

Advice to reduce dietary salt for prevention of cardiovascular disease (Review)

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[Intervention Review]

Advice to reduce dietary salt for prevention of cardiovascular disease

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ABSTRACT

Background

Restricting sodium intake in hypertensive patients over short periods of time reduces blood pressure. Long term effects (on mortality, morbidity or blood pressure) of advice to reduce salt in patients with elevated or normal blood pressure are unclear.

Objectives

To assess in adults the long term effects (mortality, cardiovascular events, blood pressure, quality of life, weight, urinary sodium excretion, other nutrients and use of anti-hypertensive medications) of advice to restrict dietary sodium using all relevant randomised controlled trials.

Search methods

The Cochrane Library, MEDLINE, EMBASE, bibliographies of included studies and related systematic reviews were searched for unconfounded randomised trials in healthy adults aiming to reduce sodium intake over at least 6 months. Attempts were made to trace unpublished or missed studies and authors of all included trials were contacted. There were no language restrictions.

Selection criteria

Inclusion decisions were independently duplicated and based on the following criteria: 1) randomisation was adequate; 2) there was a usual or control diet group; 3) the intervention aimed to reduce sodium intake; 4) the intervention was not multifactorial; 5) the participants were not children, acutely ill, pregnant or institutionalised; 6) follow-up was at least 26 weeks; 7) data on any of the outcomes of interest were available.

Data collection and analysis

Decisions on validity and data extraction were made independently by two reviewers, disagreements were resolved by discussion or if necessary by a third reviewer. Random effects meta-analysis, sub-grouping, sensitivity analysis and meta-regression were performed.

Main results

Three trials in normotensives (n=2326), five in untreated hypertensives (n=387) and three in treated hypertensives (n=801) were included, with follow up from six months to seven years. The large, high quality (and therefore most informative) studies used intensive behavioural interventions.

Deaths and cardiovascular events were inconsistently defined and reported; only 17 deaths equally distributed between intervention and control groups occurred. Systolic and diastolic blood pressures were reduced at 13 to 60 months in those given low sodium advice as compared with controls (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), as was urinary 24 hour sodium excretion (by 35.5 mmol/ 24 hours, 95% CI 47.2 to 23.9). Degree of reduction in sodium intake and change in blood pressure were not related. People on anti-hypertensive medications were able to stop their medication more often on a reduced sodium diet as compared with controls, while maintaining similar blood pressure control.

Authors' conclusions

Intensive interventions, unsuited to primary care or population prevention programmes, provide only minimal reductions in blood pressure during long-term trials. Further evaluations to assess effects on morbidity and mortality outcomes are needed for populations as a whole and for patients with elevated blood pressure.

A low sodium diet may help in maintenance of lower blood pressure following withdrawal of antihypertensives. If this is confirmed, with no increase in cardiovascular events, then targeting of comprehensive dietary and behavioural programmes in patients with elevated blood pressure requiring drug treatment would be justified.

PLAIN LANGUAGE SUMMARY

The long term effects of advice to cut down on salt in food on deaths, cardiovascular disease and blood pressure in adults

Intensive support and encouragement to reduce salt intake did lead to reduction in salt eaten. It also lowered blood pressure but only by a small amount (about 1 mmHg for systolic blood pressure, less for diastolic) after more than a year. This reduction was not enough to expect an important health benefit. It was also very hard to keep to a low salt diet. However, the reduction in blood pressure appeared larger for people with higher blood pressure.

There was not enough information to assess the effect of these changes in salt intake on health or deaths.

Evidence from a large and small trial showed that advice to reduce salt helps to maintain lower blood pressure following withdrawal of antihypertensive medication. If this is confirmed, with no increase in cardiovascular events, then comprehensive dietary and behavioural programmes in patients with elevated blood pressure requiring drug treatment would be justified.

See also the Cochrane review of short-term salt reduction trials: [Jurgens 2003](#).

BACKGROUND

There is evidence from published systematic reviews that restricting sodium intake in people with elevated blood pressure leads to reductions in blood pressure of about 4 mm hg systolic and 2 mm hg diastolic ([Law 1991](#); [Midgley 1996](#); [Cutler 1997](#); [Graudal 1998](#); [Alam 1999](#); [Jurgens 2003](#)). However, within these reviews many included trials are short term, neither allowing for complete adjustment of blood pressure to altered sodium intake or to reduced motivation for following dietary restrictions over time. Also,

some trials increased sodium intake in one arm and compared this with a reduced sodium intake in the other arm and so do not estimate likely effects of cutting down on sodium in a normal diet. In addition, some reviews suggest that the level of blood pressure reduction achieved over a longer period in free-living adults is less impressive than in the short term ([Ebrahim 1996](#); [Ebrahim 1998](#); [Graudal 1998](#)).

A decrease in blood pressure is only important if it results in a

decrease in cardiovascular events and deaths. The published systematic reviews on the effect of salt restriction on blood pressure and other risk factor outcomes have expressed different interpretations with regard to the significance of these changes in relation to cardiovascular events and deaths. This systematic review and meta-analysis aimed to draw together information on the effect of long-term dietary salt reduction on health outcomes.

OBJECTIVES

This systematic review aimed to study the effects of restricting sodium intake over at least six months in free-living adults, compared with a normal or usual sodium intake.

The specific objectives were to assess, in people with normal and elevated blood pressure, the effect of advice and/or support to reduce dietary sodium intake, on deaths and cardiovascular events; number and dose of anti-hypertensive medications used; quality of life; weight; systolic and diastolic blood pressure; and urinary sodium excretion and other nutrient intakes in free-living adults at least six months after the initial intervention was commenced.

The effects of potential modifiers of salt restriction (i.e. initial level of blood pressure, categorization into normal or elevated blood pressure, degree of sodium reduction, gender, race and age) were also investigated.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled clinical trials (randomisation of individuals, or into at least six clusters) with at least 26 weeks of follow up from initiation of intervention.

Types of participants

Studies of adults (16 years or older) with normal or raised blood pressure were accepted. Participants were of either gender, but those institutionalised, acutely ill or pregnant were excluded.

Types of interventions

The interventions included were designed to reduce sodium intake. The control group received a placebo intervention or no active intervention. Studies were not included if they used a multiple risk factor intervention intending to alter lifestyle or dietary factors other than sodium (unless the effect of the low sodium diet

could be separated out from the other interventions). For example, interventions that aimed to reduce sodium and increase potassium were excluded, whilst in factorial interventions aiming to reduce sodium intake and reduce weight, the low sodium arm (without weight intervention) was compared to the control group (without sodium or weight interventions).

Types of outcome measures

Primary outcomes:

The main outcomes were total mortality and combined cardiovascular events (including fatal and non-fatal myocardial infarction, stroke, angina, heart failure, peripheral vascular events, sudden death and non-scheduled cardiovascular interventions - coronary artery bypass surgery or angioplasty). Both of these outcomes were examined as relative risk in the intervention vs control group at the latest time point available.

Secondary outcomes:

Changes in systolic and diastolic blood pressure (mm Hg), quality of life, weight (kg), nutrient intakes, urinary sodium excretion (mmol/24 hours) and numbers and doses of anti-hypertensive medication used. These were assessed at intermediate (6 months to and including 12 months), late (13 to 60 months) and very late follow up (over 60 months).

Search methods for identification of studies

Two searches were conducted, titles and abstracts scanned and papers retrieved independently of each other. For the first search (LH) the results of a previous large-scale search (Hooper 2000) for dietary trials were used. This search scanned for trials on any dietary intervention and cardiovascular disease and included searching of the Cochrane Library, MEDLINE, EMBASE, CAB Abstracts, CVRCT registry, SIGLE to May 1998 plus bibliographies of collected papers and reviews. It was updated for this review by searching for systematic reviews or randomised controlled trials on sodium manipulation and blood pressure in The Cochrane Library and MEDLINE (using randomised controlled trial filters):

DIET-SODIUM-RESTRICTED*:ME

SODIUM-DIETARY*:ME

(DIET* near (SALT* or SODIUM*))

((#1 or #2) or #3)

HYPERTENSION*:ME

HYPERTENS*

(#5 or #6)

(#4 and #7)

The second search (CB) looked specifically for trials on salt or sodium restriction and blood pressure, and was run on MEDLINE, EMBASE and The Cochrane Library. The Cochrane search strategy (below) was used in conjunction with special search filters to find randomised controlled trials on MEDLINE and EMBASE. HYPERTENS*

HYPERTENSION*:ME
 (BLOOD near PRESSURE)
 ((#1 or #2) or #3)
 DIET-SODIUM-RESTRICTED*:ME
 SODIUM-CHLORIDE*:ME
 (DIET* near ((SALT or SODIUM) or CHANGE))
 (DIET* near (THERAPY or INTERVENTION))
 (RESTRICT* near (SALT or SODIUM))
 (LOWER* near (SALT or SODIUM))
 (INTAKE* near (SALT or SODIUM))
 (REDUC* near (SALT or SODIUM))
 ((((((#5 or #6) or #7) or #8) or #9) or #10) or #11) or #12)
 (#4 and #13)

Neither search was limited by language. Systematic reviews on dietary sodium and blood pressure were retrieved and bibliographies of these and included studies scanned for further trials of at least six months duration. Attempts were made to contact authors of all included studies for details of further relevant trials that may have been missed (either published or unpublished).

Data collection and analysis

Two reviewers (LH, CB) independently screened each article or trial report with regard to the inclusion criteria. Articles were only rejected on initial screen if the reviewer could determine from the title and abstract that the article was not a report of a randomised controlled trial; or the trial did not address a low sodium diet, or the trial was exclusively in children less than 16 years old, pregnant women or the critically ill; or the control group was not on usual diet or placebo intervention; or the trial was of less than six months duration; or the intervention was multi-factorial. When a title or abstract could not be rejected with certainty the full text of the article was obtained for further evaluation.

Data extraction and quality assessment were performed independently by two reviewers (CB, LH) onto forms designed for the review (except for data on weight and other nutrients, which were extracted by LH only). Disagreements were resolved by discussion or if necessary by a third reviewer (SE).

Data extraction included details on population characteristics, intervention and control procedures and outcomes of interest. Mortality and cardiovascular event data were collected as events per number of participants randomised to control and intervention groups. Change in blood pressure, weight, other nutrient intakes and sodium excretion from baseline to assessment period were collected as continuous variables - number of subjects, mean change in the outcome variable and standard deviation of the change for both intervention and control groups. Data were collected on systolic and diastolic blood pressure changes, and urinary sodium excretion, at intermediate (latest data point available from 6 to 12 months), late (latest data point available between 13 and 60 months) and very late (after 60 months) follow up.

Four trials (Costa 1981; Arroll 1995; Alli 1992; Morgan 1987) provided baseline and follow-up values, with standard deviation or standard errors, but no standard deviation for the change from baseline. Using all of the three studies (Morgan 1978; TOHP phase I; TOHP phase II) in which data were provided at baseline, follow-up and mean differences given, values for the correlations between baseline and change values (for the control and experimental groups for systolic and diastolic blood pressure values but not for urinary sodium excretion) were computed (Follman 1992). A conservative estimate (lowest correlation) was used to compute the standard deviation for the mean change for four studies (only two of these were used in the meta-analyses). Correlations varied (0.11 to 0.47 for systolic blood pressure in control groups, 0.07 to 0.56 for systolic blood pressure in experimental groups, -5.79 to 0.17 for diastolic blood pressure in control groups and -5.22 to 0.19 for diastolic blood pressure in experimental groups). The negative correlations for diastolic blood pressure were due to extremely narrow ranges of diastolic blood pressure at baseline, resulting in very small standard deviations, so that the assumption that standard deviations at trial end would be similar were invalid. For this reason calculated standard deviations were used only for systolic blood pressure.

In factorial trials of calorie and sodium reduction only data from the sodium reduction and control groups were used as, of three such factorial trials (TOHP phase II; HPT; TONE), one reported statistically significant interactions between the two interventions (TOHP phase II), and another reported a 'suggestion of diminished effect on blood pressure when sodium and calorie counseling were combined' (although this effect was not statistically significant) (HPT). The exception was within the TONE trial, where data on urinary sodium excretion were only available for the combined groups, but where included event and medication data excluded participants on calorie reduction interventions.

Quality assessment included information on randomisation procedure, allocation concealment, blinding of participants, providers of care and outcome assessors and losses to follow up (Anonymous 2000). Where those recruiting participants into a trial appeared unaware of the treatment allocation of those participants until after recruitment was complete and where it was not possible to alter allocation after treatment was assigned allocation concealment was judged 'adequate'. Other possibilities were 'inadequate' or 'unclear'. Blinding of participants to their assigned treatment was not possible, awareness of outcome assessors to the recipients assigned treatment was judged 'no' (equivalent to 'blinded'), 'yes', or 'unclear'. Numbers of participants lost to follow-up in each arm were noted, as was the method used in the data analysis to adjust for these losses.

Disagreements in data extraction or quality assessment were discussed and referred to another reviewer (SE) where necessary. Attempts were made to contact all authors of included studies for further information on trial characteristics, quality and outcomes

(where further information was not available numbers were extracted from available published figures and graphs).

Quantitative data synthesis

Primary measures of interest were the effects of dietary advice to reduce sodium intake on

1. total mortality and
2. cardiovascular events and interventions.

For mortality and cardiovascular events, relative risks were used to examine differences between low sodium and control groups using the random effects model. For continuous outcomes, weighted mean differences were examined, again using the random effects model, on Cochrane Collaboration Review Manager 4.1 software. Meta-analyses were checked for heterogeneity by visual inspection and by Cochran's test.

Two trials were identified as being cluster randomised. In one small trial, [Alli 1992](#), 19 general practitioners were randomised to deliver simple low salt advice or no advice to a total of 77 patients. Patient numbers in the intervention and control groups were reduced to an effective sample size as described by [Hauck 1991](#), assuming the intraclass correlation (appropriate for nonfamilial clusters such as randomised practice units) to be 0.5 ([Donner 1982](#)). The other cluster randomised trial was Thaler (which consisted of one publication, but the unpublished data provided were separated into data for men, referred to as [Thaler men 1982](#) and data for women, [Thaler women 1982](#)). Individually randomised 'index' men and women included members of their families in the trial. Only the 'index' participants were used in this meta-analysis.

Random effects meta-regression ([Berkley 1995](#)) was used to assess the effect of initial level of systolic blood pressure, degree of sodium reduction achieved, percentage female participants, percentage white participants and initial mean age on systolic blood pressure (there were insufficient data on the primary endpoints, death or cardiovascular events to make meta-regression on these endpoints meaningful). Metaregression was performed using the STATA command `metareg` ([Sharp 1998](#)).

Sensitivity analysis was carried out to assess the robustness of the results to a) the exclusion of the data for which standard deviation of the change was imputed, b) use of the largest correlations to estimate these standard deviations, c) the exclusion of trials with unknown or inadequate allocation concealment ([Anonymous 2000](#)) and d) inclusion of the weight and salt reduction arms of factorial trials (where data for the appropriate [weight loss + low sodium] vs [weight loss] comparison were added to a meta-analysis plot beside the already included [low sodium] vs [control] comparison).

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

The 11 studies included within the review are described in the table 'characteristics of included studies'. The number of publications assessed to come to these 11 studies and the outcomes that were available in the 11 studies are shown in the Quorum Flow Diagram which can be seen at this website: <http://www.ti.ubc.ca/PDF/A019QFD.pdf>

Three trials in normotensives (n=2326, [HPT](#); [TOHP phase I](#); [TOHP phase II](#)), five in untreated hypertensives (n=387, [Morgan 1978](#); [Costa 1981](#); Thaler ([Thaler men 1982](#); [Thaler women 1982](#)); [Silman 1983](#); [Alli 1992](#)) and three in treated hypertensives (n=801, [Morgan 1987](#); [Arroll 1995](#); [TONE](#)) were included, with follow up from six months to seven years.

The three normotensive trials were in healthy people (predominantly white, male, mean age 40) with high normal blood pressure. Entry criteria varied between trials, but included those with diastolic blood pressure from 78 to 89 mm hg, with a narrow range of means from 83 to 86 mm hg diastolic and 124 to 127 mm hg systolic. All of the studies were conducted in the USA and included from 392 to 1190 randomised participants.

All three studies (as well as [TONE](#), below) ran comprehensive dietary and behaviour change programmes led by experienced personnel, including group counseling sessions, regularly over several months, with newsletters between sessions, self assessment, goal setting, food tasting and recipes. Control groups received no active intervention. Sodium excretion goals were set at 70-80 mmol/24 hours. For example, the [HPT](#) study ran ten weekly group counseling 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 counseling 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 five trials in untreated hypertensives included people from 16 to 64 years, were carried out in Australia, New Zealand, Italy and the UK and ranged in size from 28 to 164 participants. Entry criteria ranged from unspecified 'untreated borderline hypertension' ([Costa 1981](#)), diastolic blood pressure ranges within 90 to 109 mm hg ([Morgan 1978](#); [Silman 1983](#); [Alli 1992](#)) and systolic blood pressure 137-180 mm hg (Thaler 1982). 42 to 100% of participants were male (not specified in two trials, [Costa 1981](#); [Silman 1983](#)) and no trial described the ethnicity of its participants.

Interventions in the studies on untreated hypertensives included:

- individual counseling and a leaflet provided by a general practitioner with reinforcement at each clinic visit, while the control group maintained their usual diet ([Alli 1992](#)),
- a salt restriction programme for the whole family led by a

nutritionist including a cookbook and individual counseling (some at the family home) with provision of low sodium baking powder and baking soda and low sodium bread provided weekly by a local baker, while the control group were asked to eat their usual diet (Thaler 1982),

- a general health education package (on healthy eating, smoking, exercise and stress control) with teaching about a low fat diet (diet sheet provided) compared with the general health education package only in the control group (Silman 1983),
- given a low salt diet (no details provided) compared with advice on a diet with free salt in the control group (Costa 1981),
- instructions to reduce dietary sodium chloride intake, with advice repeated at 3 months (no further details provided) compared with no intervention in the control group (Morgan 1978).

Sodium goals varied from <80 mmol/24 hours to <100 mmol/24 hours of urinary sodium excretion, 3 g NaCl per day and 70-100 mmol/24 hours of sodium intake.

The three trials in treated hypertensives had mean ages of 55 to 67 years, were carried out in Australia, New Zealand and the USA and ranged in size from 20 to 641 participants. Entry criteria varied, diastolic blood pressure was 70-105 mm hg or systolic blood pressure 155-180 mm hg while taking antihypertensive treatment (Arroll 1995), diastolic blood pressure <85 mm hg while taking antihypertensive treatment and >100 mm hg without treatment (Morgan 1987) or <85 mm hg diastolic and <145 mm hg systolic blood pressure while taking antihypertensive medication (TONE). 49-100% of participants were male and 76% were white in the TONE study (ethnicity was not mentioned in the other studies).

Interventions in trials of treated hypertensives included:

- being asked to reduce use of high salt foods, salt at table and in cooking, given an article on blood pressure and salt restriction, a leaflet and a book with sodium contents of common foods, compared with no intervention in the control group (Arroll 1995),
- a low sodium diet (no further details provided) compared with a normal diet in the control group (Morgan 1987), and
- an individual nutrition and behavioural counseling programme (as above) or no such programme but with invitations to meetings on unrelated topics in the control group (TONE).

Sodium goals were dietary intake of 50-75 mmol/24 hours (Morgan 1987), urinary sodium < 80 mmol/24 hours (TONE) and unspecified (Arroll 1995).

Excluded studies (where the full text paper was collected) were excluded on the basis of no follow up after six or more months (28 studies), having a multifactorial intervention where the effects of salt reduction advice could not be separated from other interventions (17 studies), lack of randomisation (10 studies), lack of an appropriate 'usual diet' control group (10 studies) or inclusion

of children (one study). Studies were often excluded for several reasons, but one main reason has been provided for each study in the list above.

Risk of bias in included studies

Trial quality as judged by allocation concealment appeared higher in the trials on normotensives (allocation concealment adequate in three of three trials, compared to one of three trials in treated hypertensives and zero of five trials in untreated hypertensives). Other aspects of trial quality assessed included blinding of outcome assessment and losses to follow up. Different methods of dealing with missing data associated with losses to follow up were apparent. The majority of trials attempted to blind outcome assessors. For further details of individual study quality see the 'Notes' section of the Table of Characteristics of Included Studies.

Effects of interventions

Mortality and cardiovascular events

These outcomes were inconsistently reported in trials (see Table 1). No differences in periods of hospitalisation were seen between intervention groups in the HPT study (no further data were provided). Morgan 1978 reported that three control participants were treated for cardiac failure, as were two on low sodium diets, with four cardiovascular deaths in the low sodium group and two in the control group. TONE recorded cardiovascular events (including stroke, transient ischaemic attack, myocardial infarction, angina, congestive heart failure, arrhythmia and 'other' events) of participants. Cardiovascular events occurred in 46 control participants and 36 of those on low sodium diets. Pooling the two studies suggests no significant difference in cardiovascular morbidity between low sodium and control groups (relative risk 0.82, 95% CI 0.56 to 1.21).

The trials report few deaths, altogether only 9 deaths in control groups and 8 in low sodium groups (relative risk 0.90, 95% CI 0.36 to 2.24). The available data are shown in metanalysis.

Blood pressure

Changes in blood pressure and urinary sodium excretion at intermediate and late assessments are given in Table 2 and meta-analysis results in Table 3. Systolic blood pressure was reduced on a low salt diet at both intermediate (by 2.5 mm hg, 95% CI 3.8 to 1.2) and late follow up (by 1.1 mm hg, 95% CI 1.8 to 0.4). Diastolic blood pressure was also reduced at intermediate follow up (by 1.2 mm hg, 95% CI 1.8 to 0.6), less so later (by 0.6 mm hg, 1.5 to -0.3).

The few participants with very late follow up (seven years) had non-significant reductions in systolic (by 3.8 mm hg, 95% CI 7.9 to -0.3) and diastolic (by 2.2 mm hg, 95% CI 4.8 to -0.4) blood pressure. It should be noted that this late follow up of the TOHP phase I study was technically after the end of the trial.

TOHP phase I ran for 18 months with a consistent intervention to help the low sodium group stick to a low sodium diet. The 7-year results are described as 'posttrial' results, and as 7 years follow up, and the trialists implied that they were assessing the long term effect of their 18 month intervention. We (as reviewers) felt that if the trial just stopped intervening, without altering the diets of either the intervention or control groups then we could include data from the later follow up (in many studies the intervention only happens once or twice at the beginning, but the effect is measured months later). The paper states that 'after 18-months, there was no further contact with the trial participants to enhance the intervention effect'. We could not contact the reviewers to confirm that there were no suggested alterations to the diets of the participants after the eighteen month intervention, so the data are included here but with this note of caution.

Statistical heterogeneity was present for systolic blood pressure at intermediate follow up and diastolic blood pressure at late follow up, but was resolved when sensitivity analyses removed trials with inadequate or unclear allocation concealment, or with imputed standard deviations, or when trials were sub-grouped into normotensive or hypertensive at baseline.

Sensitivity analysis, excluding trials with inadequate allocation concealment, resulted in all trials on untreated hypertensives being removed. As these trials were small, the effect on pooled estimates of blood pressure change was minor. Adding in data for the weight reduction arms of factorial trials strongly reduced the effect of low sodium advice on blood pressure, and slightly reduced the effect on sodium excretion (Table 3).

