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Reduced dietary salt for the prevention of cardiovascular disease (Review)

Adler AJ, Taylor F, Martin N, Gottlieb S, Taylor RS, Ebrahim S

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Reduced dietary salt for the prevention of cardiovascular disease

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A B S T R A C T

Background

This is an update of a Cochrane review that was first published in 2011 of the effects of reducing dietary salt intake, through advice to reduce salt intake or low-sodium salt substitution, on mortality and cardiovascular events.

Objectives

1. To assess the long-term effects of advice and salt substitution, aimed at reducing dietary salt, on mortality and cardiovascular morbidity.

2. To investigate whether a reduction in blood pressure is an explanatory factor in the effect of such dietary interventions on mortality and cardiovascular outcomes.

Search methods

We updated the searches of CENTRAL (2013, Issue 4), MEDLINE (OVID, 1946 to April week 3 2013), EMBASE (OVID, 1947 to 30 April 2013) and CINAHL (EBSCO, inception to 1 April 2013) and last ran these on 1 May 2013. We also checked the references of included studies and reviews. We applied no language restrictions.

Selection criteria

Trials fulfilled the following criteria: (1) randomised, with follow-up of at least six months, (2) the intervention was reduced dietary salt (through advice to reduce salt intake or low-sodium salt substitution), (3) participants were adults and (4) mortality or cardiovascular morbidity data were available. Two review authors independently assessed whether studies met these criteria.

Data collection and analysis

A single author extracted data and assessed study validity, and a second author checked this. We contacted trial authors where possible to obtain missing information. We extracted events and calculated risk ratios (RRs) and 95% confidence intervals (CIs).
Main results

Eight studies met the inclusion criteria: three in normotensives (n = 3518) and five in hypertensives or mixed populations of normo- and hypertensives (n = 3766). End of trial follow-up ranged from six to 36 months and the longest observational follow-up (after trial end) was 12.7 years.

The risk ratios (RR) for all-cause mortality in normotensives were imprecise and showed no evidence of reduction (end of trial RR 0.67, 95% confidence interval (CI) 0.40 to 1.12, 60 deaths; longest follow-up RR 0.90, 95% CI 0.58 to 1.40, 79 deaths n=3518) or in hypertensives (end of trial RR 1.00, 95% CI 0.86 to 1.15, 565 deaths; longest follow-up RR 0.99, 95% CI 0.87 to 1.14, 674 deaths n=3085).

There was weak evidence of benefit for cardiovascular mortality (hypertensives: end of trial RR 0.67, 95% CI 0.45 to 1.01, 106 events n=2656) and for cardiovascular events (hypertensives: end of trial RR 0.76, 95% CI 0.57 to 1.01, 194 events, four studies, n = 3397; normotensives: at longest follow-up RR 0.71, 95% CI 0.42 to 1.20, 200 events; hypertensives: RR 0.77, 95% CI 0.57 to 1.02, 192 events; pooled analysis of six trials RR 0.77, 95% CI 0.63 to 0.95, n = 5912). These findings were driven by one trial among retirement home residents that reduced salt intake in the kitchens of the homes, thereby not requiring individual behaviour change.

Advice to reduce salt showed small reductions in systolic blood pressure (mean difference (MD) -1.15 mmHg, 95% CI -2.32 to 0.02 n=2079) and diastolic blood pressure (MD -0.80 mmHg, 95% CI -1.37 to -0.23 n=2079) in normotensives and greater reductions in systolic blood pressure in hypertensives (MD -4.14 mmHg, 95% CI -5.84 to -2.43 n=675), but no difference in diastolic blood pressure (MD -3.74 mmHg, 95% CI -8.41 to 0.93 n=675).

Overall many of the trials failed to report sufficient detail to assess their potential risk of bias. Health-related quality of life was assessed in one trial in normotensives, which reported significant improvements in well-being but no data were presented.

Authors’ conclusions

Despite collating more event data than previous systematic reviews of randomised controlled trials, there is insufficient power to confirm clinically important effects of dietary advice and salt substitution on cardiovascular mortality in normotensive or hypertensive populations. Our estimates of the clinical benefits from advice to reduce dietary salt are imprecise, but are larger than would be predicted from the small blood pressure reductions achieved. Further well-powered studies would be needed to obtain more precise estimates. Our findings do not support individual dietary advice as a means of restricting salt intake. It is possible that alternative strategies that do not require individual behaviour change may be effective and merit further trials.

Plain Language Summary

Reduced dietary salt for the prevention of cardiovascular disease

Cardiovascular disease includes heart attacks and strokes and is a major cause of premature death and disability. This is an update of a review first published in 2011. This review sets out to assess whether intensive support and encouragement to cut down on salt in foods, and substituting low-sodium salt, reduces the risk of death or cardiovascular disease. This update includes two new studies and eliminates one problematic study, giving a total of eight trials with 7284 participants.

Dietary advice and salt substitution did reduce the amount of salt eaten, which led to a small reduction in blood pressure by six months. There was weak evidence of benefit for cardiovascular events, but these findings were inconclusive and were driven by a single trial among retirement home residents, which reduced salt intake in the kitchens of the homes.

The findings of our review do not mean that advising people to reduce salt should be stopped. However, additional measures - reducing the amount of hidden salt in processed foods, for example - will make it much easier for people to achieve a lower salt diet. Overall many of the trials failed to report sufficient detail to assess their potential risk of bias. Further evidence of the effects of different ways of reducing dietary salt on clinical events is needed from experimental and observational studies to underpin public health policies.
BACKGROUND

In 2010 it was estimated that nearly 12.9 million deaths (a quarter of the global total) were due to ischaemic heart disease and stroke (Lozano 2012). Morbidity data are more difficult to collect because there are so many different measures of cardiovascular morbidity. However, in 2010 ischaemic heart disease was globally the number one cause of disability adjusted life years (DALYs) lost each year, with nearly 130 million DALYs (Allender 2008). Similarly, high blood pressure was the number one risk factor, with over 170 million DALYs lost globally each year (Mente 2013).

Globally, high blood pressure is a leading risk factor for cardiovascular disease, contributing over 7% of the global DALYs in 2010 (Lim 2012). The relationship of salt intake to blood pressure is the basis for the belief that restriction of dietary sodium intake will prevent blood pressure-related cardiovascular events (Elliot 1996). The public health recommendations of a decade ago remain in place: to reduce salt intake by about half, i.e. from approximately 10 to 5 g/day (Dietary Guidelines for Americans 2010; He 2010; SACN 2003; Whelton 2002; Whelton 2012), and they have also been endorsed in current World Health Organization guidelines on sodium intake (WHO 2012).

Data from observational studies have indicated that a high dietary intake of salt is an important risk factor for cardiovascular disease (He 2002; He 2010). Short-term intervention studies, including the Dietary Approaches to Stop Hypertension (DASH) trials, have shown decreases in systolic blood pressure in all groups (Sacks 2001). This was confirmed by a systematic review and meta-analysis of 13 prospective studies including 177,000 participants, which reported a greater risk of stroke in those with higher salt intakes (relative risk 1.23, 95% CI 1.06 to 1.43) (Strazzullo 2009). However, in this review the association between salt intake and all cardiovascular events was smaller (relative risk 1.14, 95% CI 0.99 to 1.31) and with the exclusion of one study statistical significance was achieved (relative risk 1.17, 95% CI 1.02 to 1.32), but all-cause mortality was not reported. The interpretation of this observational evidence base is complicated by the heterogeneity in estimating sodium intake (diet or urinary salt excretion), types of participants (healthy, hypertensive, obese and non-obese), end-points and the definition of outcomes across studies (Alderman 2010). A more recent review of observational studies reported no strong evidence of an effect on all-cause mortality (relative risk 1.06, 95% CI 0.94 to 1.20) and similar inconclusive effects on cardiovascular disease (relative risk 1.12, 95% CI 0.93 to 1.34), noting that the quality of evidence was generally low due to non-randomised designs (Aburto 2013).

Following publication of the 2011 Cochrane review, commentators have put forward a view that the relationship between dietary sodium intake and cardiovascular events may be J-shaped, suggesting that lowering sodium beyond a certain point may not be beneficial (Alderman 2011; Alderman 2012; Mente 2013). Several prospective cohort studies have been published recently that overcome the problem of dietary sodium assessment by using urinary sodium excretion as an index of dietary intake. These have shown a possible J-shaped relationship: low sodium intake (< 3 g/day) is associated with no lower rate of cardiovascular disease, and perhaps a higher rate (Ekinçi 2011; O’Donnell 2011; Stolarz-Skrzypek 2011). In light of these studies, the US Institute of Medicine reviewed the evidence and found that it supported population-based efforts to lower excessive dietary salt intake, but not the lowering of intakes to < 2.3 g sodium/day (Institute of Medicine 2013). Commentary on the new recommendations has suggested that the scientific debates, our earlier Cochrane review and difficulties in interpreting the evidence only provide opportunities for the food industry to avoid regulation of salt in their products (Neal 2013). Others consider that we still have insufficient evidence to decide whether to advise people to reduce their salt intake below current average levels (Mente 2013). A recent review of four decades of the salt and health debate concludes that the evidence available from different eras has been unable to resolve the debate satisfactorily (Bayer 2012).

A number of meta-analyses of randomised controlled trials of salt reduction and blood pressure have been undertaken (He 2004; Jürgens 2004). Whilst these analyses consistently report a reduction in the level of blood pressure with reduced salt intake, the level of blood pressure reduction achieved is less impressive in the longer term. The 2004 Cochrane review of dietary salt restriction intervention studies of at least six months’ duration found that intensive support and encouragement to reduce salt intake lowered blood pressure at 13 to 60 months, but only by a small amount (systolic by 1.1 mmHg, 95% CI 1.8 to 0.4; diastolic by 0.6 mmHg, 95% CI 1.5 to -0.3) (Hooper 2004). These findings of small blood pressure reductions among normotensive people were confirmed in a recent Cochrane review, which demonstrated much smaller blood pressure reductions in normotensives (about 1% in systolic blood pressure) and greater reductions in hypertensive people (around 3.5%) (Graudal 2011). Certainly the very large estimated effects of salt reduction using both trial and observational data are no longer considered plausible (Law 1991). The most recent review has continued the questionable practice of combining both short and longer duration trials: among 34 trials of 3230 participants with four or more weeks (median four to five weeks) of follow-up, the mean change in blood pressure was -4 mmHg for systolic and -2 mmHg for diastolic blood pressure, although heterogeneity was marked with I² estimates of between 68% and 75% (He 2013a; He 2013b). Such estimates are unlikely to reflect the reductions in blood pressure that can be obtained in the general normotensive population in practice. However, even small sustained reductions in mean blood pressure of 2 to 3 mmHg would be sufficient for important population reductions in cardiovascular events (Elliot 1991).
patients with heart failure was included (Paterna 2008). We have now excluded this trial following the retraction by the editors of Heart journal of a meta-analysis including this paper (Editor’s Note 2013). Trials of salt restriction in heart failure are no longer within the scope of this review.

Whilst our earlier Cochrane review also sought to assess the impact of dietary salt restriction advice on mortality and cardiovascular events, across the 11 randomised controlled trials included there were only 17 deaths spread evenly across groups and 46 cardiovascular events in the controls compared with 36 in the low-sodium diet groups (Hooper 2004). The small number of events limited the ability of this earlier review to detect small to moderate reductions in the risk of cardiovascular events.

Given that the effect of interventions to reduce dietary salt on blood pressure is well established and health policy in the area of salt reduction has advanced, the primary focus of this review is to confirm whether reducing dietary salt through advice or substitution is associated with improvements in mortality and cardiovascular events.

**OBJECTIVES**

1. To assess the long-term effects of advice and salt substitution, aimed at reducing dietary salt, on mortality and cardiovascular morbidity.

2. To investigate whether a reduction in blood pressure is an explanatory factor in the effect of such dietary interventions on mortality and cardiovascular outcomes.

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**

Randomised controlled trials (RCTs), individual or cluster level, with follow-up of at least six months.

**Types of participants**

Studies in adults (18 years or older), irrespective of gender or ethnicity. We excluded studies in patients with heart failure, children or pregnant women.

**Types of interventions**

Reducing dietary salt intake, either by advice from health professionals or provision of low-sodium salt substitution. The comparison group could include usual, control or placebo diet, or no intervention.

**Types of outcome measures**

**Primary outcomes**

1. All-cause mortality.
2. Cardiovascular mortality.
3. Cardiovascular morbidity (including fatal and non-fatal myocardial infarction, stroke, angina, heart failure, peripheral vascular events, sudden death, revascularisation (coronary artery bypass surgery or angioplasty with or without stenting) and cardiovascular-related hospital admissions).

We assessed primary outcomes at study end and also at the latest trial follow-up, where participants had been followed observationally after the end of the original trial.

**Secondary outcomes**

In studies that reported the primary outcomes we also sought the following secondary outcomes:

1. Changes in systolic and diastolic blood pressure.
2. Urinary salt excretion (or other method of estimation of salt intake).
3. Health-related quality of life using a validated outcome measure (e.g. Short Form 36, McHorney 1993).

**Search methods for identification of studies**

**Electronic searches**

We updated the searches, initially run in 2008 (Appendix 1), and re-ran these on 1 May 2013 (Appendix 2). We searched the following databases:

- Cochrane Central Register of Controlled Trials (CENTRAL) (2013, Issue 4);
- MEDLINE (OVID, 1946 to April week 3 2013);
- EMBASE Classic + EMBASE (OVID, 1947 to 30 April 2013);
- CINAHL Plus with Full Text (EBSCO, to 1 April 2013);
- PsycINFO (OVID, 1806 to October 2008 - not updated as resources were limited);
- Health Technology Assessment (HTA) on The Cochrane Library (2008, Issue 4 - not updated as resources were limited);
- Database of Abstracts of Reviews of Effects (DARE) on The Cochrane Library (2008, Issue 4 - not updated as resources were limited).
Searches conducted in MEDLINE, EMBASE, CINAHL and PsycINFO included a controlled trials filter in 2008. We updated this in 2013 to the Cochrane sensitivity-maximising RCT filter for MEDLINE and adaptations of it for EMBASE and CINAHL (Lefebvre 2011). We limited the searches in MEDLINE, EMBASE and CINAHL by entry dates/weeks to identify only newly added records since the last search. We limited the CENTRAL search by publication dates. We applied no language restrictions.

**Searching other resources**

We searched reference lists of all eligible trials and relevant systematic reviews for additional studies.

**Data collection and analysis**

**Selection of studies**

Two authors (KA and RST) independently screened the titles and abstracts of studies identified by the original search and discarded clearly irrelevant studies. In order to be selected, abstracts had to identify clearly the study design, an appropriate population and a relevant intervention/exposure, as described above. We obtained the full-text reports of all potentially relevant studies and two authors (KA and RST) assessed these independently for eligibility, based on the defined inclusion criteria. We resolved any disagreement by discussion or where agreement could not be reached, by consultation with an independent third person (LH). For the update, two authors (AJA, FCT or NM) independently screened half the abstracts. A third author (NM) checked 10% of all studies. Two authors (AJA and FCT) checked full-text articles of potentially relevant studies. A third author (NM) checked all excluded studies.

**Data extraction and management**

We used standardised data extraction forms. We extracted relevant data regarding inclusion criteria (study design, participants, intervention/exposure and outcomes), risk of bias (see below) and outcome data. A single author (KA or RST) carried out data extraction and a second author (RST or KA) checked this. We resolved disagreements by discussion or if necessary with a third author (LH). We extracted outcomes at the latest follow-up point within the trial, and also at the latest follow-up after the trial where this was available, as we reasoned this would maximise the number of events reported. We contacted all included study authors to clarify any missing outcome data or issues of ‘Risk of bias’ assessment. For the update, two authors (AJA or FCT and SE) carried out data extraction independently.

**Assessment of risk of bias in included studies**

Factors considered included random sequence generation and allocation concealment, description of drop-outs and withdrawals, blinding (participants, personnel and outcome assessment) and selective outcome reporting. In addition we sought evidence that the groups were balanced at baseline, that intention-to-treat analysis was undertaken and that the period over which the salt intervention lasted and follow-up of outcome were equivalent. A single author (KA) assessed the risk of bias of the included studies and a second author (RST) checked this. We resolved disagreements by discussion or if necessary with a third author (LH). Two authors (AJA and FCT) independently checked risk of bias in the update.

