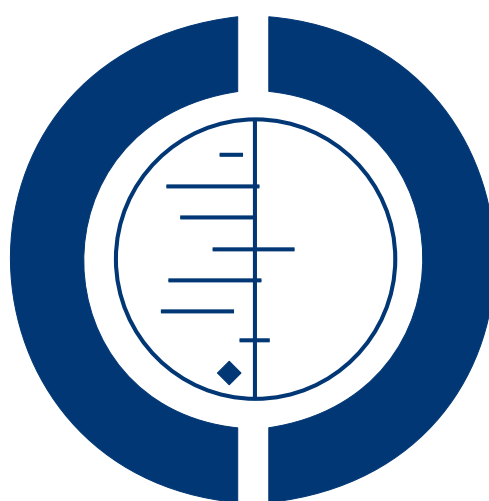# Reduced dietary salt for the prevention of cardiovascular disease (Review)

Taylor RS, Ashton KE, Moxham T, Hooper L, Ebrahim S

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Reduced dietary salt for the prevention of cardiovascular disease

Rod S Taylor[1], Kate E Ashton[2], Tiffany Moxham[3], Lee Hooper[4], Shah Ebrahim[5]

[1]Peninsula College of Medicine and Dentistry, Universities of Exeter & Plymouth, Exeter, UK. [2]PenTAG, Peninsula Medical School, University of Exeter, Exeter, UK. [3]Wimberly Library, Florida Atlantic University, Boca Raton, Florida, USA. [4]Norwich Medical School, University of East Anglia, Norwich, UK. [5]Department of Non-communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK

Contact address: Rod S Taylor, Peninsula College of Medicine and Dentistry, Universities of Exeter & Plymouth, Veysey Building, Salmon Pool Lane, Exeter, EX2 4SG, UK. rod.taylor@pms.ac.uk.

ABSTRACT

Background

An earlier Cochrane review of dietary advice identified insufficient evidence to assess effects of reduced salt intake on mortality or cardiovascular events.

Objectives

1. To assess the long term effects of interventions aimed at reducing dietary salt on mortality and cardiovascular morbidity.

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

Search strategy

The Cochrane Library (CENTRAL, Health Technology Assessment (HTA) and Database of Abstracts of Reviews of Effect (DARE)), MEDLINE, EMBASE, CINAHL and PsycInfo were searched through to October 2008. References of included studies and reviews were also checked. No language restrictions were applied.

Selection criteria

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

Data collection and analysis

Data extraction and study validity were compiled by a single reviewer, and checked by a second. Authors were contacted where possible to obtain missing information. Events were extracted and relative risks (RRs) and 95% CIs calculated.

Main results

Seven studies (including 6,489 participants) met the inclusion criteria - three in normotensives (n=3518), two in hypertensives (n= 758), one in a mixed population of normo- and hypertensives (n=1981) and one in heart failure (n=232) with end of trial follow-up of seven to 36 months and longest observational follow up (after trial end) to 12.7 yrs. Relative risks for all cause mortality in normotensives (end of trial RR 0.67, 95% CI: 0.40 to 1.12, 60 deaths; longest follow up RR 0.90, 95% CI: 0.58 to 1.40, 79 deaths) and hypertensives (end of trial RR 0.97, 95% CI: 0.83 to 1.13, 513 deaths; longest follow up RR 0.96, 95% CI; 0.83 to 1.11, 565 deaths) showed strong evidence of any effect of salt reduction. Cardiovascular morbidity in people with normal blood pressure (longest follow-up RR 0.71, 95% CI: 0.42 to 1.20, 200 events) or raised blood pressure at baseline (end of trial RR 0.84, 95% CI: 0.57 to 1.23, 93 events) also showed no strong evidence of benefit. Salt restriction increased the risk of all-cause death in those with congestive heart failure (end of trial relative risk: 2.59, 95% 1.04 to 6.44, 21 deaths). We found no information on participants health-related quality of life.

Authors' conclusions

Despite collating more event data than previous systematic reviews of randomised controlled trials (665 deaths in some 6,250 participants), there is still insufficient power to exclude clinically important effects of reduced dietary salt on mortality or cardiovascular morbidity in normotensive or hypertensive populations. Further RCT evidence is needed to confirm whether restriction of sodium is harmful for people with heart failure. Our estimates of benefits from dietary salt restriction are consistent with the predicted small effects on clinical events attributable to the small blood pressure reduction achieved.

P L A I N   L A N G U A G E   S U M M A R Y

Cutting down on the amount of salt has no clear benefits in terms of likelihood of dying or experiencing cardiovascular disease

Cardiovascular disease includes heart attacks, strokes, and the need for heart surgery and is a major cause of premature death and disability. This review set out to assess whether advice to cut down on salt in foods on altered our risk of death or cardiovascular disease. Intensive support and encouragement to reduce salt intake did lead to a reduction in salt eaten and a small reduction in blood pressure after more than six months. There was not enough information to understand the effect of these changes in salt intake on deaths or cardiovascular disease. Further research in needed to confirm our finding that dietary advice to reduce salt may increase deaths in people with heart failure.

B A C K G R O U N D

In 2002 it was estimated that nearly 17 million deaths globally per year result from cardiovascular disease (CVD) (Mackay 2004). Data on morbidity is more difficult to collect because there are so many different measures of cardiovascular morbidity. However, in 2002 it was estimated that over 34 million disability adjusted life years (DALYs) are lost each year to CVD in Europe (Allender 2008).

The current public health recommendations in most developed countries are to reduce salt intake by about half, i.e. from approximately 10 to 5 g/day (He 2010; SACN 2003; Whelton 2002).

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). This was confirmed by a recently published systematic review and meta-analysis of 13 prospective studies including 177,000 participants. A high salt intake was associated with a greater risk of stroke (relative risk, 1.23, 95% CI: 1.06 to 1.43) (Starzzullo 2009). However, there was no association between salt intake and all cardiovascular events, and total mortality was not reported. Furthermore, 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), different end points, and definition of outcomes across studies (Alderman 2010).

The relationship of salt intake to blood pressure is the basis for the belief that restriction in dietary sodium intake will prevent blood pressure related cardiovascular events (Elliot 1996). A number of

meta-analyses of randomised controlled trials of salt reduction and blood pressure have been undertaken (He 2004; Jurgens 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 mm Hg, 95% CI: 1.8 to 0.4, diastolic by 0.6 mm Hg, 95% CI: 1.5 to -0.3) (Hooper 2004). The reduction in blood pressure appeared larger for people with higher blood pressure. A decrease in blood pressure is only important if it results in a decrease in cardiovascular events and deaths. Sustained reductions in mean blood pressure of 2-3 mmHg are necessary for important population reductions in cardiovascular events (Elliot 1991).

Whilst the Cochrane review also sought to assess the impact of dietary salt restriction on mortality and cardiovascular events, across the included 11 RCTs there were only 17 deaths spread evenly across groups and 46 cardiovascular events in the controls compared with 36 in low sodium diet groups. This extremely low number of events substantially limited the ability of this 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, the primary focus of this review is to confirm whether such changes in diet are associated with improvements in mortality and cardiovascular events.

O B J E C T I V E S

1. To assess the long term effects of interventions 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.

Interventions to reduce dietary salt were compared with usual, control or placebo diets, or no intervention.

M E T H O D S

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 of adults (18 years or older), irrespective of gender or ethnicity. Studies of children or pregnant women were excluded.

Types of interventions

The desired intervention was reduced dietary salt and could include studies that involved participants receiving a dietary intervention that restricted salt or studies where the intervention was advice to reduce salt intake. The comparison group could include usual, control or placebo diet, or no intervention.

Types of outcome measures

Primary outcomes

Mortality (overall and cardiovascular), 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). Primary outcomes were assessed 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 primary outcomes we also sought the following secondary outcomes: systolic and diastolic blood pressure, and urinary salt excretion (or other method of estimation of salt intake) and 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

Randomised controlled trials were identified by searching the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library (Issue 4, 2008), MEDLINE (Ovid, 1950 to 29 October 2008), EMBASE (Ovid, 1980 to 30 October 2008), CINAHL (Ovid, 2001 to 3 November 2008), and PsycINFO (Ovid, 1806 to October 2008), Health Technology Assessment (HTA) and Abstracts of Reviews of Effects (DARE) databases were searched via The Cochrane Library (Issue 4, 2008). Searches conducted in MEDLINE, EMBASE, CINAHL, and PsycINFO included a controlled trials filter. Additional filters were applied to restrict searches to non-animal studies in MEDLINE and EM-BASE and to exclude certain publication types from the search results [Medline: case reports/letters, EMBASE: letters/editorials,

and PsycInfo: editorials/letters]. No language or additional limits or filters were utilized. See Appendix 1 for details of the search strategies.

Searching other resources

Reference lists of all eligible trials and relevant systematic reviews were searched for additional studies.

Data collection and analysis

Selection of studies

The titles and abstracts of studies identified by the search were independently screened by two reviewers (KA & RST) and clearly irrelevant studies discarded. In order to be selected, abstracts had to clearly identify the study design, an appropriate population and a relevant intervention/exposure, as described above. The full text reports of all potentially relevant studies were obtained and assessed independently for eligibility, based on the defined inclusion criteria, by two reviewers (KA & RST). Any disagreement was resolved by discussion or where agreement could not be reached, by consultation with an independent third person (LH).

Data extraction and management

Standardised data extraction forms were used. Relevant data regarding inclusion criteria (study design, participants, intervention/exposure, and outcomes), risk of bias (see below) and outcome data were extracted. Data extraction was carried out by a single reviewer (KA or RST) and checked by a second reviewer (RST or KA). Disagreements were resolved by discussion or if necessary by a third reviewer (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. All included authors were contacted to clarify any missing outcome data or issues of risk of bias assessment.

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 evidence was sought that the groups were balanced at baseline, that intention to treat analysis was undertaken and whether the period over which the salt intervention lasted and follow up of outcome were equivalent. The risk of bias of included studies was assessed by a single reviewer (KA)

and checked by a second reviewer (RST). Disagreements were resolved by discussion or if necessary by a third reviewer (LH).

Data synthesis

Data were processed as described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2009). For mortality and cardiovascular events, risk ratio and 95% confidence intervals were calculated for each trial. For blood pressure and urinary sodium excretion, mean group differences and 95% confidence intervals were calculated using weighted mean difference. Heterogeneity amongst included studies was explored qualitatively (by comparing the characteristics of included studies), and quantitatively (using the Chi^2 statistic of heterogeneity and I^2 statistic). Results from included studies were combined 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 after the end of the randomisation period). A fixed-effect meta-analysis was used except where statistical heterogeneity (Chi ^{2} P $\leq$ 0.05 and I^2 value $\geq$ 50%) was identified, in which case methodological and clinical reasons for heterogeneity were considered and a random-effects model was used.

Subgroup analysis and investigation of heterogeneity

It was planned to use stratified meta-analysis to explore the differential effects that occur as a result of: individual advice vs. population level interventions, baseline risk of cardiovascualr disease (CVD), and salt reduction only interventions vs. multi-component dietary interventions that include salt restriction; and meta-regression to assess the effects of level of salt reduction achieved, baseline blood pressure (BP) and change in BP on mortality and CV event outcomes.

R E S U L T S

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Our electronic and reference list searches identified a total of 2,649 titles of which 2,605 were excluded on title and abstract. After examining the full texts of the remaining 44 papers, seven trials were included (38 reports) (Chang 2006 [31 mo]; HPT 1989 [36 mo]; Morgan 1978 [7-71 mo]; Paterna 2008 [6.4 mo]; TOHP I 1992 [18 mo]; TOHP II 1997 [36 mo]; TONE 1998 [30 mo]). The study selection process is summarised in the flow diagram shown in Figure 1.

Figure 1. Study flow diagram

Five studies from an earlier Cochrane review (Hooper 2004) met the inclusion criteria (TOHP I 1992 [18 mo]; TOHP II 1997 [36 mo]; TONE 1998 [30 mo]; HPT 1989 [36 mo]; Morgan 1978 [7-71 mo]). The other six included studies from Hooper 2004 were excluded as they did not report mortality or cardiovascular events (Alli 1992; Arroll 1995; Costa 1981; Morgan 1987; Silman 1983; Thaler 1982). Studies that were assessed in full text, but excluded, are listed in Characteristics of excluded studies section. Responses to our request for additional details were obtained from three of the included trial authors i.e. TOHP I and II and TONE.

Included studies

The seven included studies are described in Characteristics of included studies section. Three trials in people with normotension (n=3518, HPT 1989 [36 mo]; TOHP I 1992 [18 mo]; TOHP II 1997 [36 mo]), two in people with hypertension (n=758, Morgan 1978 [7-71 mo]; TONE 1998 [30 mo]), one in a mixed population of people with normo- and hypertension (n=1981, Chang 2006 [31 mo]) and one in people with heart failure (n=232, Paterna 2008 [6.4 mo]) were included. Post-randomisation follow up varied from up to six to nine months (Morgan 1978 [7-71 mo]; Paterna 2008 [6.4 mo]), to ~three-years (Chang 2006 [31 mo]; HPT 1989 [36 mo]) and 10-15 years (TOHP I 1992 [18 mo]; TOHP II 1997 [36 mo]; TONE 1998 [30 mo]).

The three normotensive trials were in healthy people (predominantly [>75%] white, male [75%], median age 40) conducted in the USA. Entry criteria varied between trials, but included those with diastolic blood pressure from 78 to 89 mmHg, with a narrow range of means from 83 to 86 mmHg diastolic and 124 to 127 mmHg systolic and the number of participants included ranged from 392 to 2382.

All three studies (as well as TONE, below) in normotensives aimed to reduce salt by a comprehensive dietary and behaviour change programmes led by experienced personnel, including group counselling sessions, regularly over several months, with newsletters between sessions, self assessment, goal setting, food tasting and recipes. For example, the HPT study ran ten 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). 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 in the TONE study to some 36 months in TOHP II study. Control groups received no active intervention. Sodium excretion goals were set at less than 70 to

80mmol/24 hours.