Meta-regression of blood pressure change up to 12 months using all trials with relevant data (or trials with adequate allocation concealment, effectively trials on normotensives) showed no relationship with change in urinary sodium excretion, baseline systolic blood pressure or age (Table 4). However, the meta-analyses sub-grouping by 'normotensive' or 'hypertensive' participants at baseline did suggest a consistently greater effects of salt restriction on blood pressure in hypertensives. Insufficient data were available of effects on specific races or genders to enable statistical exploration of these factors.

Quality of Life

Information on quality of life was patchy, with no common outcome measures. HPT asked participants whether they were having problems with their diets. 69% of those in the low sodium group reported problems at some time during the 3 years of the trial, and problems were reported at 42% of clinic visits. Problems related to the diet being inconvenient, conflicting with schedules, lack of time for planning, and difficulty in adherence while eating out.

TOHP phase I reported psychological well-being scores. These improved significantly in participants in the low sodium groups at 18 months compared with the non-intervention control group ($p < 0.01$). It was stated that the improvement was generally consistent across race and sex subgroups but no further information was provided.

Thaler (Thaler men 1982; Thaler women 1982) reported that stopping adding salt at table was not difficult for participants, but many found cutting down on salt in cooking harder. The majority found their low salt bread (salt cut from 2.1% to 1.0% dry weight) and salt-free butter acceptable. Only 13% of participants reported their salt restricted diet as unpleasant or worse.

TONE found that the most common non-cardiovascular event recorded was headache: the low sodium group had a significant reduction in headaches as compared to the control group.

Thaler (Thaler men 1982; Thaler women 1982) asked about presence or absence of muscle cramps in control and low sodium participants. At eight months 13% of control subjects reported getting cramps a lot or sometimes (as opposed to occasionally or never) whilst this outcome was reported in 30% of the low sodium group.

Overall drop out rates were very similar (relative risk 1.04, 95% CI 0.86 to 1.25) in low sodium compared with control groups.

Weight

The suggestion from food diaries in HPT was that men on a low sodium diet take in roughly 240 kcal less per day than their control counterparts. Women on low sodium diets take in 120 fewer kcal per day. This did not result in a large difference in weight; at 3 years those in the control group had gained about 1 kg on average more than those in the low sodium group.

TOHP phase I observed significantly greater weight loss in the low sodium group compared with control at six (1.2 kg) and twelve (0.8 kg) months, but the difference at 18 months (0.4 kg) was no longer significant. Similarly, in TOHP phase II those on a low sodium diet lost more weight initially (1.2 kg difference at 6 months, $p < 0.001$), but the difference had disappeared by 36 months.

Arroll 1995 found a weight loss of 1.4 kg in the low sodium group relative to the controls at six months. However, Morgan 1987, Thaler (Thaler men 1982; Thaler women 1982), and Silman 1983, found no change in weight in either control or low sodium groups.

In TONE eight participants not assigned to a weight loss intervention experienced excessive weight loss, but it is not clear how many of these were in the control or low sodium groups.

Overall, in the larger studies, where one is more likely to see any real effect, there appeared to be initial weight reductions accompanying the low sodium diet, but the effect was lost over several years.

Urinary sodium excretion

Meta-analysis demonstrated a reduction in urinary 24 hour sodium excretion at intermediate (48.9 mmol/ 24 hours, 95% CI 65.4 to 32.5), and late follow up (35.5 mmol/ 24 hours, 95% CI 47.2 to 23.9) in those advised to follow a low sodium diet compared with control. Significant heterogeneity was seen in results at intermediate and late assessment, and was not resolved by sensitivity analysis leaving out trials with unclear or inadequate allocation concealment. The one trial to assess very late outcomes (TOHP phase I, in normotensives) found that at seven years sodium ex-

cretion in a small subset of their original sample was similar in intervention and control groups.

Other nutrients

The relationship between low sodium dietary advice and other dietary components has not been fully explored in these studies. Potassium is the most reported component, usually measured as urinary excretion alongside sodium. Other nutrients were measured as dietary intakes using food record and recall systems.

Minerals

Potassium. In **HPT** potassium excretion was consistently greater in low sodium than control groups (about 6 mmol/24 hours at 3 years) but whether this difference was statistically significant is not clear. In **TONE** potassium intake was also greater in the low sodium group than in control (by 160 mg/24 hours, 95% CI 25 to 295). The rest of the trials found no significant differences in reported intakes or excretion of potassium including: **TOHP phase I**, **TOHP phase II**, **Thaler men 1982**, **Thaler women 1982**, **Morgan 1978**, **Morgan 1987** and **Silman 1983**.

Magnesium. **TONE** found a higher intake of magnesium in low salt as compared with control groups (by 24 mg/24 hour, 95% CI 8 to 39), whereas **TOHP phase I** reported no significant difference between groups.

Calcium. **TONE** found a significant fall in calcium intake in the low salt as compared with the control group (of 71 mg/24 hours, 95% CI 119 to 23). **HPT** found a reduction in salt from dairy foods (suggested in all groups, but only significant in normal weight men), while **TOHP phase I** reported no significant net differences in reported intake of calcium.

Iron. **TOHP phase I** reported lower intakes of iron (3.6 mg/day at 18 months) in the low sodium group. The differences in iron were due to differences in men (women were similar between low sodium and control groups) and the reported iron intakes (15 mg/day at 18 months in men) in the low sodium group were still well over the RDA (10 mg/day for men). **TONE** also found lower iron intakes in the low sodium group (lower by 2.8 mg/24 hours, 95% CI 3.8 to 1.8).

Phosphorus and zinc were not significantly different in low sodium and control groups in **TONE**.

Vitamins

TOHP phase I reported no significant net differences in reported intakes of vitamin A, vitamin C, thiamine, riboflavin or niacin. **TONE** found lower intakes of thiamine (0.12 mg/24 hours, 95% CI 0.22 to 0.02) and riboflavin (0.2 mg/24 hours, 95% CI 0.3 to 0.1) in low sodium groups, but no significant differences in vitamins A, Bs, C, D, E, folate or niacin (excluding supplements).

Macronutrients

Energy. **TOHP phase I** reported significantly lower daily intakes of total energy (207 kcal) in the low sodium group, as did **TONE** (by 119 kcal/24 hours, 95% CI 197 to 41).

Fats. Lower intakes of total fat (by 5.8 g/24 hours, 95% CI 10.1 to 1.5), saturated fat (by 2.4 g/24 hours, 95% CI 4.0 to 0.8) and monounsaturated fat (by 2.2 g/24 hours, 95% CI 4.0 to 0.4) were

seen in the low sodium group of **TONE**. No significant differences were seen in polyunsaturated fat intake. **TOHP phase I** reported significantly lower daily intakes of total fat (11.4 g) in the low sodium group, but no significant net differences in saturated fat. Alcohol. **TOHP phase II** reported that there were no differences between the low sodium and usual care groups in alcohol intake, while **Arroll 1995** reported an increased intake of alcohol in the control group (2.4 g/day), though it was not clear whether this was statistically significant. **TOHP phase I** reported no significant net differences in reported intake of alcohol.

Protein and carbohydrates were not significantly different in the low sodium and control groups in **TONE**.

Overall, there is a trend towards increases in potassium and magnesium, and a fall in calcium, iron, some B vitamins, total energy, total and saturated fats in low sodium groups.

Anti-hypertensive medications used

Two trials in patients with elevated blood pressure considered the ability of low salt diets to maintain blood pressure control after stopping anti-hypertensive medication. In the smaller trial (**Morgan 1987**) anti-hypertensive therapy was stopped two months after randomisation to usual or low sodium diet, but restarted if diastolic blood pressure rose. After six months, four of ten men on low sodium diet were taking anti-hypertensive medication, compared to nine of ten on usual diet (relative risk 0.44, 95% CI 0.20 to 0.98).

In the larger study (**TONE**, 975 participants, including those on weight reduction interventions) withdrawal of medication was attempted 3 months after randomisation to low sodium diet (with behavioural therapy) or usual care. The primary combined endpoint (a combination of high blood pressure at any visit, restarting of anti-hypertensive medication or any clinical cardiovascular event) was less common in the low sodium group, relative risk 0.83 (95% CI 0.75 to 0.92), ARR 14%, NNT 7.

DISCUSSION

Eleven long term randomised controlled trials of dietary salt reduction (including 3514 participants) provided few data on mortality (17 deaths in total), cardiovascular events or quality of life, but did demonstrate a significant decrease in systolic blood pressure (1.1 mm hg, 95% CI 1.8 to 0.4) and urinary sodium excretion (35.5 mmol/24 hours, 95%CI 47.2 to 23.9) at 13 to 60 months after initial advice. The decrease in diastolic blood pressure was smaller (0.6 mm hg, 95% CI 1.5 to -0.3). The data suggest that a low salt diet may help people on anti-hypertensives to stop their medication without losing blood pressure control. The data from **TONE** suggest that for every 7 patients assigned a goal of achieving a sodium intake of less than 80 mmol/day, one would remain off antihypertensive medication with a BP less than 150/90 mm hg and with no adverse cardiovascular events.

Effects of low salt dietary advice on mortality and cardiovascular morbidity

Health promotion interventions involve several stages before any health outcome is seen. First, the advice must result in changed behaviour (cutting down on salt in foods) and secondly that behaviour must result in an improved health outcome (reduced cardiovascular illness, increased life expectancy). A major weakness of this review is that we were not able to assess the overall effect of advice to reduce dietary sodium on mortality or morbidity (as not enough events have been accumulated to see any definitive answer). Instead we have tried to follow the process by assessing several intermediate outcomes including urinary sodium excretion and blood pressure; however there may be effects on other risk factors.

It is not clear what effects a low sodium diet has on cardiovascular events and mortality. It has been suggested that lowering sodium intake may have adverse effects on the vascular endothelium through stimulation of the renin-angiotensin system (Alderman 1997), and adverse effects on serum total and LDL cholesterol levels (Graudal 1998) have been suggested. In cohort studies, lower salt intake in hypertensives has been associated with higher levels of cardiovascular disease (Alderman 1995) and in general populations (Alderman 1998; Tunstall-Pedoe 1997) with greater all-cause mortality. However, among obese people lower salt intake may be associated with reduced risk of cardiovascular events (He 1999; Tuomilehto 2001). These apparently contradictory findings emphasizes the fact that we do not know whether long-term salt restriction is beneficial or harmful.

Effects of low salt dietary advice on sodium excretion

The review suggests that sodium reduction of about a quarter of usual sodium intake in US and UK populations (MAFF 1999) can be achieved long term. This may be exaggerated. For example, HPT found that 48% of participants ate differently on the day of their food record, eating less food, and substituting simpler foods. Several people in the low sodium group also reported eating less salt on days salt intake was recorded. Whether food adjustment also occurred when urine samples were collected (and whether these were complete) is not known. Male participants in Thaler's trial (Thaler men 1982) were believed to have relaxed their salt restriction between urine samples (O. Simpson, personal communication, 2001).

Is it realistic to ask people to alter their salt intake long term? Advice to reduce dietary salt is common in primary care if the British Hypertension Society's Guidelines (Ramsay 1999; Ramsay 1999a) are being followed. These guidelines advise that 'reduced use of salt when preparing food and elimination of excessively salty foods from the diet' 'be offered to all hypertensive people and those with a strong family history of hypertension'. It does appear that the degree of salt restriction attained attenuates over time (Table 3) and this occurs despite a great deal of ongoing encouragement

and support (comprehensive interactive programmes of dietary and behavioural education involving specialized and highly trained staff, vast input of skills, time and materials) in all of the four large high quality trials. The resulting falls of 1.1 mm hg systolic and 0.6 mm hg in diastolic blood pressure may be useful at a population level; however the intensity of intervention applied to individuals required to achieve this is not realistic for community control of high blood pressure, which would need to be through changes in food production and catering practices.

Effects of low salt dietary advice on blood pressure

While both urinary sodium excretion and blood pressure fell, the salt reduction may not have caused the fall in blood pressure. Alterations in diet aimed at reducing salt intake may perhaps systematically affect other dietary components (such as alcohol, potassium, calcium, fat or energy intake) that may themselves alter blood pressure (Cappuccio 1991; Allender 1996; Whelton 1997; Ebrahim 1998; Brand 1999; Griffith 1999). The only available data suggest that potassium is not consistently affected by a low sodium diet, and that weight may be reduced in the medium term, but is unlikely to be exerting much effect on blood pressure by three years. Very little information is available on alcohol (suggesting no major effect), calcium (TOHP phase I reported no significant changes in intake of calcium, but HPT reported a reduction in salt from dairy foods) or fat (suggesting that significant reductions may be occurring in low sodium groups, reported in only one large trial). The significant reduction in weight of people given low sodium dietary advice in the medium, but not the longer term, may explain why the effect of a low sodium diet on blood pressure 'drops off' so much between intermediate and late follow up in this review. It may also explain why, in this review, no relationship is seen between the degree of reduction in sodium excretion and change in blood pressure. However the number of trials is small and relating a mean change in blood pressure to a mean change in urinary sodium is statistically weak. In previous meta-analyses (Table 5) a relationship has been seen in some cases but not in others. Individual participant data are required to take this issue further.

We expected that short duration trials would achieve larger falls in blood pressure that would attenuate over time, in line with attenuation of salt restriction. Trials in normotensives in the Graudal review (Graudal 1998) (Table 5) had a median length of 8 days, a reduction of 160 mmol/24 hours in urinary sodium excretion and a fall of 1.2 mm hg in systolic blood pressure, while in this review (median trial length 36 months, 34 mmol/24 hours difference in sodium excretion) systolic blood pressure fell by 1.1 mm hg. In hypertensives our results are less easy to interpret due to the low quality of included studies, but there is no clear suggestion that blood pressure effects diminish with longer duration trials or with smaller reductions in sodium excretion. This suggests that home-

ostatic mechanisms (Navar 1997) do not operate over the longer term to re-set usual blood pressure levels as might be expected. It has been suggested that 'usual' blood pressure may be set in utero or early childhood (Barker 1998) so it is possible that dietary salt intake in early childhood has a greater role in determining adult blood pressure than salt intake in adulthood; however the evidence is mixed (Lucas 1988; Hofman 1983; Singhal 2001), and open to varying interpretations (He 2001). A systematic review in this area would be helpful.

Part of the blood pressure lowering effect at longer follow up may be due to lower sodium diets preventing blood pressure rise with age. The Intersalt observational study (Elliott 1996) suggested that a population excreting 100 mmol/day less sodium would experience a 10 and 6 mm hg lower rise in systolic and diastolic blood pressure over 30 years. This review suggests that voluntary reduction of only 35 mmol Na/ 24 hours is realistic for periods of over one year. This would prevent 3-4 mm hg systolic (2 mm hg diastolic) blood pressure rise over thirty years. However, the sodium reduction achieved may decline over time so this additional protective effect of low salt advice may be limited.

The sodium reduction arms of the DASH (Sacks 2001) study are not included in this review as their intervention periods were only 30 days; however the strength of the study was in providing all food for participants and so tightly regulating sodium (as well as potassium and calorie) intake. Participants in the 'control intermediate sodium' arm reduced their sodium excretion by 35 mmol/day compared with the 'control normal sodium' arm, reducing systolic (2.1 mm hg, 95% CI 3.4 to 0.8 mm hg) and diastolic (1.1 mm hg, 95% CI 1.9 to 0.2 mm hg) blood pressure by amounts similar to those seen in 13-60 month follow up in this review. With greater reductions in sodium, systolic blood pressure decreased by a greater amount (6.7 mm hg, 95% CI 5.4 to 8.0).

Effects of low salt dietary advice on other outcomes

There is evidence that a low sodium diet improves the chance of maintaining controlled blood pressure following withdrawal of antihypertensives.

There are several reasons for assessing levels of other nutrients in a low sodium diet. Altering any one component of a complex diet will in turn alter the intake of many other micro and macro-nutrients. It is important to ensure that a low sodium diet is nutritionally adequate. It is also necessary to be aware that changes in many nutrients have their own long term effects on blood pressure and other aspects of cardiovascular health. The available data are scant but suggest increases in potassium and magnesium intake, and reductions in energy and total fat intakes, all of which might be expected to help reduce blood pressure in their own right as well as protecting against cardiovascular disease in other ways. This is good news for health, but raises further questions about the extent of the effect of salt reduction itself on blood pressure. It may be that the small changes in blood pressure seen in these long term

trials are due to increases in potassium and decreases in fat intake. On the other hand, the reductions in calcium and iron seen in some trials might endanger dietary adequacy for a few people, increasing the risk of osteoporosis and anaemia. It may be that the effect on blood pressure, and more generally on health, of a low sodium diet depends on the types of messages used, the specific dietary measures taken. These may differ considerably from trial to trial, or even from participant to participant.

We have included only a small number of the many randomised controlled trials on the effect of salt manipulation, and none of the intra- or inter-population surveys, cohorts or animal trials that are commonly referred to when the effect of salt reduction on health is discussed. Most of the randomised controlled trials that have been performed have been of short duration and do not assess whether dietary advice has any long term effect on health outcomes or blood pressure. Despite an extensive search, only eleven trials fulfilled our inclusion criteria (determined by our question). Where randomised controlled trials in humans are available to answer a question on health, it would be inappropriate to include animal studies, surveys or cohort studies, which have contradictory results and interpretations (Taubes 1998).

AUTHORS' CONCLUSIONS

Implications for practice

Two trials suggest that a low sodium diet helps in preventing elevated blood pressure following withdrawal of antihypertensives. If this is confirmed, with no increase in cardiovascular events, then targeting of comprehensive dietary and behavioural programmes at this group would be justified.

Long term maintenance of low sodium intake for individuals is difficult even with a great deal of support, advice and encouragement. A policy of reduction in salt intake for the entire population, through cutting salt levels in processed foods (MacGregor 1996), as recently announced by the UK's Chief Medical Officer (DoH 2001), is potentially a way of achieving small reductions in blood pressure across the whole population for sustained periods of time. Individual reduction of risk would be small, but across a whole population the effects may be substantial (Stamler 1991; Selmer 2000).

However, raised blood pressure is only one risk factor for cardiovascular disease and overall clinical benefits (or harms) of a reduced sodium diet are unclear - further research is urgently needed to explore this. Deaths and cardiovascular events in the long-term RCTs published to date were too infrequent to answer whether the benefits of sodium restriction outweigh the harms.

Implications for research

Follow up of all participants of the large trials some years later to

assess long term effects of low sodium dietary advice on mortality and cardiovascular morbidity would be a cost effective and timely way to assess the clinical effect of low sodium advice. There remains a strong justification for a large, long term RCT to explore the effect of reduced sodium advice on these outcomes in people with borderline and mild elevations of blood pressure.

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REFERENCES

References to studies included in this review

Alli 1992 {published data only}

* Alli C, Avanzini F, Bettelli G, Bonati M, Colombo F, Corso R, Di Tullio M, Gentile MG, Sangalli L, Taioli E, Tognoni G. Feasibility of a long-term low-sodium diet in mild hypertension. *Journal of Human Hypertension* 1992;**6**(4):281–286. [MEDLINE: 93059176]

Arroll 1995 {published and unpublished data}

* Arroll B, Beaglehole R. Salt restriction and physical activity in treated hypertensives. *N Z Med J* 1995;**108**(1003):266–268. [MEDLINE: 95365076]

Costa 1981 {published data only}

* Costa FV, Ambrosioni E, Montebugnoli L, Paccaloni L, Vasconi L, Magnani B. Effects of low-salt diet and of acute salt loading on blood pressure and intralymphatic sodium concentration in young subjects with borderline hypertension. *Clinical Science* 1981;**61**(Supplement 7): 21s–23s. [MEDLINE: 82094132]

HPT {published and unpublished data}

Borhani NO, Tonascia J, Schlundt DG, Prineas RJ, Jefferys JL. Recruitment in the Hypertension Prevention trial. Hypertension Prevention Trial Research Group. *Controlled Clin Trials* 1989;**10**(3 Suppl):30S–39S. [MEDLINE: 90031597]

Brown KM, Oberman A, Van Natta ML, Forster JL. Baseline characteristics in the hypertension prevention trial. *Controlled Clinical Trials* 1989;**10**(3 supplement):40S–64S. [MEDLINE: 90031598]

Forster JL, Jeffery RW, VanNatta M, Pirie P. Hypertension prevention trial: do 24-h food records capture usual eating behavior in a dietary study?. *Am J Clin Nutr* 1990;**51**(2): 253–257. [MEDLINE: 90164468]

* Hypertension Prevention Trial Research Group. The Hypertension Prevention Trial: three-year effects of dietary changes on blood pressure. *Arch Intern Med* 1990;**150**(1): 153–162. [MEDLINE: 90120838]

Jeffery RW, French SA, Schmid TL. Attributions for dietary failures: problems reported by participants in the

Hypertension Prevention Trial. *Health Psychol* 1990;**9**(3): 315–329. [MEDLINE: 90255462]

Jeffery RW, Tonascia S, Bjornson BW, Schlundt DG, Sugars C for the Hypertension Prevention Trial Research Group. Treatment in the Hypertension Prevention Trial. *Controlled Clin Trials* 1989;**10**(3 Suppl):65S–83S. [MEDLINE: 90031599]

Meinert CL, Borhani NO, Langford HG. Design, methods, and rationale in the Hypertension Prevention Trial. Hypertension Prevention Trial Research Group. *Controlled Clin Trials* 1989;**10**(3 Suppl):1S–29S. [MEDLINE: 90031596]

Prud'homme GJ, Canner PL, Cutler JA. Quality assurance and monitoring in the Hypertension Prevention Trial. Hypertension Prevention Trial Research Group. *Controlled Clin Trials* 1989;**10**(3 Suppl):84S–94S. [MEDLINE: 90031600]

Schmid TL, Jeffery RW, Onstad L, Corrigan SA. Demographic, knowledge, physiological, and behavioral variables as predictors of compliance with dietary treatment goals in hypertension. *Addictive Behaviors* 1991;**16**(3-4): 151–160. [MEDLINE: 91289809]

Shah M, Jeffery RW, Laing B, Savre SG, Van NM, Strickland D. Hypertension Prevention Trial (HPT): food pattern changes resulting from intervention on sodium, potassium, and energy intake. Hypertension Prevention Trial Research Group. *J Am Diet Assoc* 1990;**90**(1):69–76. [MEDLINE: 90110778]

Morgan 1978 {published and unpublished data}

* Morgan T, Adam W, Gillies A, Wilson M, Morgan G, Carney S. Hypertension treated by salt restriction. *Lancet* 1978;**1**(8058):227–230. [MEDLINE: 78091122]

Morgan TO, Adams WR, Hodgson M, Gibberd RW. Failure of therapy to improve prognosis in elderly males with hypertension. *Medical Journal of Australia* 1980;**2**(1): 27–31. [MEDLINE: 81051857]

Morgan 1987 {published data only}

* Morgan T, Anderson A. Sodium restriction can delay the return of hypertension in patients previously well-controlled on drug therapy. *Can J Physiol Pharmacol* 1987;**65**(8):

1752–1755. [MEDLINE: 88079620]

Silman 1983 *{published data only}*

Silman AJ, Locke C, Humpherson P. Salt restriction and no drug treatment in mild to moderate hypertension [letter]. *Lancet* 1982;**1**(8277):903–904. [MEDLINE: 82172148]

* Silman AJ, Locke C, Mitchell P, Humpherson P. Evaluation of the effectiveness of a low sodium diet in the treatment of mild to moderate hypertension. *Lancet* 1983;**1**(8335):1179–1182. [MEDLINE: 83217784]