**Data synthesis**

We processed data as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). For mortality and cardiovascular events, we calculated the risk ratio and 95% confidence interval (CI) for each trial. For blood pressure and urinary sodium excretion, we calculated mean group differences and 95% CI using the mean difference. We explored heterogeneity amongst included studies qualitatively (by comparing the characteristics of included studies) and quantitatively (using the Chi² test of heterogeneity and the I² statistic). We combined results from included studies for each outcome to give an overall estimate of treatment effect at the latest point available within the randomised trial and, as a secondary analysis, at the latest point available (including where participants were followed up after the end of the randomisation period). We used a fixed-effect meta-analysis except where statistical heterogeneity was identified (Chi² P value ≤ 0.05 and I² value ≥ 50%), in which case we considered methodological and clinical reasons for heterogeneity and used a random-effects model.

**Subgroup analysis and investigation of heterogeneity**

We planned to use stratified meta-analysis to explore the differential effects that might occur as a result of: individual advice versus group advice, salt substitution versus advice and baseline risk of cardiovascular disease. We used meta-regression to assess the effects of the level of salt reduction achieved, baseline blood pressure and change in blood pressure on mortality and cardiovascular event outcomes.

**Sensitivity analysis**

We conducted sensitivity analysis of the primary outcomes to determine whether cluster and individually randomised trial designs influenced the effects observed.

**Results**
Description of studies

Results of the search
The searches in 2013 retrieved 2439 references and 1861 remained after de-duplication. We excluded 1737 references based on screening the title and abstract. We retrieved the remaining 124 references in full text, two of which met the inclusion criteria (two reports) (CSSS 2007; Kwok 2012). We also identified three additional reports for previously included studies.

The searches in 2008 identified a total of 2649 titles, of which we excluded 2605 on title and abstract. After examining the full texts of the remaining 44 papers, we included six trials (26 reports) (Chang 2006; HPT 1990; Morgan 1978; TOHP I 1992; TOHP II 1997; TONE 1998).

Five studies from an earlier Cochrane review, Hooper 2004, met the inclusion criteria (HPT 1990; Morgan 1978; TOHP I 1992 (18 months); TOHP II 1997; TONE 1998). We excluded the other six included studies from Hooper 2004, as they did not report mortality or cardiovascular events (Alli 1992; Arroll 1995; Costa 1981; Morgan 1987; Silman 1983; Thaler 1982).

In total, we included eight trials (reported in 31 papers) and one ongoing study (Aung 2012).

We obtained responses to our requests for additional details from four of the included trial authors (Kwok 2012; TOHP I 1992; TOHP II 1997; TONE 1998).

The study selection process is summarised in the flow diagram shown in Figure 1.
Figure 1. Study flow diagram for review and update

Total study reports identified: N = 5088
Electronic database search: N = 5059
Reference list search: N = 29

Records excluded as duplicates: N = 578

Records screened by title and abstract: N = 4510

Records excluded: N = 4342

Studies not included after examining full text: N = 136

Full-text reports ordered for detailed review: N = 168

Studies meeting inclusion criteria: N = 8 (reported in papers: N = 31)
Ongoing studies: N = 1 (reported in papers: N = 1)
Included studies

The eight included studies are described in the Characteristics of included studies table.

We included three trials in people with normotension (n = 3518) (HPT 1990; TOHP I 1992; TOHP II 1997), two in people with hypertension (n = 748) (Morgan 1978; TONE 1998), and three in a mixed population of people with normo- and hypertension (n = 3018) (Chang 2006; CSSS 2007; Kwok 2012). For the purposes of analysis, we included studies in mixed normo- and hypertensive individuals with the hypertensive studies.

Post-randomisation follow-up varied from up to six to nine months (Morgan 1978; HPT 1990), and long-term post-trial end follow-up of 10 to 15 years (TOHP I 1992; TOHP II 1997; TONE 1998).

The three normotensive trials were in healthy people (predominantly white (> 75%), male (75%), median age 40) and were conducted in the USA. Entry criteria varied between trials, but included those with diastolic blood pressure from 78 mmHg to 89 mmHg, with a narrow range of means from 83 mmHg to 86 mmHg diastolic and 124 mmHg to 127 mmHg systolic. The number of participants included ranged from 392 to 2382. All three trials in normotensives (as well as TONE 1998, below) aimed to reduce salt by comprehensive dietary and behaviour change programmes led by experienced personnel, including regular group counselling sessions over several months, with newsletters between sessions, self assessment, goal setting, food tasting and recipes. For example, the Hypertension Prevention Trial (HPT) ran 10 weekly group counselling sessions on food selection, food preparation and behaviour management skills, followed by semi-monthly and then bi-monthly meetings throughout the trial (with newsletters in the months where no meetings occurred) (HPT 1990). Sessions were run by nutritionists and behavioural scientists and individual counselling was provided, where participants missed sessions or had special needs. Techniques used in the sessions included group discussions, instructions for dietary record keeping, goal setting, individual diet analysis for each participant, cooking demonstrations, provision of recipe books and tasting of new foods. The intervention duration ranged from seven months (TONE 1998) to 36 months (TOHP II 1997). Control groups received no active intervention. Sodium excretion goals were set at less than 70 to 80 mmol/24 hours. Only two studies used salt substitution; one gradually increased the use of a potassium-enriched salt substitute over several weeks, although this was done in kitchens by cooks without requiring participants to alter their behaviours (Chang 2006), and the other advised participants to use a low-sodium salt substitute (CSSS 2007).

The five trials that included hypertensives included one trial in treated hypertensive participants (TONE 1998), two that included participants with untreated hypertension (Chang 2006; Morgan 1978), one study with a proportion of treated participants (CSSS 2007) and one unspecified (Kwok 2012). In the mixed studies, the per cent with hypertension ranged from 40% (Chang 2006) to 60% (Kwok 2012). Studies were carried out in Australia, China, Hong Kong, Taiwan and the USA and ranged in size from 77 to 1981 participants. Between 15% and 100% of participants were male, with a median age of 60 years. Most studies did not report ethnicity. At study entry mean diastolic blood pressure ranged from 71 mmHg (Chang 2006; TONE 1998, on treatment) to 97 mmHg (Morgan 1978, untreated) and systolic blood pressure ranged from approximately 131 mmHg (Chang 2006, untreated; TONE 1998, on treatment) to 162 mmHg (Morgan 1978, untreated).

Sodium goals varied from < 80 mmol/day (TONE 1998) to 70 to 100 mmol/day and unspecified sodium intake (Chang 2006).

Excluded studies

Studies that were close to meeting but did not meet our inclusion criteria are listed in the Characteristics of excluded studies table.

Risk of bias in included studies

A number of studies failed to give sufficient detail to assess their potential risk of bias.

Details of the generation and concealment of the random allocation sequence were particularly poorly reported (Figure 2; Figure 3). However, in all cases there was objective evidence of balance in the baseline characteristics of the intervention and control participants.
Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.
Figure 3. 'Risk of bias' summary: review authors’ judgements about each risk of bias item for each included study.
For blinding of outcome assessment we assumed there to be low risk of bias, as the primary outcomes of mortality and major cardiovascular disease morbidity are unlikely to be wrongly assessed based on participant allocation.

While studies reported loss to follow-up and reasons for loss to follow-up, only a few undertook a sensitivity or imputation analysis to assess the impact of these losses, followed up participants for event outcomes and described reasons for loss to follow-up for other outcomes. In the Trial of Nonpharmacologic Intervention in the Elderly (TONE) trial, the authors stated that data were collected via psychological questionnaires at randomisation and a number of the follow-up visits (TONE 1998). However, none of these data were found in the trial reports. Although often not stated, all studies appeared to undertake an intention-to-treat analysis in that groups were analysed according to initial random allocation.

All studies assessed compliance with the salt reduction intervention using diet diaries or monitoring of use. However, in the longer-term post-trial end follow-up of the TOHP I (11.5 years), TOHP II (eight years) and TONE (12.7 years) trials, such compliance data were not reported beyond the official end of the study (TOHP I 1992; TOHP II 1997; TONE 1998). Therefore it was unclear whether intervention groups were encouraged to continue their low-salt diets long-term, or returned to their pre-trial diet. Similarly, in the control groups it is not clear whether they were left to continue with their usual diet or advised to reduce their salt at the end of the trial.

**Effects of interventions**

Given the heterogeneity of populations and the likelihood that normotensives and hypertensives would differ in their adherence to dietary interventions, the results are presented and pooled separately for studies of people with normotension and hypertension. We pooled outcomes at end of trial and at the longest follow-up point unless otherwise indicated.

**Primary outcomes**

**All-cause mortality**

All-cause mortality was reported at the end of the trial in seven of the included studies (Chang 2006; CSSS 2007; HPT 1990; Kwok 2012; Morgan 1978; TOHP I 1992; TOHP II 1997). Trials were homogeneous and therefore we pooled them using a fixed-effect model. There was no strong evidence of a reduction in the number of deaths in the reduced salt group relative to controls for the normotensive (fixed-effect risk ratio (RR) 0.67, 95% confidence interval (CI) 0.40 to 1.12, 60 deaths in total, I² = 0%) or hypertensive populations (fixed-effect RR 1.00, 95% CI 0.86 to 1.15, 565 deaths in total, I² = 0%) (Analysis 1.1).

A longer observational follow-up following the end of the randomised trial period was reported for the Trials of Hypertension Prevention (TOHP) I (11.5 years) and TOHP II (eight years) trials (Cook 2007). We were also able to obtain longer observational unpublished data from the authors from the Trial of Nonpharmacologic Intervention in the Elderly (TONE) study (12.7 years) (TONE 1998). Trials remained homogeneous. At longest follow-up, there was still no evidence of a reduction in the number of deaths in the reduced salt group relative to controls, for the normotensive (fixed-effect RR 0.90, 95% CI 0.58 to 1.40, 79 deaths in total, I² = 0%) or hypertensive populations (fixed-effect RR 0.99, 95% CI 0.87 to 1.14, 674 deaths; I² = 0%) (Analysis 1.2).

**Cardiovascular mortality**

Cardiovascular mortality was reported in three studies including hypertensive patients. Chang 2006 reported a lower proportion of cardiovascular deaths in the intervention group than in the control group (27 versus 66) and contributed 90% weight to this analysis. Importantly, dietary salt was substituted gradually with a potassium-rich, low-salt product in the kitchens used by residents in retirement homes. Morgan 1978 reported only one cardiovascular death in the intervention group and none in the control group, but in a subsequent publication two cardiovascular deaths were reported in each of the intervention and control groups (Morgan 1980). There was no difference in the other study (CSSS 2007). The pooled risk ratio shows weak, inconclusive evidence of benefit (fixed-effect RR 0.67, 95% CI 0.45 to 1.01, 106 cardiovascular deaths, I² = 0%) (Analysis 1.3).

**Cardiovascular morbidity**

We assessed cardiovascular events (both fatal and non-fatal) at end of trial. The definition of non-fatal cardiovascular events varied from trial to trial, although it broadly consisted of a composite of myocardial infarction, stroke, coronary artery bypass and percutaneous transluminal coronary angioplasty. Data at end of trial were only available in trials of hypertensives (Chang 2006; CSSS 2007; Morgan 1978; TONE 1998), and demonstrated weak evidence of a decrease in events (fixed-effect RR 0.76, 95% CI 0.57 to 1.01, 192 events, I² = 0%) (Analysis 1.4). Cardiovascular events at longest follow-up were also examined to maximise the number of events available for analysis and gain data for normotensives. Data were available from six trials (Chang 2006; CSSS 2007; HPT 1990; Morgan 1978; TOHP I 1992; TOHP II 1997). Following long-term observational follow-up, TOHP I and II reported no strong evidence of risk reduction, with heterogeneity of effect between the two trials in normotensive participants (random-effects RR 0.71, 95% CI 0.42 to 1.20, 200 events, I² = 63%). We found...
weak evidence of benefit in hypertensive individuals (fixed-effect RR 0.77, 95% CI 0.57 to 1.02, 192 events, $I^2 = 0\%$) (Analysis 1.5). Pooling across normotensive and hypertensive trials gives modest evidence of benefit for cardiovascular events at longest follow-up (random-effects RR 0.77, 95% CI 0.63 to 0.95, 392 events, $I^2 = 0\%$, $P$ value $< 0.01$).

**Secondary outcomes**

**Changes in systolic and diastolic blood pressure**

End of trial blood pressure was reported by five studies (HPT 1990; Morgan 1978; TOHP I 1992; TOHP II 1997; TONE 1998). CSSS 2007 reported end of trial blood pressure but did not provide standard deviations (SD), so we imputed the median SD of the other studies to include the findings in the pooled analysis using the methodology outlined in section 7.7.3.3 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). Kwok 2012 did not report end of trial blood pressure but stated that there was no difference between intervention and control groups. For systolic blood pressure there was evidence of substantial statistical heterogeneity in the normotensive groups, but not the hypertensive studies. Systolic blood pressure was reduced in all intervention arms: normotensives (random-effects mean difference (MD) -1.15 mmHg, 95% CI -2.32 to 0.02, $I^2 = 64\%$) and hypertensives (random-effects MD -4.14 mmHg, 95% CI -5.84 to -2.43, $I^2 = 0\%$). Combining normotensives and hypertensives resulted in substantial heterogeneity ($I^2 = 74\%$) and moderate evidence of benefit (random-effects MD -1.79 mmHg, 95% CI -3.23 to -0.36). Diastolic blood pressure was also reduced in normotensives (random-effects MD -0.80 mmHg, 95% CI -1.37 to -0.23, $I^2 = 0\%$), but not in hypertensives (random-effects MD -3.74 mmHg, 95% CI -8.41 to 0.93, $I^2 = 67\%$). In this analysis there was no heterogeneity in normotensives, but substantial heterogeneity in hypertensives. Pooled analysis of normotensives and hypertensives showed moderate evidence of an effect (random-effects MD -1.17 mmHg, 95% CI -2.08 to -0.26) (Analysis 1.6; Analysis 1.7).

**Urinary salt excretion (or other method of estimation of salt intake)**

Changes in urinary sodium excretion at the end of trial were reported by six studies (HPT 1990; Kwok 2012; Morgan 1978; TOHP I 1992; TOHP II 1997; TONE 1998). There was substantial evidence of statistical heterogeneity, which may reflect different approaches to the assessment of 24-hour urinary sodium excretion. In the study by Morgan, results were only reported as samples and therefore comprised repeated observations for a number of patients (Morgan 1978). As for blood pressure, in a number of studies the last urinary sodium excretion value available was at a time point much preceding the timing of the reported mortality or cardiovascular events (blood pressure follow-up time: six months (Morgan 1978); 30 months (TON 1998); 18 months (TOHP I 1992); 36 months (TOHP II 1997)). Urinary 24-hour sodium excretion was reduced by a similar amount across the study subgroups: normotensives (random-effects MD -34.19 mmol/24 hours, 95% CI -49.61 to -18.78, $I^2 = 76\%$); hypertensives (random-effects MD -20.48 mmol/24 hours, 95% CI -53.68 to 12.73, $I^2 = 98\%$) and pooled analysis (random-effects MD -27.21 mmol/24 hours, 95% CI -49.85 to -4.57, $I^2 = 97\%$) (Analysis 1.8).

**Health-related quality of life**

One study in normotensives reported that significant improvements in the Psychological General Well-Being scale were observed at six and 18 months, but no data were presented (TOHP I 1992).

**Subgroup analyses and investigation of heterogeneity**

In order to take account of the heterogeneity in populations and cardiovascular baseline risk, we stratified meta-analyses according to whether studies were undertaken in normotensive or hypertensive populations. As one of the studies involved a kitchen salt substitution rather than requiring participants to change their behaviours, we conducted a subgroup analysis excluding this trial (Chang 2006). This resulted in reductions in the pooled effects observed (cardiovascular mortality at end of trial: RR 0.87, 95% CI 0.30 to 2.55; cardiovascular events at end of trial: RR 0.86, 95% CI 0.57 to 1.30; cardiovascular events at longest follow-up: RR 0.81, 95% CI 0.63 to 1.03). As this trial did not measure blood pressure or urinary sodium excretion we were not able to explore its effects on these outcomes.

**Small study bias**

Given the small number of included studies it was not possible to assess small study bias either statistically or using a funnel plot.

**Sensitivity analysis**

We conducted sensitivity analysis for the primary outcomes by removing the Kwok 2012 and Chang 2006 studies as they were cluster-randomised trials. Both studies were carried out in hypertensives, so results for normotensives remained unchanged. Chang 2006 was the largest study conducted in hypertensives, so the overall result of removing it was to reduce the sample size and considerably decrease the precision of the estimate. For the primary outcome all-cause mortality at end of trial, the two removed trials had accounted for 86.9% of the weight, thus the sensitivity analysis increased the relative weight of the TOHP I 1992 and TOHP II 1997 trials. As a result, even though the pooled estimate...
for hypertensives was higher in sensitivity analysis, the pooled estimate was lower than the main analysis but with less precision (RR 0.73, 95% CI 0.45 to 1.17, 69 events, 4193 participants) (Analysis 2.1). For cardiovascular mortality, removing the cluster-randomised trials decreased the effect estimate and decreased the precision (RR 0.87, 95% CI 0.29 to 2.64, 13 events, 675 participants) (Analysis 2.2). For cardiovascular disease events at end of trial, removing Chang 2006 resulted in TONE 1998 increasing in weight to 84.5% of the estimate, and resulted in salt reduction showing less evidence of an effect (RR 0.86, 95% CI 0.57 to 1.30, 101 events, 1416 participants) (Analysis 2.3).

