Effect of longer-term modest salt reduction on blood pressure (Review)

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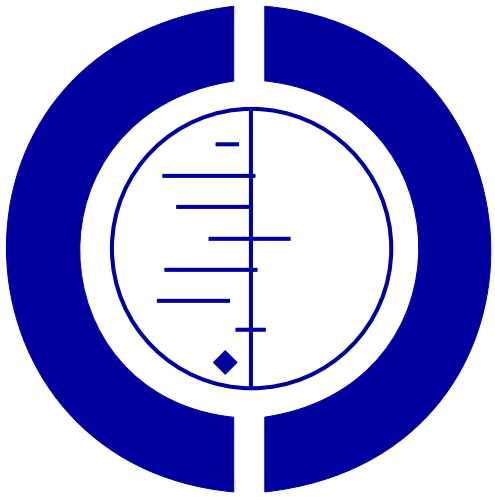

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ABSTRACT

Background
Many randomised trials assessing the effect of salt reduction on blood pressure show reduction in blood pressure in individuals with high blood pressure. However, there is controversy about the magnitude and the clinical significance of the fall in blood pressure in individuals with normal blood pressure. Several meta-analyses of randomised salt reduction trials have been published in the last few years. However, most of these included trials of very short duration (e.g. 5 days) and included trials with salt loading followed by salt deprivation (e.g. from 20 to 1 g/day) over only a few days. These short-term experiments are not appropriate to inform public health policy which is for a modest reduction in salt intake over a prolonged period of time. A meta-analysis (Hooper 2002) is an important attempt to look at whether advice to achieve a long-term salt reduction (i.e. more than 6 months) in randomised trials causes a fall in blood pressure. However, most trials included in this meta-analysis achieved a small reduction in salt intake; on average, salt intake was reduced by 2 g/day. It is, therefore, not surprising that this analysis showed a small fall in blood pressure, and that a dose-response to salt reduction was not demonstrable.

Objectives
To assess the effect of the currently recommended modest salt reduction on blood pressure in individuals with elevated and normal blood pressure.
To assess whether there is a dose-response to salt reduction.

Search strategy
We searched MEDLINE, EMBASE, Cochrane library and reference list of original and review articles.

Selection criteria
We included randomised trials with a modest reduction in salt intake and duration of 4 or more weeks.

Data collection and analysis
Data were extracted independently by two persons. Mean effect sizes were calculated using both fixed and random effects model. Weighted linear regression was performed to examine the relationship between the change in urinary sodium and the change in blood pressure.

Main results
Twenty trials in individuals with elevated blood pressure (n=802) and 11 trials in individuals with normal blood pressure (n=2220) were included. In individuals with elevated blood pressure the median reduction in urinary sodium was 78 mmol/24h (4.6 g/day of salt), the mean reduction in blood pressure was -5.06 mmHg (95%CI:-5.81 to -4.31) for systolic and -2.70 mmHg (95% CI:-3.16 to -2.24) for diastolic. In individuals with normal blood pressure the median reduction in urinary sodium was 74 mmol/24h (4.4 g/day of salt), the mean reduction in blood pressure was -2.03 mmHg (95% CI: -2.56 to -1.50) for systolic and -0.99 mmHg (-1.40 to -0.57) for diastolic. Weighted linear regression showed a significant relationship between the reduction in urinary sodium and the reduction in blood pressure.

Authors' conclusions

Our meta-analysis demonstrates that a modest reduction in salt intake for a duration of 4 or more weeks has a significant and, from a population viewpoint, important effect on blood pressure in both individuals with normal and elevated blood pressure. These results support other evidence suggesting that a modest and long-term reduction in population salt intake could reduce strokes, heart attacks, and heart failure. Furthermore, our meta-analysis demonstrates a correlation between the magnitude of salt reduction and the magnitude of blood pressure reduction. Within the daily intake range of 3 to 12 g/day, the lower the salt intake achieved, the lower the blood pressure.

PLAIN LANGUAGE SUMMARY

Current public health recommendations in most developed countries are to reduce salt intake by about half, i.e. from approximately 10 grams per day to 5 grams per day. Our pooled analysis of randomised trials of 4 weeks or more in duration showed that reduction in salt intake lowers blood pressure both in individuals with elevated blood pressure and in those with normal blood pressure. These results support other evidence for a modest and long term reduction in population salt intake. If this occured it would result in a lower population blood pressure, and a reduction in strokes, heart attacks and heart failure. Furthermore, our study is consistent with the fact that the lower the salt intake, the lower the blood pressure. The current recommendations to reduce salt intake to 5 grams per day will lower blood pressure, but a further reduction to 3 grams per day will lower blood pressure more.

BACKGROUND

The current public health recommendations in most developed countries are to reduce salt intake by about half, i.e. from approximately 9-12 to 5-6 g/day (WHO 2003; SACN 2003; Whelton 2002). This is because salt intake is thought to play an important role in regulating blood pressure based on epidemiological, migration, intervention, genetic and animal studies (Elliott 1996; Poulter 1990; Forte 1989; Lifton 1996; Denton 1995). In addition, many trials assessing the effect of salt reduction on blood pressure have shown consistent reductions in blood pressure in individuals with elevated blood pressure. There is, however, controversy about the magnitude of the fall in blood pressure in those with normal blood pressure. Several meta-analyses of these salt reduction trials have been performed (Law 1991; Cutler 1991; Midgley 1996; Cutler 1997; Graudal 1998; Hooper 2002). In two meta-analyses (Midgley 1996; Graudal 1998), it was claimed that the results showed that salt reduction had no or very little effect on blood pressure in individuals with normal blood pressure. The authors concluded that a reduction in population salt intake is not warranted. Furthermore, these papers were used as the basis of a commentary in Science (Taubes 1998) casting doubt on the link between salt intake and blood pressure, and have also been used to oppose public health recommendations for a reduction in salt intake (Swales 2000).

Detailed examination of these two meta-analyses (Midgley 1996; Graudal 1998) shows that they are flawed. Both meta-analyses included trials of very short duration of salt restriction, many for only 5 days. On average, the median duration of salt reduction in individuals with normal blood pressure was only 8 days in one meta-analysis (Graudal 1998) and 14 days in the other (Midgley 1996). Furthermore, around half of these trials compared the effects of acute salt loading to abrupt and severe salt restriction, e.g. from 20 to less than 1 gram/day of salt (Graudal 1998). These acute and large changes in salt intake cause an increase in sympathetic activity, plasma renin activity, and angiotensin II concentration (He 2001), which would counteract the effects on blood pressure. It is also known that most blood pressure-lowering drugs do not exert their maximal effect within 5 days; this is particularly true with diuretics which are likely to work by a similar mechanism to that of a reduction in salt intake. For these reasons it is inappropriate to include the acute salt restriction trials in a meta-analysis that attempts to apply them to public health recommendations for a longer-term modest reduction in salt intake.

A more recent meta-analysis (Hooper 2002) is an important attempt to look at whether advice to achieve long term salt reduction (i.e. more than 6 months) in randomised trials causes a fall in blood pressure. However, most trials included in this meta-analysis only achieved a very small reduction in salt intake (on average, salt intake was only reduced by 2 g/day). It is, therefore, not surprising that there was only a small, but still statistically significant fall in blood pressure. Furthermore, this meta-analysis did not demonstrate a relationship between the magnitude of salt reduction and the magnitude of blood pressure reduction.