The three trials that included hypertensives included one trial in treated hypertensive participants (TONE 1998 [30 mo]) and two for participants with untreated hypertension (Chang 2006 [31 mo]; Morgan 1978 [7-71 mo]). Some 40 percent of participants in the Chang study were defined as hypertensive. Studies were carried out in Australia, Taiwan and USA and ranged in size from 77 to 1,981 participants. 58 to 100% of participants were male with median age of 66 yrs and 76% were white in the TONE study and 100% were Asian in the Chang study (ethnicity was not reported in Morgan study). At study entry mean diastolic blood pressure ranged from 71 mmHg (Chang 2006 [31 mo]; TONE 1998 [30 mo] on treatment) to 97 mmHg (Morgan 1978 [7-71 mo], untreated) and systolic blood pressure ranged from approximately 131mmHg (Chang 2006 [31 mo] untreated; TONE 1998 [30 mo] on treatment) to 162 mmHg (Morgan 1978 [7-71 mo], untreated).

Interventions in the three studies included:

- a dietary programme by the cook of the kitchen to which they were assigned (clustered random allocation), to 'high potassium salt' containing 49% sodium chloride, 49% potassium chloride, and 2% other additives or control prepared diet using 'usual salt' containing 99.6% sodium chloride and 0.4% other additives (Chang 2006 [31 mo]).

- advice to reduce dietary sodium chloride intake, with advice repeated at 6 months compared with no dietary intervention in the control group (Morgan 1978 [7-71 mo]). Anti-hypertensive medication was stopped two months after randomisation to intervention or control, but restarted if diastolic blood pressure rose. After 6 months, four out of 10 men on low sodium diet were taking anti-hypertensive medication, compared to nine of the ten controls (relative risk: 0.44, 95% CI: 0.20 to 0.98).

- a four-month 'intensive' plus three-month 'extended' individual nutrition and behavioural counselling programme (as above) or no such programme but with invitations to meetings on unrelated topics in the control group (TONE 1998 [30 mo]). In the TONE study hypertensive medication withdrawal could be attempted began at three-months post randomisation. The primary composite outcome (high blood pressure at any visit, restarting anti-hypertensive medication or a cardiovascular event) was less common in the sodium reduction group than control (relative risk 0.83, 95% CI: 0.75 to 0.92). The proportions of individuals restarting medication was not separately reported.

Sodium goals varied from <80 mmol/day (TONE 1998 [30 mo]) to 70-100 mmol/day and unspecified (Chang 2006 [31 mo]) sodium intake.

The final study was undertaken in Italy and included a population of participants diagnosed with uncompensated heart failure

(NYHA class III or IV) (Paterna 2008 [6.4 mo]). The majority of participants were male with a mean age of 73, mean diastolic blood pressure of 82.5 mmHg and mean systolic blood pressure of 125.5 mmHg. The intervention group received written standard diet sheets containing 80mmol of sodium daily prepared by dietitians and the control group received the same dietary advice but with the addition of 40mmol of sodium per day. In addition to either low-sodium or control diet, both groups received a high dose diuretic (furosemide, 250-500 mg bid).

Risk of bias in included studies

A number of studies failed to give sufficient detail to assess their potential risk of bias. Details of generation and concealment of random allocation sequence were particularly poorly reported (Figure 2; Figure 3). However, in all cases there was objective evidence of balance in baseline characteristics of intervention and control participants. While studies reported loss to follow up and reasons for loss for follow, 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 TONE trial, the authors stated that data were collected via psychological questionnaires at randomisation and a number of the follow-up visits. However, none of these data were found in 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 to salt reduction intervention using diet diaries or monitoring USE. However, in the longer term follow up of the TOHP I (11.5 yrs), TOHP II (8 yrs) and TONE (12.7 yrs) trials such compliance data was not reported beyond the official end of the study. Therefore it was unclear whether intervention groups encouraged to continue their low salt diets, or return to their pre-trial diet. Similarly, control groups may have been left to continue with their usual diet or advised to reduce their salt at the end of the trial.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.
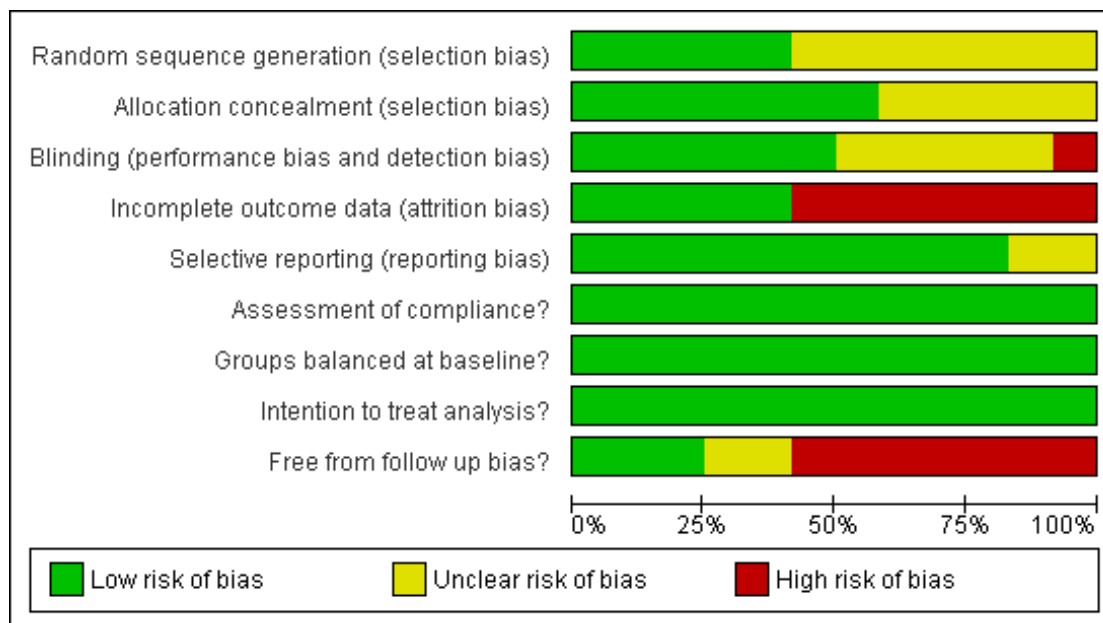
Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Effects of interventions

Given the heterogeneity in populations, results are presented and pooled separately for studies of people with normotension, hypertension and heart failure. Outcomes were pooled at end of trial and at longest follow up point unless otherwise indicated.

Mortality

All cause mortality was reported at the end of the trial in five of the included studies (HPT 1989; TOHP I 1992; TOHP II 1997; Chang 2008; Morgan 1978). Trials were homogeneous and therefore pooled using a fixed effect model. There was weak evidence of a reduction in the number of deaths in the reduced salt group relative to controls for normotensives (fixed effects RR 0.67, 95% CI: 0.40 to 1.12, 60 deaths in total, Chi² p-value=0.96,I² = 0%) and hypertensive populations (fixed effects RR 0.97, 95% CI: 0.83 to 1.13, 513 deaths, Chi² p-value = 0.98, I² = 0%). Compared to control there was an increase in deaths with dietary salt reduction in the single heart failure study (relative risk: 2.59, 95% CI: 1.04 to 6.44, 21 deaths). See Analysis 1.1

A longer observational follow up following the end of the randomised trial period was reported for the TOHP I (11.5 yrs) and TOHP II (8 yrs) trials (Cook 2007) and we were able to obtain longer observational unpublished data from the authors from the TONE study (12.7 yrs). Trials remained homogeneous. At longest follow up, there was still no strong evidence of a reduction in the number of deaths in the reduced salt group relative to controls, for the normotensives (fixed effects RR 0.90, 95% CI: 0.58 to 1.40, 79 deaths in total, Chi² p-value=1.00,I² = 0%) or hypertensive populations (fixed effects RR 0.96, 95% CI: 0.83 to 1.11, 565 deaths, Chi² p-value = 0.92); I² = 0%). See Analysis 1.2

Cardiovascular mortality was only reported in two studies of hypertensive patients. Both studies only reported trial end data. Chang reported a lower proportion of cardiovascular deaths in reduced salt group (27 died; 1310.0 per 100,000 person years) than in the control group (66 died; 2,140 per 100,000 person years). Morgan reported only five cardiovascular deaths, three in the intervention and two in control group. The pooled relative risk was consistent with a halving of the relative risk of cardiovascular deaths or a small increase (fixed effects RR 0.69, 95% CI: 0.45 to 1.05, 98 cardiovascular deaths, Chi² p-value = 0.26, I² = 0%). See Analysis 1.3

Cardiovascular morbidity

Overall cardiovascular morbidity was available for four trials. There was some evidence of statistical heterogeneity which may reflect that the definition of CV morbidity varied from trial to trial, although it broadly consisted of a composite of myocardial infarction, stroke, coronary artery bypass, PTCA, or death from a cardiovascular cause. At longer term observational follow up, TOHP I reported a relative risk reduction of cardiovascular events of 49% (95% CI: 9% to 71%) with reduced salt although when pooled with long term observational follow up of TOHP II there was no strong evidence of benefit in normotensive participants (random effects relative risk: 0.71, 95% CI: 0.42 to 1.20, 200 events, Chi² p-value = 0.10; I² = 63%). There were no reports of cardiovascular morbidity during or at the end of the randomised period for TOHP I or II trials. We found no strong evidence of benefits of salt reduction in hypertensive individuals (fixed effects relative risk: 0.84, 95% CI: 0.57 to 1.24, 93 events, Chi² p-value = 0.53; I² = 0%) at end of trial. See Analysis 1.4

Individual cardiovascular morbidity outcomes were infrequently reported and at trial end only. Paterna et al reported 39 cardiovascular-related hospital admissions (30 intervention, nine control) in their study of congestive heart failure patients (Paterna 2008 [6.4 mo]). In TONE, three patients experienced strokes (one intervention, two control); six experienced a myocardial infarction (two intervention, four control); three developed heart failure (two intervention, one control) and 26 suffered from angina (nine intervention, 17 control) (TONE 1998 [30 mo]).

Blood pressure

End of trial blood pressure was reported by all studies. There was evidence of substantial statistical heterogeneity. Systolic blood pressure was reduced in all intervention arms - normotensives (random effects mean difference 1.1 mmHg, 95% CI -0.1 to 2.3, Chi² p-value = 0.05, I² = 67%), hypertensives (fixed effect mean difference 4.1 mmHg, 95% CI 2.4 to 5.8, Chi² p-value = 0.64; I² = 0%) and those with heart failure (by 4.0 mmHg, 95% CI 0.7 to 7.3). Diastolic blood pressure was also reduced in normotensives (fixed effect mean difference 0.8 mmHg, 95% CI 0.2 to 1.4, Chi² p-value = 0.39); I² = 0%) but not in hypertensives (random effect mean difference -3.7 mmHg, 95% CI: 0.9 to -8.4, Chi² p-value = 0.08; I² = 67%) or those with heart failure (mean difference -2.0 mmHg, 0.70 to -4.80). See Analysis 1.5 and Analysis 1.6.

Urinary sodium excretion

Changes in urinary sodium excretion (USE) at the end of trial were reported by all studies. There was some evidence of statistical heterogeneity which may reflect different approaches to the assessment of 24-hr urinary sodium excretion. In the study by Morgan (Morgan 1978 [7-71 mo]), results were only reported as samples and therefore contained repeated observations for a number of patients. As for BP, in a number of studies, the last USE available was at a time point much preceding the timing of the reported mortality or CV events (BP follow up time: Morgan - six mo;

TONE - 30 mo, TOHP I - 18 mo, TOHP II - 36 mo). Urinary 24-hour USE was reduced by a similar amount across the three study subgroups - normotensives (by random effects 34.2 mmol/ 24 hrs, 95% CI: 18.8 to 49.6, Chi² p-value = 0.03, I² = 76%), hypertensive (by fixed effects 39.1 mmol/24 hrs, 95% CI: 31.1 to 47.1, Chi² p-value = 0.35; I² = 0%) and heart failure (by 27.0 mmol/24hrs, 95% CI: 24.5 to 29.5). See Analysis 1.7

Health-related quality of life

No studies reported outcomes using a validated health-related quality of life instrument.

Subgroup analyses and investigation of heterogeneity

In order to take to take account of the heterogeneity in populations and CV baseline risk, we stratified meta-analyses according to whether studies were undertaken in normotensive, hypertensive or heart failure populations. However, there was insufficient variability and number of studies to formally investigate heterogeneity. For example, as all studies applied participant level salt reduction interventions, we were unable to compare the effect of individual vs. population level interventions.

Small study bias

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

D I S C U S S I O N

Summary of main results

This Cochrane review identified seven randomised controlled trials that assessed the long-term (> six-months) effects of interventions aimed at reducing dietary salt on mortality and cardiovascular morbidity. Three trials were in normotensives (HPT 1989 [36 mo]; TOHP I 1992 [18 mo]; TOHP II 1997 [36 mo], n= 3518 participants), two in hypertensives (Morgan 1978 [7-71 mo]; TONE 1998 [30 mo], n=758 participants), one in a mixed population of normo- and hypertensives (Chang 2006 [31 mo], n= 1981 participants) and one in heart failure (Paterna 2008 [6.4 mo], n=232 participants).
We found no strong evidence that salt reduction reduced all-cause mortality in normotensives (end of trial RR 0.67, 95% CI 0.40 to 1.12, 60 deaths, 3518 participants; longest follow up - relative risk: 0.90, 95% CI: 0.58 to 1.40, 79 deaths, 3518 participants) or hypertensives (end of trial - relative risk: 0.97, 95% CI 0.83 to 1.13, 513 deaths, 2058 participants; longest follow up - relative risk: 0.96, 95% CI; 0.83 to 1.11, 565 deaths, 2349 participants). A

single RCT showed increase the risk of all-cause death in one study (relative risk: 2.59, 95% 1.04 to 6.44, 21 deaths, 232 participants) in those with congestive heart failure receiving a low salt diet. Few cardiovascular events were reported, and the lack of a statistically significant effect of reduced salt on cardiovascular morbidity in people with normal blood pressure (end of trial - relative risk: 0.71, 95% CI: 0.42 to 1.20, 200 events, 2502 participants) and high blood pressure (end of trial - relative risk: 0.84, 95% CI: 0.57 to 1.23, 93 events, 720 participants). We found no information on participant's health-related quality of life assessed using either validated generic or disease-specific instruments.
The interventions were capable of reducing 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 some 1 mmHg in normotensives and by an average of 2 to 4 mmHg in hypertensives and those with heart failure. Sustained long-term reductions of blood pressure of 1 and 4 mmHg would be predicted to reduce CVD mortality by 5% and 20% respectively (MacMahon 1990). Our point estimates are consistent with effects of this size but have wide confidence intervals owing to the relatively small number of events.