**DISCUSSION**

**Summary of main results**

This Cochrane review identified eight randomised controlled trials that assessed the long-term (more than six months) effects of interventions aimed at reducing dietary salt on mortality and cardiovascular morbidity. Three trials were in normotensives (HPT 1990; TOHP I 1992; TOHP II 1997, n = 3518 participants), two in hypertensives (Morgan 1978; TONE 1998, n = 748 participants) and three in mixed populations of normo- and hypertensives (Chang 2006; CSSS 2007; Kwok 2012, n = 3018 participants).

We found no strong evidence that dietary advice or substitution to reduce salt intake reduced all-cause mortality in normotensives (end of trial risk ratio (RR) 0.67, 95% confidence interval (CI) 0.40 to 1.12, 60 deaths, 3518 participants; longest follow-up RR 0.90, 95% CI 0.58 to 1.40, 79 deaths, 3518 participants), or in hypertensives (end of trial RR 1.00, 95% CI 0.86 to 1.15, 565 deaths, 3085 participants; longest follow-up RR 0.99, 95% CI 0.87 to 1.14, 674 deaths, 3680 participants).

There was weak evidence that cardiovascular mortality and cardiovascular events were reduced among hypertensives (cardiovascular mortality: end of trial RR 0.67, 95% CI 0.45 to 1.01, 106 deaths, 2656 participants; cardiovascular events: end of trial RR 0.76, 95% CI 0.57 to 1.01, 194 deaths, 3397 participants), however these results were strongly driven by the Chang 2006 study, which accounted for 88% of the weight in the cardiovascular mortality analysis and 49% of the weight in cardiovascular events analysis. There was no strong evidence that cardiovascular events (fatal and non-fatal combined) were reduced in people with normal blood pressure (longest follow-up RR 0.71, 95% CI 0.42 to 1.20, 200 events, 2505 participants), but in hypertensives there was weak evidence of benefit (longest follow-up RR 0.77, 95% CI 0.57 to 1.02, 192 events, 3407 participants). Maximising the available data by pooling across normotensive and hypertensive groups and using the data collected by some trials after the trial end date gave a ‘significant’ result (RR 0.77, 95% CI 0.63 to 0.95, P value < 0.01). This result was driven by the trial of residents in institutions where salt reduction was achieved by changes in salt used in the institution kitchens (Chang 2006). Excluding this trial from the analysis gave an overall effect of RR 0.81 (95% CI 0.63 to 1.03) for cardiovascular events at longest follow-up. Both TOHP I 1992 and TOHP II 1997 were carried out in overweight individuals (average body mass index (BMI) in TOHP I 27.1, mean BMI in TOHP II 30.9 in both intervention and control), so the effects of dietary advice to reduce salt found in this trial may not be applicable to non-overweight people.

Although no data were published on participant’s health-related quality of life, in one trial among normotensives it was reported that there were significant improvements in quality of life in the intervention group (TOHP I 1992).

The interventions reduced urinary sodium excretion and indicated that participants continued to comply with sodium restriction in the long term, at least to some degree, although, as noted in a previous Cochrane review, the degree of sodium restriction is likely to attenuate over time (Hooper 2004). End of trial systolic and diastolic blood pressure were reduced by an average of 1 mmHg in normotensives and by an average of 2 to 4 mmHg in hypertensives. Sustained long-term reductions of diastolic blood pressure of 1 mmHg and 4 mmHg would be predicted to reduce cardiovascular disease mortality by 5% and 20% respectively (MacMahon 1990).

Our point estimates among hypertensives are consistent with effects of this size, but have wide confidence intervals owing to the relatively small number of events. Among normotensives our point estimate of benefit is rather larger (about a 30% risk reduction in cardiovascular events), which probably reflects the use of the long-term follow-up data from the TOHP I and II trials. These provide the only relevant data but they may be biased by losses to follow-up for non-fatal events and no data on blood pressure or urinary sodium excretion were available to assess the extent to which participants had maintained trial values (Cook 2007).

The systolic blood pressure reduction in the TOHP I and II trials was between 1 mmHg and 2 mmHg, which would not be expected to produce such a large reduction in cardiovascular events. Findings from sensitivity analysis excluding cluster-randomised trials are less precise, but overall are consistent with the main analysis.

**Overall completeness and applicability of evidence**

A previous Cochrane review was limited by the lack of reported events (17 deaths, 93 cardiovascular events) (Hooper 2004). In this review, because of longer observational follow-up (up to 10 to 15 years) of three of the trials included in the previous Cochrane review (TOHP I 1992; TOHP II 1997 (eight years); TONE 1998 (12.7 years)) and inclusion of one more recent randomised controlled trial (RCT) (Chang 2006), we have gathered more evidence on mortality and cardiovascular outcomes (approximately 7200
participants, 753 deaths and 392 cardiovascular events). Nevertheless, the total amount of evidence on events remains limited. The question arises of how much more evidence would be required to give a conclusive answer on the benefits of advice to reduce salt intake. Assuming a 15% risk of suffering a cardiovascular event over 10 years (consistent with mild hypertension at age 60 in a man), a trial with 80% power and a significance level of 5% would require randomisation of about 25,000 people to intervention and control arms with follow-up for 10 years to detect a 10% reduction in cardiovascular events. However, targeting a 20% reduction in cardiovascular events - similar to the effects of antihypertensives or statins in primary prevention of cardiovascular disease - and a shorter follow-up of five years would require a more feasible trial of 12,000 participants. The randomised evidence to support antihypertensive drug treatment comprises over 120,000 participants followed for about five years and provides conclusive evidence of benefit. Despite over a decade of advocacy for salt reduction as a major public health strategy, it is remarkable that an evidence base a 10th of the size of the equivalent pharmacological database has been produced. Doing better than this is considered impracticable because of logistic, financial and ethical issues (He 2011).

More recently, the US Institute of Medicine, in its review of the evidence on salt and health, has recommended further trials to examine the effects of a range of sodium levels on the risk of cardiovascular events, stroke and mortality among patients in controlled environments, where randomised trials may be more feasible, and in natural experiments (Institute of Medicine 2013). In response to this the TOHP I and II trial investigators reported long-term observational findings from the control groups of these trials, which did not show a J-shaped association but indicated that urinary sodium excretion is linearly associated with cardiovascular events, although only 10% of the participants had urinary sodium excretions of below 2300 mg/24 hours (Cook 2014), a little higher than the level of 2000 mg/24 hours recommended by the World Health Organization (WHO 2012). In contrast, an observational cohort analysis was unable to demonstrate a clear linear relationship between urinary sodium excretion and coronary heart disease events, although a weak interaction between urinary sodium excretion and plasma N-terminal pro-B-type natriuretic peptide on coronary heart disease events was reported (Joosten 2014). Reviewing these new studies, Whelton stated that "... the potential for reverse causality, bias in assessment of sodium intake, absent or insufficient adjustment for confounding variables, and random error" all contribute to inconsistent findings (Whelton 2014). 

Potential biases in the review process

We searched comprehensively for randomised controlled trials of dietary sodium reduction, with a duration of six months or more and which reported mortality or cardiovascular events. We attempted to contact all authors of included studies to verify events. Nevertheless, we were unable to report all relevant outcomes for all trials. The small number of included studies prevented us from being able to assess the presence of small study or publication bias. By incorporating data from the longest follow-up point, we sought to maximise the number of deaths and cardiovascular events that might be affected by alterations in dietary salt. However, in doing so we may have introduced a source of bias as not all trials conducted long-term follow-up. For three large studies (TOHP I 1992, TOHP II 1997 (eight years), TONE 1998 (12.7 years)), the longest follow-up was considerably beyond the official end of the trial and therefore can no longer be assumed to represent a randomised comparison. It was unclear if the intervention groups continued their low-salt diets and whether control groups were left to continue with dietary advice or advised to reduce their salt. For this reason we consider the trial end findings to be a more robust, albeit less precise, source of evidence.

In common with previous systematic reviews of dietary interventions, we observed marked heterogeneity across studies in terms of their population, sample size and follow-up. Whilst we stratified meta-analysis by differing sub-populations (normotensives and hypertensives) and pooled studies using weighting based on sample size, we did not account for the duration of follow-up. A previous Cochrane review suggests that over time the sodium reduction achieved is greatly reduced, as is the effect on blood pressure and therefore the effect on events is potentially diminished (Hooper 2004). In a systematic review of trials of dietary salt reduction, sodium excretion was about half that in the two trials of

Quality of the evidence

Although all included studies were RCTs, only two of the eight included studies provided sufficient detail to be judged as having adequate random sequence generation, allocation concealment and outcome blinding. One cluster-randomised trial was analysed as if it was individually randomised (Chang 2006). Nevertheless, all trials provided evidence of baseline balance. Although lack of blinding is unlikely to alter outcome assessment when outcomes include mortality and cardiovascular events, failure to blind participants may have led to a positive change in the lifestyle and dietary behaviours of control participants, leading to a reduction in the difference between groups.

Most trials appeared to be free from dietary changes in the intervention and control groups, apart from dietary sodium. The one major exception was the trial by Chang where sodium was replaced by a high-potassium substitute (Chang 2006). Potassium has beneficial effects on blood pressure but may have adverse effects in individuals with renal disease (Cappuccio 2000). Two studies in hypertensives allowed changes in antihypertensive medication during the period of the trial (Morgan 1978; TONE 1998). In both trials, lower levels of hypertensive medication in the intervention group compared to control may have reduced the blood pressure-lowering effect of reduced dietary sodium and therefore offset mortality and cardiovascular morbidity benefits.

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Implications for practice

Despite collating more event data than previous systematic reviews of randomised controlled trials, there is insufficient power to confirm clinically important effects of dietary advice and salt substitution on cardiovascular mortality in normotensive or hypertensive populations. The methods of achieving salt reduction (advice and salt substitution) in the trials included in our review, and other systematic reviews, were relatively modest in their impact on sodium excretion and on blood pressure levels. They generally required considerable efforts to implement and would not be expected to have an effect on the burden of cardiovascular disease commensurate with their costs. The challenge for clinical and public health practice is to find more effective interventions for reducing salt intake that are both practicable and inexpensive.
Many countries have national authoritative recommendations, often sanctioned by government, which call for reduced dietary sodium. In the UK, the National Institute of Health and Care Excellence (NICE) has recently called for an acceleration of the reduction in salt intake of the general population from a maximum intake of 6 g per day per adult by 2015 to 3 g by 2025 (NICE 2010).

Implications for research

Further long-term follow-up of existing trials (as done by Trials of Hypertension Prevention (TOHP) I, TOHP II and Trial of Nonpharmacologic Intervention in the Elderly (TONE)) may contribute further events to allow assessment of the long-term effects of reduced dietary salt advice on mortality, cardiovascular morbidity and hormonal and lipid outcomes, although the intensive dietary advice interventions evaluated in trials over the last three decades are of less relevance to current policy initiatives. Our findings support the recent US Institute of Medicine recommendation for further rigorous, large, long-term studies, capable of demonstrating the cardiovascular benefit of dietary salt reduction beyond reasonable doubt using a range of plausible interventions. Such trials need to assess population level (e.g. workplace, institutional, regulatory) interventions that might be more likely to lead to sustained reductions in salt intake and which would provide evidence relevant to current public health guidelines. It will also be important to evaluate the effects of voluntary and regulatory salt reduction by food industries (such as the UK’s reduction of salt in processed foods) on dietary salt intake and blood pressure, as these may hold greater opportunities for practicable and inexpensive means of reducing salt intake in the population at large.

Acknowledgements

This review was supported by a UK NIHR Cochrane Collaboration Programme grant: ’Cochrane Heart Public Health and Prevention Reviews’ CPGS10. We would like to acknowledge the work of previous authors on this review: Kate Ashton, Tiffany Moxham and Lee Hooper.

References to studies included in this review

Chang 2006 (published data only)

CSSS 2007 (published data only)

HPT 1990 (published and unpublished data)

Kwok 2012 (published data only)

Morgan 1978 (published data only)
Reduced dietary salt for the prevention of cardiovascular disease (Review)

Bentley 2006 [unpublished data only]
Bentley BB. Dietary Sodium in Heart Failure. USA: University of Kentucky, 2006.

Knuist 1998 [published data only]

Koopman 1997 [published data only]

Licata 2003 [published data only]

Tobari 2010 [published data only]
Reduced dietary salt for the prevention of cardiovascular disease (Review)

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van der Post 1997 (published data only)

Velloso 1991 (published data only)

References to ongoing studies

Aung 2012 (published data only)

Additional references

Aburto 2013

Alderman 2010

Alderman 2011

Alderman 2012

Allender 2008

Alli 1992

Arroll 1995

Bayer 2012

Cappuccio 2011

Cappuccio 2000

Cobiac 2010

Cook 2007

Cook 2014

Costa 1981

Dietary Guidelines for Americans 2010

Editor’s Note 2013

Ekinci 2011

Elliot 1991

Elliot 1996

Graudal 2011
Graudal NA, Hubeck-Graudal T, Jurgens G. Effects of low sodium diet versus high sodium diet on blood pressure,
Reduced dietary salt for the prevention of cardiovascular disease (Review)

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Institute of Medicine 2013


Jürgens 2004


Law 1991


Lefebvre 2011


Lim 2012


Lozano 2012


Mackay 2004


MacMahon 1990


McHorney 1993


Mente 2013


Millett 2012


Moius 2013

Morgan 1980

Morgan 1987

Murray 2013

Neal 2013

NICE 2010

O’Donnell 2011

Paterna 2008

Sacks 2001

SACN 2003

Silman 1983

Stolarz-Skrzypek 2011

Strazzullo 2009

Taylor 2011

Thaler 1982

Webster 2011

Whelton 2002

Whelton 2012

Whelton 2014

WHO 2012

* Indicates the major publication for the study
## Characteristics of included studies [ordered by study ID]

### Chang 2006

<table>
<thead>
<tr>
<th>Methods</th>
<th>Cluster-RCT (5 kitchens)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participants</strong></td>
<td><strong>N randomised:</strong> 1981 (N = 768 intervention, 2 kitchens; N = 1213 control, 3 kitchens) <strong>Baseline blood pressure:</strong> intervention: SBP mean 131.3 (SD 19.7), DBP mean 71.2 (SD 10.8); control: SBP mean 130.7 (SD 20.4), DBP mean 71.4 (SD 10.8) <strong>Case mix:</strong> intervention: 40.2% hypertension; control: 40.4% hypertension <strong>Age:</strong> mean 75.6 (SD 7.7), 74.8 (7.0), in kitchens 2 and 3 (intervention group) 74.8 (7.3), 74.6 (6.7), 74.6 (6.1) in kitchens 1, 4 and 5 (control group) respectively <strong>Cardiovascular diagnoses:</strong> none reported <strong>Percentage male:</strong> 100% <strong>Percentage white:</strong> not reported <strong>Inclusion/exclusion criteria:</strong> <strong>Inclusion:</strong> veterans registered in a retirement home in Northern Taiwan <strong>Exclusion:</strong> bed-ridden veterans, high serum creatinine (i.e. &gt;= 3.5 mg/dL) <strong>Funder:</strong> Taiwan Salt Work, Tainan, Taiwan, ROC</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td><strong>Intervention</strong> <strong>Total duration:</strong> average of 31 months <strong>Salt reduction/advice component:</strong> ate food prepared by the cook of the kitchen to which they were assigned, using salt containing 49% sodium chloride, 49% potassium chloride and 2% other additives. The ‘potassium enriched salt’ replaced the regular salt in the selected kitchens in a gradual manner. It was mixed with regular salt in a 1:3 ratio for the first week; it was then increased to 1:1 for the second week and 3:1 for the third week. By the 4th week the cooks solely used the potassium-enriched salt <strong>Other dietary component:</strong> other condiments and spices such as soy sauce and monosodium glutamate were not limited because reasonably priced low-sodium soy sauce and monosodium glutamate were not available at the time of the trial <strong>Comparator</strong> <strong>Dietary:</strong> ate food prepared by the cook of the kitchen to which they were assigned using ‘regular salt’ containing 99.6% sodium chloride and 0.4% other additives at all times. Other condiments and spices such as soy sauce and monosodium glutamate were not limited because reasonably priced low-sodium soy sauce and monosodium glutamate were not available at the time of the trial</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Deaths (all-cause and CVD); costs of CVD health care</td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td>Average 31 months</td>
</tr>
<tr>
<td><strong>Country and setting</strong></td>
<td>Taiwan - veterans’ retirement home</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>Outcomes are not reported by kitchen so not possible to quantify the effect of clustering. The authors reported the number of deaths due to cardiovascular disease and elsewhere in the table of number of deaths due to other heart problems. In the most current update we included these deaths under cardiovascular mortality. Also, the authors included deaths</td>
</tr>
</tbody>
</table>
due to diabetes under deaths due to cardiovascular disease. We emailed the authors to ask about this inclusion and they replied, “As to diabetes, we included it in CVD because we knew locally at the time our coders coded death to be due to diabetes as long as diabetes is related and diabetes occurred earlier. For example, if a person has diabetes and stroke, the code would be diabetes. That is why we grouped diabetes in the CVD category which can be viewed as the cardiometabolic death. A large proportion of dm death is due to CVD.”