Thaler men 1982 *{published and unpublished data}*

* Thaler BI, Paulin JM, Phelan EL, Simpson FO. A pilot study to test the feasibility of salt restriction in a community. *N Z Med J* 1982;**95**(721):839–842. [MEDLINE: 83142430]

Thaler women 1982 *{published and unpublished data}*

* Thaler BI, Paulin JM, Phelan EL, Simpson FO. A pilot study to test the feasibility of salt restriction in a community. *N Z Med J* 1982;**95**(721):839–842. [MEDLINE: 83142430]

TOHP phase I *{published data only}*

Cook NR, Kumanyika SK, Cutler JA. Effect of change in sodium excretion on change in blood pressure corrected for measurement error. *Am J Epidemiol* 1998;**148**(5):431–444. [MEDLINE: 98407573]

He J, Whelton PK, Appel LJ, Charleston J, Klag MJ. Long-term effects of weight loss and dietary sodium reduction on incidence of hypertension. *Hypertension* 2000;**35**(2):544–550. [MEDLINE: 20145848]

Kumanyika SK, Hebert PR, Cutler JA, Lasser VI, Sugars CP, Steffen BL, Brewer AA, Cameron M, Shepek LD, Cook NR, et al. Feasibility and efficacy of sodium reduction in the Trials of Hypertension Prevention, phase I. Trials of Hypertension Prevention Collaborative Research Group. *Hypertension* 1993;**22**(4):502–512. [MEDLINE: 94011135]

Sacks FM, Hebert P, Appel LJ, Borhani NO, Applegate WB, Cohen JD, Cutler JA, Kirchner KA, Kuller LH, Roth KJ, et al. The effect of fish oil on blood pressure and high-density lipoprotein-cholesterol levels in phase I of the Trials of Hypertension Prevention. Trials of Hypertension Prevention Collaborative Research Group. *J Hypertens Suppl* 1994;**12**(7):S23–S31. [MEDLINE: 95287279]

Satterfield S, Cutler JA, Langford HG, Applegate WB, Borhani NO, Brittain E, Cohen JD, Kuller LH, Lasser NL, Oberman A, Rosner B, Taylor JO, Vogt TM, Walker G, and Whelton PK for the Trials of Hypertension Prevention Collaborative Research Group. Trials of hypertension prevention. Phase I design. *Ann Epidemiol* 1991;**1**(5):455–471. [MEDLINE: 94093770]

Stevens VJ, Corrigan SA, Obarzanek E, Bernauer E, Cook NR, Hebert P, Mattfeldt BM, Oberman A, Sugars C, Dalcin AT, Whelton PK for the TOHP Collaborative Research Group. Weight loss intervention in phase 1 of the Trials of Hypertension Prevention. *Arch Intern Med* 1993;**153**(7):849–858. [MEDLINE: 93221340]

* The Trials of Hypertension Prevention Collaborative Research Group. The effects of nonpharmacologic

interventions on blood pressure of persons with high normal levels: results of the Trials of Hypertension Prevention, Phase I. *JAMA* 1992;**267**(9):1213–1220. [MEDLINE: 92167528]

Whelton PK, Buring J, Borhani NO, Cohen JD, Cook N, Cutler JA, Kiley JE, Kuller LH, Satterfield S, Sacks FM and Taylor JO for the Trials of Hypertension Prevention (TOHP) Collaborative Research Group. The effect of potassium supplementation in persons with a high-normal blood pressure. Results from phase I of the Trials of Hypertension Prevention (TOHP). Trials of Hypertension Prevention (TOHP) Collaborative Research Group. *Ann Epidemiol* 1995;**5**(2):85–95. [MEDLINE: 95316194]

Whelton PK, Hebert PR, Cutler J, Applegate WB, Eberlein KA, Klag MJ, Keough ME, Hamill S, Borhani NO, Hollis J and Oberman A for the Trials of Hypertension Prevention Collaborative Research Group et al. Baseline characteristics of participants in phase I of the Trials of Hypertension Prevention. *Ann Epidemiol* 1992;**2**(3):295–310. [MEDLINE: 94101134]

Whelton PK, Kumanyika SK, Cook NR, Cutler JA, Borhani NO, Hennekens CH, Kuller LH, Langford H, Jones DW, Satterfield S, Lasser NL, Cohen JD. Efficacy of nonpharmacologic interventions in adults with high-normal blood pressure: results from phase 1 of the Trials of Hypertension Prevention. Trials of Hypertension Prevention Collaborative Research Group. *Am J Clin Nutr* 1997;**65**(2 Suppl):652S–660S. [MEDLINE: 97174901]

Yamamoto ME, Applegate WB, Klag MJ, Borhani NO, Cohen JD, Kirchner KA, Lakatos E, Sacks FM, Taylor JO, Hennekens CH. Lack of blood pressure effect with calcium and magnesium supplementation in adults with high-normal blood pressure. Results from Phase I of the Trials of Hypertension Prevention (TOHP). Trials of Hypertension Prevention (TOHP) Collaborative Research Group. *Ann Epidemiol* 1995;**5**(2):96–107. [MEDLINE: 95316195]

TOHP phase II *{published data only}*

Appel LJ, Hebert PR, Cohen JD, Obarzanek E, Yamamoto M, Buring J, Stevens V, Kirchner K, Borhani NO. Baseline characteristics of participants in phase II of the Trials of Hypertension Prevention (TOHP II). Trials of Hypertension Prevention (TOHP) Collaborative Research Group. *Ann Epidemiol* 1995;**5**(2):149–155. [MEDLINE: 95316191]

Hebert PR, Bolt RJ, Borhani NO, Cook NR, Cohen JD, Cutler JA, Hollis JF, Kuller LH, Lasser NL, Oberman A, Miller ST, Morris C, Whelton PK, Hennekens CH, for the Trials of Hypertension Prevention (TOHP) Collaborative Research Group. Design of a multicenter trial to evaluate long-term life-style intervention in adults with high-normal blood pressure levels. Trials of Hypertension Prevention (Phase II). *Ann Epidemiol* 1995;**5**(2):130–139. [MEDLINE: 95316189]

Hollis JF, Satterfield S, Smith F, Fouad M, Allender PS, Borhani N, Charleston J, Hirlinger M, King N, Schultz R, Sousoulas BG, on behalf of Trials of Hypertension Prevention (TOHP) Collaborative Research Group.

Recruitment for phase II of the Trials of Hypertension Prevention. Effective strategies and predictors of randomization. *Ann Epidemiol* 1995;**5**(2):140–148. [MEDLINE: 95316190]

Hunt SC, Cook NR, Oberman A, Cutler JA, Hennekens CH, Allender PS, Walker WG, Whelton PK, Williams RR. Angiotensinogen genotype, sodium reduction, weight loss, and prevention of hypertension. Trials of Hypertension Prevention, Phase II. *Hypertension* 1998;**32**(3):393–401. [MEDLINE: 98413188]

Lasser VI, Raczynski JM, Stevens VJ, Mattfeldt-Beman M, Kumanyika S, Evans M, Danielson E, Dalcin A, Batey DM, Belden LK and Brewer AA for the Trials Of Hypertension Prevention (TOPH) Collaborative Research Group. Trials of Hypertension Prevention, phase II. Structure and content of the weight loss and dietary sodium reduction interventions. Trials of Hypertension Prevention (TOHP) Collaborative Research Group. *Ann Epidemiol* 1995;**5**(2): 156–164. [MEDLINE: 95316192]

* The Trials of Hypertension Prevention Collaborative Research Group. Effects of weight loss and sodium reduction intervention on blood pressure and hypertension incidence in overweight people with high-normal blood pressure. The Trials of Hypertension Prevention, phase II. *Arch Intern Med* 1997;**157**(6):657–667. [MEDLINE: 97236001]

TONE {published data only}

Appel LJ, Espeland M, Whelton PK, Dolecek T, Kumanyika S, Applegate WB, Ettinger WH Jr, Kostis JB, Wilson AC, Lacy C, Miller ST. Trial of Nonpharmacologic Intervention in the Elderly (TONE). Design and rationale of a blood pressure control trial. *Ann Epidemiol* 1995;**5**(2):119–129. [MEDLINE: 95316188]

Appel LJ, Espeland MA, Easter L, Wilson AC, Folmar S, Lacy CR. Effects of reduced sodium intake on hypertension control in older individuals. Results from the Trial of Nonpharmacological Interventions in the Elderly (TONE). *Arch Intern Med* 2001;**161**(5):685–693. [MEDLINE: 21152543]

Bahnon JL, Whelton PK, Appel LJ, Espeland MA, Wofford JL, Rosen R, Wilson AC, Lacey CR, Rutan G, Hogan P, Tayback M, Dolecek TA, Shindler D. Baseline characteristics of randomized participants in the trial of nonpharmacologic intervention in the elderly (TONE). *Disease Management and Clinical Outcomes* 1997;**1**(2): 61–68. [EMBASE Accession number is 1998019109]

Espeland MA, Whelton PK, Kostis JB, Bahnon JL, Ettinger WH, Cutler JA, Appel LJ, Kumanyika S, Farmer D, Elam J, Wilson AC, Applegate WB. Predictors and mediators of successful long-term withdrawal from antihypertensive medications. *Arch Fam Med* 1999;**8**(3): 228–236. [MEDLINE: 99266360]

Kostis JB, Espeland MA, Appel LJ, Johnson KC, Pierce J, James L. Does withdrawal of antihypertensive medication increase the risk of cardiovascular events?. *Am J Cardiol* 1998;**82**(12):1501–1508. [MEDLINE: 99089451]

* Whelton PK, Appel LJ, Espeland MA, Applegate WB,

Ettinger WH Jr, Kostis JB, Kumanyika S, Lacy CR, Johnson KC, Folmar S, Cutler JA for the TONE Collaborative Research Group. Sodium reduction and weight loss in the treatment of hypertension in older persons: a randomized controlled trial of nonpharmacologic interventions in the elderly (TONE). *JAMA* 1998;**279**(11):839–846. [MEDLINE: 98175759]

Whelton PK, Bahnon J, Appel LJ, Charleston J, Cosgrove N, Espeland MA, Folmar S, Hoagland D, Krieger S, Lacy C, Lichtermann L, Oates WF, Tayback M, Wilson AC. Recruitment in the Trial of Nonpharmacologic Intervention in the Elderly (TONE). *J Am Geriatr Soc* 1997;**45**(2): 185–193. [MEDLINE: 97185836]

References to studies excluded from this review

Aberg 1989 {published data only}

* Aberg H, Tibblin G. Addition of non-pharmacological methods of treatment in patients on antihypertensive drugs: results of previous medication, laboratory tests and life quality. *Journal of Internal Medicine* 1989;**226**(1):39–46. [MEDLINE: 89328303]

Ambard 1904 {published data only}

Ambard L. Causes de l'hypertension arterielle. *Archives of General Medicine* 1904;**1**:520–533.

Ambrosioni 1982 {published data only}

Ambrosioni E, Costa F, Borghi C, montebugnoli M, Giordani M, Vasconi L. Effects of moderate salt restriction and high potassium intake on intralymphocytic sodium content and pressor response to stress in borderline hypertension. *Clinical Science* 1982;**63**:231S–234S.

Anderson 1990 {published data only}

* Anderson A, Morgan T. Interaction of enalapril with sodium restriction, diuretics, and slow-channel calcium-blocking drugs. *Nephron* 1990;**55**(Suppl 1):70–72. [MEDLINE: 90265449]

Berglund 1989 {published data only}

Berglund A, Andersson OK, Berglund G, Fagerberg B. Antihypertensive effect of diet compared with drug treatment in obese men with mild hypertension. *BMJ* 1989; **299**(6697):480–485. [MEDLINE: 90001793]

Bompiani 1988 {published data only}

Bompiani GD, Cerasola G, Morici M, Condorelli M, Trimarco B, de Luca N, Leonetti G, Sampieri L, Cuspidi C, Cottone S, D'Ignoto G. Effects of moderate low sodium / high potassium diet on essential hypertension: results of a comparative study. *Int Journal of Clinical Pharmacology, Therapy and Toxicology* 1988;**26**(3):129–132. [MEDLINE: 88314399]

Cappuccio 1997 {published data only}

* Cappuccio FP, Markandu ND, Carney C, Sagnella GA, MacGregor GA. Double-blind randomised trial of modest salt restriction in older people [see comments]. *Lancet* 1997; **350**(9081):850–854. [MEDLINE: 97456646]

Carney 1975 {published data only}

Carney S, Morgan T, Wilson M, Matthews G, Roberts R. Sodium restriction and thiazide diuretics in the treatment

- of hypertension. *Medical Journal of Australia* 1975;**1**(26): 803–807. [MEDLINE: 75215971]
- Corcoran 1951** *{published data only}*
 * Corcoran AC, Taylor RD, Page IH. Controlled observations on the effect of low sodium dietotherapy in essential hypertension. *Circulation* 1951;**III**:1–16.
- Dahl 1958** *{published data only}*
 Dahl L, Silver L, Christie R. The role of salt in the fall of blood pressure accompanying reduction in obesity. *New England Journal of Medicine* 1958;**258**:1186–1192. [MEDLINE: 58095969]
- DASH** *{published data only}*
 Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, Bray GA, Vogt TM, Cutler JA, Windhauser MM, Lin PH, Karanja N. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. *N Engl J Med* 1997;**336**(16):1117–1124. [MEDLINE: 97238752]
 Sacks FM, Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Bray GA, Vogt TM, Cutler JA, Windhauser MM, Lin PH, Karanja N. A dietary approach to prevent hypertension: a review of the dietary approaches to stop hypertension (DASH) study. *Clinical Cardiology* 1999;**22**(7 Supplement):III 6–10. [MEDLINE: 99338488]
 Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, Obarzanek E, Conlin PR, Miller ERI, Simons-Morton DG, Karanja N, Lin P-H, Aickin M, Most-Windhauser MM, Moore TJ, Proschan MA, Cutler JA. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. *New England Journal of Medicine* 2001;**344**(1):3–10. [MEDLINE: 21012263]
 Svetkey LP, Simons-Morton DG, Vollmer WM, Appel LJ, Conlin PR, Ryan DH, Ard J, Kennedy BM. Effects of dietary patterns on blood pressure: subgroup analysis of the dietary approaches to stop hypertension (DASH) randomized clinical trial. *Archives of Internal Medicine* 1999;**159**(3):285–293. [MEDLINE: 99142647]
- DISH** *{published data only}*
 * Blafox MD, Langford HG, Oberman A, Hawkins CM, Wassertheil SS, Cutter GR. Effect of dietary change on the return of hypertension after withdrawal of prolonged antihypertensive therapy (DISH). Dietary Intervention Study of Hypertension. *J Hypertens Suppl* 1984;**2**(3): S179–S181. [MEDLINE: 86199066]
 Langford HG, Blafox MD, Oberman A, Hawkins CM, Curb JD, Cutter GR, Wassertheil SS, Pressel S, Babcock C, Abernethy JD, et al. Dietary therapy slows the return of hypertension after stopping prolonged medication. *JAMA* 1985;**253**(5):657–664. [MEDLINE: 85108285]
 Wassertheil SS, Blafox MD, Langford HG, Oberman A, Cutter G, Pressel S. Prediction of response to sodium intervention for blood pressure control. *J Hypertens Suppl* 1986;**4**(5):S343–S346. [MEDLINE: 87197751]
 Wassertheil SS, Langford HG, Blafox MD, Oberman A, Hawkins M, Levine B, Cameron M, Babcock C, Pressel S, Caggiula A, et al. Effective dietary intervention in hypertensives: sodium restriction and weight reduction. *J Am Diet Assoc* 1985;**85**(4):423–430. [MEDLINE: 85158652]
- Dole 1951** *{published data only}*
 Dole V, Dahl L, Cotzias G, Dziewiatkowski D, Harris C. Dietary treatment of hypertension. II Sodium depletion as related to the therapeutic effect. *Journal of Clinical Investigation* 1951;**30**:584–595.
- Dubbert 1995** *{published data only}*
 Dubbert PM, Cushman WC, Meydrech EF, Rowland AK, Maury P. Effects of dietary instruction and sodium excretion feedback in hypertension clinic patients. *Behavior Therapy* 1995;**26**(4):721–732. [MEDLINE: 1995342245]
- Erwteman 1984** *{published data only}*
 * Erwteman TM, Nagelkerke N, Lubsen J, Koster M, Dunning AJ. Beta blockade, diuretics, and salt restriction for the management of mild hypertension: a randomised double blind trial. *Br Med J Clin Res Ed* 1984;**289**(6442): 406–409. [MEDLINE: 84281599]
- Evers 1987** *{published data only}*
 Evers SE, Bass M, Donner A, McWhinney IR. Lack of impact of salt restriction advice on hypertensive patients. *Preventive Medicine* 1987;**16**(2):213–220. [MEDLINE: 87231784]
- Fagerberg 1984** *{published data only}*
 * Fagerberg B, Andersson OK, Isaksson B, Bjornorp P. Blood pressure control during weight reduction in obese hypertensive men: separate effects of sodium and energy restriction. *Br Med J Clin Res Ed* 1984;**288**(6410):11–14. [MEDLINE: 84081362]
- Geleijnse 1995** *{published data only}*
 * Geleijnse JM, Witteman JC, Bak AA, den BJ, Grobbee DE. Long-term moderate sodium restriction does not adversely affect the serum HDL/total cholesterol ratio. *J Hum Hypertens* 1995;**9**(12):975–979. [MEDLINE: 96362947]
- Gillum 1983** *{published data only}*
 * Gillum RF, Prineas RJ, Jeffery RW, Jacobs DR, Elmer PJ, Gomez O, Blackburn H. Nonpharmacologic therapy of hypertension: the independent effects of weight reduction and sodium restriction in overweight borderline hypertensive patients. *Am Heart J* 1983;**105**(1):128–133. [MEDLINE: 83097284]
- Grimm 1990** *{published data only}*
 * Grimm RH Jr, Neaton JD, Elmer PJ, Svendsen KH, Levin J, Segal M, Holland L, Witte LJ, Clearman DR, Kofron P, La Bounty RK, Crow R, Prineas RJ. The influence of oral potassium chloride on blood pressure in hypertensive men on a low-sodium diet. *N Engl J Med* 1990;**322**(9):569–574. [MEDLINE: 90158725]
- HCP** *{published data only}*
 Stamler R, Grimm RH Jr, Dyer AR, Talano JV, Prineas R, Crow R, Berman R, Gosch FC, Elmer P, Stamler J. Cardiac status after four years in a trial on nutritional therapy

- for high blood pressure. *Arch Intern Med* 1989;**149**(3): 661–665. [MEDLINE: 89149275]
- Stamler R, Stamler J, Grimm R, Dyer A, Gosch FC, Berman R, Elmer P, Fishman J, Van Heel N, Civinelli J, Hoeksema R. Nonpharmacological control of hypertension. *Prev Med* 1985;**14**(3):336–345. [MEDLINE: 86042572]
- Stamler R, Stamler J, Grimm R, Gosch F, Dyer A, Berman R, Civinelli J, Elmer P, Fishman J, Van Heel N, McDonald A, McKeever P. Trial on control of hypertension by nutritional means: three-year results. *J Hypertens Suppl* 1984;**2**(3):S167–S170. [MEDLINE: 87141518]
- Stamler R, Stamler J, Grimm R, Gosch FC, Elmer P, Dyer A, Berman R, Fishman J, Van Heel N, Civinelli J, McDonald A. Nutritional therapy for high blood pressure. Final report of a four-year randomized controlled trial--the Hypertension Control Program. *JAMA* 1987;**257**(11): 1484–1491. [MEDLINE: 87141518]
- Stamler R, Stamler J, Grimm R, Gosch FC, Elmer P, Dyer A, Berman R, Fishman J, Van Heel N, Civinelli J, McDonald A. Nutritional therapy for high blood pressure. Final report of a four-year randomized controlled trial--the Hypertension Control Program. *JAMA* 1987;**257**(11): 1484–1491. [MEDLINE: 86199063]
- Henningsen 1980** *{published data only}*
- * Henningsen NC. Salt and essential hypertension. [Swedish]. *Var Foda* 1980;**32**(6/7):345–354.
- Holly 1981** *{published data only}*
- * Holly JM, Goodwin FJ, Evans SJ, Vandenburg MJ, Ledingham JM. Re-analysis of data in two Lancet papers on the effect of dietary sodium and potassium on blood pressure. *Lancet* 1981;**2**(8260-61):1384–1387. [MEDLINE: 82079762]
- Iwaoka 1994** *{published data only}*
- * Iwaoka T, Umeda T, Inoue J, Naomi S, Sasaki M, Fujimoto Y, Gui C, Ideguchi Y, Sato T. Dietary NaCl restriction deteriorates oral glucose tolerance in hypertensive patients with impairment of glucose tolerance. *Am J Hypertens* 1994;**7**(5):460–463. [MEDLINE: 94338640]
- Jula 1990** *{published data only}*
- * Jula A, Ronnema T, Rastas M, Karveti RL, Maki J. Long-term nopharmacological treatment for mild to moderate hypertension. *J Intern Med* 1990;**227**(6): 413–421. [MEDLINE: 90278339]
- Jula 1992a** *{published data only}*
- * Jula A, Ronnema T, Tikkanen I, Karanko H. Responses of atrial natriuretic factor to long-term sodium restriction in mild to moderate hypertension. *J Intern Med* 1992;**231**(5): 521–529. [MEDLINE: 92291706]
- Jula 1992b** *{published data only}*
- * Jula AM, Ronnema TE, Piha SJ, Maki JP. Response of diastolic blood pressure to long-term sodium restriction is posture related. *Scandinavian Journal of Clinical and Laboratory Investigation* 1992;**52**(3):159–167. [MEDLINE: 9303401]
- Jula 1994** *{published data only}*
- * Jula AM, Karanko HM. Effects on left ventricular hypertrophy of long-term nonpharmacological treatment with sodium restriction in mild-to-moderate essential hypertension. *Circulation* 1994;**89**(3):1023–1031. [MEDLINE: 94170458]
- Koopman 1990** *{published data only}*
- * Koopman H, Spreeuwenberg C, Westerman RF, Donker AJ. Dietary treatment of patients with mild to moderate hypertension in a general practice: a pilot intervention study (2). Beyond three months. *J Hum Hypertens* 1990;**4**(4):372–374. [MEDLINE: 91080076]
- Koopman H, Spreeuwenberg C, Westerman RF, Donker AJM. Dietary treatment of patients with mild to moderate hypertension in a general practice: a pilot intervention study. (2) Beyond 3 months. *Journal of Human Hypertension* 1990;**4**(4):372–374. [MEDLINE: 91080076]
- Korhonen 1999** *{published data only}*
- Korhonen MH, Litmanen H, Rauramaa R, Vaisanen SB, Niskanen L, Uusitupa J. Adherence to the salt restriction diet among people with mildly elevated blood pressure. *European Journal of Clinical Nutrition* 1999;**53**(11): 880–885. [MEDLINE: 20025972]
- Logan 1986** *{published and unpublished data}*
- Logan AG. Sodium manipulation in the management of hypertension. The view against its general use. *Canadian Journal of Physiology and Pharmacology* 1986;**64**(6): 793–802. [MEDLINE: 87001697]
- * Logan AG, Flanagan PT, Haynes RB. Effect of dietary sodium restriction alone in the treatment of mild hypertension. unpublished.
- MacGregor 1982a** *{published data only}*
- MacGregor GA, Markandu ND, Sagnella GA. Dietary sodium restriction in normotensive subjects and patients with essential hypertension. *Clin Sci* 1982;**63**:399S–402S.
- MacGregor 1982b** *{published data only}*
- MacGregor GA, Markandu ND, Best FE, Elder DM, Cam JM, Sagnella GA, Squires M. Double-blind randomised crossover trial of moderate sodium restriction in essential hypertension. *Lancet* 1982;**1**(8268):351–355. [MEDLINE: 82123995]
- MacGregor 1989** *{published data only}*
- * MacGregor GA, Markandu ND, Sagnella GA, Singer DR, Cappuccio FP. Double-blind study of three sodium intakes and long-term effects of sodium restriction in essential hypertension. *Lancet* 1989;**2**(8674):1244–1247. [MEDLINE: 90065792]
- Magnani 1976** *{published data only}*
- Magnani B, Ambrosioni E, Agosta R, Racco F. Comparison of the effects of pharmacological therapy and a low-sodium diet on mild hypertension. *Clin Sci Mol Med Suppl* 1976;**3**: 625S–626S. [MEDLINE: 77161090]
- McDonald 1988** *{published data only}*
- * McDonald AM, Dyer AR, Liu K, Stamler R, Gosch FC, Grimm R, Berman R, Stamler J. Sodium, lithium-countertransport and blood pressure control by nutritional