OBJECTIVES

Our systematic review aimed to assess the effect of a longer-term modest reduction in salt intake on blood pressure in individuals with both elevated and normal blood pressure. We also assessed whether there was a dose-response to salt reduction. Furthermore,

we aimed to study the effect of a longer-term modest reduction in salt intake on plasma renin activity, aldosterone, noradrenaline, and lipids.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

For inclusion, trials needed to satisfy the following criteria:

1. Random allocation either to a modestly reduced salt intake or usual salt intake (i.e. control).

2. No concomitant interventions (i.e. nonpharmacololgical interventions, antihypertensive or other medications) in either group.

3. Net reduction in 24-h urinary sodium must be equal to or greater than 40 mmol (2.4 g/day of salt). Net reduction in 24-h urinary sodium was calculated as UNa (Post) - UNa (Pre) for crossover trials, where UNa (Post) designated to the average 24-h urinary sodium at the end of the reduced salt intake period and UNa (Pre) designated to the average 24-h urinary sodium at the end of the usual salt intake period (i.e. control period). In parallel trials net change in urinary sodium was calculated as {[UNa (Post) - UNa (Pre)] reduced salt group} - {[UNa (Post) - UNa (Pre)] usual salt group}, where UNa (Post) designated to the average 24-h urinary sodium at the end of follow-up and UNa (Pre) designated to the average 24-h urinary sodium at baseline.

4. Duration of salt reduction must have been for 4 or more weeks. By excluding trials with very short duration, we excluded most of the trials with severe reductions in salt intake.

Types of participants

Studies of adults (18 years or older) with normal or elevated blood pressure, irrespective of gender and ethnicity, were included. Children or pregnant women were excluded.

Types of intervention

The interventions included were to reduce salt intake. Studies with concomitant interventions (i.e. nonpharmacololgical interventions, antihypertensive or other medications) were excluded. One trial with factorial design (i.e. the Trials of Hypertension Prevention, Phase II) was included (TOHPRG 1997), however, in this trial the low salt arm (without weight intervention) was compared to the control group (without salt or weight intervention).

Types of outcome measures

The main outcome measures extracted were the net changes in systolic and diastolic blood pressure, and 24h urinary sodium excretion. These were calculated as the differences between the reduced salt and usual salt groups for mean change from baseline for parallel trials. For crossover trials, the net changes were calculated as the mean differences between the end of reduced salt and usual salt period. Other variables recorded were plasma renin activity, aldosterone, noradrenaline, and lipids.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Hypertension Group methods used in reviews.

In our first meta-analysis (He 2002), we developed a search strategy (Table 01) to search for randomised salt reduction trials from electronic database - MEDLINE (1966 to September 2001), EMBASE (1980 to September 2001), and CINAHL (1982 to June 2001). We also searched the Cochrane library with terms of “dietary sodium”, or “dietary salt”, or “sodium restriction”, or “salt restriction”. Furthermore, we reviewed reference list of original and review articles to search for more trials. There were no language restrictions.

For this review, we performed a repeated search from electronic database - MEDLINE, EMBASE and the Cochrane library, using the same search strategy in April 2005 through January 2001. This search revealed additional 12 randomised salt reduction trials. Among these 12 trials, 1 met our inclusion criteria and has been included in the meta-analysis (Gates 2004). The other 11 did not meet the inclusion criteria and have, therefore, been excluded. Another randomised double-blind trial from our own group which has been accepted by Hypertension (Swift 2005), also met the inclusion criteria, and has been included in this updated review. An additional randomised double-blind trial by Meland et al published in 1997 (Meland 1997), met the inclusion criteria, but was missed out in our first review. This trial is now included in the updated review.

METHODS OF THE REVIEW

Data Extraction Data were extracted independently by two persons (F. He and L. Ruddock) using a standard form and differences were resolved by discussion with a third reviewer (G.A. MacGregor). Relevant data recorded were characteristics of the study, design (parallel or crossover), type of the study (open, single-blind or double-blind), method of blinding (use of placebo, random-zero or automated sphygmomanometers, or blood pressure observers-blind), study duration, pre- and post-intervention results. For the purpose of pooled analyses, statistics that could be used to estimate the variances of the outcome measures were also recorded.

Statistical Analyses For each trial, we calculated the treatment effect for systolic and diastolic blood pressure. For crossover trials, the treatment effect was the difference in blood pressure between the end of reduced salt period and the end of usual salt (i.e. control) period. For parallel trials, the treatment effect was the difference

between the two treatment groups in the change in blood pressure from baseline to the end of follow-up.

For each trial, we also calculated the variance of the treatment effect for systolic and diastolic blood pressure. This was derived from standard deviations or standard errors of paired differences between baseline and the end of follow-up for each group in a parallel trial (Cappuccio 1991) or between the two treatment periods in a crossover trial, or if these statistics were not given, from confidence intervals, exact t or p values. If the exact variance of paired difference was not derivable, it was imputed either by inverting a boundary p value (e.g. $p<0.05$ became $p=0.05$) or assuming a correlation coefficient of 0.5 between the initial and final blood pressure (Follmann 1992). Among the 31 trials included in our meta-analysis, 10 had to have variance imputed (Table: "Characteristics of included studies").

Mean effect sizes were calculated using both fixed and random effects model on Cochrane Collaboration Review Manager 4.2.1 software. To examine whether there was a dose response relationship between the change in 24-h urinary sodium and the change in blood pressure, we performed weighted linear regression assuming a zero intercept. The assumption for using this model was that absence of a change in urinary sodium would be associated with no change in blood pressure, i.e. all other factors being equal between two randomised treatments. Furthermore, when we performed weighted linear regression without fixing the origin, the intercepts were not significantly different from zero. We used funnel plot asymmetry to detect publication and other biases in the meta-analysis (Egger 1997; Sterne 2001).

DESCRIPTION OF STUDIES

Thirty-one trials with 3022 subjects were found that fitted the inclusion criteria. A total of 112 trials were excluded, and the reasons for exclusion were 1) duration of salt reduction less than 4 weeks (n=63); 2) with concomitant intervention (medication or nonpharmacololgical intervention) (n=30); 3) studies in children (n=9), or pregnant women (n=2); 4) urinary sodium not measured (n=4); 5) net reduction in 24 h urinary sodium less than 40 mmol (n=3); 6) extreme change in salt intake (i.e. urinary sodium was changed from 309 to 24 mmol/24h) (n=1).

Among the 31 trials included in the meta-analysis, 20 were in patients with elevated blood pressure and 11 in individuals with normal blood pressure. For 3 papers where both elevated and normal blood pressure were studied, the data for the two categories were recorded separately and each of these papers was counted as two studies in this meta-analysis (Sacks 2001 (H); Sacks 2001 (N); Puska 1983 (H); Puska 1983 (N); Cappuccio 1997 (H); Cappuccio 1997 (N)) . For 2 papers (MacGregor 1989; Sacks 2001 (H); Sacks 2001 (N)) where 3 levels of salt intakes were studied, we included the high and intermediate levels (i.e. urinary sodium reduced from 190 to 108 mmol/24h) in one trial (MacGregor 1989) and in the other (DASH-Sodium study) (Sacks 2001 (H); Sacks 2001 (N)) we included the high and low levels (i.e. urinary sodium reduced from 145 to 65 mmol/24h in individuals with elevated blood pressure and from 139 to 64 mmol/24h in individuals with normal blood pressure on the normal American diet). In 3 studies (Morgan 1981 (F); Morgan 1981 (M); Nestel 1993 (F); Nestel 1993 (M); Watt 1985 (HH) offspring of two parents with elevated blood pressure; Watt 1985 (LL) offspring of two parents with low blood pressure) where subgroup data were reported only, they were entered for subgroups separately. The characteristics of the trials included in the meta-analysis are summarised in Table: "Characteristics of included studies".