<table>
<thead>
<tr>
<th>Risk of bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Quote: “The simplest randomisation method, i.e., drawing lots, was used.”</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not reported</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Low risk</td>
<td>Quote: “The veterans were told about the trial, but were not told to which salt they were assigned.”</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Low risk</td>
<td>Not stated, however primary outcomes are clinical and unlikely to be affected by outcome assessors</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>High risk</td>
<td>It appears that all subjects were followed up for the deaths outcome. A consort diagram and reasons for losses to follow-up for other outcomes are given. No sensitivity analysis or imputation was carried out to assess the impact of missing data</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>All outcomes described in the methods are reported in the results</td>
</tr>
<tr>
<td>Assessment of compliance?</td>
<td>Low risk</td>
<td>Subjects ate food that was prepared for them</td>
</tr>
<tr>
<td>Groups balanced at baseline?</td>
<td>Low risk</td>
<td>Quote: “The ages of persons in different kitchens were not significantly [different] at entry (P=0.24). The results also indicated that weight, height, body mass index, blood pressure, and electrolytes for a subsamples of persons in the experimental and control groups were not significantly different at baseline. Persons in [the experimental kitchens] had slightly longer follow-up times than did their counterparts [in the control kitchens]; however, the difference did not reach statistical significance (P=0.11).”</td>
</tr>
<tr>
<td>Intention-to-treat analysis?</td>
<td>Low risk</td>
<td>Not specifically reported, but on the basis of the consort diagram, subjects did appear to be analysed according to the groups to which they were originally allocated</td>
</tr>
</tbody>
</table>
### Chang 2006 (Continued)

<table>
<thead>
<tr>
<th>Free from follow-up bias?</th>
<th>Low risk</th>
<th>The dietary intervention was applied over the period of event outcome follow-up</th>
</tr>
</thead>
</table>

### CSSS 2007

<table>
<thead>
<tr>
<th>Methods</th>
<th>RCT</th>
</tr>
</thead>
</table>
| Participants | N randomised: 608; intervention: 302, control: 306  
Baseline blood pressure: intervention: 159/93 (25/14), control: 159/93 (26/14)  
Case mix: mixed  
Age: mean 60 years; intervention: 59 (10), control: 61 (9.7)  
Cardiovascular diagnoses: history of vascular diseases, intervention: 62%, control: 66%  
Percentage male: 44% male; intervention: 48%, control: 42%  
Percentage white: not reported  
Inclusion/exclusion criteria:  
Inclusion: individuals with a high risk of future vascular disease based on a doctor's diagnosis of any of the following: coronary, cerebral or peripheral vascular disease, diabetes and aged 55 years or older or a systolic blood pressure of 160 mmHg or higher. In addition, all participants were required to have an estimated daily sodium intake of 260 mmol/day or more and an expectation that at least half of the dietary salt could be replaced with the study salt or salt substitute. Participants were required to have no established clear indication for, or contra-indication to, the use of the study salt substitute, such as use of a potassium-sparing medication or significant renal impairment  
Exclusion: any individual with a blood test result considered to be possibly abnormal. Any patient with a family member who had a contra-indication to the salt substitute  
Funding: the George Institute for International Health (Australia), the Clinical Trials Research Unit (New Zealand), the Capital Medical Science Development Fund (China) and the National Health and Medical Research Council of Australia |
| Interventions | Salt reduction/advice component: salt substitute. The salt substitute was 65% sodium chloride, 25% potassium chloride and 10% magnesium sulphate  
Comparison:  
100% sodium chloride |
| Outcomes | Death, BP, urinary sodium excretion |
| Follow-up | 1, 2, 3, 6, 9 and 12 months after randomisation |
| Country and setting | China; 39 sites in 6 regional co-ordinating centres |
| Notes | 2 lost to follow-up in the control group; 6 lost to follow-up and 1 withdrew in the intervention group. Do not report enough data for us to calculate standard deviations for MD in SBP and DBP |

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
</tr>
</thead>
</table>

**Reduced dietary salt for the prevention of cardiovascular disease (Review)**

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**Random sequence generation (selection bias)**

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Randomisation done using a central, computerised randomisation service accessed by centre physicians via the study website with a back-up phone and fax service. The service was maintained by the Clinical Trials Research Unit at the University of Auckland, New Zealand.</td>
</tr>
</tbody>
</table>

**Allocation concealment (selection bias)**

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>The randomisation service provided a unique number for each individual corresponding to a treatment pack held at the centre.</td>
</tr>
</tbody>
</table>

**Blinding of participants and personnel (performance bias)**

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Treatment allocation was blinded to study investigators, participants and centre physicians until the study database was unlocked. Randomised treatment was delivered in 1 kg bags identical except for a 3-digit code corresponding to the randomisation number, with up to 3 kg a month salt substitute/salt available to each randomised participant to cover all cooking, pickling and other uses within the household. Double-blind.</td>
</tr>
</tbody>
</table>

**Blinding of outcome assessment (detection bias)**

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Treatment allocation was blinded to study investigators and centre physicians until the study database was unlocked.</td>
</tr>
</tbody>
</table>

**Incomplete outcome data (attrition bias)**

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unclear</td>
<td>Data not provided for hypertensives (61%) or those with diabetes (16% to 19%); values for urinary sodium excretion and BP not given.</td>
</tr>
</tbody>
</table>

**Selective reporting (reporting bias)**

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>No evidence of selective reporting.</td>
</tr>
</tbody>
</table>

**Assessment of compliance?**

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Participants that were randomised reported very good adherence to study salt substitute/salt with 99% of individuals stating that they used study salt substitute/salt for all or nearly all of their day-to-day food preparation with no difference between randomised groups (P value = 0.40).</td>
</tr>
</tbody>
</table>

**Groups balanced at baseline?**

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Appeared similar at baseline.</td>
</tr>
</tbody>
</table>

**Intention-to-treat analysis?**

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unclear</td>
<td>No (5% missing data so no imputations were made for missing data). Final follow-up visit attended by 96% of randomised participants and overall 98% of all post-randomisation visits completed as scheduled.</td>
</tr>
</tbody>
</table>

**Free from follow-up bias?**

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unclear</td>
<td>Follow-up very high, with no evidence of differences between groups.</td>
</tr>
</tbody>
</table>
### Methods

**Participants**

- **N randomised:** 392 (N = 196 intervention, N = 196 control)
- **Baseline blood pressure:** intervention: SBP mean 124.0 (SD NR), DBP mean 82.6 (SD NR); control: mean SBP 123.9 (SD NR), DBP mean 83.0 (SD NR)
- **Case mix:** normotensives
- **Age:** intervention: mean 39.0 (SD NR); control: mean 38.5 (SD NR)
- **Cardiovascular diagnoses:** none
- **Percentage male:** 65%
- **Percentage white:** 82%
- **Inclusion/exclusion criteria:**
  - **Inclusion:** men and women aged 25 to 49 years; DBP 78 to 89 mmHg
  - **Exclusion:** use of antihypertensive medication, evidence of CVD, BMI >= 0.0035 kg/cm², dietary requirements incompatible with any of the interventions, drank 21 or more alcoholic drinks per week, pregnant women, unable to comply with the protocol requirements

### Interventions

**Intervention**

- **Total duration:** 36 months
- **Salt reduction/advice component:** dietary counselling (in groups) aimed at sodium restriction. The groups met once a week for the first 10 weeks, once every 2 weeks for the next 4 weeks, and then once every month for the rest of treatment and follow-up. The group goal was a 50% reduction (<= 70 mmol) in mean urine sodium. Personnel delivering the interventions were trained and experienced in effecting behaviour change. Counselling included a mixture of didactic presentations and demonstrations, token incentives, telephone calls and newsletters
- **Other dietary component:** none stated

**Comparator**

- **Dietary:** no dietary counselling

### Outcomes

- **BP, urinary Na excretion, deaths (all-cause)**

### Follow-up

- **36 months**

### Country and setting

- **USA; 4 clinics**

### Notes

- Factorial design (calorie restriction and potassium supplementation not reported here
- 841 participants in total in study
- No difference in proportion of individuals in each group who began hypertensive medication (8.4% intervention versus 9.0% control) over 36 months

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Quote: “The randomisation procedure involved a fixed assignment ratio design that provided for equal numbers of assignments within clinic and weight strata in blocks (randomly ordered) of size 3, 6, or 9 for the normal weight stratum and of</td>
</tr>
</tbody>
</table>
“Randomisations were performed on demand at the individual clinic centers (using a pseudo-random number generator provided with the S/23 BASIC language) with schedules and software for issuing assignments generated by the DCC.”

<table>
<thead>
<tr>
<th>Allocation concealment (selection bias)</th>
<th>Low risk</th>
<th>Quote: “Randomisations were performed on demand at the individual clinic centers (using a pseudo-random number generator provided with the S/23 BASIC language) with schedules and software for issuing assignments generated by the DCC. Clinic personnel had to key all [Baseline 1 and Baseline 2 visit] data and those contained on part I of the [Baseline 3 visit] data before an assignment could be obtained (via the S/23)”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>Quote: “In order to reduce observer bias, data collection and treatment visits for dietary counselling were not held in the same week for a given participant, and data collection (i.e., interviews, measurements, food record review, and the like) were carried out by personnel not involved in treatment.” “Participants were asked not to […] divulge or discuss their dietary counselling with data collection personnel.”</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>Not stated, but as primary outcomes are clinical they are unlikely to be affected by outcome assessor’s risk of bias</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>High risk</td>
<td>Numbers in each group at each assessment time point were reported. The only reasons given for losses to follow-up were non-attendance at follow-up visits or death. No sensitivity analysis or imputation undertaken to assess the impact of loss to follow-up</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>All outcomes described in methods are reported in results</td>
</tr>
</tbody>
</table>
| Assessment of compliance? | Low risk | Quote: “Attendance during the first 12 counselling sessions ranged from a high of 86.5% for the Na treatment group in the sodium-calorie component at session 1 to a low of 46.8% for that same treatment group at session 12. Attendance for all counselling groups declined with time (test for linear decline, P<.001). Generally, attendance over the 12 sessions was better for the two treatment groups involving calorie restriction […] than for the other two dietary treatment groups [including the sodium reduction group].” “For the purposes of this article, we use progress toward or attainment of dietary treatment goals as indices of compliance. […] As a first level of exploratory analysis, univariate and multiple linear regressions were conducted comparing 34 baseline and process variables with urine sodium excretion […] as [one of the] dependent variables. […] In the second level of analysis,
compliance was defined in terms of achieving treatment goals. For the sodium reduction groups, compliance was defined as having a 24-hr urine excretion of less than or equal to 70mEq.”

Groups balanced at baseline? | Low risk
---|---
Quote: “Except for sex there were no marked baseline differences among the treatment groups.”

Intention-to-treat analysis? | Low risk
---|---
Quote: “All results are presented by original treatment assignment.”

Free from follow-up bias? | Low risk
---|---
Duration of intervention same as follow-up time for event outcomes

### Kwok 2012

#### Methods

Cluster-RCT

#### Participants

N randomised: 429 (14 hostels); intervention: 204 (6 hostels), control: 225 (8 hostels)

Baseline blood pressure: intervention: SBP 139.2 (16.6), DBP 78.9 (9.3); control: SBP 141.0 (18.5), DBP 78.4 (8.7)

Case mix: intervention: 55.4%, control: 64.4%

Age: 75+, average age intervention: 83.1 (5.7), control: 83.3 (5.5)

Cardiovascular diagnoses: none

Percent male: intervention: 22.1%, control: 9.3%

Percent white: not stated

Inclusion/exclusion criteria:

Inclusion: men and women 75 years and older in old age hostels run by 2 non-government organisations

Exclusion: tube-fed residents, individuals on a special diet due to chronic renal failure

Funding: Tung Wah group and private donations

#### Interventions

Total duration: 33 months

Salt reduction/advice component:

1) Research dietician gave a 1-hour talk to residents and staff on the prevention of dementia and promoted the 'brain preservation diet' with the following targets including avoidance of salty foods

2) Trained dietician conducted dietary support groups to reinforce the brain preservation diet (group size ranged from 10 to 15 subjects), totalling 20 times in the first year, each group session lasting 45 minutes. In the subsequent 21 months, the frequency of dietary groups was reduced to once in 6 weeks to reinforce the intervention

3) The dietician also liaised closely with the hostel staffs and kitchen staff on the hostel menu and cooking methods. Instead of using salt or other salty seasoning like fermented tofu and oyster sauce, they suggested using peppers, ginger, onion, spring onion, garlic, coriander and Chinese 5 spices powder. The hostel staff also helped to promote the 'brain preservation diet’ in their homes

Comparator

1) Research dietician gave a 1-hour talk to residents and staff on the prevention of dementia and promoted the 'brain preservation diet' with the following targets including avoidance of salty foods
Kwok 2012  (Continued)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Mortality, BP, urinary sodium excretion, health-related quality of life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up</td>
<td>12 months, 24 months, 33 months</td>
</tr>
<tr>
<td>Country and setting</td>
<td>Hong Kong: 14 old age hostels</td>
</tr>
<tr>
<td>Notes</td>
<td>Did not provide information on BP and health-related quality of life; only said that there were no significant differences at 33 months</td>
</tr>
</tbody>
</table>

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Not stated; “randomly assigned”</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not stated</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>High risk</td>
<td>Not possible for patients and caregivers to be blinded</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low risk</td>
<td>Not possible for outcome assessors to be blinded, however as primary outcomes all clinical, unlikely to be affected by risk of bias</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Unclear risk</td>
<td>Not stated</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Appeared to report on all outcomes, although did not give data for some of the outcomes, only stating that there were no differences</td>
</tr>
<tr>
<td>Assessment of compliance?</td>
<td>High risk</td>
<td>Stated that “The dietary intervention was not successful in reducing salt intake. Although salty foods in the menu of the intervention homes were reduced significantly, the residents had the option of adding salty flavouring, for example, soya sauce to their foods.”</td>
</tr>
<tr>
<td>Groups balanced at baseline?</td>
<td>Unclear risk</td>
<td>More males in the treatment group, slightly higher BP in the control group</td>
</tr>
<tr>
<td>Intention-to-treat analysis?</td>
<td>Low risk</td>
<td>Done</td>
</tr>
<tr>
<td>Free from follow-up bias?</td>
<td>Low risk</td>
<td>Yes</td>
</tr>
</tbody>
</table>
**Methods** | Individual RCT
---|---

**Participants**

**N randomised:** 4-arm trial. 2 arms were of drug treatments and not considered here. The dietary sodium restriction arm and control arm are used here. 67 (N = 34 intervention, N = 33 control). Morgan 1980 reports on a longer follow-up and gives 42 allocated to control and 33 to intervention arms

**Baseline blood pressure:** intervention: SBP mean 160 (SD 23), DBP 97 (SD 8); control: SBP mean 165 (SD 17), DBP mean 97 (SD 8)

**Case mix:** untreated hypertensives

**Age:** intervention: mean 57.1 (SD NR); control: mean 58.6 (SD NR)

**Cardiovascular diagnoses:** borderline hypertensives (DBP 95 to 109 mmHg) and hypertensives (DBP 110+ mmHg)

**Percentage male:** 100%

**Percentage white:** not reported

**Inclusion/exclusion criteria:**

- **Inclusion:** males with borderline hypertension on admission to hospital or outpatient visit
- **Exclusion:** malignant disease, severe psychiatric disturbances, severe physical incapacity or a disease likely to be fatal in the next 2 years, serum-creatinine levels > 0.18 mmol/l, abnormal liver function tests, in cardiac failure or on diuretic therapy

**Funding:** Australian Department of Veterans’ Affairs, the Australian National Heart Foundation, Merck, Sharp & Dohme (Aust), Pty Ltd and ICI Australia Ltd