- intervention in 'mild' hypertension. *J Hypertens* 1988;**6**(4): 283–291. [MEDLINE: 88244364]
- Morgan 1988** {published data only}
Morgan T, Anderson A. Interaction in hypertensive men between sodium intake, converting enzyme inhibitor (enalapril), plasma renin and blood pressure control. *Journal of Human Hypertension* 1988;**1**(4):311–315. [MEDLINE: 89125550]
- Muhlhauser 1993** {published data only}
* Muhlhauser I, Sawicki PT, Didjurgeit U, Jorgens V, Trampisch HJ, Berger M. Evaluation of a structured treatment and teaching programme on hypertension in general practice. *Clin Exp Hypertens* 1993;**15**(1):125–142. [MEDLINE: 93222829]
- Myers 1989** {published data only}
Myers JB. Reduced sodium chloride intake normalises blood pressure distribution. *Journal of Human Hypertension* 1989;**3**(2):97–104. [MEDLINE: 89342389]
- Nestel 1993** {published data only}
* Nestel PJ, Clifton PM, Noakes M, McArthur R, Howe PR. Enhanced blood pressure response to dietary salt in elderly women, especially those with small waist:hip ratio. *Journal of Hypertension* 1993;**11**(12):1387–1394. [MEDLINE: 94179778]
- Neyses 1985** {published data only}
* Neyses L, Dorst K, Michaelis J, Berres M, Philipp T, Distler A, Losse H, Vetter H, Epstein FH, Vetter W. Compliance with salt restriction as a limiting factor in the primary prevention of hypertension. *J Hypertens Suppl* 1985;**3**(1):S87–S90. [MEDLINE: 87253502]
- Nicholson 1986** {published data only}
* Nicholson JP, Resnick LM, Laragh JA. The impact of dietary sodium intake on the hypotensive response of verapamil in essential hypertension. *J Clin Hypertens* 1986;**2**(3 Suppl):143S–147S. [MEDLINE: 87085718]
- Nicholson 1987** {published data only}
* Nicholson JP, Resnick LM, Laragh JH. The antihypertensive effect of verapamil at extremes of dietary sodium intake. *Ann Intern Med* 1987;**107**(3):329–334. [MEDLINE: 87297036]
- Nowson 1988** {published data only}
* Nowson CA, Morgan TO. Change in blood pressure in relation to change in nutrients effected by manipulation of dietary sodium and potassium. *Clinical and Experimental Pharmacology and Physiology* 1988;**15**(3):225–242. [MEDLINE: 90150703]
- Nugent 1984** {published data only}
Nugent CA, Carnahan JE, Sheehan ET, Myers C. Salt restriction in hypertensive patients. Comparison of advice, education and group management.. *Archives of Internal Medicine* 1984;**144**(7):1415–1417. [MEDLINE: 84230406]
- ODES** {published data only}
Anderssen S, Holme I, Urdal P, Hjermmann I. Diet and exercise intervention have favourable effects on blood pressure in mild hypertensives: the Oslo Diet and Exercise Study. (ODES). *Blood Pressure* 1995;**4**(6):343–349. [MEDLINE: 96356286]
- Omvik 1986** {published data only}
* Omvik P, Lund-Johansen P. Is sodium restriction effective treatment of borderline and mild essential hypertension? A long-term haemodynamic study at rest and during exercise.. *Journal of Hypertension* 1986;**4**(5):535–541. [MEDLINE: 87084739]
- Omvik 1995** {published data only}
* Omvik P, Myking OL. Unchanged central hemodynamics after six months of moderate sodium restriction with or without potassium supplement in essential hypertension. *Blood Press* 1995;**4**(1):32–41. [MEDLINE: 95253445]
- Parijs 1973** {published data only}
* Parijs J, Joossens JV, Van der Linden L, Verstreken G, Amery AK. Moderate sodium restriction and diuretics in the treatment of hypertension. *American Heart Journal* 1973;**85**(1):22–34. [MEDLINE: 73052205]
- Perera 1947** {published data only}
Perera G, Blood D. The relationship of sodium choride to hypertension. *Journal of Clinical Investigation* 1947;**26**: 1109–1117.
- Priddle 1962** {published data only}
Priddle W. Hypertension-sodium and potassium studies. *Journal of the Canadian Medical Association* 1962;**86**(1):1–9. [Medline Unique Identifier is 62090301]
- Rissanen 1985** {published data only}
* Rissanen A, Pietinen P, Siljamaki OU, Piirainen H, Reissel P. Treatment of hypertension in obese patients: efficacy and feasibility of weight and salt reduction programs. *Acta Med Scand* 1985;**218**(2):149–156. [MEDLINE: 86047190]
- Roca-Cusachs 1991** {published data only}
* Roca-Cusachs A, Sort D, Altimira J, Bonet R, Guileria E, Monmany J, Nolla J. The impact of a patient education programme in the control of hypertension. *J Hum Hypertens* 1991;**5**(5):437–441. [MEDLINE: 92122169]
- Sagnella 1987** {published data only}
* Sagnella GA, Markandu ND, Buckley MG, Singer DR, Sugden AL, Shore AC, MacGregor GA. Plasma atrial natriuretic peptide in essential hypertension: effects of changes in dietary sodium. *Br Med J Clin Res Ed* 1987;**295** (6595):417–418. [MEDLINE: 88001459]
- Shibata 1979** {published data only}
Shibata H, Hatano S. A salt restriction trial in Japan. In: Gross F, Strasser T editor(s). *Mild hypertension: natural history and management*. Bath: Pitman Medical, 1979.
- Singer 1984** {published data only}
Singer DR, Markandu ND, Cappuccio FP, Miller MA, Sagnella GA, Skrabal F, Gasser RW, Finkenstedt G, Rhomberg HP, Lochs A. Low-sodium diet versus low-sodium/high-potassium diet for treatment of hypertension. *Klinische Wochenschrift* 1984;**62**(3):124–128. [MEDLINE: 84165933]

Singer 1995 *{published data only}*

Singer DR, Markandu ND, Cappuccio FP, Miller MA, Sagnella GA, MacGregor GA. Reduction of salt intake during converting enzyme inhibitor treatment compared with addition of a thiazide. *Hypertension* 1995;**25**(5): 1042–1044. [MEDLINE: 95255896]

Stamler 1989 *{published data only}*

Stamler R, Stamler J, Gosch FC, Civinelli J, Fishman J, McKeever P, McDonald A, Dyer AR. Primary prevention of hypertension by nutritional-hygienic means. Final report of a randomized, controlled trial [published erratum appears in *JAMA* 1989 Dec 8;262(22):3132]. *JAMA* 1989;**262**(13):1801–1807. [MEDLINE: 89382841]

Stamler R, Stamler J, Gosch FC, McDonald AM. Primary prevention of hypertension—a randomized controlled trial. *Ann Clin Res* 1984;**16**(Supplement 43):136–142. [MEDLINE: 85223780]

TAIM *{published data only}*

Blaufox MD, Lee HB, Davis B, Oberman A, Wassertheil-Smoller S, Langford H. Renin predicts diastolic blood pressure response to nonpharmacologic and pharmacologic therapy. *JAMA* 1992;**267**(9):1221–1225. [MEDLINE: 92167529]

Davis BR, Blaufox MD, Oberman A, Wassertheil-Smoller S, Zimbaldi N, Cutler JA, Kirchner K, Langford HG. Reduction in long-term antihypertensive medication requirements. Effects of weight reduction by dietary intervention in overweight persons with mild hypertension. *Arch Intern Med* 1993;**153**(15):1773–1782. [MEDLINE: 93326077]

Davis BR, Oberman A, Blaufox MD, Wassertheil-Smoller S, Hawkins CM, Cutler JA, Zimbaldi N, Langford HG. Effect of antihypertensive therapy on weight loss. The Trial of Antihypertensive Interventions and Management Research Group. *Hypertension* 1992;**19**(4):393–399. [MEDLINE: 92210170]

Davis BR, Oberman A, Blaufox MD, Wassertheil-Smoller S, Zimbaldi N, Kirchner K, Wylie-Rosett J, Langford HG. Lack of effectiveness of a low-sodium/high-potassium diet in reducing antihypertensive medication requirements in overweight persons with mild hypertension. TAIM Research Group. Trial of Antihypertensive Interventions and Management. *Am J Hypertens* 1994;**7**(10 Pt 1): 926–932. [MEDLINE: 95127141]

Langford HG, Davis BR, Blaufox D, Oberman A, Wassertheil-Smoller S, Hawkins M, Zimbaldi N. Effect of drug and diet treatment of mild hypertension on diastolic blood pressure. The TAIM Research Group. *Hypertension* 1991;**17**(2):210–217. [MEDLINE: 91122830]

Oberman A, Wassertheil-Smoller S, Langford HG, Blaufox MD, Davis BR, Blaszkowski T, Zimbaldi N, Hawkins CM. Pharmacologic and nutritional treatment of mild hypertension: changes in cardiovascular risk status [see comments]. *Ann Intern Med* 1990;**112**(2):89–95. [MEDLINE: 90103317]

Wassertheil-Smoller S, Davis BR, Breuer B, Chee JC, Oberman A, Blaufox MD. Differences in precision of dietary

estimates among different population subgroups. *Ann Epidemiol* 1993;**3**(6):619–628. [MEDLINE: 95005518]

Wassertheil-Smoller S, Oberman A, Blaufox MD, Davis B, Langford H. The Trial of Antihypertensive Interventions and Management (TAIM) Study. Final results with regard to blood pressure, cardiovascular risk, and quality of life [see comments]. *Am J Hypertens* 1992;**5**(1):37–44. [MEDLINE: 92144045]

Wylie-Rosett J, Wassertheil-Smoller S, Blaufox MD, Davis BR, Langford HG, Oberman A, Jennings S, Hataway H, Stern J, Zimbaldi N. Trial of antihypertensive intervention and management: greater efficacy with weight reduction than with a sodium-potassium intervention. *J Am Diet Assoc* 1993;**93**(4):408–415. [MEDLINE: 93203528]

TOMHS *{published data only}*

* Elmer PJ, Grimm R Jr, Laing B, Grandits G, Svendsen K, Van Heel N, Betz E, Raines J, Link M, Stamler J and Neaton J for the TOMHS Research Group. Lifestyle intervention: results of the Treatment of Mild Hypertension Study (TOMHS). *Prev Med* 1995;**24**(4):378–388. [MEDLINE: 96076094]

Neaton JD, Grimm RH Jr, Prineas RJ, et al. Treatment of mild hypertension study: final results. *Journal of the American Medical Association* 1993;**270**(6):713–724. [MEDLINE: 93329754]

Stamler J, Prineas RJ, Neaton JD, et al. Background and design of the new U.S. trial on diet and drug treatment of “mild” hypertension (TOMHS). *American Journal of Cardiology* 1987;**59**(14):51G–60G. [MEDLINE: 87238420]

Treatment of Mild Hypertension Research Group. The treatment of mild hypertension study. A randomized, placebo-controlled trial of a nutritional-hygienic regimen along with various drug monotherapies. *Archives of Internal Medicine* 1991;**151**(7):1413–1423. [MEDLINE: 91290967]

Velloso 1991 *{published data only}*

* Velloso LG, Alonso RR, Ciscato CM, Barretto AC, Bellotti G, Pileggi F. [Diet with usual quantity of salt in hospital treatment of congestive heart insufficiency]. *Arq Bras Cardiol* 1991;**57**(6):465–468. [MEDLINE: 92398510]

Watt 1983 *{published data only}*

Watt GC, Edwards C, Hart JT, Hart M, Walton P, Foy CJ. Dietary sodium restriction for mild hypertension in general practice. *British Medical Journal Clinical Research*. *Ed* 1983;**286**(6363):432–436. [MEDLINE: 83102255]

Watt 1986 *{published data only}*

* Watt GC, Foy CJ, Hart JT. Dietary sodium and blood pressure in young people with and without familial predisposition to high blood pressure. *J Clin Hypertens* 1986;**2**(2):141–147. [MEDLINE: 87010734]

Weinberger 1988 *{published data only}*

* Weinberger MH, Cohen SJ, Miller JZ, Luft FC, Grim CE, Fineberg NS. Dietary sodium restriction as adjunctive treatment of hypertension. *JAMA* 1988;**259**(17):2561–2565. [MEDLINE: 88188298]

Wing 1984 {published data only}

Wing RR, Caggiula AW, Nowalk MP, Koeske R, Lee S, Langford H. Dietary approaches to the reduction of blood pressure: the independence of weight and sodium/potassium interventions. *Preventive Medicine* 1984;**13**(3): 233–244. [MEDLINE: 85038455]

Zoccali 1993 {published data only}

* Zoccali C, Mallamaci F, Leonardis D, Romeo M. Randomly allocated crossover study of various levels of sodium intake in patients with mild hypertension. *J Hypertens Suppl* 1993;**11**(Suppl 5):S326–S327. [MEDLINE: 94210208]

Additional references**Alam 1999**

Alam S, Johnson AG. A meta-analysis of randomised controlled trials (RCT) among healthy normotensive and essential hypertensive elderly patients to determine the effect of high salt (NaCl) diet of blood pressure. *J Hum Hypertens* 1999;**13**(6):367–374. [MEDLINE: 99335071]

Alderman 1995

Alderman MH, Madhavan S, Cohen H, Sealey JE, Laragh JH. Low urinary sodium is associated with greater risk of myocardial infarction among treated hypertensive men. *Hypertension* 1995;**25**(6):1144–1152. [MEDLINE: 95286216]

Alderman 1997

Alderman MH, Ooi WL, Cohen H, Madhavan S, Sealey JE, Laragh JH. Plasma renin activity: a risk factor for myocardial infarction in hypertensive patients. *American Journal of Hypertension* 1997;**10**(1):1–8. [MEDLINE: 97160946]

Alderman 1998

Alderman MH, Cohen H, Madhavan S. Dietary sodium intake and mortality: the National Health and Nutrition Examination Survey (NHANES I). *Lancet* 1998;**351**(9105): 781–785. [MEDLINE: 98178771]

Allender 1996

Allender PS, Cutler JA, Follmann D, Cappuccio FP, Pryer J, Elliott P. Dietary calcium and blood pressure: a meta-analysis of randomized clinical trials. *Annals of Internal Medicine* 1996;**124**(9):825–831. [MEDLINE: 96188897]

Anonymous 2000

Anonymous. Assessment of study quality. In: Clarke M, Oxman AD editor(s). *Cochrane Reviewer's Handbook 4.1 [updated June 2000]*. Oxford: Update Software, 2000.. Oxford: Update Software, 2000.

Barker 1998

Barker DJP. *Mothers, babies and health in later life*. Second Edition. Edinburgh: Churchill Livingstone, 1998.

Berkley 1995

Berkey CS, Hoaglin DC, Mosteller F, Colditz GA. A random-effects regression model for meta-analysis. *Statistics in Medicine* 1995;**14**(4):395–411. [MEDLINE: 95265785]

Brand 1999

Brand MB, Mulrow CD, Chiquette E, Angel L, Cornell J, Summerbell CD, Anagnostelis B, Grimm RJ. Dieting to reduce body weight for controlling hypertension in adults. *Cochrane Database of Systematic Reviews* 2000, Issue 2. [DOI: 10.1002/14651858.CD000484; MEDLINE: 10796721]

Cappuccio 1991

Cappuccio FP, MacGregor GA. Does potassium supplementation lower blood pressure? A meta-analysis of published trials. *Journal of Hypertension* 1991;**9**(5): 465–473. [MEDLINE: 91311080]

Cutler 1997

Cutler JA, Follmann D, Allender PS. Randomized trials of sodium reduction: an overview. *American Journal of Clinical Nutrition* 1997;**65**(2 Suppl):643S–651S. [MEDLINE: 97174900]

DoH 2001

Department of Health. The Annual Report of the Chief Medical Officer of the Department on Health 2001. Department of Health. London, 2001.

Donner 1982

Donner A. An empirical study of cluster randomization. *International Journal of Epidemiology* 1982;**11**(3):283–286. [MEDLINE: 83029945]

Ebrahim 1996

Ebrahim S, Davey Smith G. *Health promotion in older people for the prevention of coronary heart disease and stroke*. London: Health Education Authority, 1996.

Ebrahim 1998

Ebrahim S, Davey Smith G. Lowering blood pressure: a systematic review of sustained effects of non-pharmacological interventions. *Journal of Public Health Medicine* 1998;**20**(4):441–448. [MEDLINE: 99120827]

Elliott 1996

Elliott P, Stamler J, Nichols R, Dyer AR, Stamler R, Kesteloot H, Marmot M. Intersalt revisited: further analyses of 24 hour sodium excretion and blood pressure within and across populations. Intersalt Cooperative Research Group.[erratum appears in BMJ 1997 Aug 23;315(7106): 458.]. *BMJ* 1996;**312**(7041):1249–1253. [MEDLINE: 96225304]

Follman 1992

Follman D, Elliott P, Suh I, Cutler J. Variance imputation for overviews of clinical trials with continuous response. *J Clin Epidemiol* 1992;**45**(7):769–773. [MEDLINE: 92317975]

Graudal 1998

Graudal NA, Galloe AM, Garred P. Effects of sodium restriction on blood pressure, renin, aldosterone, catecholamines, cholesterols and triglyceride: a meta-analysis. *JAMA* 1998;**279**(17):1383–1391. [MEDLINE: 98241203]

Griffith 1999

Griffith LE, Guyatt GH, Cook RJ, Bucher HC, Cook DJ. The influence of dietary and non-dietary

- calcium supplementation on blood pressure. An updated metaanalysis of randomized controlled trials. *American Journal of Hypertension* 1999;**12**(1 Pt 1):84–92. [MEDLINE: 99173714]
- Hauck 1991**
Hauck WW, Gilliss CL, Donner A, Gortner S. Randomization by cluster. *Nursing Research* 1991;**40**(6):356–358. [MEDLINE: 92066521]
- He 1999**
He J, Ogden LG, Vupputuri S, Bazzano LA, Loria C, Whelton PK. Dietary sodium intake and subsequent risk of cardiovascular disease in overweight adults. *JAMA* 1999;**282**(21):2027–2034. [MEDLINE: 20057342]
- He 2001**
He FJ, MacGregor GA. Neonatal salt intake and blood pressure. *Lancet* 2001;**357**(9271):1880. [MEDLINE: 21307932]
- Hofman 1983**
Hofman A, Hazebroek A, Valkenburg HA. A randomized trial of sodium intake and blood pressure in newborn infants. *JAMA* 1983;**250**(3):370–373. [MEDLINE: 83216582]
- Hooper 2000**
Hooper L, Summerbell CD, Higgins JPT, Thompson RL, Clements G, Capps N, Davey Smith G, Riemersma RA, Ebrahim S. Reduced or modified dietary fat for preventing cardiovascular disease. *Cochrane Database of Systematic Reviews* 2000, Issue 2. [DOI: 10.1002/14651858.CD002137]
- Jurgens 2003**
Jurgens G, Graudal NA. Effects of low sodium diet versus high sodium diet on blood pressure, renin, aldosterone, catecholamines, cholesterols, and triglyceride. *Cochrane Database of Systematic Reviews* 2003, Issue 4. [DOI: 10.1002/14651858.CD004022.pub2]
- Law 1991**
Law MR, Frost CD, Wald NJ. By how much does dietary salt reduction lower blood pressure? III--Analysis of data from trials of salt reduction. [erratum appears in BMJ 1991 Apr 20;302(6782):939.]. *BMJ* 1991;**302**(6780):819–824. [MEDLINE: 91223292]
- Lucas 1988**
Lucas A, Morley R, Husdon GJ, Bamford MF, Boon A, Crowle P, Dossetor JF, Pearse R. Early sodium intake and later blood pressure in preterm infants. *Archives of Disease in Childhood* 1988;**63**(6):656–657. [MEDLINE: 88268226]
- MacGregor 1996**
MacGregor GA, Sever PS. Salt -- overwhelming evidence but still no action: can a consensus be reached with the food industry? CASH (Consensus Action on Salt and Hypertension).. *BMJ* 1996;**312**(7041):1287–1289. [MEDLINE: 96225315]
- MAFF 1999**
MAFF. *National Food Survey, 1998. Annual report of food expenditure, consumption and nutrient intakes.* London: HMSO, 1999.
- Midgley 1996**
Midgley JP, Matthew AG, Greenwood CM, Logan AG. Effect of reduced dietary sodium on blood pressure: a meta-analysis of randomized controlled trials. *JAMA* 1996;**275**(20):1590–1597. [MEDLINE: 96213904]
- Navar 1997**
Navar LG. The kidney in blood pressure regulation and development of hypertension. *Medical Clinics of North America* 1997;**81**(5):1165–1198. [MEDLINE: 97453984]
- Ramsay 1999**
Ramsay LE, Williams B, Johnston GD, MacGregor GA, Poston L, Potter JF, Poulter NR, Russell G. British Hypertension Society guidelines for hypertension management 1999: summary. *BMJ* 1999;**319**(7210):630–635. [MEDLINE: 99402837]
- Ramsay 1999a**
Ramsay L, Williams B, Johnston G, MacGregor G, Poston L, Potter J, Poulter N, Russell G. Guidelines for management of hypertension: report of the third working party of the British Hypertension Society. *Journal of Human Hypertension* 1999;**13**(9):569–592. [MEDLINE: 99414258]
- Sacks 2001**
Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, Obarzanek E, Conlin PR, Miller ERI, Simons-Morton DG, Karanja N, Lin P-H, Aickin M, Most-Windhauser MM, Moore TJ, Proschan MA, Cutler JA. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. *New England Journal of Medicine* 2001;**344**(1):3–10. [MEDLINE: 21012263]
- Selmer 2000**
Selmer RM, Kristiansen IS, Haglerod A, Graff-Iverson S, Larsen HK, Meyer HE, Bonna KH, Thelle DS. Cost and health consequences of reducing the population intake of salt. *Journal of Epidemiology and Community Health* 2000;**54**(9):697–702. [MEDLINE: 20400582]
- Sharp 1998**
Sharp S. Meta-analysis regression. *Stata Technical Bulletin* 1998;**42**:16–22. [ISBN 1-881228-31-2]
- Singhal 2001**
Singhal A, Cole TJ, Lucas A. Early nutrition in preterm infants and later blood pressure: two cohorts after randomised trials. *Lancet* 2001;**357**(9254):413–419. [MEDLINE: 21119870]
- Stamler 1991**
Stamler R. Implications of the INTERSALT study. *Hypertension* 1991;**17**(1 suppl):I 16-I 20. [MEDLINE: 91099886]
- Taubes 1998**
Taubes G. The (political) science of salt. *Science* 1998;**281**(5379):898–907. [MEDLINE: 98383455]
- Tunstall-Pedoe 1997**
Tunstall-Pedoe H, Woodward M, Tavendale R, A'Brook R, McCluskey MK. Comparison of the prediction by 27

different factors of coronary heart disease and death in men and women of the Scottish heart health study: cohort study. [erratum appears in BMJ 1998 Jun 20;316(7148):1881.]. *BMJ* 1997;**315**(7110):722–729. [MEDLINE: 97460376]

