomised controlled trial; SBP - systolic blood pressure; SCr - serum creatinine; UNa - urinary sodium excretion

DATA AND ANALYSES

Comparison 1. CKD stage

Outcome or sub-group title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Sodium intake/excretion	18	1383	Mean Difference (IV, Random, 95% CI)	-73.51 [-92.76, -54.27]
1.1.1 CKD	12	1048	Mean Difference (IV, Random, 95% CI)	-83.81 [-104.54, -63.08]
1.1.2 Dialysis	4	259	Mean Difference (IV, Random, 95% CI)	-27.17 [-48.59, -5.76]
1.1.3 Post-transplant	2	76	Mean Difference (IV, Random, 95% CI)	-96.99 [-148.10, -45.89]
1.2 Systolic blood pressure	19	1261	Mean Difference (IV, Random, 95% CI)	-6.91 [-8.82, -4.99]
1.2.1 CKD	12	1036	Mean Difference (IV, Random, 95% CI)	-6.10 [-8.11, -4.08]
1.2.2 Dialysis	5	149	Mean Difference (IV, Random, 95% CI)	-6.32 [-11.04, -1.60]
1.2.3 Post-transplant	2	76	Mean Difference (IV, Random, 95% CI)	-11.94 [-15.77, -8.11]
1.3 Diastolic blood pressure	19	1257	Mean Difference (IV, Random, 95% CI)	-3.91 [-4.80, -3.02]
1.3.1 CKD	12	1032	Mean Difference (IV, Random, 95% CI)	-3.47 [-4.28, -2.65]
1.3.2 Dialysis	5	149	Mean Difference (IV, Random, 95% CI)	-3.46 [-6.39, -0.54]
1.3.3 Post-transplant	2	76	Mean Difference (IV, Random, 95% CI)	-7.13 [-9.46, -4.79]
1.4 Proteinuria [ln mg/d]	6		Mean Difference (IV, Random, 95% CI)	-0.41 [-0.58, -0.25]
1.4.1 CKD	6		Mean Difference (IV, Random, 95% CI)	-0.41 [-0.58, -0.25]
1.5 Albuminuria [ln mg/d]	6		Mean Difference (IV, Random, 95% CI)	-0.44 [-0.58, -0.30]
1.5.1 CKD	5		Mean Difference (IV, Random, 95% CI)	-0.47 [-0.60, -0.34]
1.5.2 Post-transplant	1		Mean Difference (IV, Random, 95% CI)	-0.03 [-0.63, 0.57]
1.6 eGFR [mL/min/1.73 m²]	7	559	Mean Difference (IV, Random, 95% CI)	-0.82 [-2.31, 0.66]
1.6.1 CKD	6	515	Mean Difference (IV, Random, 95% CI)	-1.00 [-2.85, 0.85]
1.6.2 Post-transplant	1	44	Mean Difference (IV, Random, 95% CI)	-0.50 [-3.00, 2.00]
1.7 Creatinine clearance	7	529	Mean Difference (IV, Random, 95% CI)	-4.70 [-6.94, -2.47]
1.7.1 CKD	6	485	Mean Difference (IV, Random, 95% CI)	-5.06 [-7.40, -2.72]
1.7.2 Post-transplant	1	44	Mean Difference (IV, Random, 95% CI)	-1.00 [-8.50, 6.50]