**Interventions**

**Intervention**

- **Total duration:** 24 months
- **Salt reduction/advice component:** patients were instructed to reduce their sodium chloride intake and were given a diet that should have reduced their sodium intake to 70 to 100 mmol/day. The advice about diet was repeated at 6 months. No details on who gave advice

- **Other dietary component:** at each 6-month review visit, if serum potassium levels < 3.4 mmol/L, potassium supplements were given

- **Comparator:** No treatment, reviewed at 6 months (as intervention)

- **Other:** not given any treatment, but reviewed at 6-monthly intervals and if DBP rose above 115 mmHg treatment was started

**Outcomes**

Deaths (all-cause and CVD); BP; urinary Na excretion

**Follow-up**

BP at 24 months; clinical outcomes at 24 months (end of trial) and at extra follow-up to 70 months

**Country and setting**

Australia - single hospital

**Notes**

Cardiovascular morbidity and mortality data taken from review of Morgan 1978 and Morgan 1980

Taking antihypertensive medication (at 6 months): intervention 4/10 versus control 9/10 (RR 0.44, 95% CI 0.20 to 0.98)

Longer-term follow-up reported in Med J Australia 1980. Note that denominators for long-term findings are taken from this report
## Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Quote: “[patients] were randomly divided into 4 subgroups”</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not reported</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Unclear risk</td>
<td>Not reported</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low risk</td>
<td>Not reported but as primary outcomes clinical unlikely to be affected by risk of bias</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>Quote: “Information regarding life or death was not known for two patients, who were excluded from the study. All patients included in the study were seen at the initial visit, and at a subsequent six-month visit. Patients who did not report back on at least one occasion have not been analysed. Five patients died in the first six months; these have been included in the analysis. There were no other known deaths in this time interval in the patients who did not report back. More than 90% of initially allocated patients reported back at the end of the first six-month period.” The only reason given for losses to follow-up was patients not reporting back. No sensitivity analysis or imputation undertaken to assess the impact of loss to follow-up</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>All outcomes described in the methods are reported at some point in the results</td>
</tr>
<tr>
<td>Assessment of compliance?</td>
<td>Low risk</td>
<td>Urinary sodium is measured and although it is not specifically stated that this was used to assess compliance, it is implied. Quote: “Patients in the dietary therapy group who continued to have a high sodium excretion were advised about their diet.”</td>
</tr>
<tr>
<td>Groups balanced at baseline?</td>
<td>Low risk</td>
<td>Quote: “At the start of the study the groups were similar in age, weight, height, pulse-rate, and serum electrolytes, urea, creatinine, uric acid, glucose, and cholesterol. The initial systolic and diastolic blood-pressures, supine and standing, did not differ among the groups”.</td>
</tr>
<tr>
<td>Intention-to-treat analysis?</td>
<td>Low risk</td>
<td>Although the term ITT is not used by the authors it appears that groups were analysed as randomised  Quote: ”[Morgan et al’s (1980)] report does not exclude patients</td>
</tr>
</tbody>
</table>
Morgan 1978  (Continued)

who changed therapy or ceased therapy. It evaluates the proposition: “Did the decision to implement therapy alter the mortality rate in patients with mild hypertension?”

<table>
<thead>
<tr>
<th>Free from follow-up bias?</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Longest event follow-up for mortality was 71 months but last stated diet advice stated as 6 months. No urinary sodium excretion data available at longest follow-up</td>
</tr>
</tbody>
</table>

TOHP I 1992

<table>
<thead>
<tr>
<th>Methods</th>
<th>Individual RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>N randomised: 744 (intervention: 327 and control: 417) Baseline blood pressure: intervention: SBP mean 124.8 (SD 8.5), DBP mean 83.7 (SD 2.7); control: SBP mean 125.1 (SD 8.1), DBP mean 83.9 (SD 2.8) Case mix: normotensives Age: intervention: 43.4 (SD 6.6); control: 42.6 (SD 6.5) Cardiovascular diagnoses: none Percentage male: 71.4% Percentage white: 77.2% Inclusion/exclusion criteria: Inclusion: aged 30 to 54: mean DBP 80 to 89 mmHg without antihypertensive medication; ability to complete and return a satisfactory 24-hour urine collection and food frequency questionnaire Exclusion: long list of exclusion criteria, generally designed to eliminate patients with: evidence of medically diagnosed hypertension (DBP &gt;= 90 mmHg or use of BP medications within 2 months of first evaluation), cardiovascular or other life-threatening or disabling diseases, gross obesity (BMI &gt; 36.14), a contraindication to any of the phase I interventions, or might have difficulty complying with the treatment or follow-up requirements of the trial</td>
</tr>
<tr>
<td>Interventions</td>
<td>Intervention Total duration: 18 months Salt reduction/advice component: dietary and behavioural counselling on how to identify sodium in the diet, self-monitor intake and select or prepare low-sodium foods and condiments suited to personal preferences. Individual and weekly group counselling sessions were provided during the first 3 months, with additional less frequent counselling and support for the remainder of follow-up. Sessions were provided by nutritionists, psychologists, or other experienced counsellors. The objective was to reduce urinary sodium excretion in the intervention group to 80 mmol/24 hours Comparator Dietary: usual diet. General guidelines for healthy eating were given</td>
</tr>
<tr>
<td>Outcomes</td>
<td>All-cause mortality, cardiovascular morbidity, BP and 24-hour urinary sodium excretion</td>
</tr>
<tr>
<td>Follow-up</td>
<td>11.5 years (&quot;additional ~10 yrs observational follow up&quot;)</td>
</tr>
<tr>
<td>Country and setting</td>
<td>USA; 6 clinics</td>
</tr>
</tbody>
</table>
### TOHP I 1992 (Continued)

<table>
<thead>
<tr>
<th>Notes</th>
<th>TOHP I design included allocation to other interventions (weight loss, stress management and supplements, e.g. fish oil)</th>
</tr>
</thead>
</table>

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Not reported</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;the clinic notified the coordinating center [of participant eligibility] by telephone and obtained a randomisation assignment. Clinics were also provided with sealed envelopes containing randomization assignments for use when telephone contact with the coordinating center was not possible. “adherence to the appropriate assignment sequence was monitored by the coordinating center.”</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>Quote: &quot;To minimize bias, [BP] observers were blinded to treatment allocation. Persons certified to measure BP were not involved with intervention aspects of the trial, nor were they allowed access to data that would reveal group assignment. When possible, separate facilities or entrances were used for data collection visits as compared to intervention visits.”</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;In order to reduce observer bias, data collectors were blinded to the treatment assignment of the participants.&quot; Primary outcomes all clinical and are unlikely to be affected by risk of bias</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>Quote: &quot;In the analyses shown, participants with no follow-up visits [...] were assigned a zero value for BP change ([intention-to-treat] analysis). These results did not differ appreciably from those in which missing BP values were treated as missing at random and excluded from the analysis. “The effect of missing urinary sodium excretion data at follow-up on estimates of the absolute change from baseline was assessed by assuming no change (the baseline sodium excretion value was imputed). To reduce the likelihood that estimates of treatment group differences were influenced by the inclusion of incomplete samples, mean differences in urinary sodium excretion at 6, 12, and 18 months were recalculated excluding urine values associated with a volume less than 500g or, in separate analyses, associated with creatinine or creatinine per kilogram of body weight less than 85% of the within-person average. Mean treatment group differences with these exclusions were very similar to each other and to those calculated when all samples were included.”</td>
</tr>
</tbody>
</table>

Reduced dietary salt for the prevention of cardiovascular disease (Review)

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### TOHP I 1992

<table>
<thead>
<tr>
<th>Selective reporting (reporting bias)</th>
<th>Low risk</th>
<th>All outcomes described in methods are reported in results</th>
</tr>
</thead>
</table>

**Assessment of compliance?**  
Low risk  
Quote: "Twenty-four-hour urine samples were used to monitor sodium reduction" [...] In addition, food frequency questionnaire and 24-hour dietary recall estimates of sodium intake were obtained from all life-style participants." 
"Compliance with the three life-style interventions was satisfactory, both in terms of attendance at counselling sessions and in reaching specific goals. [...] The group difference [in urinary Na excretion] was maximal (58mmol/24h) at 6 months, [...] the mean reduction [in urinary Na excretion] was well-maintained." 
"The Data Coordinating Center provided guidelines for estimating adherence to the counselling goal of 60mmol sodium /24hr from the average sodium excretion in two 8-hour urine samples collected at least 2 days apart.”

<table>
<thead>
<tr>
<th>Groups balanced at baseline?</th>
<th>Low risk</th>
<th>Quote: &quot;Baseline characteristics were evenly distributed, except for age, which was higher in the sodium reduction intervention group”</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Intention-to-treat analysis?</th>
<th>Low risk</th>
<th>Quote: &quot;In a sensitivity analysis using logistic regression we performed an intention to treat analysis treating non-responders as non-events. Because mortality follow-up was virtually complete, we included all randomised participants in analyses of mortality alone in a full intention to treat analysis.”</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Free from follow-up bias?</th>
<th>High risk</th>
<th>Longest event follow-up for mortality and cardiovascular morbidity was approximately 11.5 years but last stated diet advice stated as 18 months. No urinary sodium excretion data available at longest follow-up</th>
</tr>
</thead>
</table>

### TOHP II 1997

**Methods**  
Individual RCT

**Participants**  
N randomised: 2382 (intervention: 1191; control: 1191)  
Baseline blood pressure: intervention: mean SBP 127.5 (SD 6.6), DBP mean 86.0 (SD 1.9); control: SBP mean 127.4 (SD 6.2), DBP SD 85.9 (SD 1.9)  
Case mix: normotensives  
Age: intervention: mean 43.9 (SD 6.2); control: mean 43.3 (SD 6.1)  
Cardiovascular diagnoses: none  
Percentage male: 65.7%  
Percentage white: 79.3%  
Inclusion/exclusion criteria:  
**Inclusion**: 30 to 54-year old adults with no evidence of medically diagnosed hypertension, who were moderately overweight (men: between 26.1 and 37.4 kg/m²; women: between 24.4 and 37.4 kg/m²), and had average DBP between 83 to 89 mmHg, and
a SBP < 140 mmHg. Participants also had to demonstrate compliance with the more difficult data collection tasks

**Exclusion:** evidence of current hypertension. History of CVD, diabetes mellitus, malignancy other than non-melanoma skin cancer during the past 5 years, or any other serious life-threatening illness that requires regular medical treatment. Current use of prescription medications that affect BP, as well as non-prescription diuretics. Serum creatinine level >= 1.7 mg/dL for men or 1.5 mg/dL for women, or casual serum glucose >= 200mg/dL. Current alcohol intake > 21 drinks/week. Pregnancy, or intent to become pregnant during the study. Plans to move or inability to co-operate

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Total duration:</strong> 36 months</td>
</tr>
<tr>
<td></td>
<td><strong>Salt reduction/advice component:</strong> individual and weekly group counselling sessions were provided initially followed by additional less intensive counselling and support for the remainder of follow-up. Mini-modules to reinforce the content of the counselling session were offered in the later years of the intervention. The content of sessions included sodium information, self management and social support components. Sessions were provided by registered dieticians mainly, plus a few psychologists, or other experienced counsellors. The objective was to reduce urinary sodium excretion in the intervention group to 80 mmol/24 hours</td>
</tr>
<tr>
<td></td>
<td><strong>Other:</strong> the salt reduction intervention was combined with a weight loss intervention or alone</td>
</tr>
<tr>
<td></td>
<td><strong>Comparator</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Dietary:</strong> no advice</td>
</tr>
<tr>
<td></td>
<td><strong>Other:</strong> usual care or weight loss intervention alone</td>
</tr>
</tbody>
</table>

| Outcomes | All-cause mortality, cardiovascular morbidity (a composite of myocardial infarction, stroke, coronary revascularisation or cardiovascular death), BP, urinary excretion |

| Follow-up | 36 months |

| Country and setting | USA; 9 clinics |

| Notes | This study had a 2 x 2 factorial design in which the groups were: weight loss alone, sodium reduction alone, a combination of weight loss and sodium reduction, and a usual care group. The long-term effects of the sodium reduction intervention were analysed by grouping data for the 2 sodium reduction interventions (alone or with weight loss) and for the 2 non-sodium reduction groups (usual care and weight loss alone) |

<table>
<thead>
<tr>
<th>Risk of bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Not reported</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Quote: “The clinic then notified the coordinating center [of participant eligibility] by telephone and obtained a randomisation assignment. In those cases where random assignment was not</td>
</tr>
</tbody>
</table>
done by phone, clinics also were provided with sealed randomization envelopes for use when contact with the coordinating center was not possible.”

<table>
<thead>
<tr>
<th>Blinding of participants and personnel (performance bias)</th>
<th>Low risk</th>
<th>Quote: “With respect to the determination of categorical endpoints, in order to minimize bias in the ascertainment of hypertension, an Endpoints Subcommittee conducts a blind review of study forms, and as necessary, the medical records of participants who are considered to have had hypertensive events. Potential hypertensive end points identified are either confirmed or refuted by the subcommittee.”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low risk</td>
<td>Quote: “[Data collectors] were masked to participants’ intervention assignments.” Primary outcomes all clinical and are unlikely to be affected by risk of bias</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>Quote: “For those with BP measurements but without urinary sodium excretion data at the corresponding follow-up visit, a 0 change in urinary sodium excretion was imputed in a secondary analysis.” “For the small number of participants with no useable BP readings after randomisation (n=99, of whom 57% were treated early with BP medications by their physicians), measures from a randomly selected participant in the usual care group were imputed under the assumption that having little or no exposure to the intervention programs would produce similar results to that of the usual care group.”</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>All outcomes described in methods are reported in results</td>
</tr>
<tr>
<td>Assessment of compliance?</td>
<td>Low risk</td>
<td>Quote: “Intervention attendance also is collected for participants within each of the active intervention groups. The dietary data are collected on random samples of equal numbers of participants across the treatment groups. The 24-hour urine specimens for sodium, potassium and creatinine measurements are collected from all participants at 18 and 36 months. An additional 24-hour urine specimen, collected on a 25% sample of trial participants at 6 months, was added to more fully assess sodium intakes at this time as compared to baseline levels.” “Urinary sodium excretion and weight change are collected as intermediate end points for all participants. These intermediate end points were selected to evaluate compliance to specific interventions”</td>
</tr>
<tr>
<td>Groups balanced at baseline?</td>
<td>Low risk</td>
<td>Quote: “Baseline characteristics were evenly distributed, except for age, which was higher in the sodium reduction intervention group”</td>
</tr>
</tbody>
</table>
### TOHP II 1997

| Intention-to-treat analysis? | Low risk | Quote: “In a sensitivity analysis using logistic regression we performed an intention to treat analysis treating non-responders as non-events. Because mortality follow-up was virtually complete, we included all randomised participants in analyses of mortality alone in a full intention to treat analysis.” |

| Free from follow-up bias? | Unclear risk | Longest event follow-up for mortality and cardiovascular morbidity was approximately 8 years but last stated diet advice stated as 36 months. No urinary sodium excretion data available at longest follow-up |

### TONE 1998

#### Methods

| Individual RCT |

#### Participants

| N randomised: 681 (N = 340 intervention, N = 341 control) - part of a factorial design study |

| Baseline blood pressure: SBP 128.0 (9.4), DBP 71.3 (7.3) mmHg |

| Case mix: treated hypertensives |

| Age: 65.8 (SD 4.6) |

| Cardiovascular diagnoses: none |

| Percentage male: 53% |

| Percentage white: 76% |

#### Inclusion/exclusion criteria:

**Inclusion:** healthy, aged 60 to 80 years, SBP < 145 mmHg and DBP < 85 mmHg while taking a single antihypertensive medication or a single combination regimen consisting of a diuretic agent and a non-diuretic agent. Individuals taking 2 antihypertensive medications were also eligible if they were successfully weaned off one of them during the screening phase. Independence in activities of daily living. Capacity to alter diet and physical activity in accordance with the requirements of any TONE intervention

**Exclusion:** diagnosis or treatment of cancer within the last 5 years; treatment with diuretics, ACE inhibitors, or digitalis for CHF or unknown reason; drug therapy with nitrates, beta-blockers or calcium channel blockers for CHD or reason other than hypertension; MI or stroke within 6 months; “active” CHD (e.g. angina pectoris); CHF; atrial fibrillation; second- or third-degree heart block without permanent pacemaker; drug therapy for ventricular arrhythmias; self report of heart valve replacement; clinically important valvular heart disease; insulin-dependent diabetes mellitus; severe hypertension; current or recent (within 6 months) drug therapy for asthma or chronic obstructive lung disease; use of corticosteroid therapy for > 1 month; serious mental or physical illness; unexplained or involuntary weight loss (≥ 4.5 kg) during the previous year; BMI < 21 in men or women, or > 33 in men or > 37 in women; serum creatinine > 2 mg/dL; non-fasting blood glucose level of > 260 mg/dL; hyperkalaemia (> 5.5 mmol/L); anaemia (Hb level < 110 g/L); > 14 alcoholic drinks per week (assessed by self report); severe visual or hearing impairment; other reason making it difficult for the participant to comply fully with any part of the study protocol.
**Interventions**

**Intervention**

*Total duration:* 4-month “intensive” phase, plus 3-month “extended” phase, and then a maintenance phase (duration of this phase is unclear)

**Salt reduction/advice component:** individual and group sessions with an interventionist (typically a registered dietician) who provided information using both centrally and locally prepared materials, motivated participants to make and sustain long-term lifestyle changes, and frequently monitored progress of groups and individuals. Individualised feedback was provided. Participants learned about sources of sodium, in particular those foods with a high salt content, and they learned about possible alternatives. They also learned how to adapt the recommendations for a low-salt diet to their own lifestyle. The goal of this intervention for the group was to achieve and maintain a 24-hour dietary sodium intake of 80 mmol (1800 mg) or less (as measured by 24-hour urine collection)

**Other:** attempt to withdraw hypertensive therapy began 3 months post-randomisation

**Comparator**

**Dietary:** in order to enhance retention of control participants, meetings were held on a regular basis with speakers on subjects unrelated to BP, CVD or nutrition

**Other:** drug withdrawal began at a comparable time to the intervention group

**Outcomes**

Mortality (all-cause and cardiovascular), cardiovascular morbidity (a composite of myocardial infarction, stroke, coronary artery bypass graft (CABG)), BP, urinary sodium

**Follow-up**

30 months

**Country and setting**

USA; 4 clinical academic centres

**Notes**

Unpublished all-cause mortality data at 12.7 years obtained from authors

No data specifically reported on number of individuals who stopped antihypertensive medication in 2 groups

Multifactorial design. Only used sodium reduction without weight loss. Used in both overweight and non-overweight groups

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
</table>
| Random sequence generation (selection bias) | Low risk           | Quote: “Overweight participants were randomly assigned, in a 2x2 factorial design [...] Nonoverweight participants were randomly assigned [...]”