Tuomilehto 2001

Tuomilehto J, Jousilahti P, Rastenyte D, Moltchanov V, Tanskanen A, Pietinen P, Nissinen A. Urinary sodium excretion and cardiovascular mortality in Finland: a prospective study. *Lancet* 2001;**357**(9259):848–851. [MEDLINE: 21163719]

Whelton 1997

Whelton PK, He J, Cutler JA, Brancati FL, Appel LJ, Follmann D, Klag MJ. Effects of oral potassium on blood

pressure. Meta-analysis of randomized controlled clinical trials. *Journal of the American Medical Association* 1997;**277**(20):1624–1632. [MEDLINE: 97311576]

References to other published versions of this review

Hooper 2002

Hooper L, Bartlett C, Davey Smith G, Ebrahim S. Longer electronic version of this review on BMJ website, <http://bmj.com/> [Systematic review of long term effects of advice to reduce dietary salt in adults]. *British Medical Journal* 2002;**325**(7365):628–632. [EMBASE Accession Number is 2002347601]

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Alli 1992

Methods	RCT: GPs were 'selected at random' (GPs were randomised, not participants, 9 gave dietary advice and 10 did not)
Participants	Untreated hypertensives, Italy, mean age 48 years, 42% male, ?% white, BMI<30. Inclusion criteria: DBP 90-104 mmHg over 6 weeks, not on AHTM
Interventions	LS: received low sodium dietary advice (individual counselling by GP, reinforced at each clinic visit. Main messages (leaflet) don't add salt at table or in cooking, restrict salty processed foods, eat more fresh/ frozen foods and seasoning advice), USE Target: <=80, C maintained usual diet
Outcomes	BP & USE at 1,3,6, 9 & 12 mo
Notes	PB: no. OAB: no AL: Losses excluded. Assigned: LS 40, C 37 Follow up: LS 26, C 30 (12 mo)

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	No	C - Inadequate

Arroll 1995

Methods	RCT: 'factorial type RCT design'.
Participants	Treated hypertensives, New Zealand, mean age 55 years, 52% male, ?% white. Inclusion criteria: AHTM treated hypertension (DBP >70 to 105 mmHg or SBP >155 to 180 mmHg)
Interventions	LS: on medication, asked to reduce use of high salt foods, salt added at table and in cooking (led by whom? , group or individual?). Each given an article on BP and salt restriction, a leaflet and a book with the Na content of common foods , USE Target: Not specified, C: on medication, no intervention
Outcomes	BP & AHTM levels following withdrawal of AHTM at 0 and 6 mo, USE at 6 mo
Notes	PB: no OAB: yes AL: Losses excluded from BP measurement. No adjustment made for those who decreased or stopped medication

Arroll 1995 (Continued)

	Assigned: LS 51, C 49 Follow up: LS 44, C 43 (6 mo)	
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Costa 1981

Methods	RCT: 'randomly divided into 2 groups'.
Participants	Untreated hypertensives, Italy, age range 16-31 years, ?% male, ?% white. Inclusion criteria: untreated borderline hypertension
Interventions	LS: given a low salt diet (no data on who gave advice, group or individual counselling, materials used, or main messages), Target: 3 g NaCl/day, C: advised on diet with free salt intake
Outcomes	BP & intra-lymphocytic sodium at 0 & 12 mo
Notes	PB: no. OAB: unclear. AL: Not specified. Assigned: LS 21, C 20 Follow up: LS 20, C 21 (sic)

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

HPT

Methods	RCT: randomisation code 'centrally generated by computer'.
Participants	Normotensives, USA, mean age 39 years, 62% male, 84% white. Inclusion criteria: high normotensive, DBP 78-89, not on AHTM
Interventions	LS: on dietary and behavioural change programme (led by personnel trained and experienced in effecting behaviour change related to food, group sessions with individual counselling if sessions missed, newsletter between sessions, self assessment, goal setting, participant manual, food counter, cookbook, food demonstrations and tasting, team building exercises, tokens of accomplishment), USE Target: ≤ 70 , C: no dietary counselling

HPT (Continued)

Outcomes	BP & USE at 0, 6, & 36 mo, % on anti-hypertensive medication
Notes	PB: no OAB: yes AL: Participants with no follow-ups excluded; others given reading from last visit (or treated BP if higher) . Assigned: LS 196, C 196 Follow up: LS 174, C 191 (6 mo), LS 175, C 178 (36 mo)

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Morgan 1978

Methods	RCT: 'were divided randomly into 4 subgroups'.
Participants	Untreated hypertensives, Australia, >50 years, 100% male, ethnicity not stated. Inclusion criteria: borderline hypertension, no AHTM (DBP 95-109 mmHg as a mean of 2 or 4 readings)
Interventions	LS: instructed to reduce their dietary sodium chloride intake, advice repeated at 3 months (no data on who gave advice, group or individual counselling, materials used, or main messages), DSI Target: 70-100, C: no dietary treatment, reviewed 6 monthly as LS group
Outcomes	BP & USE at 0, 6, 12, 18, 24 mo
Notes	PB: no. OAB: yes AL: Those with no follow-up excluded. Reading at last visit used for remainder. Assigned: LS 34, C 33 for BP (LS 35, C 42 for mortality) Follow up: LS 26, C 21 (24 mo) (all followed re mortality)

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Morgan 1987

Methods	RCT: 'randomised in blocks of 4'
Participants	Treated hypertensives, Australia, mean age 61 years, 100% male, ?% white. Inclusion criteria: hypertension (DBP <85 mmHg) while on AHTM (DBP >100 uncontrolled)
Interventions	LS: withdrawal of AHTM after 3 months on low sodium diet (led by whom?, no details of programme), DSI Target: 50-75, C: withdrawal of anti-hypertensives after 3 months, maintained normal diet
Outcomes	Necessity to restart AHTM following withdrawal, USE at 0 & 9 mo
Notes	PB: no. OAB: yes AL: Last BP reading before reinstatement was used; all had at least one follow-up. Assigned: LS 10, C 10 Follow up: LS 10, C 10 (9 mo)

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Silman 1983

Methods	RCT: 'randomisation after stratification by practice'.
Participants	Untreated hypertensives, UK, aged 50 to 64, ?% male, ?% white. Inclusion criteria: hypertension (DBP 95 - 104 mmHg over one year)
Interventions	LS: general health education group package with spouses (eating sensibly, stopping smoking, regular exercise, stress avoidance) plus taught diet (diet sheet given) lead by researcher, USE Target: 100, C: general health education group package only
Outcomes	BP & USE at 0, 1, 2, 3, 6 & 12 mo
Notes	PB: no, OAB: unclear. AL: Losses excluded. Baseline readings for "excluded" compared with those for "included". Assigned: LS 12, C 16 Follow up: LS 10, C 15 (12 mo)

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Thaler men 1982

Methods	RCT: index subjects were subdivided into two groups in such a way that the following factors were kept balanced: sex, decade of age, SBP, AHTM, number of index persons per family, number of other persons in family. The two groups were randomly assigned to control and salt restriction respectively'
Participants	Untreated hypertensives, New Zealand, mean age 41 years, 48% male, ethnicity not stated. Inclusion criteria: For index subjects, SBP 137-180 mmHg, some (21%) on AHTM. Family members also included
Interventions	LS: salt restriction programme for the whole family (led by a nutritionist, gradually introduced, individual counselling, some at the family home, main messages to stop adding salt, cut out salt in cooking and restrict high sodium foods, low sodium baking powder and baking soda were provided and a local baker made low sodium bread, cookbook provided), USE Target: not stated, C: asked to eat usual diet
Outcomes	USE at 0 & 8 mo
Notes	PB: no. OAB: unclear. AL: losses excluded. Assigned: LS 80 (38 index + 42 family), C 84 (39 index + 45 family) . Follow up: LS 69 (37 index, 19 men & 18 women), C 67 (35 index, 17 men & 18 women) (8 mo)

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Thaler women 1982

Methods	as Thaler men
Participants	as Thaler men
Interventions	as Thaler men
Outcomes	as Thaler men
Notes	as Thaler men

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

TOHP phase I

Methods	RCT: 'randomisation assignments were obtained from the co-ordinating center by telephone... when telephone contact not possible sealed opaque envelopes were used'
Participants	Normotensives, USA, mean age 43 years, 71% male, 77% white. Inclusion criteria: High normal (DBP 80 to 89 mmHg over 9 readings), not on AHTM
Interventions	Regimen: LS group nutrition and behavioural counselling programme (led by nutritionists, including food tasting and samples, problem solving exercises, shopping lists and guides, peer support and family involvement, field trips to shops and restaurants, motivational activities, food diaries and self assessment of sodium intake), USE Target: 80, C: no intervention
Outcomes	BP & USE at 0, 6, 12 & 18 mo
Notes	PB: no OAB: yes AL: Participants with no follow-up reading taken as zero change; others given reading from last visit. Assigned: LS 327, C 417 Follow up: LS 301, C 392 (12 mo), LS 304, C 395 (18 mo)

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

TOHP phase II

Methods	RCT: by telephone to TOHP co-ordinating center or sealed, opaque envelope
Participants	Normotensives, USA, mean age 44 years, 67% male, 81% white. Inclusion criteria: High normal (DBP 83 to 89 mmHg, SBP<=140 mmHg), not on AHTM. (People unwilling to comply with intervention excluded.)
Interventions	LS: dietary and behavioural change programme (led by dietitians, psychologists and health counselors, programme as TOHP I with individual counselling as well as group sessions) intensive early on, contact maintained later, USE Target: 70, C: no active intervention
Outcomes	BP & USE at 0, 6, 18 & 36 mo (42 or 48 mo sometimes)
Notes	PB: no. OAB: yes AL: Those with no follow-up reading given random value from range of results; others given reading from last visit. Assigned: LS 594, C 596 Follow up: LS 529, C 538 (6 mo), LS 515, C 514 (36 mo)

TOHP phase II (Continued)

<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

TONE

Methods	RCT: 'using a computer program each participants eligibility was confirmed prior to enrollment in the trial, randomisation was stratified by clinic and weight status'
Participants	Treated hypertensives, USA, mean age 67 years, 49% male, 76% white. Inclusion criteria: AHTM-treated HT (DBP <85 mmHg, SBP <145 mmHg)
Interventions	LS: attempted withdrawal of AHTM, group plus individual nutrition and behavioural counselling programme (led by nutritionists), USE Target: <80, C: attempted withdrawal of anti-hypertensives, no counselling but invited to meetings on unrelated topics
Outcomes	Combined BP, use of AHTM & CV events. USE at 0, 9, 18 & 30 mo
Notes	PB: no. OAB: yes AL: Used survival analysis with censoring to project proportions free of endpoints. Assigned: LS 340, C 341 Follow up: LS 310, C 314 (30 mo)

<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

LS = low salt or intervention group, C= control group, AHTM = anti-hypertensive medication, BP = blood pressure, in mmHg, SBP = systolic blood pressure, in mmHg, DBP = diastolic blood pressure, in mmHg, HT = hypertension, USE = urinary sodium excretion, in mmol/ 24 hours, DSI = dietary sodium intake, in mmol/ 24 hours, Mo = months, CV = cardiovascular, AC = allocation concealment, PB = participants blinded?, OAB = outcome assessors blinded?, AL = adjustment for losses

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

Study	Reason for exclusion
Aberg 1989	Multifactorial management programme (dietary changes, stress management and increased physical activity)
Ambard 1904	Not randomised.
Ambrosioni 1982	Less than 6 months follow up from initial intervention
Anderson 1990	Less than 6 months follow up from initial intervention
Berglund 1989	Multifactorial management programme, less than 6 months follow up from initial intervention
Bompiani 1988	Less than 6 months follow up from initial intervention
Cappuccio 1997	Less than 6 months follow up from initial intervention
Carney 1975	Not randomised.
Corcoran 1951	Not randomised.
Dahl 1958	Not randomised.
DASH	Less than 6 months follow up from initial intervention
DISH	Multifactorial, reduces sodium intake, but also increases potassium intake
Dole 1951	Not randomised.
Dubbert 1995	Less than 6 months follow up from initial intervention
Erwtelman 1984	Less than 6 months follow up from initial intervention
Evers 1987	Multifactorial management programme
Fagerberg 1984	Less than 6 months follow up from initial intervention
Geleijnse 1995	Multifactorial, reduces sodium intake, but also increases potassium intake
Gillum 1983	Less than 6 months follow up from initial intervention, no control group
Grimm 1990	All on salt restriction, no 'usual diet' control
HCP	Multifactorial management programme, reduction of sodium with weight loss and alcohol reduction
Henningsen 1980	Less than 6 months follow up from initial intervention (follow up between 4 and 8 months of intervention) - suggests that later results will be published but none found and contact not established with the author

(Continued)

Holly 1981	Less than 6 months follow up from initial intervention
Iwaoka 1994	Less than 6 months follow up from initial intervention
Jula 1990	Multifactorial management programme (sodium reduction with fat reduction)
Jula 1992a	Multifactorial management programme (sodium reduction with weight and fat reduction)
Jula 1992b	Multifactorial management programme (sodium reduction with weight and fat reduction)
Jula 1994	Multifactorial management programme (sodium reduction with weight and fat reduction)
Koopman 1990	The randomised part of the study only lasted 3 months, multifactorial intervention
Korhonen 1999	Less than 6 months follow up from initial intervention
Logan 1986	Compares an intensive intervention with a less intensive intervention to restrict sodium intake, but no 'usual diet' control group used. (This is a randomised clinical trial lasting 6 months)
MacGregor 1982a	Not randomised.
MacGregor 1982b	Less than 6 months follow up from initial intervention
MacGregor 1989	All on salt restriction, no 'usual diet' control
Magnani 1976	No 'usual diet' control
McDonald 1988	Multifactorial management programme (sodium reduction with weight and alcohol reduction)
Morgan 1988	Less than 6 months follow up from initial intervention
Muhlhauser 1993	Multifactorial management programme
Myers 1989	Less than 6 months follow up from initial intervention
Nestel 1993	Less than 6 months follow up from initial intervention
Neyses 1985	Children included
Nicholson 1986	Less than 6 months follow up from initial intervention
Nicholson 1987	Less than 6 months follow up from initial intervention
Nowson 1988	Less than 6 months follow up from initial intervention
Nugent 1984	Comparison of two different methods of salt restriction, no 'usual diet' control

(Continued)

ODES	Multifactorial management programme
Omvik 1986	All on salt restriction, no 'usual diet' control
Omvik 1995	All on salt restriction, no 'usual diet' control
Parijs 1973	Not randomised.
Perera 1947	Not randomised.
Priddle 1962	Not randomised.
Rissanen 1985	No 'usual diet' controls
Roca-Cusachs 1991	Multifactorial management programme, reduces sodium and also reduces weight, fat and alcohol
Sagnella 1987	Less than 6 months follow up from initial intervention
Shibata 1979	Not randomised.
Singer 1984	Less than 6 months follow up from initial intervention
Singer 1995	Less than 6 months follow up from initial intervention
Stamler 1989	Multifactorial management programme, reduces sodium as well as weight and alcohol with increased exercise
TAIM	Multifactorial, reduces sodium intake, but also increases potassium intake
TOMHS	All on salt restriction, no 'usual diet' control
Velloso 1991	Less than 6 months follow up from initial intervention
Watt 1983	Less than 6 months follow up from initial intervention
Watt 1986	Less than 6 months follow up from initial intervention
Weinberger 1988	All on salt restriction, no 'usual diet' control. Less than 6 months follow up from initial intervention
Wing 1984	Less than 6 months follow up from initial intervention
Zoccali 1993	Less than 6 months follow up from initial intervention

DATA AND ANALYSES

Comparison 1. Mortality and cardiovascular morbidity

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	4	2393	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.36, 2.24]
2 Cardiovascular morbidity	2	748	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.56, 1.21]

Comparison 2. Systolic blood pressure

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Trials with 6 to 12 months of follow up	7	2303	Mean Difference (IV, Random, 95% CI)	-2.51 [-3.82, -1.21]
1.1 Normotensives	3	2124	Mean Difference (IV, Random, 95% CI)	-2.31 [-3.06, -1.55]
1.2 Hypertensives	4	179	Mean Difference (IV, Random, 95% CI)	-8.01 [-15.78, -0.24]
2 Trials with 13 to 60 months of follow up	4	2347	Mean Difference (IV, Random, 95% CI)	-1.12 [-1.83, -0.41]
2.1 Normotensives	3	2285	Mean Difference (IV, Random, 95% CI)	-1.09 [-1.92, -0.26]
2.2 Hypertensives	1	62	Mean Difference (IV, Random, 95% CI)	-1.50 [-12.60, 9.60]
3 Trials with more than 60 months of follow up	1	128	Mean Difference (IV, Random, 95% CI)	-3.80 [-7.91, 0.31]
3.1 Normotensives	1	128	Mean Difference (IV, Random, 95% CI)	-3.80 [-7.91, 0.31]
3.2 Hypertensives	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable

Comparison 3. Diastolic blood pressure

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Trials with 6 to 12 months of follow up	5	2211	Mean Difference (IV, Random, 95% CI)	-1.21 [-1.84, -0.59]
1.1 Normotensives	3	2124	Mean Difference (IV, Random, 95% CI)	-1.16 [-1.77, -0.56]
1.2 Hypertensives	2	87	Mean Difference (IV, Random, 95% CI)	-4.65 [-9.33, 0.04]
2 Trials with 13 to 60 months of follow up	4	2347	Mean Difference (IV, Random, 95% CI)	-0.62 [-1.54, 0.31]
2.1 Normotensives	3	2285	Mean Difference (IV, Random, 95% CI)	-0.52 [-1.05, 0.01]
2.2 Hypertensives	1	62	Mean Difference (IV, Random, 95% CI)	-7.0 [-12.53, -1.47]
3 Trials with more than 60 months of follow up	1	128	Mean Difference (IV, Random, 95% CI)	-2.2 [-4.83, 0.43]
3.1 Normotensives	1	128	Mean Difference (IV, Random, 95% CI)	-2.2 [-4.83, 0.43]

3.2 Hypertensives	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
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Comparison 4. Urinary sodium excretion

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Urinary sodium excretion at different times following intervention	7		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 6-12 months following initiation of intervention	7	2166	Mean Difference (IV, Random, 95% CI)	-48.94 [-65.42, -32.46]
1.2 13 to 60 months following initiation of intervention	4	2787	Mean Difference (IV, Random, 95% CI)	-35.53 [-47.22, -23.85]
1.3 More than 60 months following initiation of intervention	1	120	Mean Difference (IV, Random, 95% CI)	10.5 [-13.83, 34.83]

Comparison 5. Dropouts

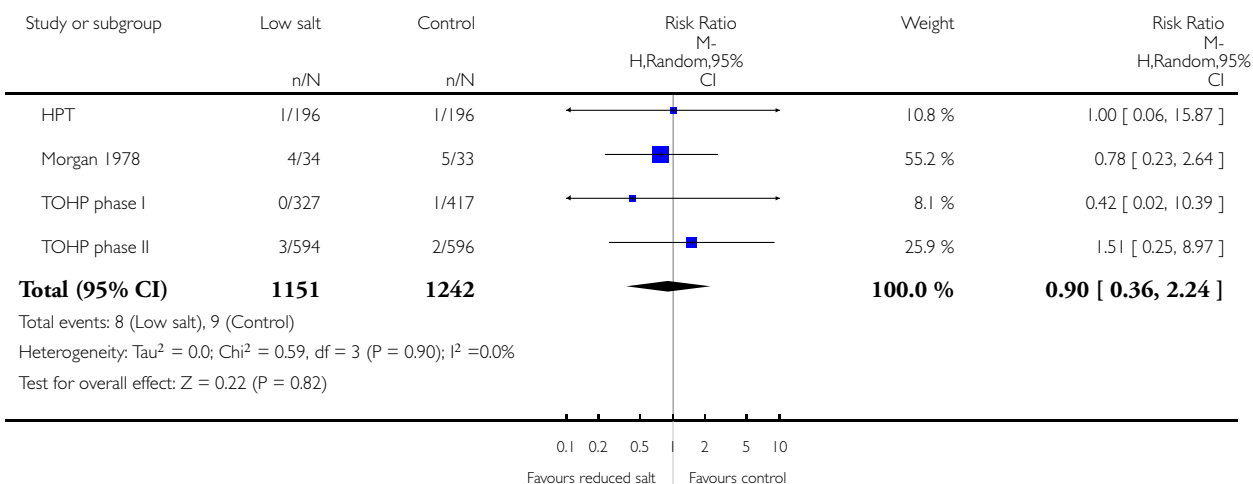
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Comparison of dropouts at longest follow up	10	3463	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.86, 1.25]

Analysis 1.1. Comparison 1 Mortality and cardiovascular morbidity, Outcome 1 Mortality.

Review: Advice to reduce dietary salt for prevention of cardiovascular disease

Comparison: 1 Mortality and cardiovascular morbidity

Outcome: 1 Mortality

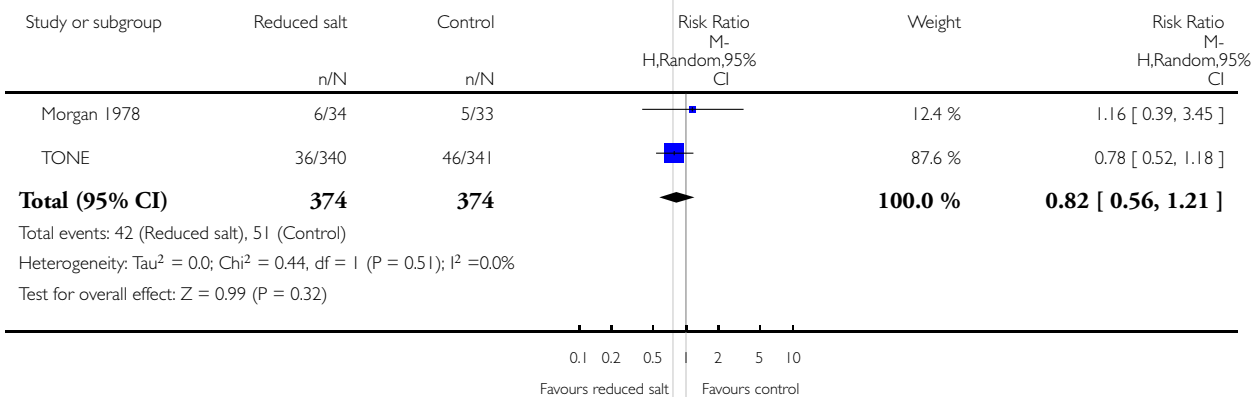


Analysis 1.2. Comparison 1 Mortality and cardiovascular morbidity, Outcome 2 Cardiovascular morbidity.