Outcome or sub-group title	No. of studies	No. of participants	Statistical method	Effect size
1.8 Serum creatinine	7	519	Mean Difference (IV, Random, 95% CI)	4.46 [0.08, 8.83]
1.8.1 CKD	6	487	Mean Difference (IV, Random, 95% CI)	4.86 [0.95, 8.76]
1.8.2 Post-transplant	1	32	Mean Difference (IV, Random, 95% CI)	-11.00 [-32.30, 10.30]
1.9 Filtration fraction	2	160	Mean Difference (IV, Random, 95% CI)	-0.40 [-0.87, 0.07]
1.9.1 CKD	2	160	Mean Difference (IV, Random, 95% CI)	-0.40 [-0.87, 0.07]
1.10 Weight	12	759	Mean Difference (IV, Random, 95% CI)	-1.32 [-1.94, -0.70]
1.10.1 CKD	8	634	Mean Difference (IV, Random, 95% CI)	-1.47 [-2.42, -0.53]
1.10.2 Dialysis	3	81	Mean Difference (IV, Random, 95% CI)	-0.67 [-1.37, 0.04]
1.10.3 Post-transplant	1	44	Mean Difference (IV, Random, 95% CI)	-2.00 [-3.00, -1.00]
1.11 Inter-dialytic weight gain	2	187	Mean Difference (IV, Random, 95% CI)	-0.11 [-0.28, 0.06]
1.11.1 Dialysis	2	187	Mean Difference (IV, Random, 95% CI)	-0.11 [-0.28, 0.06]
1.12 Extracellular fluid volume	3	187	Mean Difference (IV, Random, 95% CI)	-0.87 [-1.17, -0.58]
1.12.1 CKD	2	148	Mean Difference (IV, Random, 95% CI)	-0.89 [-1.20, -0.59]
1.12.2 Dialysis	1	39	Mean Difference (IV, Random, 95% CI)	-0.30 [-1.87, 1.27]
1.13 Presence of oedema	2	191	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.31, 0.90]
1.13.1 CKD	2	191	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.31, 0.90]
1.14 Plasma renin activity	2	142	Mean Difference (IV, Random, 95% CI)	1.08 [0.51, 1.65]
1.14.1 CKD	2	142	Mean Difference (IV, Random, 95% CI)	1.08 [0.51, 1.65]
1.15 Aldosterone (plasma or serum)	2	142	Mean Difference (IV, Random, 95% CI)	6.20 [3.82, 8.58]
1.15.1 CKD	2	142	Mean Difference (IV, Random, 95% CI)	6.20 [3.82, 8.58]
1.16 Reduction in anti-hypertensive dose	7	664	Risk Ratio (M-H, Random, 95% CI)	2.45 [0.98, 6.08]
1.16.1 CKD	5	588	Risk Ratio (M-H, Random, 95% CI)	1.53 [0.62, 3.78]
1.16.2 Post-transplant	2	76	Risk Ratio (M-H, Random, 95% CI)	7.52 [1.45, 39.04]
1.17 Symptomatic hypotension	6	478	Risk Ratio (M-H, Random, 95% CI)	6.70 [2.40, 18.69]

Outcome or sub-group title	No. of studies	No. of participants	Statistical method	Effect size
1.17.1 CKD	5	433	Risk Ratio (M-H, Random, 95% CI)	6.26 [2.08, 18.81]
1.17.2 Post-transplant	1	45	Risk Ratio (M-H, Random, 95% CI)	10.54 [0.62, 180.07]
1.18 Total cholesterol	7	473	Mean Difference (IV, Random, 95% CI)	-0.11 [-0.31, 0.10]
1.18.1 CKD	5	390	Mean Difference (IV, Random, 95% CI)	-0.06 [-0.30, 0.19]
1.18.2 Dialysis	1	39	Mean Difference (IV, Random, 95% CI)	-0.42 [-0.99, 0.15]
1.18.3 Post-transplant	1	44	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.54, 0.39]

Analysis 1.1. Comparison 1: CKD stage, Outcome 1: Sodium intake/excretion

Analysis 1.2. Comparison 1: CKD stage, Outcome 2: Systolic blood pressure

Analysis 1.3. Comparison 1: CKD stage, Outcome 3: Diastolic blood pressure

Analysis 1.4. Comparison 1: CKD stage, Outcome 4: Proteinuria [ln mg/d]

Analysis 1.5. Comparison 1: CKD stage, Outcome 5: Albuminuria [ln mg/d] **Analysis 1.6. Comparison 1: CKD stage, Outcome 6: eGFR [mL/min/1.73 m²]**