METHODOLOGICAL QUALITY

Criteria for assessment of trial quality were as follows:

1. Concealment of Allocation Sequences (Jüni 2001)
The allocation sequences were defined as adequately concealed if participants and investigators can not foresee assignment, e.g. a prior numbered or coded drug containers of identical appearance prepared by an independent pharmacy; central randomisation, and as inadequately concealed if participants and investigators can foresee assignment, e.g. open list of random numbers.

2. Blinding
We distinguished trials by the methods of blinding, i.e. double-blind, blood pressure observer blind, or open study.

3. Completeness of Follow-up
We defined trials as using intention-to-treat analysis if all subjects were analysed in the groups to which they were randomly allocated, and as not using intention-to-treat analysis if only subjects who completed the trial were included in the analysis. We also recorded the number of subjects who were lost of follow-up after randomisation.

RESULTS

Effect on blood pressure

Trials in individuals with elevated blood pressure

Eight hundred and two individuals with elevated blood pressure were studied in 20 trials (Table: "Characteristics of included studies"). Median age was 50 years (ranging from 24 to 73 years). Of the 20 trials, 14 employed crossover design and 6 used paralleled comparisons. Twelve out of the 20 trials were double blind, 7 were blood pressure observer blind, and 1 did not report any blinding procedure. The study duration varied from 4 weeks to 1 year (median: 5 weeks). The median blood pressure on usual salt intake was 149/94 mmHg. The median 24-h urinary sodium on the usual salt intake was 162 mmol (9.5 g/day of salt), ranging from 125

to 191 mmol (7.4 to 11.2 g/day of salt) and on the reduced salt intake it was 87 mmol (5.1 g/day of salt), ranging from 57 to 125 mmol (3.4 to 7.4 g/day of salt). The median net change in 24-h urinary sodium was -78 mmol (4.6 g/day of salt), ranging from -53 to -117 mmol (3.1 to 6.9 g/day of salt). This average reduction in salt intake is similar to that of the current public health recommendations.

Figure 01-01 and Figure 01-02 show the net change in blood pressure in individual trials included in the meta-analysis and the mean effect size using the fixed effect model. The pooled estimates of changes in blood pressure are -5.06 mmHg (95% CI: -5.81 to -4.31) for systolic and -2.70 mmHg (95% CI: -3.16 to -2.24) for diastolic.

Using the random effects model, the pooled estimates of changes in blood pressure are -5.27 mmHg (95% CI: -6.69 to -3.85) for systolic and -2.76 mmHg (95% CI: -3.55 to -1.97) for diastolic.

The dose response analysis with the y-intercept fixed at zero shows a significant dose response to salt reduction for both systolic and diastolic blood pressure (Figure 1a; Figure 1b). A reduction of 100 mmol/day (6 g/day) in salt intake predicts a fall in blood pressure of 7.2 mmHg (95% CI: 5.6 to 8.8) for systolic and 3.8 mmHg (95%CI: 2.8 to 4.7) for diastolic blood pressure.

Trials in individuals with normal blood pressure

Two thousand two hundred and twenty individuals with normal blood pressure were studied in 11 trials (Table: "Characteristics of included studies"). Median age was 47 years (ranging from 22 to 67 years). Of the 11 trials, 6 employed crossover design and 5 used paralleled comparisons. Seven of the 11 trials were double blind and 4 were blood pressure observer blind. The study duration varied from 4 weeks to 3 years (median: 4 weeks). The median blood pressure on usual salt intake was 127/78 mmHg. The median 24-h urinary sodium on the usual salt intake was 154 mmol (9.1 g/day of salt), ranging from 128 to 200 mmol (7.5 to 11.8 g/day of salt) and on the reduced salt intake it was 82 mmol (4.8 g/day of salt), ranging from 56 to 135 mmol (3.3 to 7.9 g/day of salt). The median net change in 24-h urinary sodium was -74 mmol (4.4 g/day of salt), ranging from -40 to -118 mmol (2.4 to 6.9 g/day of salt). This average reduction in salt intake is similar to that of the current public health recommendations. It is important to note that in the only two longer-term trials (18 months and 3 years) (TOHPRG 1992; TOHPRG 1997) the reduction in salt intake was about half that found in the trials of 4 to 6 weeks.

Figure 01-01 and Figure 01-02 shows the net change in blood pressure in individual trials included in the meta-analysis and the mean effect size using the fixed effect model. The pooled estimates of changes in blood pressure are -2.03 mmHg (95% CI: -2.56 to -1.50) for systolic and -0.99 mmHg (95% CI: -1.40 to -0.57) for diastolic.

Using random effects model, the pooled estimates of change in blood pressure are -2.31 mmHg (95% CI: -3.48 to -1.14) for systolic and -0.84 mmHg (95% CI: -1.72 to 0.03) for diastolic.

The dose response analysis with the y-intercept fixed at zero shows a dose response to salt reduction for both systolic and diastolic blood pressure (Figure 1a; Figure 1b). A reduction of 100 mmol/day (6 g/day) in salt intake predicts a fall in blood pressure of 3.6 mmHg (95%CI: 1.9 to 5.2) for systolic and 1.7 mmHg (95%CI: 0.3 to 3.0) for diastolic.

Trials in all individuals

When taking all individuals together, there were 3022 subjects, among whom 27% had elevated blood pressure. Median age was 50 years (ranging from 22 to 73 years). The study duration varied from 4 weeks to 3 years (median: 5 weeks). The pooled estimates of changes in blood pressure, using a fixed effect model, are -3.03 mmHg (95% CI: -3.46 to -2.59) for systolic and -1.76 mmHg (95% CI: -2.07 to -1.46) for diastolic. Using a random effects model, the pooled estimates of changes in blood pressure are -3.99 mmHg (95% CI: -5.05 to -2.93) for systolic and -1.92 mmHg (95% CI: -2.59 to -1.26) for diastolic.

Effect on hormones and lipids

Plasma renin activity

Of the 31 trials, 11 reported the data of plasma renin activity (8 in hypertensives and 3 in normotensives) (Table: "Characteristics of included studies"). The median plasma renin activity was 0.97 ng/ml/hr on the usual salt and 1.53 ng/ml/hr on the reduced salt intake. The pooled estimate of the change in plasma renin activity was 0.13 ng/ml/hr (95% CI: 0.09 to 0.18) using the fixed effect model, and 0.29 ng/ml/hr (0.15 to 0.42) using random effects model.

Aldosterone

Of the 31 trials, 9 had plasma aldosterone measured (7 in hypertensives and 2 in normotensives) (Table: "Characteristics of included studies"). One trial (Benetos 1992) was excluded from the aldosterone analysis as the plasma aldosterone was extremely high after the unit conversion (235277.8 pmol/l on the usual salt and 269166.7 pmol/l on the reduced salt intake). The median plasma aldosterone was 298 pmol/l on the usual salt and 399 pmol/l on the reduced salt intake. The pooled estimate of the change in aldosterone was 90.7 pmol/l (95% CI: 68.1 to 113.3) using the fixed effect model and 122.3 pmol/l (95% CI: 60.7 to 183.8) using random effects model.

Noradrenaline

Plasma noradrenaline was measured in 6 trials (Table: "Characteristics of included studies"). Only 1 trial showed a significant increase (increased by 79 pg/ml, $P<0.05$) (Ruppert 1993), and the others showed no significant changes.