“We used a variable block length randomization algorithm.” (from investigators)

<p>| Allocation concealment (selection bias)    | Low risk           | Quote: “Assignments were made via computers at the clinic sites, after eligibility criteria were confirmed. The sequences were concealed from clinic staff?only known to statisticians at the coordinating center.” (from investigators) |</p>
<table>
<thead>
<tr>
<th></th>
<th>Risk</th>
<th></th>
</tr>
</thead>
</table>
| **Blinding of participants and personnel (performance bias)** All outcomes | Unclear risk | Quote: “To facilitate masking of the data collectors, intervention visits were conducted at separate times and places from the data collection visits.”  
 “An end point committee, masked to intervention assignment, made final decisions concerning the end point status of each participant.”  
 “Outcome information was obtained by staff members who were blind to the participants’ intervention assignment, at different times and different locations from those used for the intervention visits. Participants were instructed not to reveal their intervention assignment to the data collection staff.”  
 “Intervention staff members were masked with respect to the participants’ BP and drug withdrawal status.”  
 “When questioned at the final follow-up visit, the data collectors guessed the correct treatment assignment in 31% of the obese participants (compared with an expected rate of 25% on the basis of chance) and in 45% of the nonobese participants (compared with expected rate of 50% on the basis of chance).” |
| **Blinding of outcome assessment (detection bias)** All outcomes | Low risk | Primary outcomes all clinical and are unlikely to be affected by risk of bias               |
| **Incomplete outcome data (attrition bias)** All outcomes | High risk | The only reason given for losses to follow-up was non-attendance at follow-up visits. No sensitivity analysis or imputation undertaken to assess the impact of loss to follow-up |
| **Selective reporting (reporting bias)** | Unclear risk | The authors report that data were collected via psychological questionnaires at randomisation and a number of the follow-up visits, but none of the data from these appear to be reported, unless they are in a separate publication |
| **Assessment of compliance?** | Low risk | Quote: “Monitoring adherence (Reduced sodium life-style): Attendance; urinary data; food and behaviour records; adherence-related incentives. Monitoring adherence (Usual (control) lifestyle): Attendance.” |
| **Groups balanced at baseline?** | Low risk | Quote: “There was no evidence of a substantial imbalance between the reduced sodium and UL [usual lifestyle] groups [at baseline]” |
| **Intention-to-treat analysis?** | Low risk | Quote: “Analyses were conducted on an intention-to-treat basis.” |
| **Free from follow-up bias?** | High risk | Mortality outcome provided by authors at 12.7 years average follow-up. No urinary sodium excretion data available at longest follow-up |
ACE: angiotensin-converting enzyme  
BMI: body mass index  
BP: blood pressure  
CHF: coronary heart failure  
CHD: coronary heart disease  
CSSS: China Salt Substitute Study  
CVD: cardiovascular disease  
DBP: diastolic blood pressure  
Hb: haemoglobin  
HPT: Hypertension Prevention Trial  
ITT: intention-to-treat  
MD: mean difference  
MI: myocardial infarction  
Na: sodium  
NR: not reported  
RCT: randomised controlled trial  
ROC: Republic of China  
RR: risk ratio  
SBP: systolic blood pressure  
SD: standard deviation  
TOHP: Trials of Hypertension Prevention  
TONE: Trial of Nonpharmacologic Intervention in the Elderly

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bentley 2006</td>
<td>Inadequate follow-up duration</td>
</tr>
<tr>
<td>Knuist 1998</td>
<td>Pregnant women</td>
</tr>
<tr>
<td>Koopman 1997</td>
<td>No appropriate outcomes</td>
</tr>
<tr>
<td>Licata 2003</td>
<td>Not dietary salt reduction intervention</td>
</tr>
<tr>
<td>Tobari 2010</td>
<td>No cardiovascular events</td>
</tr>
<tr>
<td>van der Post 1997</td>
<td>Pregnant women</td>
</tr>
<tr>
<td>Velloso 1991</td>
<td>Inadequate follow-up duration</td>
</tr>
</tbody>
</table>
### Characteristics of ongoing studies  *(ordered by study ID)*

**Aung 2012**

<table>
<thead>
<tr>
<th>Trial name or title</th>
<th>RESIP-CVD Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Cluster-randomised trial</td>
</tr>
<tr>
<td>Participants</td>
<td>High CVD risk patients stratified by the Framingham general CVD risk scoring system (&gt; 15%)</td>
</tr>
<tr>
<td>Interventions</td>
<td>Education regarding salt content in foods, subsequent cooking classes</td>
</tr>
<tr>
<td>Outcomes</td>
<td>BP, CVD events, CVD mortality</td>
</tr>
<tr>
<td>Starting date</td>
<td>Not stated</td>
</tr>
<tr>
<td>Contact information</td>
<td>-</td>
</tr>
<tr>
<td>Notes</td>
<td>-</td>
</tr>
</tbody>
</table>

BP: blood pressure  
CVD: cardiovascular disease
<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 All-cause mortality at end of trial</td>
<td>7</td>
<td>6603</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.96 [0.83, 1.10]</td>
</tr>
<tr>
<td>1.1 Normotensive</td>
<td>3</td>
<td>3518</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.67 [0.40, 1.12]</td>
</tr>
<tr>
<td>1.2 Hypertensive</td>
<td>4</td>
<td>3085</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.00 [0.86, 1.15]</td>
</tr>
<tr>
<td>2 All-cause mortality at longest follow-up</td>
<td>8</td>
<td></td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>2.1 Normotensive</td>
<td>3</td>
<td>3518</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.90 [0.58, 1.40]</td>
</tr>
<tr>
<td>2.2 Hypertensive</td>
<td>5</td>
<td>3680</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.99 [0.87, 1.14]</td>
</tr>
<tr>
<td>3 Cardiovascular mortality at end of trial</td>
<td>3</td>
<td></td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>3.1 Hypertensive</td>
<td>3</td>
<td>2656</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.67 [0.45, 1.01]</td>
</tr>
<tr>
<td>4 Cardiovascular events at end of trial</td>
<td>4</td>
<td>3397</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.76 [0.57, 1.01]</td>
</tr>
<tr>
<td>4.1 Hypertensive</td>
<td>4</td>
<td>3397</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.76 [0.57, 1.01]</td>
</tr>
<tr>
<td>5 Cardiovascular disease events at longest follow-up</td>
<td>6</td>
<td>5912</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.77 [0.63, 0.95]</td>
</tr>
<tr>
<td>5.1 Normotensive</td>
<td>2</td>
<td>2505</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.71 [0.42, 1.20]</td>
</tr>
<tr>
<td>5.2 Hypertensive</td>
<td>4</td>
<td>3407</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.77 [0.57, 1.02]</td>
</tr>
<tr>
<td>6 Systolic blood pressure at end of trial</td>
<td>6</td>
<td>3362</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>-1.79 [-3.23, -0.36]</td>
</tr>
<tr>
<td>6.1 Normotensive</td>
<td>3</td>
<td>2079</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>-1.15 [-2.32, 0.02]</td>
</tr>
<tr>
<td>6.2 Hypertensive</td>
<td>3</td>
<td>1283</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>-4.14 [-5.84, -2.43]</td>
</tr>
<tr>
<td>7 Diastolic blood pressure at end of trial</td>
<td>5</td>
<td>2754</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>-1.17 [-2.08, -0.26]</td>
</tr>
<tr>
<td>7.1 Normotensive</td>
<td>3</td>
<td>2079</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>-0.80 [-1.37, -0.23]</td>
</tr>
<tr>
<td>7.2 Hypertensive</td>
<td>2</td>
<td>675</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>-3.74 [-8.41, 0.93]</td>
</tr>
<tr>
<td>8 Urinary sodium excretion at end of trial</td>
<td>6</td>
<td>3047</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>-27.21 [-49.85, -4.57]</td>
</tr>
<tr>
<td>8.1 Normotensive</td>
<td>3</td>
<td>1812</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>-34.19 [-49.61, -18.78]</td>
</tr>
<tr>
<td>8.2 Hypertensive</td>
<td>3</td>
<td>1235</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>-20.48 [-53.68, 12.73]</td>
</tr>
</tbody>
</table>
Comparison 2. Sensitivity analysis: individual RCTs

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 All-cause mortality at end of trial</td>
<td>5</td>
<td>4193</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.73 [0.45, 1.17]</td>
</tr>
<tr>
<td>1.1 Normotensive</td>
<td>3</td>
<td>3518</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.67 [0.40, 1.12]</td>
</tr>
<tr>
<td>1.2 Hypertensive</td>
<td>2</td>
<td>675</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>1.20 [0.34, 4.24]</td>
</tr>
<tr>
<td>2 Cardiovascular mortality at end of trial</td>
<td>2</td>
<td>675</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.87 [0.29, 2.64]</td>
</tr>
<tr>
<td>2.2 Hypertensive</td>
<td>2</td>
<td>675</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.87 [0.29, 2.64]</td>
</tr>
<tr>
<td>3 Cardiovascular events at end of trial</td>
<td>3</td>
<td>1416</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.86 [0.57, 1.30]</td>
</tr>
<tr>
<td>3.1 Hypertensives</td>
<td>3</td>
<td>1416</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.86 [0.57, 1.30]</td>
</tr>
</tbody>
</table>

Analysis 1.1. Comparison 1 Reduced salt versus control, Outcome 1 All-cause mortality at end of trial.

Review: Reduced dietary salt for the prevention of cardiovascular disease

Comparison: 1 Reduced salt versus control

Outcome: 1 All-cause mortality at end of trial

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Intervention n/N</th>
<th>Control n/N</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Normotensive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPT 1990</td>
<td>1/196</td>
<td>1/196</td>
<td></td>
<td>0.3 %</td>
<td>1.00 [0.06, 15.87]</td>
</tr>
<tr>
<td>TOHP I 1992</td>
<td>6/327</td>
<td>12/417</td>
<td></td>
<td>3.5 %</td>
<td>0.64 [0.24, 1.68]</td>
</tr>
<tr>
<td>TOHP II 1997</td>
<td>16/1191</td>
<td>24/1191</td>
<td></td>
<td>7.9 %</td>
<td>0.67 [0.36, 1.25]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>1714</strong></td>
<td><strong>1804</strong></td>
<td></td>
<td><strong>11.6 %</strong></td>
<td><strong>0.67 [0.40, 1.12]</strong></td>
</tr>
<tr>
<td></td>
<td>Total events: 23 (Intervention), 37 (Control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heterogeneity: Chi² = 0.09, df = 2 (P = 0.96); I² =0.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test for overall effect: Z = 1.53 (P = 0.13)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Hypertensive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chang 2006</td>
<td>192/768</td>
<td>312/1213</td>
<td></td>
<td>79.1 %</td>
<td>0.97 [0.83, 1.14]</td>
</tr>
<tr>
<td>CSSS 2007</td>
<td>4/302</td>
<td>4/306</td>
<td></td>
<td>1.3 %</td>
<td>1.01 [0.26, 4.01]</td>
</tr>
<tr>
<td>Kwok 2012</td>
<td>27/204</td>
<td>25/225</td>
<td></td>
<td>7.8 %</td>
<td>1.19 [0.72, 1.98]</td>
</tr>
<tr>
<td>Morgan 1978</td>
<td>1/34</td>
<td>0/33</td>
<td></td>
<td>0.2 %</td>
<td>2.91 [0.12, 69.08]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>1308</strong></td>
<td><strong>1777</strong></td>
<td></td>
<td><strong>88.4 %</strong></td>
<td><strong>1.00 [0.86, 1.15]</strong></td>
</tr>
<tr>
<td></td>
<td>Total events: 224 (Intervention), 341 (Control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heterogeneity: Chi² = 1.01, df = 3 (P = 0.80); I² =0.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(Continued . . . )
### Analysis 1.2. Comparison 1 Reduced salt versus control, Outcome 2 All-cause mortality at longest follow-up.

**Review:** Reduced dietary salt for the prevention of cardiovascular disease

**Comparison:** 1 Reduced salt versus control

**Outcome:** 2 All-cause mortality at longest follow-up

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Intervention n/N</th>
<th>Control n/N</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight M-H,Fixed,95% CI</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1 Normotensive</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPT 1990</td>
<td>1/196</td>
<td>1/196</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOHP I 1992</td>
<td>10/327</td>
<td>14/417</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOHP II 1997</td>
<td>25/1191</td>
<td>28/1191</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>1714</td>
<td>1804</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>3022</td>
<td>3581</td>
<td></td>
<td></td>
<td>100.0 %</td>
</tr>
</tbody>
</table>

Test for overall effect: Z = 0.60 (P = 0.55)

Test for subgroup differences: Chi² = 2.12, df = 1 (P = 0.15), I² =53%

Heterogeneity: Chi² = 0.01, df = 2 (P = 1.00); I² =0.0%

### Continued

Reduced dietary salt for the prevention of cardiovascular disease (Review)
### Analysis 1.3. Comparison 1 Reduced salt versus control, Outcome 3 Cardiovascular mortality at end of trial.

**Review:** Reduced dietary salt for the prevention of cardiovascular disease  
**Comparison:** 1 Reduced salt versus control  
**Outcome:** 3 Cardiovascular mortality at end of trial

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Intervention</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>1603</td>
<td>2077</td>
<td>100.0 %</td>
<td>0.99</td>
<td>[0.87, 1.14]</td>
</tr>
</tbody>
</table>
| Total events: 278 (Intervention), 396 (Control)  
Heterogeneity: Chi² = 0.58, df = 4 (P = 0.97); I² = 0.0%  
Test for overall effect: Z = 0.08 (P = 0.93) |
### Analysis 1.4. Comparison 1 Reduced salt versus control, Outcome 4 Cardiovascular events at end of trial.

Review: Reduced dietary salt for the prevention of cardiovascular disease

Comparison: 1 Reduced salt versus control

Outcome: 4 Cardiovascular events at end of trial

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Reduced salt n/N</th>
<th>Control n/N</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Hypertensives</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chang 2006</td>
<td>27/768</td>
<td>66/1213</td>
<td>48.7% 0.65 [0.42, 1.00]</td>
<td></td>
</tr>
<tr>
<td>CSSS 2007</td>
<td>8/302</td>
<td>5/306</td>
<td>4.7% 1.62 [0.54, 4.90]</td>
<td></td>
</tr>
<tr>
<td>Morgan 1978</td>
<td>3/34</td>
<td>3/33</td>
<td>2.9% 0.97 [0.21, 4.47]</td>
<td></td>
</tr>
<tr>
<td>TONE 1998</td>
<td>36/370</td>
<td>46/371</td>
<td>43.7% 0.78 [0.52, 1.18]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>1474</strong></td>
<td><strong>1923</strong></td>
<td>100.0% 0.76 [0.57, 1.01]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 74 (Reduced salt), 120 (Control)

Heterogeneity: Chi² = 2.45, df = 3 (P = 0.48); I² = 0.0%

Test for overall effect: Z = 1.88 (P = 0.060)

Test for subgroup differences: Not applicable
### Analysis 1.5. Comparison 1 Reduced salt versus control, Outcome 5 Cardiovascular disease events at longest follow-up.