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 [11.5 yrs]; TOHP II 1997 [8 yrs]; TONE 1998 [12.7 yrs]) and inclusion of two more recent RCTs (Chang 2006 [31 mo]; Chang 2006 [31 mo]; Paterna 2008 [6.4 mo]) we have gathered more evidence on mortality and cardiovascular outcomes (~6,500 participants, 665 deaths, 293 cardiovascular events). Nevertheless the total amount of evidence on events remains limited. Assuming a control risk of 14% (hypertension trial control event risk in present review) we would require some 2500 cardiovascular events in over 18,000 trial participants to detect a small reduction in relative risk (0.90) with dietary salt advice (at 80% power and 5% alpha).
Although a relatively small evidence base, the external validity of the review was potentially high. Most studies included men and women at varying levels of risk of cardiovascular risk, primarily free-living in a community setting in industrialised countries. One study was undertaken in veterans in a residential setting in Taiwan, a recently graduated developing economy (Chang 2006 [31 mo]).

Quality of the evidence

Although all included studies were randomised controlled trials, only one of the seven included studies provided sufficient detail to be judged as having adequate random sequence generation, allocation concealment and outcome blinding. 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 lead to a positive change 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 group apart from dietary sodium. The one major exception was the trial by Chang where sodium was replaced by a high potassium substitute (Chang 2006 [31 mo]). Potassium has effects on blood pressure and may have deleterious effects in individuals with renal disease (Cappuccio 2000). Two studies in hypertensives allowed changes in anti-hypertensive medication during the period of the trial (Morgan 1978 [7-71 mo]; TONE 1998 [30 mo]). 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.

By incorporating data from the longest follow up point, we sought to maximise the opportunity to capture all deaths and cardiovascular events that were affected by alterations in dietary salt, not just those within the RCT period. However, in doing so we may have introduced a major source of bias. For three large studies (TOHP I 1992 [11.5 yrs], TOHP II 1997 [8 yrs], TONE 1998 [12.7 yrs]) the longest follow up was considerably beyond the official end of the trial and therefore observational. 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 included the primary analysis in each case as the latest data trial end, more robust but with slightly fewer deaths and cardiovascular events.

In summary, the overall internal validity of the evidence base in this review was limited and therefore our conclusions regarding the effect of a reduction in dietary salt may not be robust.

Potential biases in the review process

We searched comprehensively for randomised controlled trials of dietary sodium reduction, with a duration of 6-months or more and that 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.

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, hypertensives and congestive heart failure) and pooled studies using weighting based on sample size we did not account for the duration of follow up. A previous Cochrane review (Hooper 2004) suggests that over time the sodium reduction achieved is greatly reduced, as is the effect on blood pressure and therefore the effect on events potentially diminished.

Agreements and disagreements with other studies or reviews

Our finding of a lack of strong evidence of an effect of dietary sodium reduction on mortality and cardiovascular events is in contrast to Starzzullo 2009 who systematically reviewed prospective observational studies that examined the relationship between dietary sodium and cardiovascular events. They included 13 cohort studies (177,025 participants) over follow up three-17 years and found higher salt intake to be associated with greater risk of stroke (pooled relative risk: 1.23, 95% CI: 1.06 to 1.43, 5161 events) and cardiovascular events (pooled relative risk: 1.14, 95% CI: 0.99 to 1.32, 5346 events). Total and cardiovascular mortality were not reported. The inherent limitation of the Starzzullo review is the observational nature of the evidence i.e. studies describe the life course of persons who follow a chosen diet but provide no information about what might happen if that diet were experimentally allocated. People who choose a lower salt diet are likely to also eat a diet of fresh foods, lower in fats and refined carbohydrate, take more exercise and be less likely to smoke, so that their lower levels of deaths and disease may not relate to salt intake at all.

AUTHORS' CONCLUSIONS

Implications for practice

Our findings are consistent with the belief that salt reduction is beneficial in normotensive and hypertensive people. However, the methods of achieving salt reduction 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, generally required considerable efforts to implement and would not be expected to have major impacts on the burden of CVD. 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, that call for reduced dietary sodium. In UK, the National Institute of Health and Clinical Guidance (NICE) has recently called for an acceleration of the reduction in salt in the general population from a maximum intake

of 6 g per day per adult by 2015 and 3 g by 2025 (NICE 2010). Despite collating more events than previous systematic reviews of randomised controlled trials (565 deaths in almost 7,000 participants) we were unable to demonstrate a robustly estimated effect of reduced dietary salt on mortality or cardiovascular morbidity in normotensive or hypertensive populations. Including a further 79 deaths from long-term observational follow up of three trials did not improve the statistical power of the meta-analysis which is underpowered to assess the likely small relative risk reductions on all-cause mortality or cardiovascular events of dietary salt restriction.

Implications for research

In accord with the research recommendation of a previous Cochrane review, three of the large trials (TOHP I, TOHP II, TONE) have assessed the long-term effects of reduced dietary salt advice on mortality and cardiovascular morbidity. Our findings support the recent call for further rigorous large long-term randomised controlled trials, capable of definitively demonstrating the cardiovascular benefit of dietary salt reduction (Alderman 2010). Such trials need to assess population level interventions that are likely to lead to sustained reductions in salt intake and are commensurate with current public health guidelines. Further RCT evidence is needed to assess whether dietary restriction of sodium is harmful for people with heart failure. It will be important to evaluate the effects of voluntary salt reductions by food industries as these may hold greater opportunities for practicable and inexpensive means of reducing salt intake in the population at large than focusing on dietary advice for individuals.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Chang 2006 [31 mo]

Methods	Cluster RCT [5 kitchens]
Participants	**N Randomised:** 1991 (N=768, intervention, 2 kitchens; N=1213 control, 3 kitchens) **Baseline Blood Pressure:** Int.: SBP mean 131.3 (SD 19.7), DBP mean 71.2 (SD 10.8) ; Ctrl: SBP mean 130.7 (SD 20.4), DBP mean 71.4 (SD 10.8) **Case mix:** Int.: 40.2% hypertension; Ctrl.: 40.4% hypertension **Age:** mean 75.6 (SD 7.7), 74.8 (7.0), 74.8 (7.3), 74.6 (6.7), 74.6 (6.1) in kitchens 2 and 3 (int. group), and 1, 4, and 5 (ctrl group) respectively. **CV diagnoses:** None reported **Percentage male:** 100% **Percentage white:** Not reported. **Inclusion/exclusion criteria:** **Inclusion:** Veterans registered into a retired home in Northern Taiwan. **Exclusion:** Bed-ridden veterans, high serum creatinine (i.e. >=3.5mg/dL)
Interventions	***Intervention*** **Total duration:** Average of 31 months. **Salt reduction/advice component:** 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 fourth week cooks used solely the potassium enriched salt. **Other dietary component:** 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. **Comparator** **Dietary:** 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.
Outcomes	Deaths (all cause & CVD)
Notes	Outcomes are not reported by kitchen so not able to quantify effect of clustering

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	*"The simplest randomisation method, i.e., drawing lots, was used."*

Chang 2006 [31 mo]   *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	*"The veterans were told about the trial, but were not told to which salt they were assigned."* Yes - participants. Unclear - study personnel and outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	High risk	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.
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods are reported in the results.
Assessment of compliance?	Low risk	Subjects ate food that was prepared for them.
Groups balanced at baseline?	Low risk	*"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)."*
Intention to treat analysis?	Low risk	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.
Free from follow up bias?	Low risk	The dietary intervention was applied over the period of event outcome follow up

HPT 1989 [36 mo]

Methods	Individual RCT
Participants	**N Randomised:** 392 (N=196, intervention, N=196, control) **Baseline Blood Pressure:** Int.: SBP mean124.0 (SD NR), DBP mean 82.6 (SD NR); Ctrl: mean SBP 123.9(SD NR), DBP mean 83.0 (SD NR) **Case mix:** normotensives **Age:** Int. mean 39.0 (SD NR); Ctrl: mean 38.5 (SD NR) **CV diagnoses:** none **Percentage male:** 65% **Percentage white:** 82% **Inclusion/exclusion criteria:** **Inclusion:** Men and women aged 25-49yrs; DBP 78-89mmHg

HPT 1989 [36 mo]   *(Continued)*

	Exclusion: Use of antihypertensive medication, evidence of CVD, BMI >=0.0035kg/cm^2, 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 two weeks for the next four weeks, and then once every month for the rest of treatment and follow-up. The group goal was a 50% reduction (<= 70mmol) 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)
Notes	- Factorial design (calorie restriction & potassium supplementation not reported here). - No difference in proportion of individuals in each group who began hypertensive medication (8.4% intervention vs. 9/0% control) over 36 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	*"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 size 5 to 10 for the high-weight stratum.* *"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."*
Allocation concealment (selection bias)	Low risk	*"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)"*
Blinding (performance bias and detection bias) All outcomes	Low risk	*"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.*" *No - participants; Yes - data collectors; Unclear - data analysts.*
Incomplete outcome data (attrition bias) All outcomes	High risk	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 impact of loss to follow-up.
Selective reporting (reporting bias)	Low risk	All outcomes described in methods are reported in results.
Assessment of compliance?	Low risk	*"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	*"Except for sex there were no marked baseline differences among the treatment groups."*
Intention to treat analysis?	Low risk	*"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

Morgan 1978 [24 mo]

Methods	Individual RCT
Participants	*N Randomised:* 77 (N=35 intervention N=42 control) groups *Baseline Blood Pressure:* Int: SBP mean 160 (SD 23), DBP 97 (SD 8); Ctrl: SBP mean 165 (SD 17), DBP mean 97 (SD 8) *Case mix:* Untreated hypertensives *Age:* Int. mean: 57.1 (SD NR); Ctrl. mean: 58.6 (SD NR)

Morgan 1978 [24 mo]   (*Continued*)

	CV diagnoses: Borderline hypertensives (DBP = 95-109) **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 two years, serum-creatinine levels >0.18mmol/l, abnormal liver-function tests, in cardiac failure or on diuretic therapy.
Interventions	***Intervention*** **Total duration:** 6 months **Salt reduction/advice component:** Patients instructed to reduce their sodium chloride intake and were given a diet that should have reduced their sodium intake to 70-100mmol/day. The advice about diet was repeated at 6mths. No details on who gave advice. **Other dietary component:** At each 6mth review visit, if serum potassium levels <3.4mmol/L, potassium supplements were given. **Comparator** No treatment reviewed at 6 mo (as intervention) **Other:** Not given any treatment, but reviewed at six-monthly intervals and if the DBP rose above 115mmHg treatment was started
Outcomes	Deaths (all cause & CVD); BP; Urinary Na Excretion
Notes	CV morbidity and CV mortality data taken from previous Cochrane review Taking antihypertensive medication (at 6 mo): Intervention - 4/10 vs Control - 9/10 (RR: 0.44, 95% CI: 0.20 to 0.98)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	*"[patients] were randomly divided into 4 subgroups"*
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	*"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 impact of loss to follow-up.
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods are reported at some point in the results
Assessment of compliance?	Low risk	Urinary sodium is measured, and although it is not specifically stated that this was used to assess compliance, it is implied: *"Patients in the dietary therapy group who continued to have a high sodium excretion were advised about their diet."*
Groups balanced at baseline?	Low risk	*"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".*
Intention to treat analysis?	Low risk	Although the term ITT is not used by the authors it appears that groups were analysed as randomised. *"[Morgan et al.'s (1980)] report does not exclude patients 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'?"*
Free from follow up bias?	High risk	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

Morgan 1978 [6 mo]

Methods	Individual RCT
Participants	*N Randomised:* 77 (N=35 intervention N=42 control) groups **Baseline Blood Pressure:** Int: SBP mean 160 (SD 23), DBP 97 (SD 8); Ctrl: SBP mean 165 (SD 17), DBP mean 97 (SD 8) **Case mix:** Untreated hypertensives **Age:** Int. mean: 57.1 (SD NR); Ctrl. mean: 58.6 (SD NR) **CV diagnoses:** Borderline hypertensives (DBP = 95-109) **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 two years, serum-creatinine levels >0.18mmol/l, abnormal liver-function tests, in cardiac failure or on diuretic therapy.