Lipids

Five trials reported the data of total cholesterol and 3 reported the data of triglyceride, low-density-lipoprotein and high-density-

lipoprotein cholesterol (Table: "Characteristics of included studies") . None showed any significant change in total cholesterol, triglyceride, low-density-lipoprotein or high-density-lipoprotein cholesterol.

Study quality

Among the 31 trials included in our meta-analysis 23 were judged to have adequate concealment of allocation of treatments (Table: "Characteristics of included studies"). In 8 trials the information on concealment of allocation was not available. The number of trials using intention-to-treat analysis was small (7 out of 31 trials) (ANHMRC 1989 (P); ANHMRC 1989 (X); Chalmers 1986; Cobiac 1992; Sacks 2001 (H); Sacks 2001 (N); TOHPRG 1992). The percentage of subjects who were lost of follow-up after randomisation was small (6.5% on average).

We included double-blind, blood pressure observer-blind, and open studies due to the fact that 1) some trials e.g. the DASH-Sodium (Sacks 2001 (H); Sacks 2001 (N)), although non-double-blinded, were well conducted with good compliance to different diets; and 2) it is very difficult to make any dietary intervention study double-blind. In relation to salt this can only be done by the use of salt tablets (Slow Sodium and placebo). Among the 31 trials included in our meta-analysis, 19 were double-blind, 11 were blood pressure observer-blind and only one small trial in hypertensives was non-blind (Table: "Characteristics of included studies"). Re-analysing the data by excluding the non-blind study (Parijs 1973) showed that the results were unchanged. The mean net change in blood pressure for individuals with elevated blood pressure was -5.04 mmHg (95%CI: -5.79 to -4.28) for systolic and -2.72 mmHg (95%CI: -3.18 to -2.27) for diastolic when the non-blinded study was excluded.

Publication bias

We plotted the funnel plots by plotting the treatment effect against the reciprocal of the standard error of the treatment effect (Figure 2a; Figure 2b). For diastolic blood pressure the funnel plots were symmetrical about the mean effect size line (asymmetry test: P= 0.500) (Egger 1997). For systolic the graphic plot was suggestive of bias (asymmetry test: P=0.034). This asymmetry of funnel plot might be because smaller studies showing no effect were under-reported in the literature. However, in our meta-analysis it is more likely to be due to the smaller effects of two larger and longer-term trials (TOHPRG 1992; TOHPRG 1997). The smaller effects in these two trials are most likely due to the smaller reduction of salt intake achieved in the longer-term trials. When these two trials were removed from the analysis, the asymmetry test was not significant (i.e. P>0.1).

DISCUSSION

Our meta-analysis of randomised trials of longer-term modest reductions in salt intake demonstrates a significant effect on blood pressure in individuals with both elevated and normal blood pressure. The blood pressure fell, on average, by 5/3 mmHg in hypertensives and 2/1 mmHg in normotensives. These falls in blood pressure would have an immediate and significant impact on population blood pressure and would, therefore, be predicted to reduce stroke deaths by approximately 14% and ischaemic heart disease (IHD) deaths by 9% in individuals with elevated blood pressure, and in individuals with normal blood pressure reduce stroke and IHD deaths by approximately 6% and 4% respectively (Stamler 1991; MacMahon 1990). It is important to note that these reductions in stroke and IHD deaths were estimated from a previous meta-analysis of prospective observational studies (MacMahon 1990). A recent meta-analysis of 1 million adults in 61 prospective studies demonstrates that the relationship between blood pressure and cardiovascular risk is much stronger than previously estimated (PSC 2002). Therefore, the reductions in stroke and IHD with the modest reductions in salt intake might be even greater. Since raised blood pressure is also a major risk factor for heart failure, a reduction in salt intake would likely reduce the incidence of heart failure.

Dose-response to salt reduction

Weighted linear regression with the regression line forced through the origin shows a significant dose response between the reduction in salt intake and the fall in blood pressure, suggesting that the lower the salt intake achieved, the greater the effect. The reasons to force the regression line through origin were: 1) Most trials did not report confounding factors. We assumed that in randomised well-controlled studies the confounding factors did not change throughout the trial in crossover studies and were comparable between the two treatment groups in parallel studies; 2) When we performed weighted linear regression without fixing the origin, the intercepts were not significantly different from zero. Indeed the slopes (mmHg/mmol) for the data forced through the origin (0.072/0.038, systolic/diastolic) are similar to those without fixing the origin (0.120/0.025) in individuals with elevated blood pressure. Likewise in individuals with normal blood pressure the regression lines with the fixed origin (0.036/0.017) are similar to those without fixing the origin (0.033/0.011).

It is important to emphasize that the best way to study the dose-response relationship between salt intake and blood pressure is to look at the blood pressure responses to several levels of salt intake for a sufficiently long period of time. So far, there are only two controlled trials in humans that studied 3 salt intakes, each for 4 weeks (MacGregor 1989; Sacks 2001 (H); Sacks 2001 (N)). Both studies showed a clear dose response, indicating that the lower the salt intake the lower the blood pressure. The dose-response relationship observed in our meta-analysis is in agreement with these two studies with three levels of salt intake. All three studies demonstrate a consistent dose response to salt reduction, within the range of 12 to 3 g/day, the lower the salt intake, the lower the blood pressure (He 2003).

Study duration

In spite of including studies of 1 month or more, the median duration of salt reduction in our meta-analysis was 5 weeks in the hypertensives and 4 weeks in the normotensives. Whether salt reduction has exerted its maximum effect by 4 weeks is not known, but much evidence would suggest that this is unlikely (Forte 1989). The finding that the two longer-term trials (TOHPRG 1992; TOHPRG 1997) in normotensives that were included had no greater effect on blood pressure is likely to be due to the fact that salt intake was only reduced on average by 2.5 g/day, whereas in the other trials it was reduced on average by 4.4 g/day.

Heterogeneity

There is significant heterogeneity across studies in our meta-analysis. However, it is still controversial how to deal with heterogeneous data, we therefore reported the mean effect sizes based on both the fixed effect model and random effects model (Petitti 2001). These two models produced very similar results. Heterogeneity may be due to a number of factors that affect the blood pressure responses to salt reduction, e.g. differences between studies in age, ethnic group, blood pressure levels, the amount of reduction in salt intake, the duration of salt reduction, and the quality of studies. Further sensitivity analyses were not performed due to the small number of trials that met the inclusion criteria and the very limited information reported in the studies.

Any adverse effects of modest salt reduction?

The previous meta-analyses by Midgley (Midgley 1996) and Graudal (Graudal 1998) have implied that salt reduction might have adverse effects which mitigate any benefit that occurs with the reduction in blood pressure. However, it has been pointed out that there is no evidence for any adverse effects from salt reduction and this is particularly true for the more modest reductions in salt intake that are the current public health recommendations (De Wardener 1999). Our meta-analysis shows that with modest reductions in salt intake there are only very small increases in plasma renin activity and aldosterone and no detectable change in sympathetic activity, total cholesterol, triglyceride, low-density or high-density lipoprotein cholesterol.

Mortality Studies

One of the difficulties of drawing conclusions about the importance of dietary or other lifestyle changes in cardiovascular disease is the lack of morbidity and mortality evidence. One has to accept that outcome studies of dietary or lifestyle changes in the population are extremely difficult. Indeed, there is unlikely to ever be outcome evidence on mortality for the important dietary variants, e.g. fruit and vegetables, or other lifestyle changes e.g. losing weight, or exercising. For instance, a study assessing the lifetime effects of salt would need to randomise subjects at the time of conception to a lower and higher salt intake and then follow the two groups on a high and low salt intake for the rest of their lives. Such studies are impractical and would be unethical in the light of current knowledge.