Analysis 1.7. Comparison 1: CKD stage, Outcome 7: Creatinine clearance

Analysis 1.8. Comparison 1: CKD stage, Outcome 8: Serum creatinine

Analysis 1.9. Comparison 1: CKD stage, Outcome 9: Filtration fraction

Analysis 1.10. Comparison 1: CKD stage, Outcome 10: Weight

Analysis 1.11. Comparison 1: CKD stage, Outcome 11: Inter-dialytic weight gain

Analysis 1.12. Comparison 1: CKD stage, Outcome 12: Extracellular fluid volume

Analysis 1.13. Comparison 1: CKD stage, Outcome 13: Presence of oedema

Analysis 1.14. Comparison 1: CKD stage, Outcome 14: Plasma renin activity

Analysis 1.15. Comparison 1: CKD stage, Outcome 15: Aldosterone (plasma or serum)

Analysis 1.16. Comparison 1: CKD stage, Outcome 16: Reduction in antihypertensive dose

Analysis 1.17. Comparison 1: CKD stage, Outcome 17: Symptomatic hypotension

Analysis 1.18. Comparison 1: CKD stage, Outcome 18: Total cholesterol

Comparison 2. Duration

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Sodium intake/excretion	18	1383	Mean Difference (IV, Random, 95% CI)	-73.51 [-92.76, -54.27]
2.1.1 Short-term (< 4 weeks)	3	142	Mean Difference (IV, Random, 95% CI)	-111.29 [-134.25, -88.32]
2.1.2 Longer-term (≥ 4 weeks)	15	1241	Mean Difference (IV, Random, 95% CI)	-64.53 [-83.29, -45.78]
2.2 Systolic blood pressure	19	1261	Mean Difference (IV, Random, 95% CI)	-6.91 [-8.82, -4.99]
2.2.1 Short-term (< 4 weeks)	3	144	Mean Difference (IV, Random, 95% CI)	-7.91 [-11.53, -4.28]
2.2.2 Longer-term (≥ 4 weeks)	16	1117	Mean Difference (IV, Random, 95% CI)	-6.82 [-9.00, -4.64]
2.3 Diastolic blood pressure	19	1257	Mean Difference (IV, Random, 95% CI)	-3.91 [-4.80, -3.02]
2.3.1 Short-term (< 4 weeks)	3	144	Mean Difference (IV, Random, 95% CI)	-3.70 [-5.74, -1.67]
2.3.2 Longer-term (≥ 4 weeks)	16	1113	Mean Difference (IV, Random, 95% CI)	-3.99 [-5.03, -2.94]
2.4 Creatinine clearance	7	529	Mean Difference (IV, Random, 95% CI)	-4.70 [-6.94, -2.47]
2.4.1 Short-term (< 4 weeks)	2	104	Mean Difference (IV, Random, 95% CI)	-5.88 [-9.14, -2.63]
2.4.2 Longer-term (≥ 4 weeks)	5	425	Mean Difference (IV, Random, 95% CI)	-3.65 [-6.72, -0.58]
2.5 Serum creatinine	7	519	Mean Difference (IV, Random, 95% CI)	4.46 [0.08, 8.83]
2.5.1 Short-term (< 4 weeks)	1	28	Mean Difference (IV, Random, 95% CI)	17.68 [-47.51, 82.87]
2.5.2 Longer-term (≥ 4 weeks)	6	491	Mean Difference (IV, Random, 95% CI)	4.40 [-0.41, 9.20]
2.6 Weight	12	759	Mean Difference (IV, Random, 95% CI)	-1.32 [-1.94, -0.70]
2.6.1 Short-term (< 4 weeks)	2	68	Mean Difference (IV, Random, 95% CI)	-0.41 [-0.81, -0.01]
2.6.2 Longer-term (≥ 4 weeks)	10	691	Mean Difference (IV, Random, 95% CI)	-1.53 [-2.02, -1.04]

Analysis 2.1. Comparison 2: Duration, Outcome 1: Sodium intake/excretion

Analysis 2.2. Comparison 2: Duration, Outcome 2: Systolic blood pressure

Analysis 2.3. Comparison 2: Duration, Outcome 3: Diastolic blood pressure

Analysis 2.4. Comparison 2: Duration, Outcome 4: Creatinine clearance

Analysis 2.5. Comparison 2: Duration, Outcome 5: Serum creatinine

Analysis 2.6. Comparison 2: Duration, Outcome 6: Weight

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. sodium chloride:kw

(Continued)

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

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.