Morgan 1978 [6 mo] *(Continued)*

Interventions	***Intervention*** **Total duration:** 6 months **Salt reduction/advice component:** Patients instructed to reduce their sodium chloride intake and were given a diet that should have reduced their sodium intake to 70-100mmol/day. The advice about diet was repeated at 6mths. No details on who gave advice. **Other dietary component:** At each 6mth review visit, if serum potassium levels <3.4mmol/L, potassium supplements were given. **Comparator** No treatment reviewed at 6 mo (as intervention) **Other:** Not given any treatment, but reviewed at six-monthly intervals and if the DBP rose above 115mmHg treatment was started
Outcomes	Deaths (all cause & CVD); BP; Urinary Na Excretion
Notes	CV morbidity and CV mortality data taken from previous Cochrane review Taking antihypertensive medication (at 6 mo): Intervention - 4/10 vs Control - 9/10 (RR: 0.44, 95% CI: 0.20 to 0.98)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	*"[patients] were randomly divided into 4 subgroups"*
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	*"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 impact of loss to follow-up.
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods are reported at some point in the results

Morgan 1978 [6 mo]   (*Continued*)

Assessment of compliance?	Low risk	Urinary sodium is measured, and although it is not specifically stated that this was used to assess compliance, it is implied: *"Patients in the dietary therapy group who continued to have a high sodium excretion were advised about their diet."*
Groups balanced at baseline?	Low risk	*"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".*
Intention to treat analysis?	Low risk	Although the term ITT is not used by the authors it appears that groups were analysed as randomised. *"[Morgan et al.'s (1980)] report does not exclude patients 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'?"*
Free from follow up bias?	High risk	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

Morgan 1978 [7-71 mo]

Methods	Individual RCT
Participants	***N Randomised:*** 77 (N=35 intervention N=42 control) groups **Baseline Blood Pressure:** Int: SBP mean 160 (SD 23), DBP 97 (SD 8); Ctrl: SBP mean 165 (SD 17), DBP mean 97 (SD 8) **Case mix:** Untreated hypertensives **Age:** Int. mean: 57.1 (SD NR); Ctrl. mean: 58.6 (SD NR) **CV diagnoses:** Borderline hypertensives (DBP = 95-109) **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 two years, serum-creatinine levels >0.18mmol/l, abnormal liver-function tests, in cardiac failure or on diuretic therapy.
Interventions	***Intervention*** **Total duration:** 6 months **Salt reduction/advice component:** Patients instructed to reduce their sodium chloride intake and were given a diet that should have reduced their sodium intake to 70-100mmol/day. The advice about diet was repeated at 6mths. No details on who gave advice. **Other dietary component:** At each 6mth review visit, if serum potassium levels <3.4mmol/L, potassium supplements were given.

Morgan 1978 [7-71 mo]   *(Continued)*

	Comparator No treatment reviewed at 6 mo (as intervention) **Other:** Not given any treatment, but reviewed at six-monthly intervals and if the DBP rose above 115mmHg treatment was started		

Outcomes	Deaths (all cause & CVD); BP; Urinary Na Excretion
Notes	CV morbidity and CV mortality data taken from previous Cochrane review Taking antihypertensive medication (at 6 mo): Intervention - 4/10 vs Control - 9/10 (RR: 0.44, 95% CI: 0.20 to 0.98)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	*"[patients] were randomly divided into 4 subgroups"*
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	*"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 impact of loss to follow-up.
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods are reported at some point in the results
Assessment of compliance?	Low risk	Urinary sodium is measured, and although it is not specifically stated that this was used to assess compliance, it is implied: *"Patients in the dietary therapy group who continued to have a high sodium excretion were advised about their diet."*
Groups balanced at baseline?	Low risk	*"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".*

Morgan 1978 [7-71 mo]   *(Continued)*

Intention to treat analysis?	Low risk	Although the term ITT is not used by the authors it appears that groups were analysed as randomised. *"[Morgan et al.'s (1980)] report does not exclude patients 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'?"*
Free from follow up bias?	High risk	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

Paterna 2008 [6.4 mo]

Methods	Individual RCT
Participants	**N Randomised:** 232 (N=114 intervention, N=120 control) **Baseline Blood Pressure:** Int: SBP 126 (SD 15), DBP 82 (SD 13); Ctrl: SBP 125 (SD 15), DBP 83 (SD 14) **Case mix:** Congestive heart failure **Age:** mean 72.6 (SD 8) **CV diagnoses:** Treated compensated heart failure **Percentage male:** *62%* **Percentage white:** not reported **Inclusion/exclusion criteria:** **Inclusion:** Compensated patients hospitalised within previous 30 days for recently decompensated CHF. Patients had to have uncompensated CHF, NYHA functional class IV that was unresponsive to treatment with high doses of oral furosemide up to 250-500mg/day and/or combinations of diuretics, ACE-inhibitors, digitalis, beta-blockers and nitrates, and to be under this therapy at least 2 weeks prior to hospitalisation. Patients also had to have left ventricular ejection fraction (LVEF) <35%, serum creatinine <2mg/dl, blood urea nitrogen <=60mg/dl, a decreased urinary volume (<500ml/24h) and low natriuresis (<60mmol/24h), despite receiving established treatments. None of the patients had to take non-steroidal anti-inflammatory drugs (NSAIDS). All patients received high-dose furosemide (250-1000mg, twice a day), Hypertonic Saline Solution (HSS), a normal sodium diet (120mmol) and a decreased fluid intake (1000ml/day) during hospitalisation. When compensated state was achieved (NYHA class II), patients received oral furosemide (250-500mg, twice a day), a normal sodium diet (120mmol sodium) and a fluid intake of 1000ml/day. This continued after discharge, and patients were considered clinically compensated when they reached a change in NYHA functional class to at least class II and the accomplishment of an ideal body weight. Patients received tailored therapy after discharge. Only patients in NYHA class II at 30 days after discharge were included in the study and randomised. **Exclusion:** Cerebral vascular disease, dementia, cancer, uncompensated diabetes, and severe hepatic disease. Patients requiring pacemaker implantation and those with an alcoholic habit. Patients who declined to take part in the study protocol (but continued the prescribed treatment), were unable to follow the assigned treatment, did not follow the treatment protocol or attend the scheduled clinic visits, did not adhere to the fluid

Paterna 2008 [6.4 mo]   *(Continued)*

	intake of 1000ml/day, or had a reduction or discontinuation of prescribed treatments. Also, patients experiencing side effects of ACE-inhibitor treatment, even if these patients were given angiotensin II receptor blockers.
Interventions	**Intervention** **Total duration:** 6.2 months **Salt reduction/advice component:** low sodium diet (80mmol/day). Multiple written standard diets prepared by dieticians. **Other dietary component:** none stated **Other:** Oral furosemide 250-500mg b.i.d. **Comparator** **Dietary:** normal sodium diet (120mmol/day) (same diets as the intervention group with the addition of 40mmol of sodium/day) **Other:** Oral furosemide 250-500mg b.i.d. *"all patients received same amount of saturated fat, fruit and vegetables etc"*
Outcomes	Mortality, readmissions for worsening CHF, BP, 24 hour urinary sodium excretion
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	*"Randomisation was carried out using a preliminary computer algorithm?"*
Allocation concealment (selection bias)	Unclear risk	*"randomisation was performed by an external team of physicians blinded to the study protocol"*
Blinding (performance bias and detection bias) All outcomes	High risk	*"Although we attempted to perform a double-blind study, this was not possible because the patients receiving the prescribed diets perceived the difference in the amount of salt in the two diets. Another set of different physicians, also blinded to the study protocol, performed the evaluation of the programmed controls and evaluated the readmitted CHF patients during follow-up. The laboratory and neurohormonal controls were also performed by physicians blinded to the study protocol. The adherence to diet, fluid intake and doses of furosemide were also controlled by two physicians blinded to the study protocol. All of these physicians communicated the controlled results after the conclusion of the study."* No - Participants. Unclear - Study personnel and outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	High risk	Numbers in each group at each assessment time point were reported. Reasons for losses to follow-up were not given at each stage, although it looks likely that they were deaths. No sensitivity analysis or imputation undertaken to assess impact of loss to follow-up.

Paterna 2008 [6.4 mo] *(Continued)*

Selective reporting (reporting bias)	Low risk	Yes - clinical outcomes. Serum chloride, bicarbonate, albumin, urea and glucose outcomes are not reported, but these are not main outcomes.
Assessment of compliance?	Low risk	*"In addition, patients were also contacted every week during follow-up by physicians and dieticians for a telephone interview to determine the adherence to the reduced fluid intake as well as the prescribed diet."*
Groups balanced at baseline?	Low risk	Not specifically stated in the publication, but they appear to be from table 1.
Intention to treat analysis?	Low risk	*"Analysis was by intention to treat"*
Free from follow up bias?	Low risk	Patients received intervention for same duration as follow up

TOHP I 1992 [11.5 yrs]

Methods	Individual RCT
Participants	**N Randomised:** 744 (327 intervention & 417 control) **Baseline Blood Pressure:** Int: SBP mean 124.8 (SD 8.5), DBP mean 83.7 (SD 2.7); Ctrl: SBP mean 125.1 (SD 8.1), mean DBP 83.9 (SD 2.8) **Case mix:** Normotensives **Age:** Int.: 43.4 (SD 6.6); Ctrl.: 42.6 (SD 6.5) **CV diagnoses:** None **Percentage male:** 71.4% **Percentage white:** 77.2% **Inclusion/exclusion criteria:** **Inclusion:** aged 30-54: mean DBP 80-89mmHg 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 >= 90mmHg or use of BP medications within 2mths of first evaluation), cardiovascular or other life-threatening or disabling diseases, gross obesity (BMI>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.
Interventions	**Intervention** **Total duration:** 18mths **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 3mths, 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 80mmol/24h.

TOHP I 1992 [11.5 yrs]   *(Continued)*

	Comparator **Dietary:** Usual diet. General guidelines for healthy eating were given.
Outcomes	All cause mortality, CV morbidity, BP and 24hr urinary sodium excretion
Notes	TOHP I design included allocation to other interventions (weight loss, stress management & supplements e.g.. fish oil)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	*"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."*
Blinding (performance bias and detection bias) All outcomes	Low risk	*"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."* *"In order to reduce observer bias, data collectors were blinded to the treatment assignment of the participants."* No - participants; Yes - data collectors; Unclear - data analysts.
Incomplete outcome data (attrition bias) All outcomes	Low risk	*"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*

TOHP I 1992 [11.5 yrs] (*Continued*)

		these exclusions were very similar to each other and to those calculated when all samples were included."
Selective reporting (reporting bias)	Low risk	All outcomes described in methods are reported in results.
Assessment of compliance?	Low risk	*"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."*
Groups balanced at baseline?	Low risk	*"Baseline characteristics were evenly distributed, except for age, which was higher in the sodium reduction intervention group"*
Intention to treat analysis?	Low risk	*"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?	High risk	Longest event follow up for mortality and CV morbidity was ~11.5 years but last stated diet advice stated as 18 months. No urinary sodium excretion data available at longest follow up

TOHP I 1992 [18 mo]

Methods	Individual RCT
Participants	**N Randomised:** 744 (327 intervention & 417 control) **Baseline Blood Pressure:** Int: SBP mean 124.8 (SD 8.5), DBP mean 83.7 (SD 2.7); Ctrl: SBP mean 125.1 (SD 8.1), mean DBP 83.9 (SD 2.8) **Case mix:** Normotensives **Age:** Int.: 43.4 (SD 6.6); Ctrl.: 42.6 (SD 6.5) **CV diagnoses:** None **Percentage male:** 71.4% **Percentage white:** 77.2% **Inclusion/exclusion criteria:** **Inclusion:** aged 30-54: mean DBP 80-89mmHg without antihypertensive medication; ability to complete and return a satisfactory 24-hour urine collection and food frequency questionnaire.

TOHP I 1992 [18 mo]   *(Continued)*

	Exclusion: Long list of exclusion criteria, generally designed to eliminate patients with: evidence of medically diagnosed hypertension (DBP >= 90mmHg or use of BP medications within 2mths of first evaluation), cardiovascular or other life-threatening or disabling diseases, gross obesity (BMI>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.
Interventions	**Intervention** **Total duration:** 18mths **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 3mths, 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 80mmol/24h. **Comparator** **Dietary:** Usual diet. General guidelines for healthy eating were given.
Outcomes	All cause mortality, CV morbidity, BP and 24hr urinary sodium excretion
Notes	TOHP I design included allocation to other interventions (weight loss, stress management & supplements e.g.. fish oil)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	*"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."*
Blinding (performance bias and detection bias) All outcomes	Low risk	*"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."* *"In order to reduce observer bias, data collectors were blinded to the treatment assignment of the participants."* No - participants; Yes - data collectors; Unclear - data analysts.

TOHP I 1992 [18 mo]   *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	*"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."*
Selective reporting (reporting bias)	Low risk	All outcomes described in methods are reported in results.
Assessment of compliance?	Low risk	*"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."*
Groups balanced at baseline?	Low risk	*"Baseline characteristics were evenly distributed, except for age, which was higher in the sodium reduction intervention group"*
Intention to treat analysis?	Low risk	*"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?	High risk	Longest event follow up for mortality and CV morbidity was ~11.5 years but last stated diet advice stated as 18 months. No urinary sodium excretion data available at longest follow up

TOHP II 1997 [36 mo]

Methods	Individual RCT
Participants	**N Randomised:** 2382 (1191 intervention; 1191 control) **Baseline Blood Pressure:** Int: mean SBP 127.5 (SD 6.6), DBP mean 86.0 (SD 1.9); Ctrl: SBP mean 127.4 (SD 6.2), DBP SD 85.9 (SD 1.9) **Case mix:** Normotensives **Age:** Int.: mean 43.9 (SD 6.2); Ctrl.: mean 43.3 (SD 6.1) **CV diagnoses:** None **Percentage male:** 65.7% **Percentage white:** 79.3% **Inclusion/exclusion criteria:** **Inclusion:** 30-54 year old adults with no evidence of medically diagnosed hypertension who were moderately overweight (men: between 26.1-37.4kg/m^2; women: between 24.4-37.4kg/m^2), and had average DBP between 83-89mmHg, and an SBP <140mmHg. 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 nonmelanoma skin cancer during the past 5yrs, 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 >= 1.7mg/dL for men or 1.5mg/dL for women, or casual serum glucose >=200mg/dL. Current alcohol intake >21 drinks/wk. Pregnancy, or intent to become pregnant during the study. Plans to move or inability to cooperate.
Interventions	**Intervention** **Total duration:** 36 mths **Salt reduction/advice component:** 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 80mmol/24h. **Other:** The salt reduction intervention was combined with a weight loss intervention or alone. **Comparator** **Dietary:** No advice **Other:** Usual care or weight loss intervention alone.
Outcomes	All cause mortality CV morbidity (a composite of myocardial infarction, stroke, coronary revascularisation or CV death), BP, urinary excretion
Notes	This study had a 2x2 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 two sodium reduction interventions (alone or with weight loss) and for the two non-sodium reduction groups (usual care and weight loss alone)