Alderman attempted to look at the effect of salt intake on cardiovascular disease in two cohort studies, one was a follow-up study of a worksite screening project in New York (Alderman 1995), and the other was NHANES 1 - a dietary survey of US adults from the mid 1970s (Alderman 1998). These studies suggested that a low salt diet increased the risk of cardiovascular disease. However, these two analyses are flawed and have been criticised (MacGregor 1996; De Wardener 1999; De Wardener 1998; Engelman 1998; Karppanen 1998). A further analysis of the NHANES 1 data showed that a high salt intake was significantly associated with increased cardiovascular events and all cause mortality in overweight persons (He 1999).

A recent study from Finland using a random sample of the Finnish adult population showed that salt intake was directly related to increased cardiovascular mortality and total mortality (Tuomilehto 2001). For a 6 g/day increase in salt intake there were large increases in both coronary events, cardiovascular events and total mortality. Another recent population-based cohort study of Japanese men and women showed that sodium intake was positively associated with stroke death (Nagata 2004).

Other evidence in support of a reduction in population salt intake

In assessing whether salt reduction has beneficial effects on public health, it is important to look at other types of evidence. Epidemiological studies have demonstrated that salt intake is an important factor in determining population blood pressure level and the rise in blood pressure with age (Elliott 1996). Studies in migrant populations have shown an increase in blood pressure with a move from a traditional rural to an urban environment where salt intake was increased along with other changes (Poulter 1990). An intervention study in two similar villages in Portugal where salt intake was successfully reduced in one by the provision of processed foods with less salt and appropriate dietary advice demonstrated a large difference in blood pressure between the two villages by the first year and a more pronounced difference in the second year (Forte 1989). Another two intervention studies, one in Belgium (Staessen 1988) and one in North Karelia (Tuomilehto 1984), did not achieve any reduction in salt intake, so unsurprisingly, there was no change in blood pressure. Evidence in animals, particularly in chimpanzees our closest relative, also supports the role of salt in controlling blood pressure (Denton 1995). Recently described rare mutations in humans that may either cause high or low blood pressure all involve a defect in the kidney's ability to excrete salt and are exacerbated by a high and low salt intake respectively (Lifton 1996). There is also evidence early in life that humans are particularly sensitive to salt intake and a small reduction in salt intake in the first six months of life appeared to have a long-lasting effect on blood pressure (Geleijnse 1996). This evidence alone suggests that a modest reduction in salt intake throughout the population would have a large impact on population blood pressure.

From the evidence above it is likely that high salt intake has a

gradual long-term (over decades) effect to increase blood pressure with increasing age. It is also likely that these effects would not be entirely reversed by reducing salt intake for 4 to 6 weeks as demonstrated in our meta-analysis. It is therefore possible that our meta-analysis underestimates the effect of reducing salt intake over a longer period of time.

There is increasing evidence that a modest reduction in salt intake has other beneficial effects on human health e.g. a reduced risk of stomach cancer (Tsugane 2004; Beevers 2004; Joossens 1996), a direct effect to reduce stroke (Nagata 2004), and a reduction in left ventricular hypertrophy (Perry 1992; Jula 1994; Kupari 1994) . These effects are possibly independent of and additive to the effect of salt reduction on blood pressure (Antonios 1996). A recent randomised double-blind trial in 40 hypertensive blacks demonstrates that a modest reduction in salt intake not only lowers blood pressure, but also reduces urinary protein excretion which is an independent risk factor for the progression of renal disease and cardiovascular disease (Swift 2005). Another randomised double-blind trial in individuals with stage 1 isolated systolic hypertension shows that modest salt reduction lowers blood pressure, and also improves the directly measured large elastic artery compliance (Gates 2004). The results from these recent studies provide further support to the accumulating evidence that a modest reduction in salt intake not only lowers blood pressure, but also has other beneficial effects on the cardiovascular system (de Wardener 2002; Safar 2000). Reducing salt intake also decreases loss of calcium by the kidney with a reduced risk of renal stones and bone demineralisation (Cappuccio 2000).

Reducing salt intake from the current levels of 9-12 g/day to the recommended levels of 5-6 g/day is not an easy task. In most developed countries 75-80% of salt intake now comes from salt added to processed foods. In our view, the best strategy would be to have the food industry gradually reduce the salt concentration of all processed foods, starting with a 10-25% reduction which is not detectable by consumers and continuing a sustained reduction over the course of the next decade. This strategy has now been adopted in the UK both by the Department of Health and Food Standards Agency, and several leading supermarkets and food manufacturers have already started to implement such changes. Of all the dietary changes to try and prevent cardiovascular disease, a reduction in salt intake is the easiest change, however, it requires the co-operation of the food industry. Clearly it would be additionally helpful if individuals also reduced the amount of salt they add to their own cooking or to their food. If this strategy was implemented and the recommended levels of 5-6 g/day were achieved, there would likely be the predicted reductions in strokes, heart attacks and heart failure. A further reduction to 3 grams of salt per day would be expected to have additional benefits (He 2003).

AUTHORS' CONCLUSIONS

Implications for practice

Our meta-analysis demonstrates that a modest reduction in salt intake has a significant effect on blood pressure in both individuals with elevated blood pressure and to a lesser extent in individuals with normal blood pressure. These findings in conjunction with other evidence relating salt intake to blood pressure make a strong case for a reduction in salt intake for individuals with elevated blood pressure, but also for a reduction in population salt intake. The goal in both cases is to lower blood pressure with the expectation that this would be associated with a reduction cardiovascular morbidity and mortality. Furthermore, our study suggests a dose-response to salt reduction; within the range of 3 to 12 g of salt intake/day, the lower the salt intake, the lower the blood pressure. Current recommendations to reduce salt intake to 5-6 g/day will have a major effect on blood pressure and therefore cardiovascular disease, but are not ideal. Reducing salt intake further to 3 g/day will have additional large effects.

Implications for research

The totality of evidence that links salt intake to blood pressure is now overwhelming. Increasing evidence from epidemiological studies in humans and experimental studies in animals suggests that a modest reduction in salt intake may have other beneficial effects on human health. Randomised trials are needed to study these other effects, e.g. the effect on left ventricular mass, left ventricular diastolic function, 24h urinary albumin excretion, renal stones, and biochemical markers of bone metabolism. Some researchers have called for randomised trials on cardiovascular mortality. However, it is extremely difficult to conduct such long-term trials. Indeed, there is unlikely to ever be outcome evidence on mortality for any of the important dietary variants, e.g. fruit and vegetables, or other lifestyle changes e.g. losing weight, or exercising. For instance, a study on salt would need to randomise subjects at the time of conception to a lower and higher salt intake and then follow up the two groups of offspring on a high and low salt intake for the rest of their lives. Such studies are impractical and would be unethical in the light of current knowledge.

POTENTIAL CONFLICT OF INTEREST

None.