**Review:** Reduced dietary salt for the prevention of cardiovascular disease

**Comparison:** 1 Reduced salt versus control

**Outcome:** 5 Cardiovascular disease events at longest follow-up

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Reduced salt</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>H, Random, 95% CI</td>
<td></td>
<td>H, Random, 95% CI</td>
</tr>
<tr>
<td>1 Normotensive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOHP I 1992</td>
<td>17/321</td>
<td>32/311</td>
<td></td>
<td>12.7%</td>
<td>0.51 [0.29, 0.91]</td>
</tr>
<tr>
<td>TOHP II 1997</td>
<td>71/938</td>
<td>80/935</td>
<td></td>
<td>39.0%</td>
<td>0.88 [0.65, 1.20]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>1259</strong></td>
<td><strong>1246</strong></td>
<td></td>
<td><strong>51.7%</strong></td>
<td><strong>0.71 [0.42, 1.20]</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Total events: 88 (Reduced salt), 112 (Control)**

Heterogeneity: $\tau^2 = 0.09; \chi^2 = 2.71, df = 1 (P = 0.10); I^2 = 63\%$

Test for overall effect: $Z = 1.28 (P = 0.20)$

2 Hypertensive

|                   |             |         |            |        |            |
|                   |             |         | H, Random, 95% CI |        | H, Random, 95% CI |
| Chang 2006        | 27/768      | 66/1213 |             | 20.6%  | 0.65 [0.42, 1.00] |
| TONE 1998         | 36/370      | 46/371  |             | 23.1%  | 0.78 [0.52, 1.18] |
| Morgan 1978       | 2/35        | 2/42    |             | 1.2%   | 1.20 [0.18, 8.09] |
| CSSS 2007         | 8/302       | 5/306   |             | 3.5%   | 1.62 [0.54, 4.90] |
| **Subtotal (95% CI)** | **1475** | **1932** |              | **48.3%** | **0.77 [0.57, 1.02]** |
|                   |             |         |            |        |            |
|                   |             |         |            |        |            |

**Total events: 73 (Reduced salt), 119 (Control)**

Heterogeneity: $\tau^2 = 0.0; \chi^2 = 2.57, df = 3 (P = 0.46); I^2 = 0.0\%$

Test for overall effect: $Z = 1.83 (P = 0.068)$

**Total (95% CI)**

|                   |             |         |            |        |            |
|                   |             |         |            |        |            |
|                   | **2734**    | **3178** |              | **100.0%** | **0.77 [0.63, 0.95]** |

**Total events: 161 (Reduced salt), 231 (Control)**

Heterogeneity: $\tau^2 = 0.00; \chi^2 = 5.30, df = 5 (P = 0.38); I^2 = 6\%$

Test for overall effect: $Z = 2.45 (P = 0.014)$

Test for subgroup differences: $\chi^2 = 0.06, df = 1 (P = 0.81); I^2 = 0.0\%$
### Analysis 1.6. Comparison 1 Reduced salt versus control, Outcome 6 Systolic blood pressure at end of trial.

Review: Reduced dietary salt for the prevention of cardiovascular disease

Comparison: 1 Reduced salt versus control

Outcome: 6 Systolic blood pressure at end of trial

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Reduced salt</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
<td>IV,Random,95% CI</td>
</tr>
<tr>
<td>1 Normotensive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPT 1990</td>
<td>174</td>
<td>-2.8 (6.6)</td>
<td>177</td>
<td>-2.9 (6.6)</td>
<td>24.3 %</td>
</tr>
<tr>
<td>TOHP I 1992</td>
<td>304</td>
<td>-5.1 (7.9)</td>
<td>395</td>
<td>-3 (8.3)</td>
<td>25.7 %</td>
</tr>
<tr>
<td>TOHP II 1997</td>
<td>515</td>
<td>-0.7 (9)</td>
<td>514</td>
<td>0.6 (8.5)</td>
<td>26.8 %</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>993</strong></td>
<td><strong>1086</strong></td>
<td></td>
<td></td>
<td>76.8 %</td>
</tr>
</tbody>
</table>
| **Heterogeneity:** Tau² = 0.68; Chi² = 5.57, df = 2 (P = 0.06); I² =64%
| **Test for overall effect:** Z = 1.92 (P = 0.055)
| 2 Hypertensive   |             |         |              |         |                |                |
| CSSS 2007        | 302         | -4 (0)   | 306         | 3 (0)   | Not estimable |
| Morgan 1978      | 31          | -5.5 (22.3) | 31          | -4 (22.3) | 1.6 % | -1.50 [ -12.60, 9.60 ] |
| TONE 1998        | 317         | -4.6 (11.3) | 296         | -0.4 (10.5) | 21.6 % | -4.20 [ -5.93, -2.47 ] |
| **Subtotal (95% CI)** | **650**     | **633**  |              |         | 23.2 % | -4.14 [ -5.84, -2.43 ] |
| **Heterogeneity:** Tau² = 0.00; Chi² = 0.22, df = 1 (P = 0.64); I² =0.0%
| **Test for overall effect:** Z = 4.75 (P < 0.00001)
| **Total (95% CI)** | **1643**  | **1719**  |              |         | 100.0 % | -1.79 [ -3.23, -0.36 ] |

- **Heterogeneity:** Tau² = 1.70; Chi² = 15.50, df = 4 (P = 0.004); I² =74%
- **Test for overall effect:** Z = 2.45 (P = 0.014)
- **Test for subgroup differences:** Chi² = 8.04, df = 1 (P = 0.004); I² =88%

- **-10 -5 0 5 10**
  - Intervention
  - Control

Reduced dietary salt for the prevention of cardiovascular disease (Review)

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### Analysis 1.7. Comparison 1 Reduced salt versus control, Outcome 7 Diastolic blood pressure at end of trial.

**Review:** Reduced dietary salt for the prevention of cardiovascular disease

**Comparison:** 1 Reduced salt versus control

**Outcome:** 7 Diastolic blood pressure at end of trial

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Reduced salt</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
<td>IV, Random, 95% CI</td>
</tr>
<tr>
<td>Normotensive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPT 1990</td>
<td>174</td>
<td>-2.8 (9.2)</td>
<td>177</td>
<td>-2.9 (9.3)</td>
<td></td>
</tr>
<tr>
<td>TOHP I 1992</td>
<td>304</td>
<td>-4.4 (5.71)</td>
<td>395</td>
<td>-3.2 (5.8)</td>
<td></td>
</tr>
<tr>
<td>TOHP II 1997</td>
<td>515</td>
<td>-3 (6.5)</td>
<td>514</td>
<td>-2.4 (7)</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>993</td>
<td>1086</td>
<td></td>
<td>73.7 %</td>
<td>-0.80 [-1.37, -0.23]</td>
</tr>
<tr>
<td>Hypertensive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morgan 1978</td>
<td>31</td>
<td>-5 (11.1)</td>
<td>31</td>
<td>2 (11.1)</td>
<td></td>
</tr>
<tr>
<td>TONE 1998</td>
<td>317</td>
<td>-2.2 (8)</td>
<td>296</td>
<td>-0.2 (7)</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>348</td>
<td>327</td>
<td></td>
<td>26.3 %</td>
<td>-3.74 [-8.41, 0.93]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>1341</td>
<td>1413</td>
<td></td>
<td>100.0 %</td>
<td>-1.17 [-2.08, -0.26]</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.0; Chi² = 1.89, df = 2 (P = 0.39); I² = 0.0%

Test for overall effect: Z = 2.76 (P = 0.0057)

Heterogeneity: Tau² = 8.34; Chi² = 3.01, df = 1 (P = 0.08); I² = 67%

Test for overall effect: Z = 1.57 (P = 0.12)

Heterogeneity: Tau² = 0.54; Chi² = 9.51, df = 4 (P = 0.05); I² = 58%

Test for overall effect: Z = 2.52 (P = 0.012)

Test for subgroup differences: Chi² = 1.50, df = 1 (P = 0.22), I² = 33%
### Analysis 1.8. Comparison 1 Reduced salt versus control, Outcome 8 Urinary sodium excretion at end of trial.

**Review:** Reduced dietary salt for the prevention of cardiovascular disease

**Comparison:** 1 Reduced salt versus control

**Outcome:** 8 Urinary sodium excretion at end of trial

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Intervention</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normotensive</strong></td>
<td>HPT 1990</td>
<td>143</td>
<td>-15.96 (68.2)</td>
<td>16.7</td>
<td>-15.96 [-31.77, -0.15]</td>
</tr>
<tr>
<td></td>
<td>TOHP I 1992</td>
<td>232</td>
<td>-55.2 (76.9)</td>
<td>17.2</td>
<td>-43.90 [-56.87, -30.93]</td>
</tr>
<tr>
<td></td>
<td>TOHP II 1997</td>
<td>470</td>
<td>-50.9 (86.3)</td>
<td>17.4</td>
<td>-40.40 [-51.50, -29.30]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>845</td>
<td>967</td>
<td>51.3 % -34.19 [-49.61, -18.78]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hypertensive</strong></td>
<td>Kwok 2012</td>
<td>204</td>
<td>0.2 (2.5)</td>
<td>18.2</td>
<td>0.40 [-0.12, 0.92]</td>
</tr>
<tr>
<td></td>
<td>Morgan 1978</td>
<td>109</td>
<td>157 (87)</td>
<td>12.7</td>
<td>-23.00 [-57.94, 11.94]</td>
</tr>
<tr>
<td></td>
<td>TONE 1998</td>
<td>319</td>
<td>-45 (55.8)</td>
<td>17.8</td>
<td>-40.00 [-48.22, -31.78]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>632</td>
<td>603</td>
<td>48.7 % -20.48 [-53.68, 12.73]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Heterogeneity:** Tau² = 139.51; Chi² = 8.20, df = 2 (P = 0.02); I² = 76%

Test for overall effect: Z = 4.35 (P = 0.000014)

**Total (95% CI)** 1477 1570

**Heterogeneity:** Tau² = 733.39; Chi² = 193.72, df = 5 (P<0.00001); I² = 97%

Test for overall effect: Z = 2.36 (P = 0.019)

Test for subgroup differences: Chi² = 0.54, df = 1 (P = 0.46), I² = 0.0%
### Analysis 2.1. Comparison 2 Sensitivity analysis: individual RCTs, Outcome 1 All-cause mortality at end of trial

**Review:** Reduced dietary salt for the prevention of cardiovascular disease

**Comparison:** 2 Sensitivity analysis: individual RCTs

**Outcome:** 1 All-cause mortality at end of trial

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Intervention</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>M-H,Random,95% CI</td>
<td>M-H,Random,95% CI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Normotensive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPT 1990</td>
<td>1/196</td>
<td>1/196</td>
<td>3.0 %</td>
<td>1.00</td>
<td>0.06, 15.87</td>
</tr>
<tr>
<td>TOHP I 1992</td>
<td>6/327</td>
<td>12/417</td>
<td>24.4 %</td>
<td>0.64</td>
<td>0.24, 1.68</td>
</tr>
<tr>
<td>TOHP II 1997</td>
<td>16/1191</td>
<td>24/1191</td>
<td>58.2 %</td>
<td>0.67</td>
<td>0.36, 1.25</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>1714</strong></td>
<td><strong>1804</strong></td>
<td><strong>85.6 %</strong></td>
<td><strong>0.67</strong></td>
<td><strong>0.40, 1.12</strong></td>
</tr>
</tbody>
</table>

Total events: 23 (Intervention), 37 (Control)

Heterogeneity: Tau² = 0.0; Chi² = 0.09, df = 2 (P = 0.96); I² = 0.0%

Test for overall effect: Z = 1.53 (P = 0.13)

2 Hypertensive

<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>M-H,Random,95% CI</td>
<td>M-H,Random,95% CI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSSS 2007</td>
<td>4/302</td>
<td>4/306</td>
<td>12.1 %</td>
<td>1.01</td>
<td>0.26, 4.01</td>
</tr>
<tr>
<td>Morgan 1978</td>
<td>1/34</td>
<td>0/33</td>
<td>2.3 %</td>
<td>2.91</td>
<td>0.12, 69.08</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>336</strong></td>
<td><strong>339</strong></td>
<td><strong>14.4 %</strong></td>
<td><strong>1.20</strong></td>
<td><strong>0.34, 4.24</strong></td>
</tr>
</tbody>
</table>

Total events: 5 (Intervention), 4 (Control)

Heterogeneity: Tau² = 0.0; Chi² = 0.36, df = 1 (P = 0.55); I² = 0.0%

Test for overall effect: Z = 0.28 (P = 0.78)

**Total (95% CI)** | **2050** | **2143** | **100.0 %** | **0.73** | **0.45, 1.17** |

Total events: 28 (Intervention), 41 (Control)

Heterogeneity: Tau² = 0.0; Chi² = 1.16, df = 4 (P = 0.89); I² = 0.0%

Test for overall effect: Z = 1.31 (P = 0.19)

Test for subgroup differences: Chi² = 0.71, df = 1 (P = 0.40); I² = 0.0%
### Analysis 2.2. Comparison 2 Sensitivity analysis: individual RCTs, Outcome 2 Cardiovascular mortality at end of trial.

Review: Reduced dietary salt for the prevention of cardiovascular disease

Comparison: 2 Sensitivity analysis: individual RCTs

Outcome: 2 Cardiovascular mortality at end of trial

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Intervention</th>
<th>Control</th>
<th>Odds Ratio</th>
<th>Weight</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>M-H,Fixed,95% CI</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
</tr>
<tr>
<td>2 Hypertensive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSSS 2007</td>
<td>4/302</td>
<td>4/306</td>
<td>58.5 %</td>
<td>1.01 [ 0.25, 4.09 ]</td>
<td></td>
</tr>
<tr>
<td>Morgan 1978</td>
<td>2/33</td>
<td>3/34</td>
<td>41.5 %</td>
<td>0.67 [ 0.10, 4.27 ]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>335</td>
<td>340</td>
<td>100.0 %</td>
<td>0.87 [ 0.29, 2.64 ]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 6 (Intervention), 7 (Control)

Heterogeneity: Chi² = 0.12, df = 1 (P = 0.72); I² = 0.0%

Test for overall effect: Z = 0.25 (P = 0.81)

Test for subgroup differences: Not applicable
Analysis 2.3. Comparison 2 Sensitivity analysis: individual RCTs, Outcome 3 Cardiovascular events at end of trial.