(Continued)

- 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	<i>Low risk of bias:</i> 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). <i>High risk of bias:</i> 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. <i>Unclear:</i> Insufficient information about the sequence generation process to permit judgement.
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	<i>Low risk of bias:</i> Randomisation method described that would not allow investigator/participant to know or influence intervention 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). <i>High risk of bias:</i> 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. <i>Unclear:</i> 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	<i>Low risk of bias:</i> 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. <i>High risk of bias:</i> 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. <i>Unclear:</i> Insufficient information to permit judgement

(Continued)

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 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

Carry-over effect

Bias due to treatment order in cross-over studies

Low risk of bias: Sufficient time between outcome assessments in the first and second periods to ensure carryover effects are not present; insufficient time between outcome assessments in the first and second periods but treatment order effect accounted for in the analysis (by inclusion of intervention-by-time period interactions)

High risk of bias: Insufficient time between outcome assessments in the first and second periods to ensure carryover effects are not present and treatment order effect not accounted for in analysis.

Unclear: Insufficient information to permit judgement

Confounding factors

Low risk of bias: Behavioural factors that are associated with the outcome and covary with dietary sodium (e.g., potassium intake, body weight, anti-hypertensive medication dosage) are un-

(Continued)

Bias due to differences between groups other than sodium intake

changed, or changes were similar between groups, or differences between groups unlikely to modify the intervention effect estimate.

High risk of bias: Changes in confounding factors or baseline imbalances likely to have modified intervention effect estimate

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.

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.

WHAT'S NEW

Date	Event	Description
17 June 2021	New search has been performed	13 additional studies included
17 June 2021	New citation required and conclusions have changed	<p>GRADE used to assess the evidence</p> <p>Inclusion criteria modified 1) updated definition of CKD; 2) removed eligibility criterion related to measurement of 24-hour urine and achieving at least a 34 mmol difference. Previously excluded studies were re-assessed based on updated eligibility criteria.</p> <p>New analyses: proteinuria; albuminuria; inter-dialytic weight gain</p> <p>New outcome: muscle cramps</p> <p>Used results from paired analyses where possible</p>

HISTORY

Protocol first published: Issue 9, 2012

Review first published: Issue 2, 2015

CONTRIBUTIONS OF AUTHORS

1. Review protocol: EM, KC, JB, DM
2. Study selection 2019 update: EM, KC; 2015 review: EM, KC, JB
3. Data extraction 2019 update: EM; 2015 review: EM, KC
4. Data analysis: EM
5. Quality assessment: EM, KC
6. GRADE assessment: EM, JK, JB
7. Interpret analysis: EM, KC, JB, DM, JK
8. Write review: EM, KC, JB, DM, JK

DECLARATIONS OF INTEREST

- Emma J McMahon: none known
- Katrina L Campbell: none known
- Judith D Bauer: none known
- David W Mudge: none known
- Jaimon T Kelly: JK reports consultancy fees from Amgen for travel and professional presentation unrelated to the submitted work.

SOURCES OF SUPPORT

Internal sources

- Princess Alexandra Hospital, Australia
Salary (DM, KC)
- University of Queensland, Australia
Salary (JB, EH)

External sources

- NHMRC/Australian Heart Foundation Early Career Fellowship (100085), Australia

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

2015 review: Outcome sodium excretion was included.

2021 update: Inclusion criteria modified i) updated definition of CKD; ii) removed eligibility criterion related to measurement of 24-hour urine and achieving at least a 34 mmol difference. Outcome added: muscle cramps.

INDEX TERMS

Medical Subject Headings (MeSH)

Antihypertensive Agents [administration & dosage]; Blood Pressure [*drug effects] [physiology]; *Diet, Sodium-Restricted; 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