TOHP II 1997 [36 mo] *(Continued)*

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	*"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 done by phone, clinics also were provided with sealed randomization envelopes for use when contact with the coordinating center was not possible."*
Blinding (performance bias and detection bias) All outcomes	Low risk	*"With respect to the determination of categorical end points, 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."* *"[Data collectors] were masked to participants' intervention assignments."* *No - participants; Yes - data collectors; Unclear - data analysts*
Incomplete outcome data (attrition bias) All outcomes	Low risk	*"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."*
Selective reporting (reporting bias)	Low risk	All outcomes described in methods are reported in results.
Assessment of compliance?	Low risk	*"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"*

TOHP II 1997 [36 mo] (*Continued*)

Groups balanced at baseline?	Low risk	*"Baseline characteristics were evenly distributed, except for age, which was higher in the sodium reduction intervention group"*
Intention to treat analysis?	Low risk	*"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 CV morbidity was ~8years but last stated diet advice stated as 36 months. No urinary sodium excretion data available at longest follow up

TOHP II 1997 [8 yrs]

Methods	Individual RCT
Participants	**N Randomised:** 2382 (1191 intervention; 1191 control) **Baseline Blood Pressure:** Int: mean SBP 127.5 (SD 6.6), DBP mean 86.0 (SD 1.9); Ctrl: SBP mean 127.4 (SD 6.2), DBP SD 85.9 (SD 1.9) **Case mix:** Normotensives **Age:** Int.: mean 43.9 (SD 6.2); Ctrl.: mean 43.3 (SD 6.1) **CV diagnoses:** None **Percentage male:** 65.7% **Percentage white:** 79.3% **Inclusion/exclusion criteria:** **Inclusion:** 30-54 year old adults with no evidence of medically diagnosed hypertension who were moderately overweight (men: between 26.1-37.4kg/m^2; women: between 24.4-37.4kg/m^2), and had average DBP between 83-89mmHg, and an SBP <140mmHg. 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 nonmelanoma skin cancer during the past 5yrs, 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 >= 1.7mg/dL for men or 1.5mg/dL for women, or casual serum glucose >=200mg/dL. Current alcohol intake >21 drinks/wk. Pregnancy, or intent to become pregnant during the study. Plans to move or inability to cooperate.
Interventions	**Intervention** **Total duration:** 36 mths **Salt reduction/advice component:** 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

TOHP II 1997 [8 yrs]   *(Continued)*

	group to 80mmol/24h. **Other:** The salt reduction intervention was combined with a weight loss intervention or alone. **Comparator** **Dietary:** No advice **Other:** Usual care or weight loss intervention alone.
Outcomes	All cause mortality CV morbidity (a composite of myocardial infarction, stroke, coronary revascularisation or CV death), BP, urinary excretion
Notes	This study had a 2x2 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 two sodium reduction interventions (alone or with weight loss) and for the two non-sodium reduction groups (usual care and weight loss alone)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	*"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 done by phone, clinics also were provided with sealed randomization envelopes for use when contact with the coordinating center was not possible."*
Blinding (performance bias and detection bias) All outcomes	Low risk	*"With respect to the determination of categorical end points, 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."* *"[Data collectors] were masked to participants' intervention assignments."* *No - participants; Yes - data collectors; Unclear - data analysts*
Incomplete outcome data (attrition bias) All outcomes	Low risk	*"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."*

Selective reporting (reporting bias)	Low risk	All outcomes described in methods are reported in results.
Assessment of compliance?	Low risk	*"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"*
Groups balanced at baseline?	Low risk	*"Baseline characteristics were evenly distributed, except for age, which was higher in the sodium reduction intervention group"*
Intention to treat analysis?	Low risk	*"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 CV morbidity was ~8years but last stated diet advice stated as 36 months. No urinary sodium excretion data available at longest follow up

TONE 1998 [12.7 yrs]

Methods	Individual RCT
Participants	**N Randomised:** 681 (N=340, intervention & N=341, control) - part of factorial design study **Baseline Blood Pressure:** SBP 128.0 (9.4), DBP 71.3 (7.3) mm Hg **Case mix:** Treated hypertensives **Age:** 65.8 (SD 4.6) **CV diagnoses:** None **Percentage male:** 53% **Percentage white:** 76% **Inclusion/exclusion criteria:** **Inclusion:** Healthy, aged 60-80yrs, SBP <145mm Hg &DBP <85mm Hg while taking a single antihypertensive medication or a single combination regimen consisting of a diuretic agent and a non-diuretic agent. Individuals taking two antihypertensive medications were also eligible if they were successfully weaned off one of them during the screening phase. Independencein activities of daily living. Capacity to alter diet and physical activity in accordance with the requirements of any TONE intervention.

TONE 1998 [12.7 yrs]   *(Continued)*

	Exclusion: Diagnosis or treatment of cancer within the last 5yrs; 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 6mths; "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 6mths) drug therapy for asthma or chronic obstructive lung disease; use of corticosteroid therapy for >1mth; serious mental or physical illness; unexplained or involuntary weight loss (>=4.5kg) during the previous year; BMI<21 in men or women, or >33 in men or >37 in women; serum creatinine >2mg/dL; non-fasting blood glucose level of >260mg/dL; hyperkalemia (>5.5mmol/L); anaemia (Hb level <110g/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:** 4mth "intensive" phase, plus 3mth "extended" phase, and then a maintenance phase (duration of this phase is unclear) **Salt reduction/advice component:** Individual & 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 24hr dietary sodium intake of 80mmol (1800mg) or less (as measured by 24hr 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 & cardiovascular), cardiovascular morbidity (a composite of myocardial infarction, stroke, coronary artery bypass graft (CABG)), BP, urinary sodium
Notes	Unpublished all cause mortality data at 12.7 yrs obtained from authors No data specifically reported on number of individuals who stopped antihypertensive medication in 2 groups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	*"Overweight participants were randomly assigned, in a 2x2 factorial design [...] Nonoverweight participants were randomly assigned [...]"* *"We used a variable block length randomization algorithm." (from*

TONE 1998 [12.7 yrs]   *(Continued)*

		investigators)
Allocation concealment (selection bias)	Low risk	*"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)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	*"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 and expected rate of 50% on the basis of chance)."* No - participants; Yes - data collectors; Unclear - data analysts.
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 impact of loss to follow-up.
Selective reporting (reporting bias)	Unclear risk	*The authors report that data was 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	*"Monitoring adherence (Reduced sodium life-style): Attendance; urinary data; food and behaviour records; adherence-related incentives. Monitoring adherence (Usual (control) life-style): Attendance."*
Groups balanced at baseline?	Low risk	*"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	*"Analyses were conducted on an intention-to-treat basis."*
Free from follow up bias?	High risk	Mortality outcome provided by authors at 12.7 yrs average follow up. No urinary sodium excretion data available at longest follow up

TONE 1998 [30 mo] *(Continued)*

Methods	Individual RCT
Participants	**N Randomised:** 681 (N=340, intervention & N=341, control) - part of factorial design study **Baseline Blood Pressure:** SBP 128.0 (9.4), DBP 71.3 (7.3) mm Hg **Case mix:** Treated hypertensives **Age:** 65.8 (SD 4.6) **CV diagnoses:** None **Percentage male:** 53% **Percentage white:** 76% **Inclusion/exclusion criteria:** **Inclusion:** Healthy, aged 60-80yrs, SBP <145mm Hg &DBP <85mm Hg while taking a single antihypertensive medication or a single combination regimen consisting of a diuretic agent and a non-diuretic agent. Individuals taking two antihypertensive medications were also eligible if they were successfully weaned off one of them during the screening phase. Independencein 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 5yrs; 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 6mths; "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 6mths) drug therapy for asthma or chronic obstructive lung disease; use of corticosteroid therapy for >1mth; serious mental or physical illness; unexplained or involuntary weight loss (>=4.5kg) during the previous year; BMI<21 in men or women, or >33 in men or >37 in women; serum creatinine >2mg/dL; non-fasting blood glucose level of >260mg/dL; hyperkalemia (>5.5mmol/L); anaemia (Hb level <110g/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:** 4mth "intensive" phase, plus 3mth "extended" phase, and then a maintenance phase (duration of this phase is unclear) **Salt reduction/advice component:** Individual & 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 24hr dietary sodium intake of 80mmol (1800mg) or less (as measured by 24hr 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

TONE 1998 [30 mo] *(Continued)*

Outcomes	Mortality (all cause & cardiovascular), cardiovascular morbidity (a composite of myocardial infarction, stroke, coronary artery bypass graft (CABG)), BP, urinary sodium
Notes	Unpublished all cause mortality data at 12.7 yrs obtained from authors No data specifically reported on number of individuals who stopped antihypertensive medication in 2 groups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	*"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)
Allocation concealment (selection bias)	Low risk	*"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)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	*"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 and expected rate of 50% on the basis of chance)."* No - participants; Yes - data collectors; Unclear - data analysts.
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 impact of loss to follow-up.
Selective reporting (reporting bias)	Unclear risk	*The authors report that data was 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*

TONE 1998 [30 mo] *(Continued)*

		are in a separate publication.
Assessment of compliance?	Low risk	*"Monitoring adherence (Reduced sodium life-style): Attendance; urinary data; food and behaviour records; adherence-related incentives.* *Monitoring adherence (Usual (control) life-style): Attendance."*
Groups balanced at baseline?	Low risk	*"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	*"Analyses were conducted on an intention-to-treat basis."*
Free from follow up bias?	High risk	Mortality outcome provided by authors at 12.7 yrs average follow up. No urinary sodium excretion data available at longest follow up

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

Study	Reason for exclusion
Bentley 2006	Inadequate follow up duration
Knuist 1998	Pregnant women
Koopman 1997	No appropriate outcomes
Licata 2003	Not dietary salt reduction intervention
van der Post 1997	Pregnant women
Velloso 1991	Inadequate follow up duration

DATA AND ANALYSES

Comparison 1. Reduced salt vs control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All cause mortality at end of trial	6	5808	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.84, 1.12]
1.1 Normotensive	3	3518	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.40, 1.12]
1.2 Hypertensive	2	2058	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.83, 1.13]
1.3 Heart Failure	1	232	Risk Ratio (M-H, Fixed, 95% CI)	2.59 [1.04, 6.44]
2 All cause mortality at longest follow up	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Normotensive	3	3518	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.58, 1.40]
2.2 Hypertensive	3	2349	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.83, 1.11]
2.3 Heart Failure	1	232	Risk Ratio (M-H, Fixed, 95% CI)	2.59 [1.04, 6.44]
3 CV mortality at longest follow up	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Hypertensive	2	2058	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.45, 1.05]
4 CV morbidity at longest follow up	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Normotensive	2	2505	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.42, 1.20]
4.2 Hypertensive	2	720	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.57, 1.23]
5 Systolic BP at end of trial	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 Normotensive	3	2079	Mean Difference (IV, Random, 95% CI)	-1.11 [-2.34, 0.11]
5.2 Hypertensive	2	675	Mean Difference (IV, Random, 95% CI)	-4.14 [-5.84, -2.43]
5.3 Heart failure	1	211	Mean Difference (IV, Random, 95% CI)	-4.0 [-7.27, -0.73]
6 Diastolic BP at end of trial	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 Normotensive	3	2079	Mean Difference (IV, Random, 95% CI)	-0.80 [-1.37, -0.23]
6.2 Hypertensive	2	675	Mean Difference (IV, Random, 95% CI)	-3.74 [-8.41, 0.93]
6.3 Heart failure	1	211	Mean Difference (IV, Random, 95% CI)	2.0 [-0.70, 4.70]
7 Urinary sodium excretion at end of trial	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
7.1 Normotensive	3	1812	Mean Difference (IV, Random, 95% CI)	-34.19 [-49.61, -18.78]
7.2 Hypertensive	2	806	Mean Difference (IV, Random, 95% CI)	-39.11 [-47.11, -31.11]
7.3 Heart failure	1	211	Mean Difference (IV, Random, 95% CI)	-27.0 [-29.46, -24.54]

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

Review: Reduced dietary salt for the prevention of cardiovascular disease

Comparison: 1 Reduced salt vs control

Outcome: 1 All cause mortality at end of trial

Study or subgroup	Favours reduced salt n/N	Favours control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Normotensive					
HPT 1989 [36 mo]	1/196	1/196		0.3 %	1.00 [0.06, 15.87]
TOHP I 1992 [18 mo]	6/327	12/417		3.7 %	0.64 [0.24, 1.68]
TOHP II 1997 [36 mo]	16/1191	24/1191		8.3 %	0.67 [0.36, 1.25]
Subtotal (95% CI)	**1714**	**1804**		**12.3 %**	**0.67 [0.40, 1.12]**
Total events: 23 (Favours reduced salt), 37 (Favours control)					
Heterogeneity: Chi² = 0.09, df = 2 (P = 0.96); I² =0.0%					
Test for overall effect: Z = 1.53 (P = 0.13)					
2 Hypertensive					
Chang 2006 [31 mo]	192/768	312/1213		84.0 %	0.97 [0.83, 1.14]
Morgan 1978 [7-71 mo]	4/35	5/42		1.6 %	0.96 [0.28, 3.30]
Subtotal (95% CI)	**803**	**1255**		**85.6 %**	**0.97 [0.83, 1.13]**
Total events: 196 (Favours reduced salt), 317 (Favours control)					
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.98); I² =0.0%					
Test for overall effect: Z = 0.36 (P = 0.72)					
3 Heart Failure					
Paterna 2008 [6.4 mo]	15/114	6/118		2.0 %	2.59 [1.04, 6.44]
Subtotal (95% CI)	**114**	**118**		**2.0 %**	**2.59 [1.04, 6.44]**
Total events: 15 (Favours reduced salt), 6 (Favours control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.05 (P = 0.041)					
Total (95% CI)	**2631**	**3177**		**100.0 %**	**0.97 [0.84, 1.12]**
Total events: 234 (Favours reduced salt), 360 (Favours control)					
Heterogeneity: Chi² = 6.55, df = 5 (P = 0.26); I² =24%					
Test for overall effect: Z = 0.45 (P = 0.65)					
Test for subgroup differences: Chi² = 6.46, df = 2 (P = 0.04), I² =69%					

0.01   0.1   1   10   100

Favours experimental   Favours control

Analysis 1.2. Comparison 1 Reduced salt vs control, Outcome 2 All cause mortality at longest follow up.