Review: Advice to reduce dietary salt for prevention of cardiovascular disease

Comparison: 1 Mortality and cardiovascular morbidity

Outcome: 2 Cardiovascular morbidity

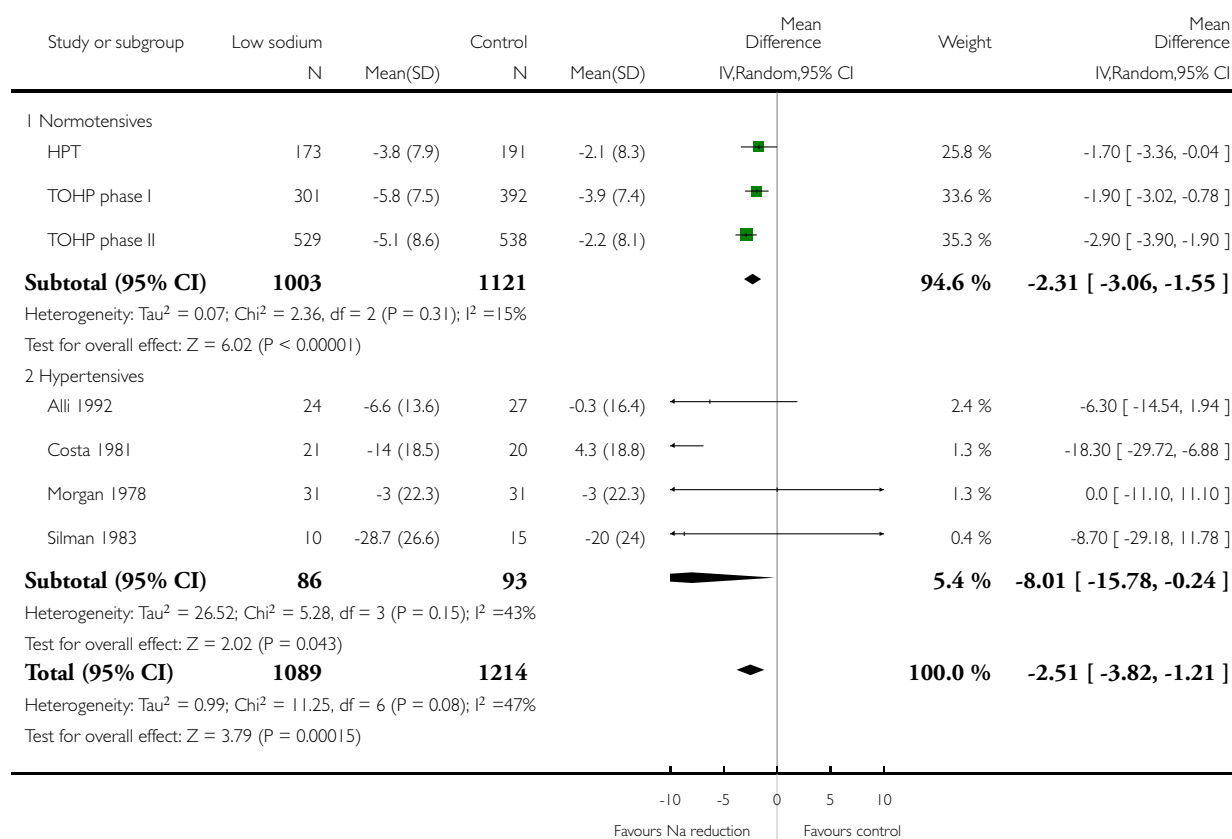


Analysis 2.1. Comparison 2 Systolic blood pressure, Outcome 1 Trials with 6 to 12 months of follow up.

Review: Advice to reduce dietary salt for prevention of cardiovascular disease

Comparison: 2 Systolic blood pressure

Outcome: 1 Trials with 6 to 12 months of follow up

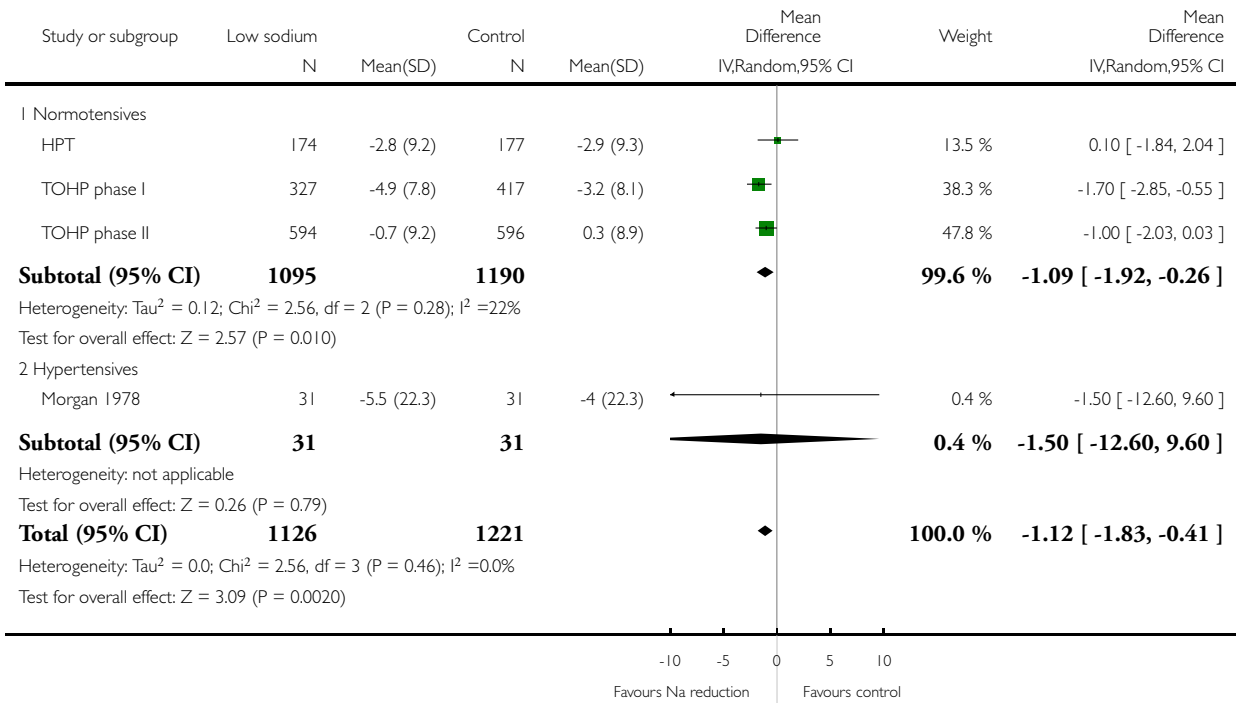


Analysis 2.2. Comparison 2 Systolic blood pressure, Outcome 2 Trials with 13 to 60 months of follow up.

Review: Advice to reduce dietary salt for prevention of cardiovascular disease

Comparison: 2 Systolic blood pressure

Outcome: 2 Trials with 13 to 60 months of follow up

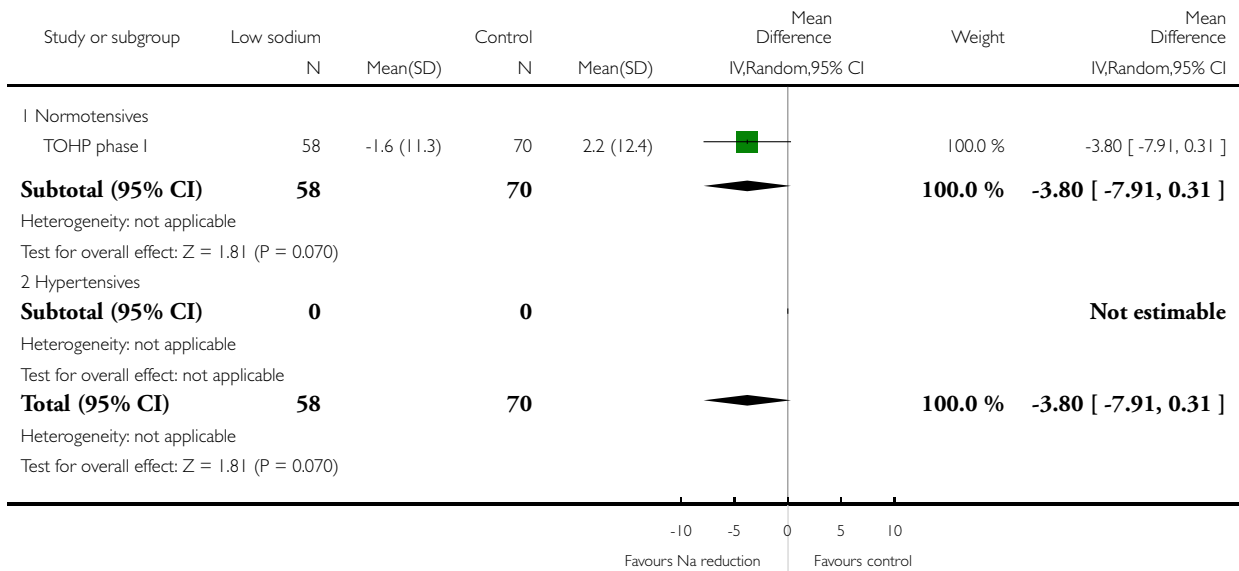


Analysis 2.3. Comparison 2 Systolic blood pressure, Outcome 3 Trials with more than 60 months of follow up.

Review: Advice to reduce dietary salt for prevention of cardiovascular disease

Comparison: 2 Systolic blood pressure

Outcome: 3 Trials with more than 60 months of follow up

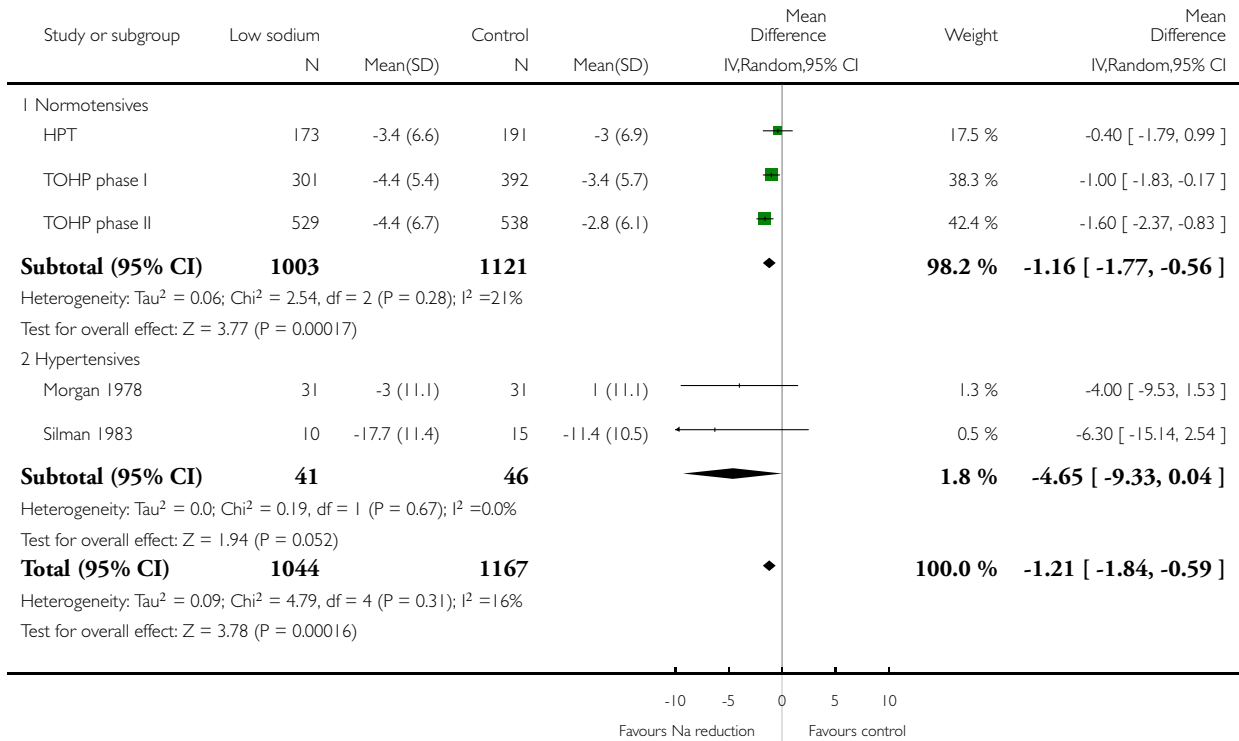


Analysis 3.1. Comparison 3 Diastolic blood pressure, Outcome 1 Trials with 6 to 12 months of follow up.

Review: Advice to reduce dietary salt for prevention of cardiovascular disease

Comparison: 3 Diastolic blood pressure

Outcome: 1 Trials with 6 to 12 months of follow up

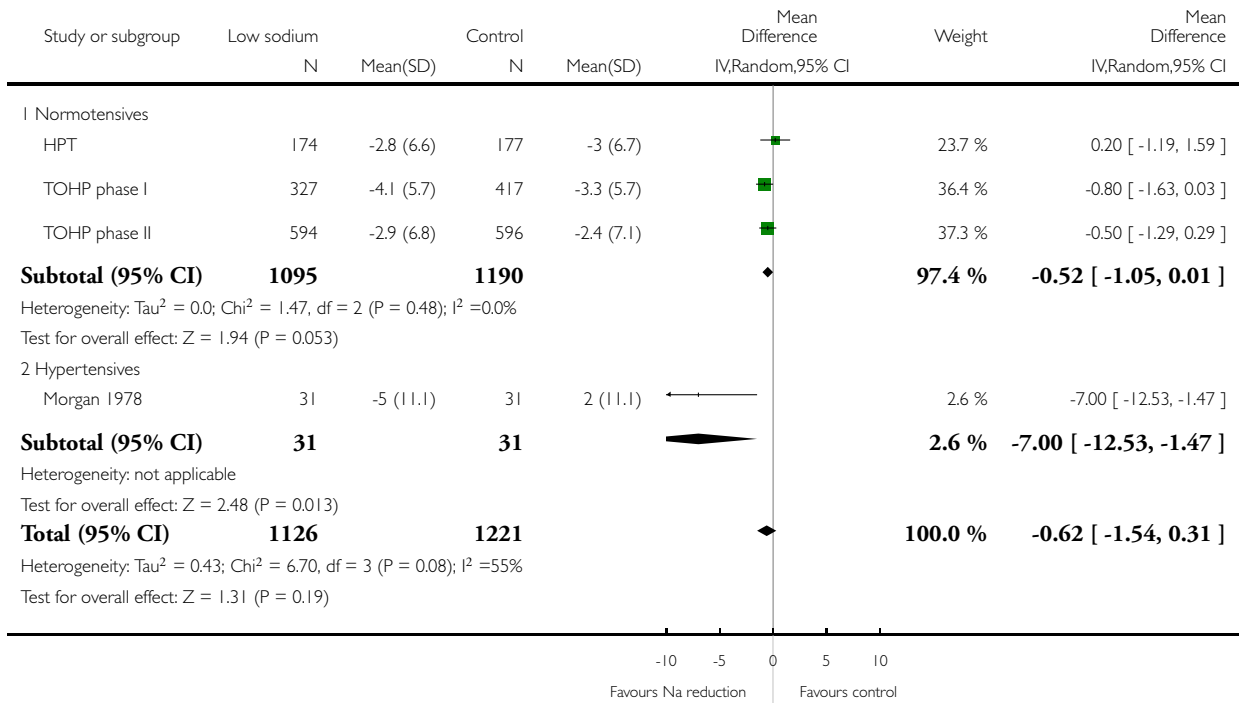


Analysis 3.2. Comparison 3 Diastolic blood pressure, Outcome 2 Trials with 13 to 60 months of follow up.

Review: Advice to reduce dietary salt for prevention of cardiovascular disease

Comparison: 3 Diastolic blood pressure

Outcome: 2 Trials with 13 to 60 months of follow up

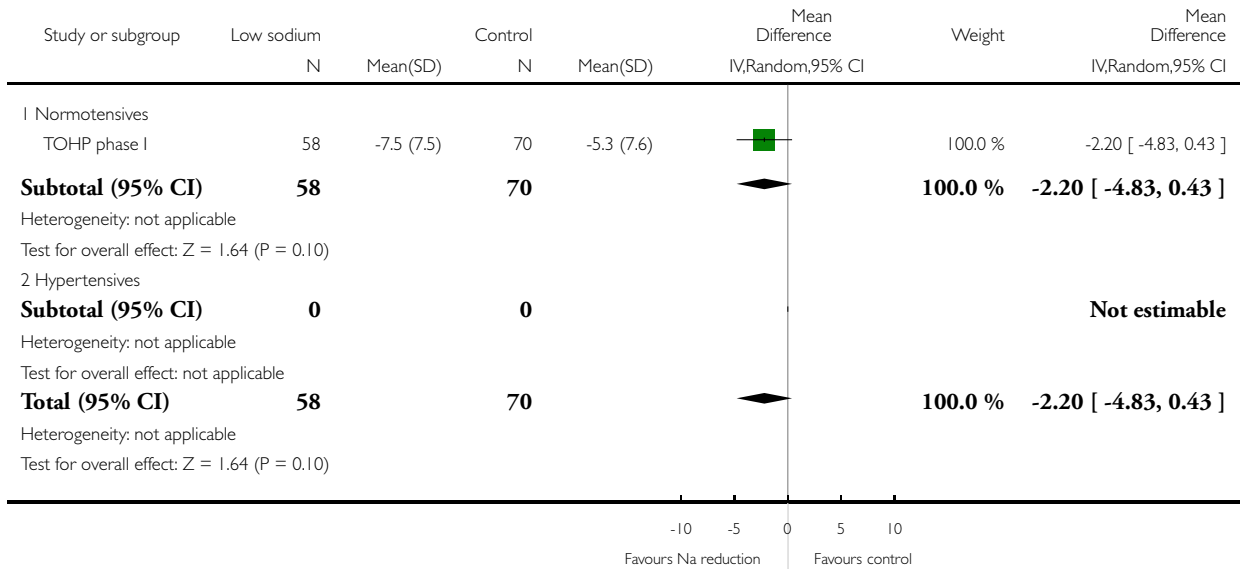


Analysis 3.3. Comparison 3 Diastolic blood pressure, Outcome 3 Trials with more than 60 months of follow up.

Review: Advice to reduce dietary salt for prevention of cardiovascular disease

Comparison: 3 Diastolic blood pressure

Outcome: 3 Trials with more than 60 months of follow up

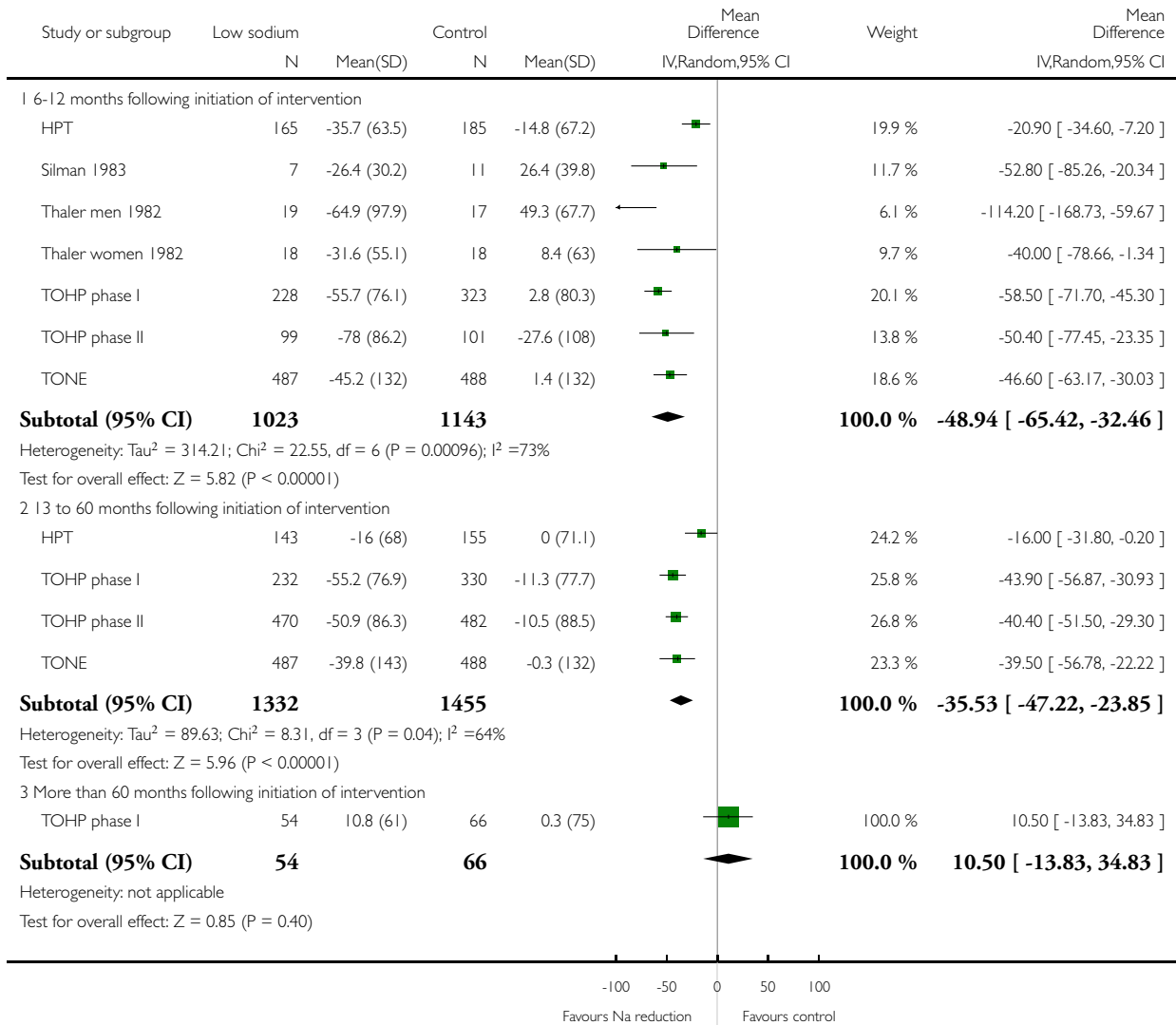


Analysis 4.1. Comparison 4 Urinary sodium excretion, Outcome 1 Urinary sodium excretion at different times following intervention.