Review: Reduced dietary salt for the prevention of cardiovascular disease

Comparison: 2 Sensitivity analysis: individual RCTs

Outcome: 3 Cardiovascular events at end of trial

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Intervention</th>
<th>Control</th>
<th>Odds Ratio</th>
<th>Weight</th>
<th>Odds Ratio</th>
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<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>Hypertensives</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSSS 2007</td>
<td>8/302</td>
<td>5/306</td>
<td></td>
<td>9.9 %</td>
<td>1.64 [ 0.53, 5.07 ]</td>
</tr>
<tr>
<td>Morgan 1978</td>
<td>3/34</td>
<td>3/33</td>
<td></td>
<td>5.7 %</td>
<td>0.97 [ 0.18, 5.18 ]</td>
</tr>
<tr>
<td>TONE 1998</td>
<td>36/370</td>
<td>46/371</td>
<td></td>
<td>84.5 %</td>
<td>0.76 [ 0.48, 1.21 ]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>706</td>
<td>710</td>
<td></td>
<td>100.0 %</td>
<td>0.86 [ 0.57, 1.30 ]</td>
</tr>
</tbody>
</table>

Total events: 47 (Intervention), 54 (Control)
Heterogeneity: Chi² = 1.54, df = 2 (P = 0.46); I² =0.0%
Test for overall effect: Z = 0.72 (P = 0.47)
Test for subgroup differences: Not applicable

A P P E N D I C E S

Appendix 1. Search strategies 2008

The Cochrane Library (2008, Issue 4)
Results for CENTRAL, Health Technology Assessment (HTA) and Database of Abstracts of Reviews of Effect (DARE)
Search date: 3 November 2008
#1 MeSH descriptor Heart Arrest explode all trees
#2 (cardiac NEAR/3 arrest*):ti,ab,kw
#3 (heart NEAR/3 arrest*):ti,ab,kw
#4 (cardiopulmonary NEAR/3 arrest*):ti,ab,kw
#5 (sudden NEAR/3 death):ti,ab,kw
#6 asystole*:ti,ab,kw
#7 (myocard* NEAR/2 contract*):ti,ab,kw
#8 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)
#9 (death* or died or dead or fatal*:ti,ab
#10 mortality:ti,ab.
#11 (#9 OR #10)
#12 MeSH descriptor Cerebrovascular Disorders explode all trees

Reduced dietary salt for the prevention of cardiovascular disease (Review)  52
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Reduced dietary salt for the prevention of cardiovascular disease (Review)

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Ovid MEDLINE(R) 1950 to October Week 4 2008

Search date: 29 October 2008
1 Randomized controlled trial.pt.
2 randomized controlled trial/
3 (random$ or placebo$).ti,ab,sh.
4 (singl$ or double$ or triple$ or treble$) and (blind$ or mask$).tw,sh.
5 or/1-4
6 "controlled clinical trial".pt.
7 (retraction of publication or retracted publication).pt.
8 6 or 7 or 5
9 exp Sodium, Dietary/
10 exp Diet, Sodium-Restricted/
11 Sodium/

Reduced dietary salt for the prevention of cardiovascular disease (Review)

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Reduced dietary salt for the prevention of cardiovascular disease (Review)

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EMBASE OVID SP <1980 to 2008 Week 43>

Search date: 30 October 2008

1 sodium intake/
2 sodium restriction/
3 Sodium/
4 Sodium Chloride/
5 3 or 4
6 (restrict* or low* or reduc* or intak* or added).tw. or diet*.mp.
7 (consum* or excess* or increas* or high*).tw.
8 6 or 7
9 5 and 8
10 (urin* or excret*).tw.
11 4 and 10
12 (restrict* adj3 (salt or sodium)).mp.
13 (low* adj3 (salt or sodium)).mp.
14 (reduc* adj3 (salt or sodium)).mp.
15 (intak* adj3 (salt or sodium)).mp.
16 (change adj3 (salt or sodium)).mp.
17 (consum* adj3 (salt or sodium)).mp.
18 (excess* adj3 (salt or sodium)).mp.
19 (sodium adj3 (urin* or excret*)).mp.
20 (increas* adj3 (salt or sodium)).mp.
21 (high* adj3 (salt or sodium)).mp.
22 (added adj3 (salt or sodium or food)).mp.
23 (diet* and (salt or sodium)).tw.
24 1 or 2 or 9 or 11 or (or/12-23)
25 exp Heart Arrest/
26 (cardiac adj3 arrest*).mp.
27 (heart adj3 arrest*).mp.
28 (cardiopulmonary adj3 arrest*).mp.
29 (sudden adj3 death).mp.
30 asystole*.mp.
31 (myocard* adj2 contract*).mp.
32 or/25-31
33 (death* or died or dead or fatal*4).ti,ab.
34 mortality.ti,ab.
35 33 or 34
36 exp Cerebrovascular Disease/
37 (stroke* or poststroke* or cva*).tw.
38 (cerebrovascular* or (cerebral adj vascular)).tw.
39 (cerebral or cerebellar or brain* or vertebrobasilar).tw.
40 (infarct* or isch?emi* or thrombo* or emboli* or apoplexy).tw.
41 (cerebral or intracerebral or intracranial or brain$ or parenchymal or intraventricular or cerebellar or infratentorial or supratentorial or subarachnoid).tw.
42 (haemorrhage or hemorrhage or bleed$ or haematoma or hematoma or aneurysm).tw.
43 40 and 39
44 41 and 42
45 trans* isch?emic attack*.tw.
46 brain attack.tw.
47 hemiplegia/
Reduced dietary salt for the prevention of cardiovascular disease (Review)

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100 ((animal$ or Nonhuman$) not human$).sh,hw.
101 letter.pt.
102 editorial.pt.
103 102 or 101 or 100
104 99 not 103
105 Randomized Controlled Trial/
106 Single Blind Procedure/
107 Double Blind Procedure/
108 Crossover Procedure/
109 105 or 106 or 107 or 108
110 (random$ or factorial$ or crossover$ or placebo$ or (cross adj over) or assign$).ti,ab.
111 ((singl$ or double$ or triple$ or treble$) and (blind$ or mask$)).ti,ab.
112 controlled clinical trial*.ti,ab.
113 112 or 110 or 111 or 109
114 104 and 113

PsycINFO (OVID) 1806 to October Week 4 2008

1 (random$ or placebo$ or rct).tw,sh.
2 ((singl$ or double$ or triple$ or treble$) and (blind$ or mask$)).tw,sh.
3 ("2000" or treatment outcome clinical trial).md.
4 (retract$ or withdraw$) adj (public$ or article$)).tw.
5 or/1-4
6 Sodium/
7 (diet and (salt or sodium)).mp.
8 (restrict* adj3 (salt or sodium)).mp.
9 (low* adj3 (salt or sodium)).mp.
10 (reduce* adj3 (salt or sodium)).mp.
11 (intak* adj3 (salt or sodium)).mp.
12 (change adj3 (salt or sodium)).mp.
13 (consum* adj3 (salt or sodium)).mp.
14 (excess* adj3 (salt or sodium)).mp.
15 (sodium adj3 (urin* or excret*)).mp.
16 (increas* adj3 (salt or sodium)).mp.
17 (high* adj3 (salt or sodium)).mp.
18 (added adj3 (salt or sodium or food)).mp.
19 or/6-18
20 exp Heart Arrest/
21 exp heart disorders/
22 (cardiac adj3 arrest*).mp.
23 (heart adj3 arrest*).mp.
24 (cardiopulmonary adj3 arrest*).mp.
25 (sudden adj3 death).mp.
26 asystole*.mp.
27 (myocard* adj2 contract*).mp.
28 or/20-27
29 (death* or died or dead or fatal*4).ti,ab.
30 mortality.ti,ab.
31 29 or 30
32 exp Cerebrovascular Disorders/
33 (stroke* or poststroke* or cva*).tw.
34 (cerebrovascular* or (cerebral adj vascular)).tw.
35 (cerebral or cerebellar or brain* or vertebrobasilar).tw.
36 (infarct* or isch?emi* or thrombo* or emboli* or apoplexy).tw.
37 (cerebral or intracerebral or intracranial or brain$ or parenchymal or intraventricular or cerebellar or infratentorial or supratentorial or subarachnoid).tw.
38 (haemorrhage or hemorrhage or bleed$ or haematoma or hematoma or aneurysm).tw.
39 36 and 35
40 37 and 38
41 32 or 33 or 34 or 39 or 40
42 trans* isch?emic attack*.tw.
43 brain attack.tw.
44 hemiplegia/
45 (hemipleg* or hemipar* or post-stroke).tw.
46 43 or 44 or 45 or 42
47 claudica*.ti,ab.
48 (peripher* adj3 (occlu* or arteri* or vascular)).ti,ab.
49 (arterial adj3 (obstruct* or occlus*)).ti,ab.
50 Atherosclerosis/
51 ((leg or limb) adj3 (isch?emia or occlusi*)).ti,ab.
52 (arteriosclerosis or atherosclerosis).ti,ab.
53 ((femoral or renal or iliac) adj3 artery).ti,ab.
54 (occlu* or obstruct*).ti,ab.
55 or/47-54
56 Heart Failure.mp.
57 ischemia/ and myocard$.tw.
58 angina.tw.
59 angor pectoris.tw.
60 myocard*.tw.
61 Ventricular Dysfunction/
62 (ventricular adj2 failure).tw.
63 revascular*.ti,ab.
64 (isch?mi? adj3 heart).ti,ab,sh.
65 coronary.ti,ab,sh.
66 heart surgery/
67 (PTCA or angioplast*).tw.
68 stenocardia*.tw.
69 (heart adj3 decompensation).tw.
70 exp Myocardial Infarction/
71 (heart adj3 infarc*).tw.
72 (heart adj3 failure).ti,ab,sh.
73 cardiac*.tw.
74 CABG.tw.
75 (heart adj3 bypass).tw,sh.
76 or/56-75
77 (cardiovascular adj3 (outcome* or morbidity or event*)).mp. [mp=title, abstract, heading word, table of contents, key concepts]
78 (hospital* or admission*).tw.
79 77 or 78
80 editorial.dt.
81 letter.dt.
82 80 or 81
83 28 or 31 or 41 or 46 or 55 or 76 or 79
84 83 and 19
85 84 and 5
86 85 not 82
87 86
CINAHL

WEB 2.0
Search date: 3 November 2008
1 SODIUM CHLORIDE, DIETARY/ OR DIET, SODIUM-RESTRICTED/
2 SODIUM/
3 SODIUM CHLORIDE/
4 ((restrict* OR low* OR reduc* OR intak* OR added) OR diet*).ti,ab
5 ((consum* OR excess* OR increas* OR high*).ti,ab
6 4 OR 5
7 6 AND (2 or 3)
8 ((urin* OR excret*).ti,ab
9 3 AND 8
12 ((restrict* AND (salt OR sodium))).ti,ab
13 ((low* AND (salt OR sodium))).ti,ab
14 ((reduc* AND (salt OR sodium))).ti,ab
15 ((intak* AND (salt OR sodium))).ti,ab
16 ((change AND (salt OR sodium))).ti,ab
17 ((consum* AND (salt OR sodium))).ti,ab
18 ((excess* AND (salt OR sodium))).ti,ab
19 ((sodium AND (urin* OR excret*))).ti,ab
20 ((increas* AND (salt OR sodium))).ti,ab
21 ((high* AND (salt OR sodium))).ti,ab
22 ((added AND (salt OR sodium OR food))).ti,ab
23 ((diet* AND (salt OR sodium))).ti,ab
24 1 OR 7 OR 9 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23
25 24 [Limit to: (Publication Type Clinical Trial or Systematic Review)]
26 ((placebo* OR random* OR rct)).ti,ab
27 (((singl* OR double* OR triple* OR treble*) AND (blind* OR mask*))).ti,ab
28 ((controlled clinical trial)).ti,ab
29 26 OR 27 OR 28
30 24 AND 29
31 25 OR 30 [Limit to: (Publication Type Clinical Trial or Systematic Review)]

Appendix 2. Search strategies 2013

CENTRAL
#1 MeSH descriptor: [Sodium, Dietary] explode all trees
#2 MeSH descriptor: [Diet, Sodium-Restricted] this term only
#3 (restrict* near/3 (salt or sodium))
#4 (low* near/3 (salt or sodium))
#5 (reduc* near/3 (salt or sodium))
#6 (intak* near/3 (salt or sodium))
#7 (change near/3 (salt or sodium))
#8 (consum* near/3 (salt or sodium))
#9 (excess* near/3 (salt or sodium))
#10 (high* near/3 (salt or sodium))
#11 (diet* and (salt or sodium))
Reduced dietary salt for the prevention of cardiovascular disease (Review)

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27. tachycardia*.tw.
28. endocardia*.tw.
29. (sick adj sinus).tw.
30. exp Stroke/
31. (stroke or stokes).tw.
32. cerebrovasc*.tw.
33. cerebral vascular.tw.
34. apoplexy.tw.
35. (brain adj2 accident*).tw.
36. ((brain* or cerebral or lacunar) adj2 infarct*).tw.
37. exp Hypertension/
38. hypertensi*.tw.
39. peripheral arter* disease*.tw.
40. ((high or increased or elevated) adj2 blood pressure).tw.
41. exp Hyperlipidemias/
42. hyperlipid*.tw.
43. hyperlipemia*.tw.
44. hypercholesterol*.tw.
45. hypercholesterolemia*.tw.
46. hyperlipoproteinemia*.tw.
47. hypertriglyceridemia*.tw.
48. exp Arteriosclerosis/
49. exp Cholesterol/
50. cholesterol.tw.
51. "coronary risk factor* ".tw.
52. Blood Pressure/
53. blood pressure.tw.
54. or/13-53
55. 12 and 54
56. randomized controlled trial.pt.
57. controlled clinical trial.pt.
58. randomized.ab.
59. placebo.ab.
60. drug therapy.fs.
61. randomly.ab.
62. trial.ab.
63. groups.ab.
64. 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63
65. exp animals/ not humans.sh.
66. 64 not 65
67. 55 and 66
68. (200810* or 200811* or 200812* or 2009* or 2010* or 2011* or 2012* or 2013*).ed.
69. 67 and 68

EMBASE

1. salt intake/
2. sodium restriction/
3. (restrict* adj3 (salt or sodium)).tw.
4. (low* adj3 (salt or sodium)).tw.
5. (reduc* adj3 (salt or sodium)).tw.
6. (intak* adj3 (salt or sodium)).tw.
7. (change adj3 (salt or sodium)).tw.
Reduced dietary salt for the prevention of cardiovascular disease (Review)

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S22 hypertensi* or peripheral arter* disease*
S21 (MH "Hypertension+")
S20 ((brain* or cerebral or lacunar) N2 infarct*)
S19 brain N2 accident*
S18 stroke or stokes or cerebrovasc* or apoplexy or cerebral next vascular
S17 (MH "Stroke+")
S16 tachycardi* or endocardi* or sick N3 sinus
S15 pericard* or ich?em* or emboli* or arrhythmi* or thrombo* or atrial fibrillat*
S14 cardio* or cardia* or heart* or coronary* or angina* or ventric* or myocard*
S13 (MH "Cardiovascular Diseases+")
S12 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11
S11 (diet* and (salt or sodium))
S10 (high* N3 (salt or sodium))
S9 (excess* N3 (salt or sodium))
S8 (consum* N3 (salt or sodium))
S7 (change N3 (salt or sodium))
S6 (intak* N3 (salt or sodium))
S5 (reduce* N3 (salt or sodium))
S4 (low* N3 (salt or sodium))
S3 (restrict* N3 (salt or sodium))
S2 (MH "Diet, Sodium-Restricted")
S1 (MH "Sodium, Dietary+")

**WHAT'S NEW**

Last assessed as up-to-date: 1 May 2013.

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
</tr>
</thead>
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<tr>
<td>1 May 2014</td>
<td>New citation required but conclusions have not changed</td>
<td>Two new studies included. Conclusions not changed.</td>
</tr>
<tr>
<td>1 May 2014</td>
<td>New search has been performed</td>
<td>Searches re-run in May 2013.</td>
</tr>
</tbody>
</table>

**HISTORY**

Review first published: Issue 7, 2011

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<th>Description</th>
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<tbody>
<tr>
<td>6 June 2013</td>
<td>Amended</td>
<td>The Paterna trial has now been retracted and we have removed the data from this trial from the review</td>
</tr>
<tr>
<td>13 March 2013</td>
<td>Amended</td>
<td>Doubts have been raised about the integrity of research from the Paterna group. The previously published results should be discounted for now</td>
</tr>
</tbody>
</table>
CONTRIBUTIONS OF AUTHORS
All the authors were involved in the design of the review.

In the original review:
TM developed the search strategy.
KA and RT selected studies for inclusion, extracted data, carried out data synthesis/analysis and wrote the first draft of the review.

For this update:
NM conducted the searches.
FCT, NM and AJA screened abstracts and selected studies for analysis.
FCT and AJA extracted trial data.
AJA did the analysis and wrote the review.
SE reviewed the data extraction, did the analysis and wrote the review.

DECLARATIONS OF INTEREST
Dr. Gottlieb owns the trademark “Greens, Beans, and Leans (R)”, a registered trademark in the United States, for a diet that is high in fibre and polyunsaturated fats, low in simple carbohydrates, saturated fats and sodium.
Shah Ebrahim’s research is supported by grants from the Wellcome Trust, IDRC, ESRC and the National Institute of Health Research.
Alma Adler, Fiona Taylor, Nicole Martin and Rod Taylor have no known conflict of interest.

SOURCES OF SUPPORT
Internal sources
- No sources of support supplied
**External sources**

- NIHR programme grant, UK.

Original review funded by a NIHR programme grant

**DIFFERENCES BETWEEN PROTOCOL AND REVIEW**

Given the small number of trials included in this review it was not possible to undertake exploration of heterogeneity using stratified meta-analysis or meta-regression.

**NOTES**

Following doubts raised about the integrity of research from the Paterna group and retraction of a publication by this group (Heart 2013), we have now removed this trial and its data from this review.

**INDEX TERMS**

**Medical Subject Headings (MeSH)**

*Diet, Sodium-Restricted; Cardiovascular Diseases [mortality; *prevention & control]; Hypertension [mortality]; Randomized Controlled Trials as Topic; Sodium Chloride, Dietary [*administration & dosage]*

**MeSH check words**

Adult; Humans