Review: Reduced dietary salt for the prevention of cardiovascular disease

Comparison: 1 Reduced salt vs control

Outcome: 2 All cause mortality at longest follow up

Study or subgroup	Favours reduced salt n/N	Favours control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Normotensive					
HPT 1989 [36 mo]	1/196	1/196		2.4 %	1.00 [0.06, 15.87]
TOHP I 1992 [11.5 yrs]	10/327	14/417		29.8 %	0.91 [0.41, 2.02]
TOHP II 1997 [8 yrs]	25/1191	28/1191		67.8 %	0.89 [0.52, 1.52]
Subtotal (95% CI)	**1714**	**1804**		**100.0 %**	**0.90 [0.58, 1.40]**
Total events: 36 (Favours reduced salt), 43 (Favours control)					
Heterogeneity: Chi² = 0.01, df = 2 (P = 1.00); I² =0.0%					
Test for overall effect: Z = 0.47 (P = 0.64)					
2 Hypertensive					
Chang 2006 [31 mo]	192/768	312/1213		88.2 %	0.97 [0.83, 1.14]
Morgan 1978 [7-71 mo]	4/35	5/42		1.7 %	0.96 [0.28, 3.30]
TONE 1998 [12.7 yrs]	24/144	28/147		10.1 %	0.88 [0.53, 1.43]
Subtotal (95% CI)	**947**	**1402**		**100.0 %**	**0.96 [0.83, 1.11]**
Total events: 220 (Favours reduced salt), 345 (Favours control)					
Heterogeneity: Chi² = 0.16, df = 2 (P = 0.92); I² =0.0%					
Test for overall effect: Z = 0.52 (P = 0.61)					
3 Heart Failure					
Paterna 2008 [6.4 mo]	15/114	6/118		100.0 %	2.59 [1.04, 6.44]
Subtotal (95% CI)	**114**	**118**		**100.0 %**	**2.59 [1.04, 6.44]**
Total events: 15 (Favours reduced salt), 6 (Favours control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.05 (P = 0.041)					

0.01   0.1   1   10   100

Favours reduced salt   Favours control

Analysis 1.3.   Comparison I Reduced salt vs control, Outcome 3 CV mortality at longest follow up.

Review: Reduced dietary salt for the prevention of cardiovascular disease

Comparison: I Reduced salt vs control

Outcome: 3 CV mortality at longest follow up

Study or subgroup	Favours reduced salt	Favours control	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% CI
I Hypertensive					
Chang 2006 [31 mo]	27/768	66/1213		96.6 %	0.65 [0.42, 1.00]
Morgan 1978 [7-71 mo]	3/35	2/42		3.4 %	1.80 [0.32, 10.17]

```
                        0.01    0.1      I      10    100
                        Favours reduced salt    Favours control
```

Analysis 1.4.   Comparison I Reduced salt vs control, Outcome 4 CV morbidity at longest follow up.

Review: Reduced dietary salt for the prevention of cardiovascular disease

Comparison: I Reduced salt vs control

Outcome: 4 CV morbidity at longest follow up

Study or subgroup	Favours reduced salt	Favours control	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Random,95% CI		M-H,Random,95% CI
I Normotensive					
TOHP I 1992 [11.5 yrs]	17/321	32/311		39.9 %	0.51 [0.29, 0.91]
TOHP II 1997 [8 yrs]	71/938	80/935		60.1 %	0.88 [0.65, 1.20]
Subtotal (95% CI)	**1259**	**1246**		**100.0 %**	**0.71 [0.42, 1.20]**

Total events: 88 (Favours reduced salt), 112 (Favours control)
Heterogeneity: Tau^2 = 0.09; Chi^2 = 2.71, df = I (P = 0.10); I^2 =63%
Test for overall effect: Z = 1.28 (P = 0.20)

2 Hypertensive					
Morgan 1978 [7-71 mo]	6/34	5/33		12.4 %	1.16 [0.39, 3.45]
TONE 1998 [30 mo]	36/322	46/331		87.6 %	0.80 [0.53, 1.21]
Subtotal (95% CI)	**356**	**364**		**100.0 %**	**0.84 [0.57, 1.23]**

Total events: 42 (Favours reduced salt), 51 (Favours control)
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.39, df = I (P = 0.53); I^2 =0.0%
Test for overall effect: Z = 0.88 (P = 0.38)

```
                        0.01    0.1      I      10    100
                        Favours reduced salt    Favours control
```

Analysis 1.5.   Comparison 1 Reduced salt vs control, Outcome 5 Systolic BP at end of trial.

Review: Reduced dietary salt for the prevention of cardiovascular disease

Comparison: 1 Reduced salt vs control

Outcome: 5 Systolic BP at end of trial

Study or subgroup	Favours reduced salt		Favours control		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
1 Normotensive							
HPT 1989 [36 mo]	174	-2.8 (6.6)	177	-3 (6.7)		30.3 %	0.20 [-1.19, 1.59]
TOHP I 1992 [18 mo]	304	-5.1 (7.9)	395	-3 (8.3)		33.6 %	-2.10 [-3.31, -0.89]
TOHP II 1997 [36 mo]	515	-0.7 (9)	514	0.6 (8.5)		36.1 %	-1.30 [-2.37, -0.23]
Subtotal (95% CI)	**993**		**1086**			**100.0 %**	**-1.11 [-2.34, 0.11]**
Heterogeneity: Tau² = 0.78; Chi² = 6.06, df = 2 (P = 0.05); I² =67%							
Test for overall effect: Z = 1.79 (P = 0.074)							
2 Hypertensive							
Morgan 1978 [24 mo]	31	-5.5 (22.3)	31	-4 (22.3)		2.4 %	-1.50 [-12.60, 9.60]
TONE 1998 [30 mo]	317	-4.6 (11.3)	296	-0.4 (10.5)		97.6 %	-4.20 [-5.93, -2.47]
Subtotal (95% CI)	**348**		**327**			**100.0 %**	**-4.14 [-5.84, -2.43]**
Heterogeneity: Tau² = 0.0; Chi² = 0.22, df = 1 (P = 0.64); I² =0.0%							
Test for overall effect: Z = 4.75 (P < 0.00001)							
3 Heart failure							
Paterna 2008 [6.4 mo]	99	107 (13)	112	111 (11)		100.0 %	-4.00 [-7.27, -0.73]
Subtotal (95% CI)	**99**		**112**			**100.0 %**	**-4.00 [-7.27, -0.73]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.40 (P = 0.017)							

-10   -5   0   5   10

Favours experimental   Favours control

Analysis 1.6.   Comparison 1 Reduced salt vs control, Outcome 6 Diastolic BP at end of trial.

Review: Reduced dietary salt for the prevention of cardiovascular disease

Comparison: 1 Reduced salt vs control
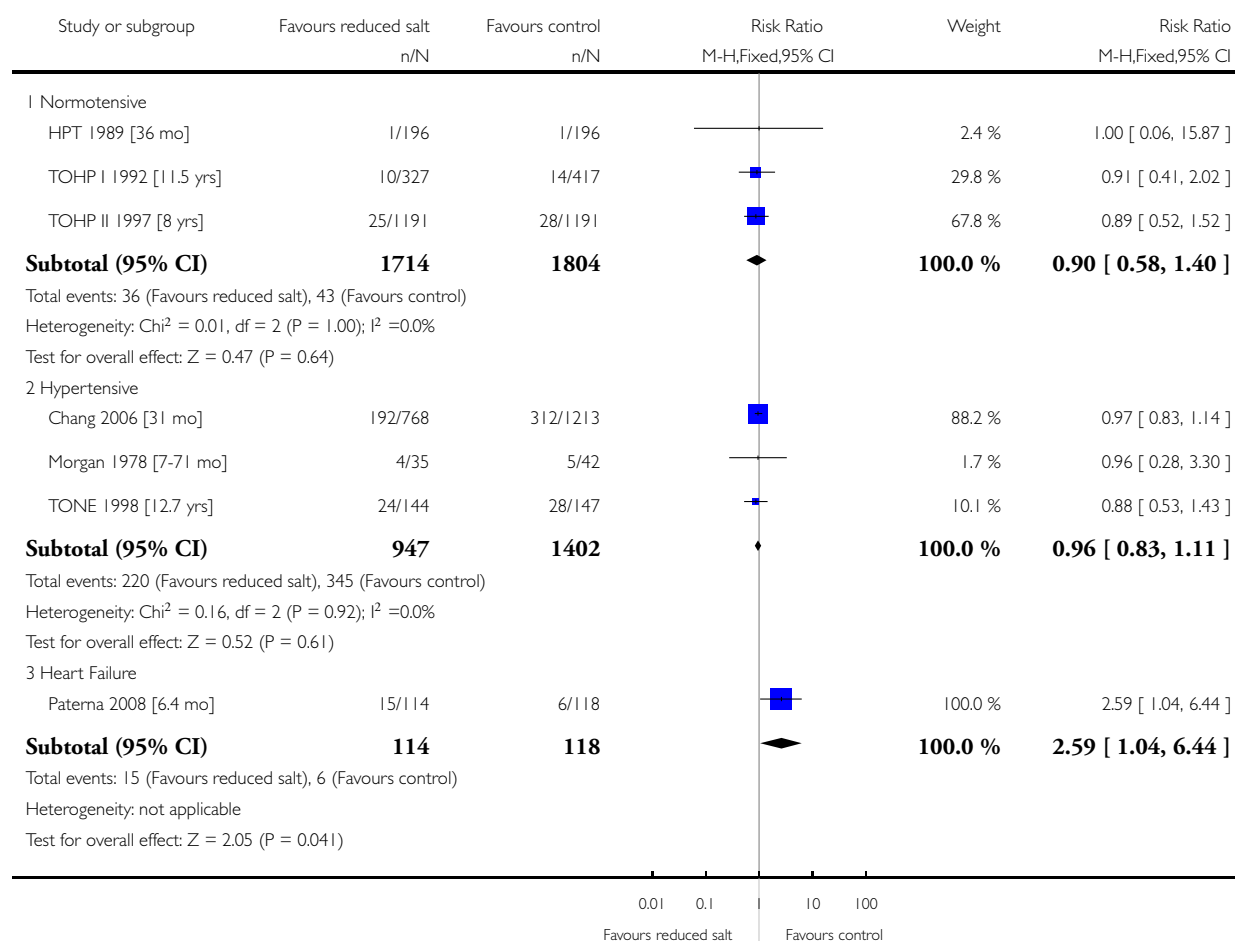
Outcome: 6 Diastolic BP at end of trial