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TABLES

Characteristics of included studies

Study	**ANHMRC 1989 (P)**
Methods	DB P
Participants	Intervention: N=50 Control: N=53 Age: 58 Male: 83% Hypertensive
Interventions	UNa: -71 mmol/24h Duration: 8 wks
Outcomes	SBP: -5.5 mmHg DBP: -2.8 mmHg
Notes	
Allocation concealment	A – Adequate

Study	**ANHMRC 1989 (X)**
Methods	DB X
Participants	N=88 Age: 59 Male: 83% Hypertensive
Interventions	UNa: -67 mmol/24h Duration: 8 wks
Outcomes	SBP: -3.6 mmHg DBP: -2.1 mmHg
Notes	
Allocation concealment	A – Adequate

Study	**Benetos 1992**
Methods	DB

	X
Participants	N=20 Age: 42 (22-55) Male: 45% Hypertensive
Interventions	UNa: -78 mmol/24h Duration: 4 wks
Outcomes	SBP: -6.5 mmHg DBP: -3.7 mmHg Noradrenaline: 52 pg/ml
Notes	Variance imputed
Allocation concealment	A – Adequate

Study	**Cappuccio 1997 (H)**
Methods	DB X
Participants	N=29 Age: 67 (60-78) Male: 51% Hypertensive
Interventions	UNa: -87 mmol/24h Duration: 4 wks
Outcomes	SBP: -6.6 mmHg DBP: -2.7 mmHg PRA: 0.32 ng/ml/h Aldo: 77 pmol/l
Notes	
Allocation concealment	A – Adequate

Study	**Cappuccio 1997 (N)**
Methods	DB X
Participants	N=18 Age: 67 (60-78) Male: 51% Normotensive
Interventions	UNa: -76 mmol/24h Duration: 4 wks
Outcomes	SBP: -8.2 mmHg DBP: -3.9 mmHg PRA: 0.36 ng/ml/h Aldo: 163 pmol/l
Notes	
Allocation concealment	A – Adequate

Study	**Chalmers 1986**
Methods	BP obs (A)

Characteristics of included studies (*Continued*)

	P
Participants	Intervention: N=48 Control: N=52 Age: 52 Male: 85% Hypertensive
Interventions	UNa: -54 mmol/24h Duration: 12 wks
Outcomes	SBP: -5.1 mmHg DBP: -4.2 mmHg
Notes	
Allocation concealment	B – Unclear

Study	**Cobiac 1992**
Methods	DB P
Participants	Intervention: N=26 Control: N=28 Age: 67 (60-80) Male: 67% Normotensive
Interventions	UNa: -73 mmol/24h Duration: 4 wks
Outcomes	SBP: -1.7 mmHg DBP: 0.8 mmHg
Notes	
Allocation concealment	A – Adequate

Study	**Erwteman 1984**
Methods	BP obs (RZ) P
Participants	Intervention: N=44 Control: N=50 Age: 46 (20-70) Male: 62% Hypertensive
Interventions	UNa: -58 mmol/24h Duration: 6 months
Outcomes	SBP: -2.7 mmHg DBP: -3.4 mmHg
Notes	
Allocation concealment	B – Unclear

Study	**Fotherby 1993**
Methods	DB X
Participants	N=17 Age: 73 (66-79)

	Male: 24% Hypertensive
Interventions	UNa: -79 mmol/24h Duration: 5 wks
Outcomes	SBP: -8.0 mmHg DBP: 0.0 mmHg PRA: 0.35 ng/ml/h Aldo: 475 pmol/l
Notes	Variance imputed
Allocation concealment	A – Adequate

Study	**Gates 2004**
Methods	DB X
Participants	N=12 Age: 64 Male: 50% Hypertensive
Interventions	UNa: -89 mmol/24h Duration: 4 wks
Outcomes	SBP: -7.0 mmHg DBP: -1.0 mmHg PRA: 0.26 ng/ml/h Chol: 0.13 mmol/l Trig: -0.10 mmol/l LDL: 0.21 mmol/l HDL: -0.05 mmol/l Noradrenaline: -6.67 pg/ml
Notes	
Allocation concealment	A – Adequate

Study	**Grobbee 1987**
Methods	DB X
Participants	N=40 Age: 18-28 Male: 85% Hypertensive
Interventions	UNa: -72 mmol/24h Duration: 6 wks
Outcomes	SBP: -0.8 mmHg DBP: -0.8 mmHg Noradrenaline: 19 pg/ml Chol: 0.0 mg/dl
Notes	Variance imputed
Allocation concealment	A – Adequate

Characteristics of included studies (*Continued*)

Study	**MacGregor 1982**
Methods	DB X
Participants	N=19 Age: 49 (30-66) Male: 59% Hypertensive
Interventions	UNa: -76 mmol/24h Duration: 4 wks
Outcomes	SBP: -10.0 mmHg DBP: -5.0 mmHg PRA: 0.64 ng/ml/h Aldo: 156 pmol/l
Notes	
Allocation concealment	A – Adequate

Study	**MacGregor 1989**
Methods	DB X
Participants	N=20 Age: 56 (43-73) Male: 55% Hypertensive
Interventions	UNa: -82 mmol/24h Duration: 4 wks
Outcomes	SBP: -8.0 mmHg DBP: -5.1 mmHg PRA: 0.20 ng/ml/h Aldo: 73 pmol/l Noradrenaline: 97 pg/ml
Notes	
Allocation concealment	A – Adequate

Study	**Mascioli 1991**
Methods	DB X
Participants	N=48 Age: 52 Male: 79% Normotensive
Interventions	UNa: -20 mmol/8h Duration: 4 wks
Outcomes	SBP: -3.6 mmHg DBP: -2.3 mmHg
Notes	
Allocation concealment	A – Adequate

Characteristics of included studies (*Continued*)

Study	**Meland 1997**
Methods	DB X
Participants	N=16 Age: 50 Male: 81% Hypertensive
Interventions	UNa: -66 mmol/24h Duration: 4 wks
Outcomes	SBP: -4.0 mmHg DBP: -2.0 mmHg
Notes	
Allocation concealment	A – Adequate

Study	**Morgan 1981 (F)**
Methods	BP obs P
Participants	Intervention: N=6 Control: N=6 Age: 38 Male: 0% Hypertensive
Interventions	UNa: -78 mmol/24h Duration: 8 wks
Outcomes	DBP: -4.0 mmHg
Notes	Variance imputed
Allocation concealment	B – Unclear

Study	**Morgan 1981 (M)**
Methods	BP obs P
Participants	Intervention: N=6 Control: N=6 Age: 40 Male: 100% Hypertensive
Interventions	UNa: -98 mmol/24h Duration: 8 wks
Outcomes	DBP: -8.0 mmHg
Notes	Variance imputed
Allocation concealment	B – Unclear

Study	**Nestel 1993 (F)**
Methods	DB P
Participants	Intervention: N=15 Control: N=15

Characteristics of included studies (*Continued*)

	Age: 65 Male: 0% Normotensive
Interventions	UNa: -94 mmol/24h Duration: 6 wks
Outcomes	SBP: -6.0 mmHg DBP: -2.0 mmHg
Notes	Variance imputed
Allocation concealment	A – Adequate

Study	**Nestel 1993 (M)**
Methods	DB P
Participants	Intervention: N=17 Control: N=19 Age: 66 Male: 100% Normotensive
Interventions	UNa: -76 mmol/24h Duration: 6 wks
Outcomes	SBP: -2.0 mmHg DBP: -1.0 mmHg
Notes	Variance imputed
Allocation concealment	A – Adequate

Study	**Parijs 1973**
Methods	NR X
Participants	N=15 Age: 41 Male: 43% Hypertensive
Interventions	UNa: -98 mmol/24h Duration: 4 wks
Outcomes	SBP: -6.7 mmHg DBP: 3.2 mmHg
Notes	Variance imputed
Allocation concealment	B – Unclear