Review: Advice to reduce dietary salt for prevention of cardiovascular disease

Comparison: 4 Urinary sodium excretion

Outcome: 1 Urinary sodium excretion at different times following intervention

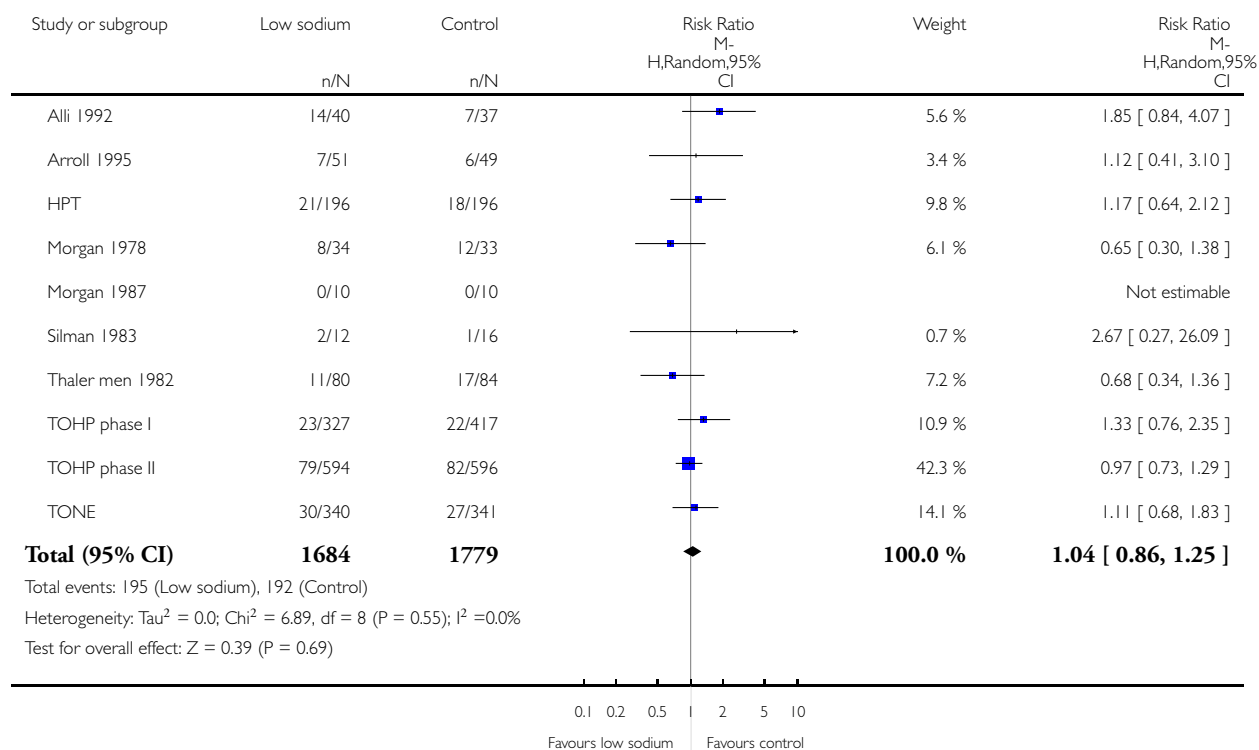


Analysis 5.1. Comparison 5 Dropouts, Outcome 1 Comparison of dropouts at longest follow up.

Review: Advice to reduce dietary salt for prevention of cardiovascular disease

Comparison: 5 Dropouts

Outcome: 1 Comparison of dropouts at longest follow up



ADDITIONAL TABLES

Table 1. Data - total deaths and cardiovascular events (including cardiovascular deaths)

Trial	Deaths, C	Deaths, LS	CV events, C	CV events, LS
TOHP phase I	1 (pancreatic cancer)	0		
TOHP phase II	2 (causes not specified)	3 (causes not specified)		
HPT	1 (no cause specified)	1 (no cause specified)	'no differences among the treatment groups in gross morbidity, as indicated by periods of hospitalization,	

Table 1. Data - total deaths and cardiovascular events (including cardiovascular deaths) (Continued)

			or in deaths'	
Morgan 1978	5 (causes of death: 1 arthritis, 1 congestive cardiac failure, 1 cerebrovascular accident, 1 pulmonary oedema and 1 unknown)	4 (causes of death: 1 cerebrovascular accident bronchospasm, 1 myocardial infarction, 1 congestive cardiac failure, 1 cardiorespiratory failure)	During first 2 years of study 3 were treated for congestive cardiac failure and 0 died of CV causes, 2 died from CV causes during the next 3 years	During the first 2 years of study 2 were treated for congestive cardiac failure and 1 person died (of CVA bronchospasm), 3 died from CV causes during the next 3 years
TONE			46 people (2 stroke, 7 TIA, 4 MI, 17 angina, 1 congestive heart failure, 3 arrhythmia and 19 other cardiovascular (further 21 CV events (no. of people unclear) in the weight loss only group))	36 people (1 stroke, 7 TIA, 2 MI, 9 angina, 2 congestive heart failure, 6 arrhythmia and 12 other cardiovascular (further 23 CV events (no. of people unclear) in the combined low sodium and weight loss group))
Alli 1992			(1 case of ischaemic heart disease in the dropouts, but not clear from controls or low salt, or whether fatal)	
Total	9	8	62	50

Table 2. Data - BP & urinary sodium ('mean (sd)' for control / 'mean (sd)' for low salt)

Trial name	initial SBP, mmHg	SBP ch, 6-12 mo	SBP ch, 13-60 mo	initial DBP, mmHg	DBP ch, 6-12mo	DBP ch, 13-60mo	initial urinary Na	Na ch, 6-12mo	Na ch, 13-60mo
HPT	123.9 / 124.0	6 months:- 2.1 (8.3) / -3.8 (7.9) (adjusted)	36 months: - 2.9 (9.3) / -2.8 (9.2) (adjusted)	83.0 / 82.6	6 months: -3.0 (6.9) / -3.4 (6.6) (adjusted)	36 months: - 3.0 (6.7) / -2.8 (6.6) (adjusted)	164.9 / 162.6 (corrected from 8 hour overnight urine samples)	6 months: -14.8 (67.2) / -35.7 (63.5) (corrected from 8 hour overnight urine samples)	36 months: 0.0 (71.1) / -16.0 (68.0) (corrected from 8 hour overnight urine samples)
TOHP phase I	125.1 (8.1) / 124.8 (8.5)	12 months: -3.9 (7.4) /	18 months: - 3.16 (8.1) /	83.9 (2.8) / 83.7 (2.7)	12 months: -3.4 (5.7) /	18 months: - 3.3 (5.7) / -	156.4 (60.5) / 154.6 (59.9)	6 months: +2.8 (80.)	18 months:

Table 2. Data - BP & urinary sodium ('mean (sd)' for control / 'mean (sd)' for low salt) (Continued)

		-5.8 (7.5)	-4.9 (7.8)		-4.4 (5.4)	4.1 (5.7)		3) / -55.7 (76.1)	-11.3 (77.7) / -55.2 (76.9)
TOHP phase II	127.3 (6.4) / 127.7 (6.6)	6 months:-2.2 (8.1) / -5.1 (8.6)	36 months:+0.3 (8.9) / -0.7 (9.2)	85.8 (1.9) / 86.1 (1.9)	6 months:-2.8 (6.1) / -4.4 (6.7)	36 months:-2.4 (7.1) / -2.9 (6.8)	188.0 (80.9) / 186.1 (80.7)	6 months:-27.6 (108.0) / -78.0 (86.2)	36 months:-10.5 (88.5) / -50.9 (86.3)
Morgan 1978	165 (16.7) / 160 (22.3)	12 months:-3 (22.3) / -3(22.3)	24 months:-4 (22.3) / -5.5 (22.3)	97 (8.6) / 97 (8.7)	12 months:+1 (11.1) / -3 (11.1)	24 months:+2 (11.1) / -5 (11.1)	191 (35) / 195 (55.0)	Not given	24 months:-11 / -38
Costa 1981	143.4 (13) / 143.3 (15)	12 months:4.3 (18.8) / -14.0 (18.5) (sd imputed)		84.1 (7) / 84.2 (9)	12 months:-0.2 (32.6) / -6.1 (31.7) (calculated sd)		Not given	Not given	
Thaler 1982, index men	139 (12) / 137 (14)	12 months:+3.4 (17.4) / -5.0 (8.3) (levels of medication altered in some participants through trial)		90(12)/86 (9)	12 months:+0.8 (9.2) / +0.6 (9.2) (levels of medication altered in some participants through trial)		159.5 (72.5) / 178.1 (76.5)	12 months:+49.3 (67.7) / -64.9 (97.9)	
Thaler 1982, index women	148 (25) / 145 (18)	12 months:+1.1 (14.4) / -11.1 (24.2) (levels of medication altered in some participants through trial)		83(12)/86 (11)	12 months:+2.8(8.5) / -6.8 (11.9) (levels of medication altered in some participants through trial)		120.1 (41.5) / 118.0 (39.9)	12 months:+8.4 (63.0) / -31.6 (55.1)	

Table 2. Data - BP & urinary sodium ('mean (sd)' for control / 'mean (sd)' for low salt) (Continued)

Silman 1983	160.5 / 165.3	12 months: -20.0 (24. 0) /-28.7 (26.6)		98.3 /98.8	12 months: - 11. 4 (10.5) / -17.7 (11. 4)		146.5 / 150.8	12 months: 26.4 (39. 8) / -26.4 (30.2)	
Alli 1992	148.3 (10. 6) / 150.8 (8.7)	12 months: -0.3 (16.4) /-6.6 (13. 6) (sd im- puted)		97.2 (3.8) / 97.0 (3.1)	12 months: - 2.7 (16.6) / -6.4 (18. 5) (sd cal- culated)		177.3 (61. 7) /177.3 (61.0)	12 months: -4.2 /+8.6 (data mea- sured off graph)	
Morgan 1987	143 (15.8) /143 (15. 8)	9 months: +35 (25.7) /+12 (21. 5) (sd im- puted, lev- els of med- ication al- tered in some par- ticipants through trial)		81 (6.3) / 83 (6.3)	9 months: +17 (28.7) /+7 (22.2) (sd calcu- lated, lev- els of med- ication al- tered in some par- ticipants through trial)		163 (50.6) /168 (37. 9)	-8 / -93	
Arroll 1995	145.3 (15. 7) /145.4 (15.9)	6 months: -6.2 (21.0) /-9.1 (21. 7) (sd im- puted, lev- els of med- ication al- tered in some par- ticipants through trial)		94.0 (9.8) / 86.4 (9.9)	6 months: -4.8 (36.1) / -1.7 (34. 9) (sd cal- cu- lated, lev- els of med- ication al- tered in some par- ticipants through trial)		Not given	Not given	
TONE	128 (9) / 129 (9)	Not given		71 (7) /72 (7)	Not given		146.2 / 145.3	9 months: +1. 4 (132) / - 45.2 (132) (data in- clude those in weight	30 months:-0. 3 (132) /- 39.8 (143) (data in- clude those in weight

Table 3. Meta-analysis, sugrouping and sensitivity analysis results (Continued)

Systolic blood pressure (mmHg)	13 to 60 months	Overall meta-analysis		4	-1.1	-1.8 to -0.4	0.46
Systolic blood pressure (mmHg)	13 to 60 months	Sensitivity analysis	Allocation concealment	3	-1.1	-1.9 to -0.3	0.28
Systolic blood pressure (mmHg)	13 to 60 months	Sensitivity analysis	Including weight arms	4	-0.5	-1.4 to 0.4	0.10
Systolic blood pressure (mmHg)	13 to 60 months	Subgrouping	Normotensives	3	-1.1	-1.9 to -0.3	0.28
Systolic blood pressure (mmHg)	13 to 60 months	Subgrouping	Untreated hypertensives	1	-1.5	-12.6 to 9.6	-
Systolic blood pressure (mmHg)	> 60 months	Overall meta-analysis		1	-3.8	-7.9 to 0.3	-
Diastolic blood pressure (mmHg)	6 to 12 months	Overall meta-analysis		5	-1.2	-1.8 to -0.6	0.31
Diastolic blood pressure (mmHg)	6 to 12 months	Sensitivity analysis	Drop imputed standard deviations	imputed standard deviations no longer used for diastolic blood pressure			
Diastolic blood pressure (mmHg)	6 to 12 months	Sensitivity analysis	Smallest calculated standard deviations	imputed standard deviations no longer used for diastolic blood pressure			
Diastolic blood pressure (mmHg)	6 to 12 months	Sensitivity analysis	Allocation concealment	3	-1.2	-1.8 to -0.6	0.28
Diastolic blood pressure (mmHg)	6 to 12 months	Sensitivity analysis	Including weight arms	7	-0.7	-1.5 to 0.1	0.05

Table 3. Meta-analysis, sugrouping and sensitivity analysis results (Continued)

Diastolic blood pressure (mmHg)	6 to 12 months	12	Subgrouping	Normotensives	3	-1.2	-1.8 to -0.6	0.28
Diastolic blood pressure (mmHg)	6 to 12 months	12	Subgrouping	Untreated hypertensives	2	-4.7	-9.3 to 0.0	0.67
Diastolic blood pressure (mmHg)	13 to 60 months	60	Overall meta-analysis		4	-0.6	-1.5 to 0.3	0.08
Diastolic blood pressure (mmHg)	13 to 60 months	60	Sensitivity analysis	Allocation concealment	3	-0.5	-1.1 to 0.0	0.48
Diastolic blood pressure (mmHg)	13 to 60 months	60	Sensitivity analysis	Including weight arms	4	-0.3	-1.0 to 0.4	0.06
Diastolic blood pressure (mmHg)	13 to 60 months	60	Subgrouping	Normotensives	3	-0.5	-1.1 to 0.0	0.48
Diastolic blood pressure (mmHg)	13 to 60 months	60	Subgrouping	Untreated hypertensives	1	-7.0	-12.5 to -1.5	-
Diastolic blood pressure (mmHg)	> 60 months		Overall meta-analysis		1	-2.2	-4.8 to 0.4	-
Sodium excretion (mmol Na/ 24 hours)	6 to 12 months	12	Overall meta-analysis		6	-48.9	-65.4 to -32.5	<0.01
Sodium excretion (mmol Na/ 24 hours)	6 to 12 months	12	Sensitivity analysis	Allocation concealment	4	-43.6	-62.6 to -24.6	<0.01
Sodium excretion (mmol Na/ 24 hours)	6 to 12 months	12	Sensitivity analysis	Including weight arms	6	-44.3	-58.4 to -30.2	<0.01
Sodium excretion (mmol Na/ 24 hours)	13 to 60 months	60	Overall meta-analysis		4	-35.5	-47.2 to -23.9	0.04

Table 3. Meta-analysis, subgrouping and sensitivity analysis results (Continued)

Sodium excretion (mmol Na/ 24 hours)	13 to 60 months	Sensitivity analysis	Allocation concealment	4	-35.5	-47.2 to -23.9	0.04
Sodium excretion (mmol Na/ 24 hours)	13 to 60 months	Sensitivity analysis	Including weight arms	4	-33.3	-42.0 to -24.6	0.05
Sodium excretion (mmol Na/ 24 hours)	> 60 months	Overall meta-analysis		1	10.5	-13.8 to 34.8	-
Dropouts	Latest follow up	Overall meta-analysis	Dropouts in low sodium vs control groups	10	Relative risk = 1.04	0.86 to 1.25	0.55

Table 4. Meta-regression results, effects on SBP at 6 to 12 months

Explanatory variable	Slope coef (95% CI)	Constant	No. of RCTs
Trials on normotensives and hypertensives			
Mean baseline SBP	-0.173 (-0.356 to 0.010)	19.5	7
Mean change in urinary sodium excretion (6 to 12 months)	0.013 (-0.049 to 0.075)	-1.68	4
Mean age of participants at baseline	0.118 (-0.188 to 0.424)	-7.46	7
Trials of normotensives only			
Mean baseline SBP	-0.362 (-0.826 to 0.102)	43.3	3
Mean change in urinary sodium excretion (6 to 12 months)	0.013 (-0.057 to 0.084)	-1.63	3
Mean age of participants at baseline	-0.213 (-0.630 to 0.203)	6.81	3

Table 5. Characteristics of systematic reviews on salt and blood pressure

Review	Inclusion criteria	RCTs only?	Normo/hypertensive	Median duration	No. trials (n)	Fall in Na excretion	WMD SBP (95%CI)	WMD DBP (95%CI)	Quality assessment
Graudal 1998	Population: mean age >15 years, Intervention: low sodium or high sodium diet, no confounding, Outcome: urinary sodium excretion measured, systolic, diastolic or mean BP reported	Yes, random allocation, parallel or crossover	Normotensive	8 (4-1100) days	56 (2581)	weighted mean 160	-1.2 (-0.6 to -1.8)	-0.26 (+0.3 to -0.9)	QA: subgrouping by open/ single blind or double blind method did not affect results. Notes: Statistical heterogeneity noted
Graudal 1998			Hypertensive	28 (4-365) days	58 (2161)	weighted mean 118	-3.9 (-3.0 to -4.8)	-1.9 (-1.3 to -2.5)	
Midgley 1996	Population: human, not on antihypertensive drugs, Intervention: dietary sodium intervention, Outcome: diastolic and systolic BP measurement, urinary sodium	Yes, randomised controlled trials (crossover or parallel design)	Normotensive	14 (4-1095) days	28 (2374)	weighted mean 125 (95% CI 95-156)	-1.6 (-2.41 to -0.89)	-0.5 (-1.18 to 0.11)	QA: Significant heterogeneity seen, reduced but not eliminated when studies subgrouped according to quality characteristics. Notes: Evidence

Table 5. Characteristics of systematic reviews on salt and blood pressure (Continued)

	excretion- Design: English language, full-length journal articles								of publica- tion bias provided
Midgley 1996			Hyperten- sive	29 (4 - 730) days	28 (1131)	Weighted mean 95 (95% CI 71-119)	-5.9(-7.77 to -4.12)	-3.8 (-4.78 to -2.9)	
Law 1991	Popula- tion: not on antihy- pertensive drugs, In- tervention: dietary sodium restriction, not con- founded, Outcome: 24 hour urine collection, systolic and/or diastolic BP	No.	Nor- motensive	1.5 (0.7 to 16) weeks	15 (?)	Not stated	Not stated	Not stated	QA: Qual- ity not as- sessed. Notes: In- di- vidual trial data com- pared with pooled ob- serva- tional data, rather than pooled to- gether
Law 1991			Hyperten- sive	5 (0.7 to 104) weeks	63 (?)	Not stated	Not stated	Not stated	
Law 1991			The review estimates that in people aged 50- 59 a re- duction in 50mmol Na /24 hours would lead to a fall of 5mmHg						

Table 5. Characteristics of systematic reviews on salt and blood pressure (Continued)

			in systolic and 2.5mmHg in diastolic BP in normotensives, and a fall of 7 and 3.5mmHg respectively in hypertensives						
Cutler 1997	Population: adult human, Intervention: sodium goals 28-273 mmol/24 hours, no confounding allowed, Outcome: lab-based measure of sodium intake, systolic and/or diastolic BP measured	Yes, randomised controlled trials (crossover or parallel design), published only	Normotensive	1 (0.5 to 36) months	12 (1689)	Median ~90 (range 16 to 210)	-1.5 (-2.1 to -1.0)	-0.8 (-1.3 to -0.3)	QA: subgrouping by double blind or not had no significant effect on overall outcome. Notes: regression analyses used for publication bias failed to reject the null hypothesis
Cutler 1997			Hypertensive	2 (1-24) months	22 (1043)	Median ~71 (range 27 to 171)	-3.8 (-4.9 to -2.8)	-2.1 (-2.8 to -1.5)	
Alam 1999	Population: human elderly (>50 years), Intervention: changes in dietary	Yes, published English-language randomised controlled trials, crossover	Normotensive (2 trials) or with essential hypertension (9 trials)	14 (9-104) weeks	11 (485)	Median 80 (range 23 to 260)	-5.6(-6.9 to -4.3)	-3.5 (-4.4 to -2.6)	QA: quality assessment score tended to be high (average score

Table 5. Characteristics of systematic reviews on salt and blood pressure (Continued)

	NaCl, Outcome: blood pressure	or parallel							>70%)
Ebrahim and Davey Smith 1998	Population: adult humans, Intervention: dietary sodium reduction vs. control, Outcome: diastolic and systolic BP measurement, urinary sodium excretion	Yes, randomised controlled trials of at least 6 months duration	Normotensive	Not stated	2 (1095)	Not stated	-1.3 (-2.7 to +0.1)	-0.8 (-1.8 to +0.2)	QA: Quality not assessed.
Ebrahim and Davey Smith 1998			Hypertensive	Not stated	6 (466)	Not stated	-2.9(-5.8 to 0.0)	-2.1 (-4.0 to -0.1)	
This review, 6 to 12 months	Population: adult human, Intervention: sodium reduced diet vs. usual diet, Outcome: urinary sodium excretion, systolic and/or diastolic BP measurements taken 6 to 12 months	Yes, parallel randomised controlled trials	Normotensive	6 (6 to 12) months	3 (2124)	Weighted mean 43 (95% CI 16 to 70)	-2.3 (-3.1 to -1.6)	-1.2 (-1.8 to -0.6)	QA: Sensitivity analysis (removing trials where allocation concealment is poor or unclear) had no effect on direction or significance of results

Table 5. Characteristics of systematic reviews on salt and blood pressure (Continued)

	or more than 12 months after intervention								
This review, 6 to 12 months			Hypertensive	12 (12 to 12) months	4(179)	weighted mean 48 (95% CI 33 to 63)	-8.0 (-15.8 to -0.2)	-4.5 (-8.7 to -0.4)	
This review, 13 to 60 months			Nor-motensive	36 (18 to 36) months	3 (2285)	weighted mean 34 (95% CI 19 to 50)	-1.1(-1.9 to -0.3)	-0.5 (-1.1 to 0.0)	
This review, 13 to 60 months			Hypertensive	24 months	1(62)	weighted mean 40 (95% CI 22 to 57)	-1.5 (-12.6 to 9.6)	-7.0 (-12.5 to -1.5)	

FEEDBACK

Comments on the Cochrane Review by Hooper et al

Summary

Previous meta-analyses have lumped both short term and long term trials together [1,2] and therefore Hooper et al's meta-analysis is an important attempt to look at whether longer term salt reduction (i.e. more than 6 months) in randomised trials causes a fall in blood pressure [3,4].

Given the inherent difficulty of reducing salt intake long term, it is not surprising that they only found a small reduction of 2 g/day in the long-term trials from an intake of around 10 g/day. This contrasts with a recommended reduction in nearly all western countries of at least 5 to 6 g/day from the now almost universal intake of 10 to 12 g/day. It would come, therefore, as no surprise that a small reduction (2 g/day) in salt intake compared to the public health recommended reduction only causes a small, but in their meta-analysis, a highly significant reduction in blood pressure. Nevertheless, this small reduction in adult population blood pressure would be expected to have a significant effect on reducing strokes, heart attacks [5,6], and heart failure, the commonest causes of death and disability in the western world.

There are important points, which Hooper et al fail to mention in the discussion section of their paper. For instance, other meta-analyses have demonstrated a dose response to salt restriction [7]. Therefore, if it was possible to reduce salt intake by a larger amount (e.g. by reducing the salt content of processed food) the fall in blood pressure and the benefits would be even larger.

There are errors and misquotation of the relevant literature in the meta-analysis. They claim that interventions used were highly intensive, but the majority of studies gave no details as to what advice was offered. The fact that very few of these studies were successful in reducing salt intake more than 1 or 2 g/day casts further doubt on this unwarranted assertion. Furthermore, as the majority of salt comes from processed foods, it is absolutely vital to provide processed foods with less salt in these studies. Unfortunately, only a few of the studies that they included provided reduced salt foods.

In the meta-analysis, the follow up study of the TOHP trial [8] was included as an over 60 months intervention trial, but salt intake was in fact only reduced for 18 months, after which all participants returned to their normal diet. It is not, therefore, as Hooper et al state, a 60-month trial of salt restriction.