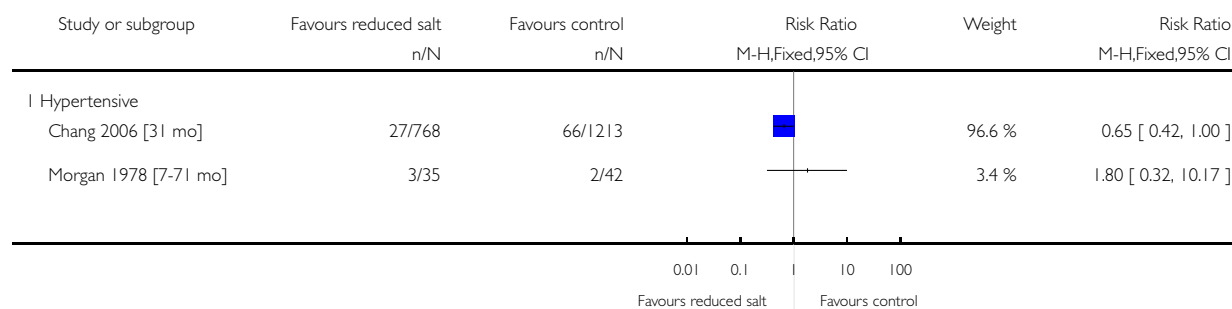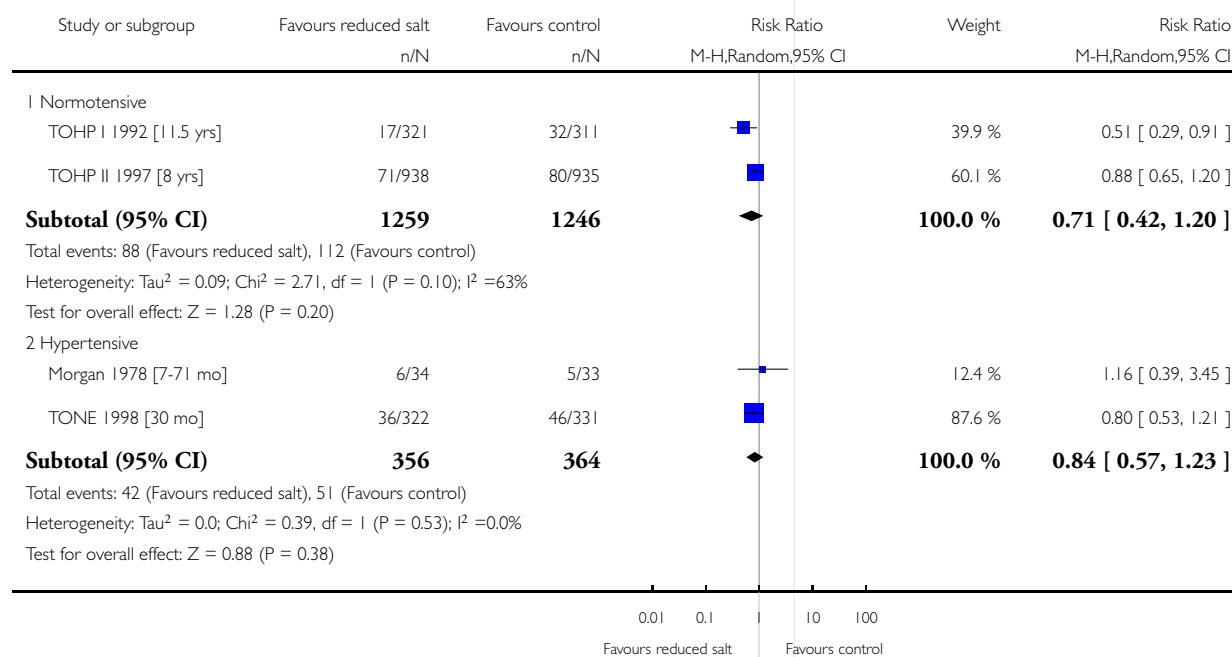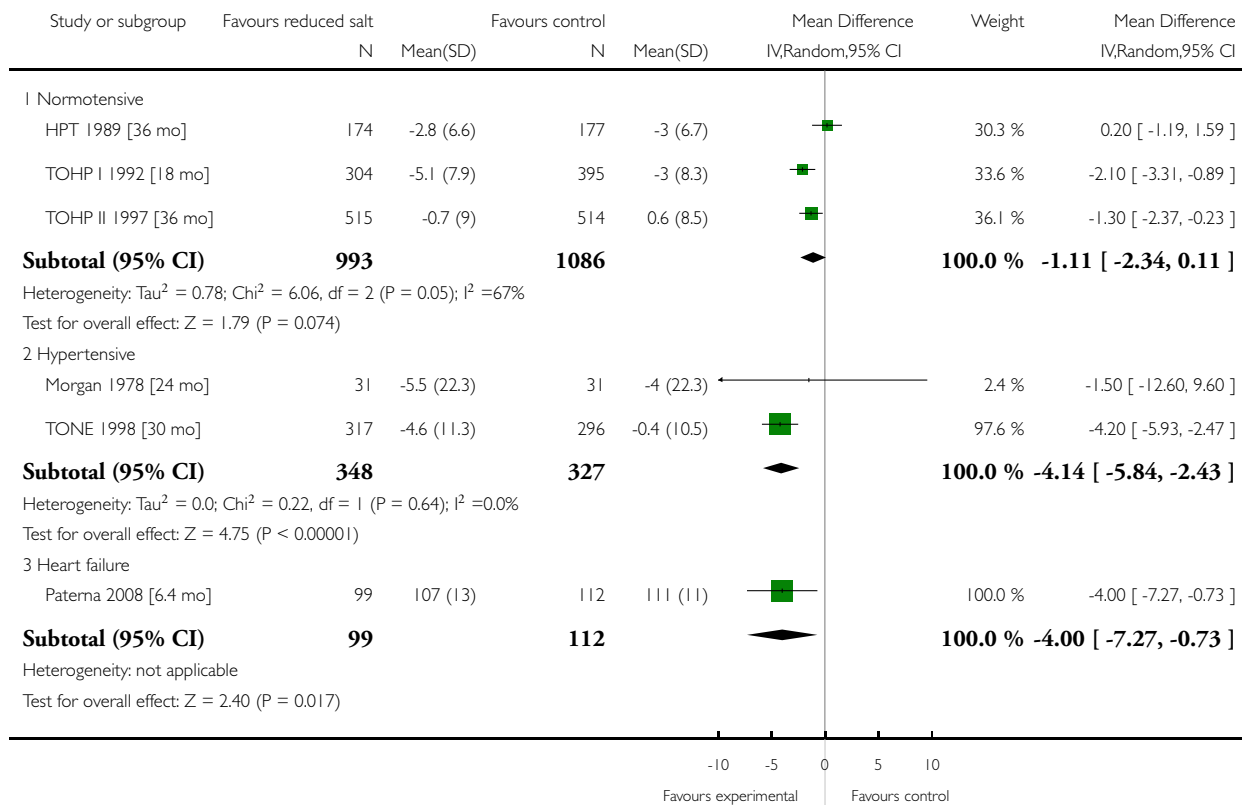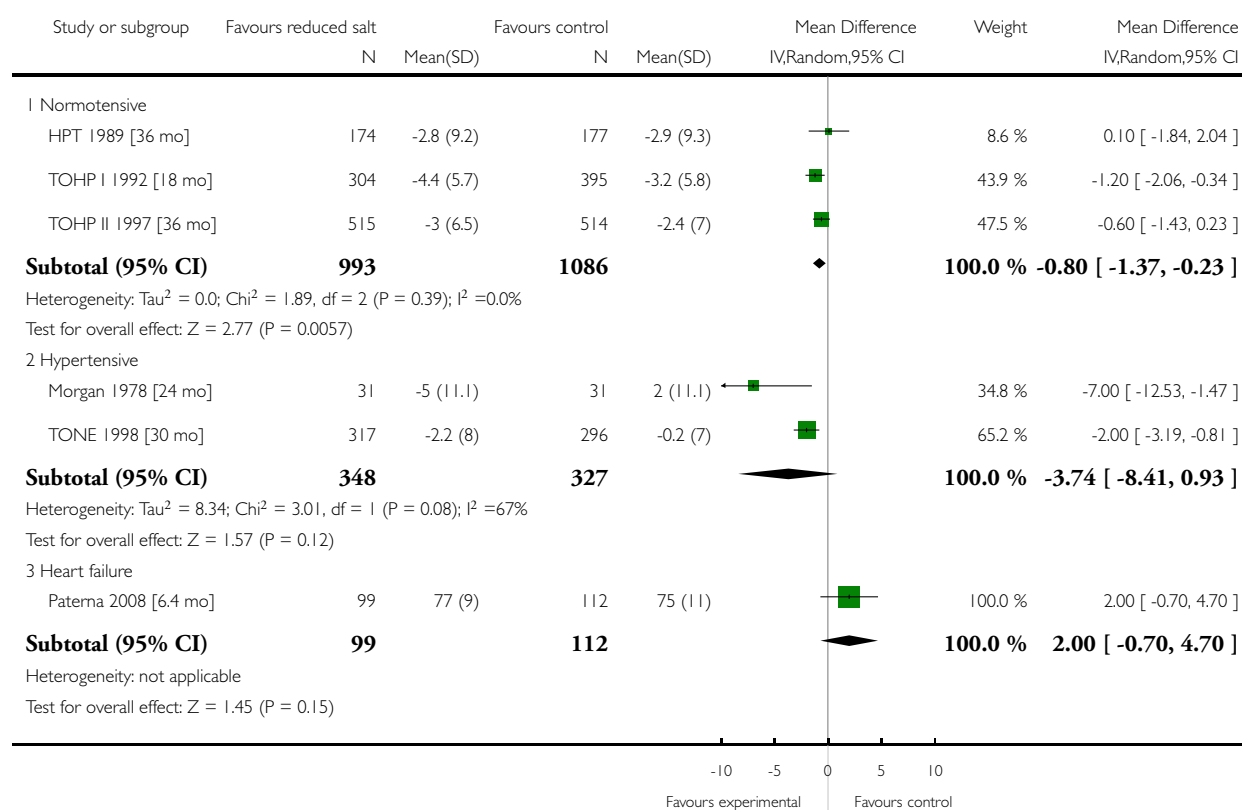| Study or subgroup	Favours reduced salt		Favours control		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
1 Normotensive							
HPT 1989 [36 mo]	174	-2.8 (9.2)	177	-2.9 (9.3)		8.6 %	0.10 [-1.84, 2.04]
TOHP I 1992 [18 mo]	304	-4.4 (5.7)	395	-3.2 (5.8)		43.9 %	-1.20 [-2.06, -0.34]
TOHP II 1997 [36 mo]	515	-3 (6.5)	514	-2.4 (7)		47.5 %	-0.60 [-1.43, 0.23]
Subtotal (95% CI)	**993**		**1086**			**100.0 %**	**-0.80 [-1.37, -0.23]**
Heterogeneity: Tau² = 0.0; Chi² = 1.89, df = 2 (P = 0.39); I² =0.0%							
Test for overall effect: Z = 2.77 (P = 0.0057)							
2 Hypertensive							
Morgan 1978 [24 mo]	31	-5 (11.1)	31	2 (11.1)		34.8 %	-7.00 [-12.53, -1.47]
TONE 1998 [30 mo]	317	-2.2 (8)	296	-0.2 (7)		65.2 %	-2.00 [-3.19, -0.81]
Subtotal (95% CI)	**348**		**327**			**100.0 %**	**-3.74 [-8.41, 0.93]**
Heterogeneity: Tau² = 8.34; Chi² = 3.01, df = 1 (P = 0.08); I² =67%							
Test for overall effect: Z = 1.57 (P = 0.12)							
3 Heart failure							
Paterna 2008 [6.4 mo]	99	77 (9)	112	75 (11)		100.0 %	2.00 [-0.70, 4.70]
Subtotal (95% CI)	**99**		**112**			**100.0 %**	**2.00 [-0.70, 4.70]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.45 (P = 0.15)							

```
        -10    -5      0      5     10
        Favours experimental   Favours control
```
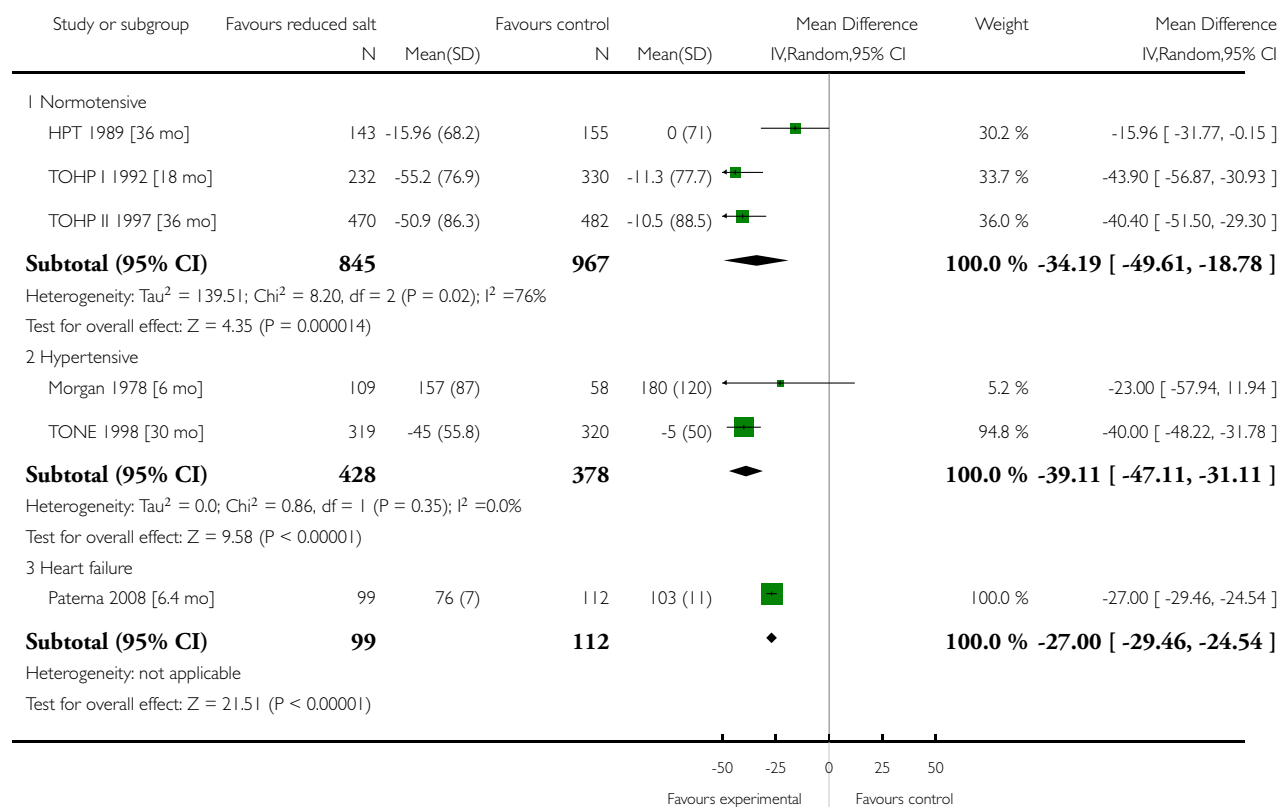
Analysis 1.7. Comparison I Reduced salt vs control, Outcome 7 Urinary sodium excretion at end of trial.