Study	**Puska 1983 (H)**
Methods	BP obs P
Participants	Intervention: N=15 Control: N=19 Age: 30-50 Hypertensive
Interventions	UNa: -117 mmol/24h

Characteristics of included studies (*Continued*)

	Duration: 6 wks
Outcomes	SBP: 1.8 mmHg DBP: 0.5 mmHg
Notes	Variance imputed
Allocation concealment	B – Unclear

Study	**Puska 1983 (N)**
Methods	BP obs P
Participants	Intervention: N=19 Control: N=19 Age: 30-50 Normotensive
Interventions	UNa: -117 mmol/24h Duration: 6 wks
Outcomes	SBP: -1.5 mmHg DBP: -2.1 mmHg
Notes	Variance imputed
Allocation concealment	B – Unclear

Study	**Richards 1984**
Methods	BP obs (A) X
Participants	N=12 Age: 19-52 Male: 67% Hypertensive
Interventions	UNa: -105 mmol/24h Duration: 4-6 wks
Outcomes	SBP: -5.2 mmHg DBP: -1.8 mmHg PRA: 0.40 ng/ml/h Aldo: 112 pmol/l Noradrenaline: 24 pg/ml
Notes	Variance imputed
Allocation concealment	B – Unclear

Study	**Ruppert 1993**
Methods	DB X
Participants	N=25 Age: 47 (27-75) Male: 40% Normotensive
Interventions	UNa: -118 mmol/24h Duration: 4 wks
Outcomes	SBP: 1.7 mmHg DBP: 1.0 mmHg

	PRA: 0.60 ng/ml/h Noradrenaline: 79 pg/ml Chol: 0.0 mg/dl Trig: -4.9 mg/dl LDL 4.8 mg/dl HDL -1.5 mg/dl
Notes	Variance imputed
Allocation concealment	A – Adequate

Study	**Sacks 2001 (H)**
Methods	BP obs (RZ) X
Participants	N=76 Age: 52 Male: 39% Hypertensive
Interventions	UNa: -80 mmol/24h Duration: 4 wks
Outcomes	SBP: -8.7 mmHg DBP: -4.5 mmHg
Notes	
Allocation concealment	A – Adequate

Study	**Sacks 2001 (N)**
Methods	BP obs (RZ) X
Participants	N=116 Age: 47 Male: 50% Normotensive
Interventions	UNa: -75 mmol/24h Duration: 4 wks
Outcomes	SBP: -5.3 mmHg DBP: -2.6 mmHg
Notes	
Allocation concealment	A – Adequate

Study	**Schorr 1996**
Methods	DB X
Participants	N=16 Age: 64 (60-72) Male: 48% Normotensive
Interventions	UNa: -71 mmol/24h Duration: 4 wks
Outcomes	SBP: -7.2 mmHg DBP: -2.9 mmHg

	PRA: 0.23 ng/ml/h Aldo: 10 pmol/l Chol: 5.0 mg/dl Trig: 17.0 mg/dl LDL: 7.0 mg/dl HDL: 3.0 mg/dl
Notes	
Allocation concealment	A – Adequate

Study	**Silman 1983**
Methods	BP obs (RZ) P
Participants	Intervention: N=10 Control: N=15 Age: 50-64 Hypertensive
Interventions	UNa: -53 mmol/24h Duration: 12 months
Outcomes	SBP: -8.7 mmHg DBP: -6.3 mmHg
Notes	
Allocation concealment	B – Unclear

Study	**Swift 2005**
Methods	DB X
Participants	N=40 Age: 50 Male: 43% Hypertensive
Interventions	UNa: -78 mmol/24h Duration: 4 wks
Outcomes	SBP: -8 mmHg DBP: -3 mmHg PRA: 0.07 ng/ml/h Aldo: 44 pmol/l
Notes	
Allocation concealment	A – Adequate

Study	**TOHPRG 1992**
Methods	BP obs (RZ) P
Participants	Intervention: N=327 Control: N=417 Age: 43 (30-54) Male: 71% Normotensive
Interventions	UNa: -44 mmol/24h

Characteristics of included studies (*Continued*)

	Duration: 18 months
Outcomes	SBP: -1.7 mmHg DBP: -0.9 mmHg
Notes	
Allocation concealment	A – Adequate

Study	**TOHPRG 1997**
Methods	BP obs (RZ) P
Participants	Intervention: N=515 Control: N=514 Age: 44 (30-54) Male: 67% Normotensive
Interventions	UNa: -40 mmol/24h Duration: 36 months
Outcomes	SBP: -1.2 mmHg DBP: -0.7 mmHg
Notes	
Allocation concealment	A – Adequate

Study	**Watt 1983**
Methods	DB X
Participants	N=18 Age: 52 (31-64) Male: 33% Hypertensive
Interventions	UNa: -56 mmol/24h Duration: 4 wks
Outcomes	SBP: -0.5 mmHg DBP: -0.3 mmHg PRA: 1.63 ng/ml/h
Notes	
Allocation concealment	A – Adequate

Study	**Watt 1985 (HH)**
Methods	DB X
Participants	N=35 Age: 22 Male: 37% Normotensive
Interventions	UNa: -74 mmol/24h Duration: 4 wks
Outcomes	SBP: -1.4 mmHg DBP: 1.2 mmHg

Characteristics of included studies (*Continued*)

Notes	
Allocation concealment	A – Adequate

Study	**Watt 1985 (LL)**
Methods	DB X
Participants	N=31 Age: 23 Male: 45% Normotensive
Interventions	UNa: -60 mmol/24h Duration: 4 wks
Outcomes	SBP: -0.5 mmHg DBP: 1.4 mmHg
Notes	
Allocation concealment	A – Adequate

UNa: urinary sodium; BP: blood pressure; X: crossover; SBP: systolic blood pressure; DBP: diastolic blood pressure; P: parallel; NR: Not reported; DB: Double blind; BP obs: blood pressure observer blinded; RZ: random zero manometer; A: automated sphygmomanometer; F: Female; M: Male; H: Hypertensive; N: Normotensive; HH: offspring of two parents with high blood pressure; LL: offspring of two parents with low blood pressure; PRA: plasma renin activity; Aldo: aldosterone; Chol: cholesterol; Trig: triglyceride; LDL: low-density lipoprotein; HDL: high-density lipoprotein.

Characteristics of excluded studies

Ambrosioni 1982	Urinary sodium not measured
Ames 2001	With concomitant intervention
Andersson 1984	With concomitant intervention
Appel 2003	With concomitant intervention
Applegate 1992	With concomitant intervention
Arroll 1995	With concomitant intervention
Barba 2000	Duration of salt reduction less than 4 weeks
Beard 1982	With concomitant intervention
Beckmann 1995	With concomitant intervention
Bruun 1990	Duration of salt reduction less than 4 weeks
Buckley 1994	Duration of salt reduction less than 4 weeks
Burnier 1993	Duration of salt reduction less than 4 weeks
Carney 1991	With concomitant intervention
Cooper 1984	Studies in children
Costa 1981	Urinary sodium not measured
Cuzzola 2001	Duration of salt reduction less than 4 weeks
Damasceno 1999	Duration of salt reduction less than 4 weeks
Davrath 1999	Duration of salt reduction less than 4 weeks
Del Rio 1993	Duration of salt reduction less than 4 weeks
Delemarre 2000	Studies in pregnant women
Dimsdale 1990	Duration of salt reduction less than 4 weeks
Dodson 1989	With concomitant intervention

Characteristics of excluded studies (*Continued*)