Alderman claimed that reducing salt intake in treated hypertensives led to myocardial infarction [9]. Detailed examination of the paper and analysis of the urinary creatinines that were provided later clearly demonstrated that the group on the low salt intake were in fact there because most of them had collected an inadequate 24 hour urine and therefore had less salt in the urine as it was an incomplete urine collection. There was no evidence that they were on a lower salt intake. Furthermore, there was only one 24 hour urine at the time of entry and no further measurements were made during the study, so the study suffered from the defect that there was no evidence that the group who were said to have been on a lower salt intake were in fact on a lower salt intake at entry and no attempt was made to measure salt intake during the rest of the study. In the second study [10] taken from the NHANES-1 Dietary Survey, the First National Health and Nutrition Examination survey in the USA, no assessment of discretionary salt (salt added to the table and cooking) was made. As the study was conducted in the 1980s, at this time approximately half of all salt intake would be in the form of discretionary salt. Therefore the assessment of total dietary salt intake is likely inadequate. Those on a lower salt intake were on a calorie intake that was equivalent to a starvation diet and yet were heavier than those who were said to be on a higher salt intake, in spite of the fact that these latter people had a much higher calorie intake. These two studies [9,10] cannot be quoted as evidence about the long-term cardiovascular effects of salt reduction. We suggest reading correspondence following these papers [11-16].

Hooper et al's meta-analysis has been previously published in the British Medical Journal [4]. It appears that their current Cochrane review has not been altered and, in particular, no attempt has been made to respond to criticism raised at the time [17,18]. For instance, Hooper et al claim that an increase in cholesterol occurs with salt restriction and quoted the meta-analysis by Graudal et al [2]. The latter meta-analysis included trials of very short term, mainly for only 5 days, and large changes in salt intake, e.g. 20 g/day. With these acute large changes in salt intake there are large changes in blood volume and it is not surprising that in the short term there is a change in cholesterol. However, it has been well demonstrated in longer-term trials of more modest reductions in salt intake that there is no change in cholesterol [7].

In spite of these problems with their meta-analysis, we agree with the conclusions that if salt intake is reduced by small amounts there are small but significant reductions in blood pressure. Indeed, these blood pressure falls fit almost exactly with the dose response that we found in a more recent meta-analysis of salt reduction [7].

In our opinion the conclusion from their study should read: "A meta-analysis of randomised longer term salt reduction trials has shown the difficulty of reducing salt intake in the long term without the provision of processed foods with less salt, as the mean salt reduction in the studies was only 2 g/day. Nevertheless, this small reduction in salt intake did cause a significant fall in blood pressure, which, on a population basis, would lead to a significant reduction in strokes, heart attacks and heart failure. Therefore, even small reductions in salt intake would be very worthwhile and in developed countries are practical to carry out. There is no evidence that this small reduction in salt intake would have any harmful effect. It could easily be implemented by the food industry in a very short time as it would only mean a 15 to 20% reduction in the salt content of all processed, canteen, restaurant and fast foods. This reduction in salt concentration of foods is not detectable and can easily be achieved, as shown by the experience of a leading supermarket in the UK where such reductions have already been implemented. If larger reductions in salt intake could be implemented in the population the benefits would be large". Indeed, the authors' own press release states that the difficulty for people to reduce their salt intake is "because most salt comes from processed and ready made foods. Efforts by the government to reduce hidden salt in foods such as bread and cereals may be more effective as no dietary change is necessary" [19].

References

1. Midgley JP, Matthew AG, Greenwood CM, Logan AG. Effect of reduced dietary sodium on blood pressure: a meta-analysis of randomised controlled trials. *JAMA* 1996;275:1590-1597.
2. Graudal NA, Galloe AM, Garred P. Effect of sodium restriction on blood pressure, renin, aldosterone, catecholamines, cholesterols, and triglyceride: a meta-analysis. *JAMA* 1998;279:1383-91.
3. Hooper L, Bartlett C, Davey Smith G, Ebrahim S. Reduced dietary salt for prevention of cardiovascular disease (Cochrane Review). In: *The Cochrane Library*, Issue 1, 2003. Oxford: Update Software.
4. Hooper L, Bartlett C, Davey Smith G, Ebrahim S. Systematic review of long term effects of advice to reduce dietary salt in adults. *BMJ* 2002; 325: 628-634.
5. Prospective studies collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;360:1903-13.
6. Murray CJL, Lauer JA, Hutubessy RCW, Niessen L, Tomijima N, Rodgers A, Lawes CMM, Evans DB. Effectiveness and costs of interventions to lower systolic blood pressure and cholesterol: a global and regional analysis on reduction of cardiovascular-disease risk. *Lancet* 2003;361:717-25.
7. He FJ, MacGregor GA. Effect of modest salt reduction on blood pressure. A meta-analysis of randomised trials. Implications for public health. *J Hum Hypertens* 2002;16:761-770.
8. He J, Whelton PK, Appel LJ, Charleston J, Klag MJ. Long-term effects of weight loss and dietary sodium reduction on incidence of hypertension. *Hypertension* 2000; 35: 544-550.

9. Alderman MH, Madhavan S, Cohen H, Sealey JE, Laragh JH. Low urinary sodium is associated with greater risk of myocardial infarction among treated hypertensive men. *Hypertension* 1995;25:1144-1152.
10. Alderman MH, Cohen H, Madhavan S. Dietary sodium intake and mortality. The National Health and Nutrition Examination Survey (NHANES 1). *Lancet* 1998;351:781-785.
11. MacGregor G. Low urinary sodium and myocardial infarction. Letter. *Hypertension* 1996;27:156.
12. de Wardener H. Salt reduction and cardiovascular risk: the anatomy of a myth. *J Human Hypertens* 1999;13:1-4.
13. de Wardener H, MacGregor GA. Sodium intake and mortality. Letter. *Lancet* 1998;351:1508.
14. Engelman K. Sodium intake and mortality. Letter. *Lancet* 1998;351:1508.
15. Karppanen H, Mervaala E. Sodium intake and mortality. Letter. *Lancet* 1998;351:1509.
16. MacGregor GA, de Wardener HE. Salt, blood pressure and health. *Int J Epidemiol* 2002;31:320-7.
17. MacGregor GA, He FJ, Perry IJ, Law MR, Wald NJ, Hooper L, Bartlett C, Davey Smith G, and Ebrahim S. Long term effects of advice to reduce dietary salt. *BMJ* 2003;326:222-4.
18. MacGregor GA, He FJ. Salt - Misleading Front Cover and Letter. <http://bmj.com/cgi/eletters/326/7382/222/a#29301>.
19. New ways of reducing salt intake needed to make a long-term impact on blood pressure. Media release. University of Bristol. <http://bris.ac.uk/Depts/Info-Office/news/archive/salt.htm>.

Reply

The Authors Reply:

The stated objective was to assess the long-term effects of advice to restrict dietary sodium, rather than the effect of the actual sodium restriction (as advice is rarely followed perfectly and over a long period of time). The effect of such advice is important as it is commonly used in primary care and is a central part of the guidelines produced by bodies such as the British Hypertension Society [1].

Despite the difficulties inherent in reducing sodium intake, individual advice does result in a significant but small reduction in blood pressure. If this small reduction could be achieved across entire populations, it would be reasonable to expect some benefits in terms of cardiovascular disease events avoided. But it is simply unrealistic to imagine that interventions as intensive as those used in the trials reviewed here could be applied population wide.

Of the 2349 people involved in the studies which measured blood pressure at 13 to 60 months (see forest plot 02, 02), 2287 had been involved in intensive and comprehensive behavioural change program to help them reduce their salt intake (for the 6 to 12 month outcome period 2124 of 2303 had intensive interventions, forest plot 02, 01). As an example, the least intensive of these programs, the HPT study, included group sessions (17 sessions over the first year, 28 over 3 years) with individual counselling if sessions were missed, a newsletter between sessions, self assessment, goal setting, a participant manual, a food counter, cookbook, food demonstrations and tastings, team building exercises and tokens of accomplishment, led by personnel trained and experienced in effecting behaviour change related to food. This type of intervention is not realistic at a population level.

Meta-analyses have only been able to demonstrate a dose response of blood pressure to sodium reduction when they have artificially forced the regression line through the origin. Where this has not been done no dose response has been seen.

See comments above on intensity of dietary advice. While several small trials were included with little information on how or what advice was provided, the majority of people involved in trials (who provided the bulk of the information on blood pressure response after 1 year) were in the larger, well documented trials with intensive interventions.

A different meta-analysis is required to assess the effect of interventions where large quantities of low sodium foods are provided to participants - this would be an unusual addition to dietary advice in primary or secondary care, but is a valid and interesting question in its own right.

These issues regarding the TOHP trial are already discussed within the results section of the review (paragraph 4).

The two cohort studies mentioned by He and MacGregor are not included in the review, but are mentioned very briefly in the discussion. The section states that a weakness of our review is its lack of ability to assess the effect of advice to reduce sodium on cardiovascular morbidity and mortality. Six cohort studies are quoted, and show a variety of conclusions about the effects of salt on death and cardiovascular health. The point being made is that we cannot be entirely sure that a reduction in blood pressure through advice to reduce salt intake will result in only beneficial effects on health. Ideally we would have some direct evidence that health benefits accrue.

Clearly, also, the cohort studies have large potential flaws, which make reliance on their conclusions unhelpful. Randomised controlled trials, and systematic reviews of randomised controlled trials are needed to understand the health effects of changes in diet.

In Graudal's review [2] 653 participants were involved in the meta-analysis which showed a significant increase in total cholesterol after around 7 days of a low sodium diet (and 517 participants were involved in the significant increase in LDL at 7 days). In the quoted review by He and MacGregor [7] only three trials contribute information on total cholesterol (81 participants) and fewer on

LDL. It would be extremely surprising if this number of participants did show a significant effect on total cholesterol or LDL. In this circumstance lack of a significant effect does not rule out a clinically important effect of salt reduction on lipids in the longer term. We disagree with the conclusions proposed by He and MacGregor; we did not assess palatability of processed food, or detectability of a 20% salt reduction in such foods. We cannot be certain from our review what the health effects of a general reduction in sodium might be. We stand by our conclusions as stated in the review.

References:

1. Ramsay LE, Williams B, Johnston GD, MacGregor GA, Poston L, Potter JF et al. Guidelines for management of hypertension: report of the third working party of the British Hypertension Society. *Journal of Human Hypertension* 1999;13:569-92.

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Comments on the Review by Hooper et al

Summary

Health care providers, researchers and policy makers need systematic reviews for rational decision making, because they are inundated with otherwise unmanageable amounts of information [1]. It follows that the title and the Reviewers' Conclusions on the front page constitute critical elements of a Cochrane Review.

In the Review by Hooper et al [2] we find both the title and conclusions misleading. This is especially regrettable since both the title and the conclusions were clear and informative in their earlier BMJ version of the same meta-analysis [3].

Their BMJ paper is entitled 'Systematic review of long-term effects of advice to reduce dietary salt in adults' and their conclusion is that the 11 trials 'provided only small reductions in blood pressure and sodium excretion'. Thus the BMJ paper clearly refers to a meta-analysis of studies of effectiveness (a measure of the extent to which an intervention has its intended effect) in which the outcome was limited by poor dietary compliance, rather than efficacy (a measure of what can be achieved when an intervention is fully implemented). Effectiveness is measured by the outcome of offering a treatment or other intervention to people who are free to accept or reject it, as they might ordinarily do [4], complying only as well as their personal inclination and social or economic circumstances allow. Efficacy is measured from the outcome when a specified treatment or other intervention is fully applied [4].

The title of the Cochrane Review no longer makes this distinction clear. The title this time is 'Reduced dietary salt for prevention of cardiovascular disease' and the conclusion is that 11 long-term trials provided 'only minimal reductions in blood pressure'. Hence, both the title and conclusion ignore the fact that the degree of dietary sodium reduction achieved in these trials was only modest, thereby limiting the effectiveness of the intervention. Their Cochrane Review implies that these authors are publishing a finding about efficacy and concludes that low salt diets are not very efficacious, which is untrue - significant reductions in blood pressure can be achieved in both hypertensives and normotensives when the dietary intervention is more fully applied, as it was in the short DASH Sodium study in which all of the food was supplied by the study organisers [5] and in longer studies where it was also more fully applied [6]. A Cochrane Review that misrepresents limited effectiveness as limited efficacy is seriously misleading to policy makers expecting guidance, and it limits the value of the Cochrane Collaboration - the very institution that commemorates the late Archie Cochrane, who made effectiveness a standard term in epidemiology [7,8]. The correspondence after their BMJ paper drew attention to good evidence of the efficacy of a lower salt intake, and the important implication for policy makers that a better supply of suitable foods will improve dietary compliance and effectiveness [9].

We discuss the fallacy of confusing effectiveness with efficacy at greater length in our comments on the Cochrane Review by Jürgens and Graudal [10].

Call for long-term randomised controlled trials

The authors conclude that we need long-term randomised controlled trials (RCTs) of a lower salt intake of a size and duration that will enable us to measure mortality and morbidity outcomes. It is unrealistic to call for such trials without suggesting ways of removing the fatal obstacles. Some of these have already been published [11], but the recommendations of JNC 7 have raised new obstacles that we consider insurmountable.

After reviewing no less than 11 inconclusive long-term effectiveness trials, Hooper et al have given no reasons for believing that the proposed long-term RCT would provide anything but yet another inconclusive effectiveness trial. The alternative of a long-term efficacy trial would explode the budget with the astronomical cost of catering for all the meals eaten throughout the day by thousands of people for one to three decades.

Moreover JNC 7 has added a new obstacle. It gave high-normal blood pressure a new name - prehypertension - for which JNC 7 has advocated nonpharmacological treatment, including the low salt diet of the intervention group [12]. This means the trial could recruit only subjects with blood pressure (BP) below 120/80, because it would be unethical to randomise subjects with prehypertension to the control group, postponing the expected late endpoints for perhaps another decade or more.

Secondly for ethical reasons it would be mandatory to give all members of the control group treatment for prehypertension as soon as their BP rose above 120/80, which would mean their having to adopt the low salt diet of the intervention group. This would result in the gradual (and probably near-complete) erosion of the control group as members leave on account of the rise of BP with age that would have provided the difference in long-term endpoints.

In our view the long-term RCT was never feasible because the ethical requirement to keep the BP of all members of the control group permanently <140/90 as soon as they became hypertensive would have greatly postponed the expected late endpoints. The new ethical requirement to treat prehypertension by allowing the control group member to share the diet of the diet group is in our view an insurmountable obstacle.

What would Cochrane's advice be today? It is easy to predict from his writings what he might have said and done. Cochrane knew that RCTs are unable to answer a large number of very important questions in public health, on account of practical, ethical, economic or other obstacles [8]. Cochrane would obtain other evidence. Some of that evidence might be observation and inference and as much as possible would be experimental. Our belief is that the existing evidence would allow Cochrane to approve of government initiatives to achieve the 50% reduction in the sodium content of processed foods that the American Public Health Association has called for (with explicit support from JNC 7).

References

1. Hooper L, Bartlett C, Davey Smith G, Ebrahim S. Reduced dietary salt for prevention of cardiovascular disease (Cochrane Review). In: The Cochrane Library, Issue 1, 2003. Oxford: Update Software. Oxford: Update Software; 2003.
2. Mulrow CD. Rationale for systematic reviews. In: Chalmers I, Altman D G. Systematic Reviews. London: BMJ Publishing Group; 1995:1.
3. Hooper L, Bartlett C, Davey Smith G, Ebrahim S. Systematic review of long-term effects of advice to reduce dietary salt in adults. *BMJ* 2002;325:628-32.
4. Fletcher RH, Fletcher SW, Wagner EH. Clinical Epidemiology: the essentials (2nd edn). Baltimore: Williams & Wilkins; 1988:132-33.
5. Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. *N Engl J Med* 2001;344:3-10.
6. MacGregor GA, Markandu ND, Sagnella GA, Singer DRJ, Cappuccio FP. Double-blind study of three sodium intakes and long-term effects of sodium restriction in essential hypertension. *Lancet* 1989;2:1244-47.
7. Last JM. A dictionary of epidemiology, 3rd edition. Oxford: Oxford University Press; 1995:52.
8. Cochrane AL. Effectiveness and efficiency: random reflections on health services. London: The Nuffield Provincial Hospitals Trust; 1972.
9. Law MR, Wald NJ. Salt needs to be reduced in manufacturing and processing food [letter]. *BMJ* 2003;326:223-24.
10. Jürgens G, Graudal NA. Effects of a low sodium diet versus high sodium diet on blood pressure, renin, aldosterone, catecholamines, cholesterols, and triglyceride (Cochrane Review). In: The Cochrane Library, Issue 1. Oxford: Update Software; 2003.
11. Chobanian AV, Hill M. National Heart, Lung, and Blood Institute Workshop on sodium and blood pressure: a critical review of current scientific evidence. *Hypertension* 2000;35:858-63.
12. Joint National Committee. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *JAMA* 2003;289:2560-72.

Reply

The Authors Reply:

"Reduced dietary salt for prevention of cardiovascular disease" is an appropriate title for a Cochrane review as it follows the recommended format of "intervention for disease". The title is not declarative and it is necessary for the reader to examine the abstract for the objectives, which make it totally clear that we are assessing the effect of dietary advice. However, after consultation with the Co-ordinating Editor of the Cochrane Hypertension Group, we have altered the title to 'Advice to reduce dietary salt for prevention of cardiovascular disease'.

The data cited which 'offers good evidence of the efficacy of a lower salt intake' is the following:

Reducing the current average salt consumption in Britain by 3 g/day (about one third) would reduce average blood pressure by about 5 mm Hg systolic in people over 50 and thereby reduce the incidence of heart attack and strokes by about 15% and 22% respectively.[1] A reduction of 6 g/day would reduce blood pressure by about twice as much with a corresponding additional reduction in the incidence of heart attacks and stroke. Reducing salt intake generally would thus have a major impact in the prevention of cardiovascular disease. Law's study from which this information is derived used a very unique methodology. Instead of pooling randomised controlled trials (and there are many reviews that do, see additional table 05), observational studies were pooled and were then compared with the results of the controlled trials (most of which were not randomised) and determines that they are not significantly dissimilar. In doing this he comes up with an effect size of a very different order than all other published systematic reviews. This is not a credible way to pool trial evidence. We drew attention to this in our response to the criticisms of our BMJ review.[2]

The estimate of the effect that this would have on mortality and morbidity was taken from evidence from a prospective study, but different prospective studies come up with very different relationships to mortality and morbidity (see discussion section of this review). It is not reasonable to pick only the evidence that supports the most optimistic view.

To assess the effect of dietary advice to reduce salt intake on cardiovascular morbidity is not necessarily difficult. Of the four large trials included in this review (those including at least 250 participants) information on cardiovascular morbidity that could be used in meta-analysis was provided by only one (TONE [3]). If details were published of the 'in study' cardiovascular morbidity for the other three (a further 2326 participants) this would be likely to provide a reasonable amount of extra information (and if the protective trend of low salt advice seen in the TONE trial was followed we may even see statistically significant protection from cardiovascular events in the low salt advice group). We did try to contact the trialists for this data but received no replies.

Although it might be argued that these trials have now been completed, long-term follow up of trial participants who received intensive dietary advice, the effects of which might reasonably be expected to induce life-long behaviour change, may be informative. However, to check the validity of such long-term evaluations, both the extent of dietary salt reduction advice provided to the control groups at the close of the studies, or since, and the maintenance of lower salt intake among the intervention groups does need to be assessed.

These are the logical first inexpensive steps to take. If these are not enough, then, a new (and large) trial of dietary advice should be contemplated. Investigators of cholesterol-lowering by either diet or drugs were not thwarted by the scale of trials necessary to demonstrate convincing effects.

The most important point is that trialists of dietary advice have failed to contribute relevant data to the public domain, and, as we found were unwilling to enter into data sharing with systematic reviewers. Perhaps the challenge is for trialists in this area to form collaboration with the aim of conducting an individual patient data meta-analysis. It should be noted we have never advocated a long-term efficacy trial.

The ethical issues inherent in any trial depend on the degree of clinical equipoise and as the salt debate illustrates, extreme views are held which makes it likely that sufficient clinicians in equipoise would be found. With ever-lower levels of "normal" blood pressure being defined it will be necessary to advance the knowledge base by conducting further trials.

What Archie Cochrane would have decided to do in these circumstances is a matter of speculation and of little relevance to the current issues. The importance of government initiatives to reduce sodium in processed foods depends on the efficacy, rather than effectiveness, of salt reduction and the DASH [4] salt study has lent serious weight to the importance of salt reduction to reduce blood pressure, but also of diets with increased fruit and vegetable intake, reduction in saturated fats, adequate whole grains, calcium, protein etc. This probably cannot all be achieved from processed foods, however low in salt they may be.

We stand by the conclusions as stated in the review.

References:

1. Law MR, Frost CD, Wald NJ. By how much does dietary salt reduction lower blood pressure? III--Analysis of data from trials of salt reduction. *BMJ*. 1991;302:819-24.
2. Hooper L, Bartlett C, Davey Smith G, Ebrahim S. Long term effects of advice to reduce dietary salt (authors reply). *BMJ* 2003;326:224.
3. Whelton PK, Appel LJ, Espeland MA, Applegate WB, Ettinger-WH J, Kostis JB et al. Sodium reduction and weight loss in the treatment of hypertension in older persons: a randomized controlled trial of nonpharmacologic interventions in the elderly (TONE). TONE Collaborative Research Group. *JAMA* 1998;279:839-46.
4. Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. *New England Journal of Medicine* 2001;344:3-10.

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WHAT'S NEW

Last assessed as up-to-date: 25 November 2003.

Date	Event	Description
12 November 2008	Amended	Contact details updated

HISTORY

Protocol first published: Issue 2, 2002

Review first published: Issue 1, 2003

Date	Event	Description
13 August 2008	Amended	Converted to new review format.
26 May 2004	Amended	Correlations used to estimate the standard deviations of change in diastolic blood pressure from baseline to 6-12 months were incorrect. These correlations are now not used for diastolic blood pressure. This alters the meta-analysis pooling of the effect on salt reduction advice compared with control on diastolic blood pressure at 6-12 months from -1.2mmHg (95% CI -1.8 to -0.7) to -1.2 mmHg (95% CI -1.8 to -0.6)
26 November 2003	New citation required but conclusions have not changed	Substantive amendment. Title of the review changed to "Advice to reduce dietary salt for prevention of cardiovascular disease" Comments and criticisms by Beard & Stowasser and by He and MacGregor were added, as well as authors' replies to the comments and criticisms

(Continued)

12 March 2003	Amended	The synopsis has been revised and references to Jurgens 2003 (a systematic review of shorter term salt reduction studies on the Cochrane Library) added
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CONTRIBUTIONS OF AUTHORS

All authors were actively involved in the design of the review, checking the data and provision of critical revisions to the manuscript, which was drafted by LH. LH and CB independently searched, decided on trial inclusion/exclusion, extracted data and assessed study quality. LH, CB and SE performed and duplicated the statistical analyses, SE and GDS were primary advisors guiding and interpreting the review. LH is the guarantor.

DECLARATIONS OF INTEREST

None of the reviewers have ever received funding in any form from food or beverage industries or anti-salt lobby groups. LH owned 285 shares in the West Indies Rum Distillery Ltd, Barbados at the time of completing the review.

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INDEX TERMS

Medical Subject Headings (MeSH)

Antihypertensive Agents [therapeutic use]; Cardiovascular Diseases [*prevention & control]; Diet, Sodium-Restricted; Hypertension [*diet therapy; drug therapy]; Randomized Controlled Trials as Topic; Sodium Chloride, Dietary [*administration & dosage]

MeSH check words

Humans