Review: Reduced dietary salt for the prevention of cardiovascular disease

Comparison: I Reduced salt vs control

Outcome: 7 Urinary sodium excretion at end of trial

Study or subgroup	Favours reduced salt		Favours control		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
I Normotensive							
HPT 1989 [36 mo]	143	-15.96 (68.2)	155	0 (71)		30.2 %	-15.96 [-31.77, -0.15]
TOHP I 1992 [18 mo]	232	-55.2 (76.9)	330	-11.3 (77.7)		33.7 %	-43.90 [-56.87, -30.93]
TOHP II 1997 [36 mo]	470	-50.9 (86.3)	482	-10.5 (88.5)		36.0 %	-40.40 [-51.50, -29.30]
Subtotal (95% CI)	**845**		**967**			**100.0 %**	**-34.19 [-49.61, -18.78]**
Heterogeneity: Tau² = 139.51; Chi² = 8.20, df = 2 (P = 0.02); I² =76%							
Test for overall effect: Z = 4.35 (P = 0.000014)							
2 Hypertensive							
Morgan 1978 [6 mo]	109	157 (87)	58	180 (120)		5.2 %	-23.00 [-57.94, 11.94]
TONE 1998 [30 mo]	319	-45 (55.8)	320	-5 (50)		94.8 %	-40.00 [-48.22, -31.78]
Subtotal (95% CI)	**428**		**378**			**100.0 %**	**-39.11 [-47.11, -31.11]**
Heterogeneity: Tau² = 0.0; Chi² = 0.86, df = 1 (P = 0.35); I² =0.0%							
Test for overall effect: Z = 9.58 (P < 0.00001)							
3 Heart failure							
Paterna 2008 [6.4 mo]	99	76 (7)	112	103 (11)		100.0 %	-27.00 [-29.46, -24.54]
Subtotal (95% CI)	**99**		**112**			**100.0 %**	**-27.00 [-29.46, -24.54]**
Heterogeneity: not applicable							
Test for overall effect: Z = 21.51 (P < 0.00001)							

```
        -50    -25     0     25    50
     Favours experimental   Favours control
```

A P P E N D I C E S

Appendix 1. Search strategies

The Cochrane Library 2008 Issue 4

Results for CENTRAL, Health Technology Assessment (HTA) and Database of Abstracts of Reviews of Effect (DARE)

Search Date: 03 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

#13 (stroke* or poststroke* or cva*):ti,ab

#14 (cerebrovascular* or (cerebral adj vascular)):ti,ab

#15 (cerebral or cerebellar or brain* or vertebrobasilar):ti,ab

#16 (infarct* or isch*emi* or thrombo* or emboli* or apoplexy):ti,ab

#17 (cerebral or intracerebral or intracranial or brain* or parenchymal or intraventricular or cerebellar or infratentorial or supratentorial or subarachnoid):ti,ab

#18 (haemorrhage or hemorrhage or bleed* or haematoma or hematoma or aneurysm):ti,ab

#19 (#15 AND #16)

#20 (#17 AND #18)

#21 (trans* isch*emic attack*):ti,ab

#22 brain attack:ti,ab

#23 MeSH descriptor Hemiplegia explode all trees

#24 (hemipleg* or hemipar* or post NEXT stroke):ti,ab

#25 (#21 OR #22 OR #23 OR #24)

#26 (#12 OR #13 OR #14 OR #19 OR #20 OR #25)

#27 MeSH descriptor Intermittent Claudication explode all trees

#28 claudica*:ti,ab

#29 MeSH descriptor Peripheral Vascular Diseases explode all trees

#30 MeSH descriptor Vascular Diseases, this term only

#31 (peripher* NEAR/3 (occlu* or arteri* or vascular)):ti,ab

#32 (arterial NEAR/3 (obstruct* or occlus*)):ti,ab

#33 MeSH descriptor Arteriosclerosis Obliterans, this term only

#34 MeSH descriptor Atherosclerosis, this term only

#35 MeSH descriptor Arterial Occlusive Diseases, this term only

#36 ((leg or limb) NEAR/3 (isch*emia or occlusi*)):ti,ab

#37 (arteriosclerosis or atherosclerosis):ti,ab

#38 MeSH descriptor Femoral Artery, this term only

#39 MeSH descriptor Popliteal Artery, this term only

#40 MeSH descriptor Iliac Artery, this term only

#41 ((femoral or renal or iliac) NEAR/3 artery):ti,ab

#42 (occlu* or obstruct*):ti,ab

#43 (#38 OR #39 OR #40 OR #41)

#44 (#42 AND #43)
#45 (#27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37)
#46 (#44 OR #45)
#47 MeSH descriptor Heart Failure explode all trees
#48 MeSH descriptor Myocardial Ischemia explode all trees
#49 angina:ti,ab
#50 (angor pectoris):ti,ab
#51 myocard*:ti,ab
#52 MeSH descriptor Ventricular Dysfunction explode all trees
#53 (ventricular NEAR/2 failure):ti,ab
#54 revascular*:ti,ab
#55 (isch*mi* NEAR/3 heart):ti,ab,kw
#56 coronary:ti,ab,kw
#57 MeSH descriptor Angioplasty explode all trees
#58 MeSH descriptor Angioplasty, Transluminal, Percutaneous Coronary, this term only
#59 (PTCA or angioplast*):ti,ab
#60 MeSH descriptor Myocardial Revascularization, this term only
#61 stenocardia*:ti,ab
#62 (heart NEAR/3 decompensation):ti,ab
#63 MeSH descriptor Myocardial Infarction explode all trees
#64 (heart NEAR/3 infarc*):ti,ab
#65 (heart NEAR/3 failure):ti,ab,kw
#66 cardiac*:ti,ab
#67 CABG:ti,ab
#68 MeSH descriptor Coronary Artery Bypass explode all trees
#69 (heart NEAR/3 bypass):ti,ab,kw
#70 (#47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60)
#71 (#61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69)
#72 (#70 OR #71)
#73 (cardiovascular NEAR/3 (outcome* or morbidity or event*)):ti,ab,kw
#74 (hospital* or admission*):ti,ab
#75 (#73 OR #74)
#76 (#8 OR #11 OR #26 OR #46 OR #72 OR #75)
#77 MeSH descriptor Sodium, Dietary explode all trees
#78 MeSH descriptor Diet, Sodium-Restricted explode all trees
#79 MeSH descriptor Sodium, this term only
#80 MeSH descriptor Sodium Chloride explode all trees
#81 (#79 OR #80)
#82 (restrict* or low* or reduc* or intak* or added or diet):ti,ab
#83 (consum* or excess* or increas* or high*):ti,ab
#84 (#82 OR #83)
#85 (#84 AND #81)
#86 (urin* or excret*):ti,ab
#87 (#80 AND #86)
#88 (restrict* NEAR/3 (salt or sodium)):ti,ab,kw
#89 (low* NEAR/3 (salt or sodium)):ti,ab,kw
#90 (reduc* NEAR/3 (salt or sodium)):ti,ab,kw
#91 (intak* NEAR/3 (salt or sodium)):ti,ab,kw
#92 (change NEAR/3 (salt or sodium)):ti,ab,kw
#93 (consum* NEAR/3 (salt or sodium)):ti,ab,kw
#94 (excess* NEAR/3 (salt or sodium)):ti,ab,kw
#95 (sodium NEAR/3 (urin* or excret*)):ti,ab,kw
#96 (increas* NEAR/3 (salt or sodium)):ti,ab,kw

#97 (high* NEAR/3 (salt or sodium)):ti,ab,kw
#98 (added NEAR/3 (salt or sodium or food)):ti,ab,kw
#99 (diet* and (salt or sodium)):ti,ab,kw
#100 (#77 OR #78 OR #85 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94 OR #95 OR #96 OR #97 OR #98 OR #99)
#101 (#76 AND #100)

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/
12 Sodium Chloride/
13 11 or 12
14 (restrict* or low* or reduc* or intak* or added).tw. or diet*.mp.
15 (consum* or excess* or increas* or high*).tw.
16 14 or 15
17 13 and 16
18 (urin* or excret*).tw.
19 12 and 18
20 (restrict* adj3 (salt or sodium)).mp.
21 (low* adj3 (salt or sodium)).mp.
22 (reduc* adj3 (salt or sodium)).mp.
23 (intak* adj3 (salt or sodium)).mp.
24 (change adj3 (salt or sodium)).mp.
25 (consum* adj3 (salt or sodium)).mp.
26 (excess* adj3 (salt or sodium)).mp.
27 (sodium adj3 (urin* or excret*)).mp.
28 (increas* adj3 (salt or sodium)).mp.
29 (high* adj3 (salt or sodium)).mp.
30 (added adj3 (salt or sodium or food)).mp.
31 (diet* and (salt or sodium)).tw.
32 9 or 10 or 17 or 19 or (or/20-31)
33 exp Heart Arrest/
34 (cardiac adj3 arrest*).mp.
35 (heart adj3 arrest*).mp.
36 (cardiopulmonary adj3 arrest*).mp.
37 (sudden adj3 death).mp.
38 asystole*.mp.
39 (myocard* adj2 contract*).mp.
40 or/33-39
41 (death* or died or dead or fatal*4).ti,ab.
42 mortality.ti,ab.
43 41 or 42

44 exp Cerebrovascular Disorders/

45 (stroke* or poststroke* or cva*).tw.

46 (cerebrovascular* or (cerebral adj vascular)).tw.

47 (cerebral or cerebellar or brain* or vertebrobasilar).tw.

48 (infarct* or isch?emi* or thrombo* or emboli* or apoplexy).tw.

49 (cerebral or intracerebral or intracranial or brain$ or parenchymal or intraventricular or cerebellar or infratentorial or supratentorial or subarachnoid).tw.

50 (haemorrhage or hemorrhage or bleed$ or haematoma or hematoma or aneurysm).tw.

51 48 and 47

52 49 and 50

53 trans* isch?emic attack*.tw.

54 brain attack.tw.

55 hemiplegia/

56 (hemipleg* or hemipar* or post-stroke).tw.

57 54 or 55 or 56 or 53

58 51 or 44 or 52 or 46 or 57 or 45

59 Intermittent Claudication/

60 claudica*.ti,ab.

61 exp Peripheral Vascular Diseases/

62 Vascular Diseases/

63 (peripher* adj3 (occlu* or arteri* or vascular)).ti,ab.

64 (arterial adj3 (obstruct* or occlus*)).ti,ab.

65 Arteriosclerosis Obliterans/

66 Atherosclerosis/

67 ARTERIAL OCCLUSIVE DISEASES/

68 ((leg or limb) adj3 (isch?emia or occlusi*)).ti,ab.

69 (arteriosclerosis or atherosclerosis).ti,ab.

70 Femoral Artery/

71 POPLITEAL ARTERY/

72 ILIAC ARTERY/

73 ((femoral or renal or iliac) adj3 artery).ti,ab.

74 (occlu* or obstruct*).ti,ab.

75 73 or 72 or 71 or 70

76 75 and 74

77 or/59-69

78 76 or 77

79 40 or 43 or 58 or 78

80 exp Heart Failure/

81 exp Myocardial Ischemia/

82 angina.tw.

83 angor pectoris.tw.

84 myocard*.tw.

85 Ventricular Dysfunction/

86 (ventricular adj2 failure).tw.

87 revascular*.ti,ab.

88 (isch?mi* adj3 heart).ti,ab,sh.

89 coronary.ti,ab,sh.

90 exp Angioplasty/

91 Angioplasty, Transluminal, Percutaneous Coronary/

92 (PTCA or angioplast*).tw.

93 Myocardial Revascularization/

94 stenocardia*.tw.

95 (heart adj3 decompensation).tw.

96 exp Myocardial Infarction/
97 (heart adj3 infarc*).tw.
98 (heart adj3 failure).ti,ab,sh.
99 cardiac*.tw.
100 CABG.tw.
101 exp coronary artery bypass/
102 (heart adj3 bypass).tw,sh.
103 or/80-102
104 (cardiovascular adj3 (outcome* or morbidity or event*)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
105 (hospital* or admission*).tw.
106 104 or 105
107 103 or 106 or 58 or 78 or 43 or 40
108 32 and 107
109 (animals not humans).sh.
110 exp Case Reports/
111 letter.pt.
112 (news or editorial).pt.
113 111 or 110 or 112
114 108 not 113
115 114 not 109
116 8 and 115

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/

48 (hemipleg* or hemipar* or post-stroke).tw.

49 46 or 47 or 48 or 45

50 43 or 36 or 44 or 38 or 49 or 37

51 Intermittent Claudication/

52 claudica*.ti,ab.

53 exp Peripheral Vascular Disease/

54 Vascular Disease/

55 (peripher* adj3 (occlu* or arteri* or vascular)).ti,ab.

56 (arterial adj3 (obstruct* or occlus*)).ti,ab.

57 Arteriosclerosis Obliterans/

58 Atherosclerosis/

59 Peripheral Occlusive Artery Disease/

60 ((leg or limb) adj3 (isch?emia or occlusi*)).ti,ab.

61 (arteriosclerosis or atherosclerosis).ti,ab.

62 Femoral Artery/

63 POPLITEAL ARTERY/

64 ILIAC ARTERY/

65 ((femoral or renal or iliac) adj3 artery).ti,ab.

66 (occlu* or obstruct*).ti,ab.

67 65 or 64 or 63 or 62

68 67 and 66

69 or/51-61

70 68 or 69

71 exp Heart Failure/

72 exp Heart Muscle Ischemia/

73 angina.tw.

74 angor pectoris.tw.

75 myocard*.tw.

76 Heart Ventricle Function/

77 (ventricular adj2 failure).tw.

78 revascular*.ti,ab.

79 (isch?mi* adj3 heart).ti,ab,sh.

80 coronary.ti,ab,sh.
81 exp Angioplasty/
82 exp Transluminal Coronary Angioplasty/
83 (PTCA or angioplast*).tw.
84 exp Heart Muscle Revascularization/
85 stenocardia*.tw.
86 (heart adj3 decompensation).tw.
87 exp Heart Infarction/
88 (heart adj3 infarc*).tw.
89 (heart adj3 failure).ti,ab,sh.
90 cardiac*.tw.
91 CABG.tw.
92 exp Coronary Artery Bypass Graft/
93 (heart adj3 bypass).tw,sh.
94 or/71-93
95 (cardiovascular adj3 (outcome* or morbidity or event*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
96 (hospital* or admission*).tw.
97 95 or 96
98 94 or 97 or 50 or 70 or 35 or 32
99 24 and 98
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

Search Date:
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 (reduc* 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
88 limit 87 to human

CINAHL

WEB 2.0
Search Date: 03 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)]

HISTORY

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CONTRIBUTIONS OF AUTHORS

All the authors were involved in the design of the review. Tiffany Moxham developed the search strategy. Kate Ashton and Rod Taylor will independently select studies for inclusion. Data extraction was carried out by Kate Ashton and Rod Taylor. Synthesis/analysis was carried out by Rod Taylor and Kate Ashton. Rod Taylor and Kate Ashton wrote the first draft of the review, with contributions and comments from all other co-authors.

DECLARATIONS OF INTEREST

None known

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Internal sources

- No sources of support supplied

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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

- Studies reporting death or cardiovascular outcomes were included regardless of the number of events in intervention and controls.