Donovan 1993	Duration of salt reduction less than 4 weeks
Egan 1991	Duration of salt reduction less than 4 weeks
Fagerberg 1984	With concomitant intervention
Feldman 1996	Duration of salt reduction less than 4 weeks
Ferri 1993	Duration of salt reduction less than 4 weeks
Ferri 1996	Duration of salt reduction less than 4 weeks
Fliser 1993	Duration of salt reduction less than 4 weeks
Forrester 2005	Duration of salt reduction less than 4 weeks
Friberg 1990	Duration of salt reduction less than 4 weeks
Fuchs 1987	Duration of salt reduction less than 4 weeks
Gillum 1981	Studies in children
Gomi 1998	Duration of salt reduction less than 4 weeks
Gow 1992	Duration of salt reduction less than 4 weeks
Grey 1996	Duration of salt reduction less than 4 weeks
HPTRG 1990	Net reduction in 24-h urinary sodium less than 40 mmol
Hargreaves 1989	Duration of salt reduction less than 4 weeks
Haythornthwaite 1992	Duration of salt reduction less than 4 weeks
Heagerty 1986	Duration of salt reduction less than 4 weeks
Hofman 1983	Studies in children
Howe 1991	Studies in children
Inoue 1996	Duration of salt reduction less than 4 weeks
Jula 1990	With concomitant intervention
Jula 1992	With concomitant intervention
Koolen 1984 (a)	Duration of salt reduction less than 4 weeks
Koolen 1984 (b)	Duration of salt reduction less than 4 weeks
Koopman 1990 (a)	With concomitant intervention
Koopman 1990 (b)	With concomitant intervention
Kurtz 1987	Duration of salt reduction less than 4 weeks
Lawton 1988	Duration of salt reduction less than 4 weeks
Logan 1986	Net reduction in 24-h urinary sodium less than 40 mmol
Luft 1990	Duration of salt reduction less than 4 weeks
MacGregor 1987	With concomitant intervention
Mallamaci 1996	Duration of salt reduction less than 4 weeks
Manunta 2001	Duration of salt reduction less than 4 weeks
Mark 1975	Duration of salt reduction less than 4 weeks
Mattila 2003	With concomitant intervention
Maxwell 1984	With concomitant intervention
McCarron 1997	With concomitant intervention
Miller 1988	Studies in children
Miller 1997	Duration of salt reduction less than 4 weeks
Morgan 1978	Net reduction in 24-h urinary sodium less than 40 mmol
Morgan 1988	Duration of salt reduction less than 4 weeks
Mtabaji 1990	Duration of salt reduction less than 4 weeks
Muhlhauser 1996	With concomitant intervention

Characteristics of excluded studies (*Continued*)

Myers 1983	Duration of salt reduction less than 4 weeks
Nakamura 2003	Urinary sodium not measured
Nowson 1988	With concomitant intervention
Nowson 2003	With concomitant intervention
Nowson 2004	With concomitant intervention
Overlack 1993	Duration of salt reduction less than 4 weeks
Overlack 1995	Duration of salt reduction less than 4 weeks
Palacios 2004	Duration of salt reduction less than 4 weeks
Palmer 1989	Urinary sodium not measured
Parker 1990	With concomitant intervention
Pedersen 1986	Duration of salt reduction less than 4 weeks
Petrie 1998	Duration of salt reduction less than 4 weeks
Pomeranz 2002	Studies in neonates
Redon-Mas 1994	With concomitant intervention
Richards 1986	Duration of salt reduction less than 4 weeks
Ruilope 1993	Duration of salt reduction less than 4 weeks
Ruppert 1991	Duration of salt reduction less than 4 weeks
Ruppert 1994	Duration of salt reduction less than 4 weeks
Schmid 1990	Duration of salt reduction less than 4 weeks
Schorr 1997	Duration of salt reduction less than 4 weeks
Sciarrone 1992	With concomitant intervention
Sharma 1990	Duration of salt reduction less than 4 weeks
Sharma 1991	Duration of salt reduction less than 4 weeks
Sharma 1993	Duration of salt reduction less than 4 weeks
Shore 1988	Duration of salt reduction less than 4 weeks
Sinaiko 1993	Studies in children
Singer 1991	With concomitant intervention
Skrabal 1981	Duration of salt reduction less than 4 weeks
Skrabal 1984	Duration of salt reduction less than 4 weeks
Skrabal 1985	Duration of salt reduction less than 4 weeks
Steegers 1991	Studies in pregnant women
Sullivan 1980	Duration of salt reduction less than 4 weeks
Takashashi 2003	With concomitant intervention
Teow 1985	Duration of salt reduction less than 4 weeks
Thaler 1982	With concomitant intervention
Wedler 1992	Duration of salt reduction less than 4 weeks
Weir 1995	Duration of salt reduction less than 4 weeks
Weir 1997	With concomitant intervention
Whelton 1998	With concomitant intervention
Whitten 1980	Studies in children
Zoccali 1993	Duration of salt reduction less than 4 weeks
Zoccali 1994	Duration of salt reduction less than 4 weeks
el Ashry 1987	Duration of salt reduction less than 4 weeks
van BergeLandry 2004	Extreme change in salt intake, uirnary sodium was changed from 309 to 24 mmol/24h
van Paassen 1996	Duration of salt reduction less than 4 weeks

ADDITIONAL TABLES

Table 01. Search strategy to identify randomised salt reduction trials

Set	Search terms
1	blood pressure
2	hypertension
3	plasma renin activity
4	renin
5	PRA
6	aldosterone
7	noradrenaline or norepinephrine
8	catecholamines
9	cholesterol
10	triglycerides
11	LDL or Lipoproteins, LDL cholesterol
12	HDL or Lipoproteins, HDL cholesterol
13	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14	sodium
15	salt
16	sodium chloride
17	14 or 15 or 16
18	diet
19	dietary
20	intake
21	restriction or reduction
22	18 or 19 or 20 or 21
23	17 and 22
24	random
25	random allocation
26	randomised
27	randomized
28	randomisation
29	randomization
30	controlled trials

Table 01. Search strategy to identify randomised salt reduction trials (*Continued*)

Set	Search terms
31	24 or 25 or 26 or 27 or 28 or 29 or 30
32	13 and 23 and 31
33	limt 32 to human

ANALYSES

Comparison 01. Mean Net Change in Blood Pressure with Salt Reduction (Fixed Effect Model)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Systolic Blood Pressure (Fixed Effect Model)	32		Net Change in SBP (Fixed) 95% CI	-3.03 [-3.46, -2.59]
02 Diastolic Blood Pressure (Fixed Effect Model)	34		Net Change in DBP (Fixed) 95% CI	-1.76 [-2.07, -1.46]

INDEX TERMS

Medical Subject Headings (MeSH)

Aldosterone [blood]; Blood Pressure [physiology]; Hypertension [blood; *diet therapy]; Lipids [blood]; Norepinephrine [blood]; Randomized Controlled Trials; Renin [blood]; Sodium Chloride, Dietary [*administration & dosage]

MeSH check words

Humans

COVER SHEET

Title	Effect of longer-term modest salt reduction on blood pressure
Authors	He FJ, MacGregor GA
Contribution of author(s)	Both authors were involved in the design of the review. Feng J He conducted the search, data extraction and statistical analyses. Graham A MacGregor supervised all aspects of the review conduct. Both authors wrote the original draft of the manuscript, contributed to the revision and final version of the paper. Both authors act as guarantors.
Issue protocol first published	/
Review first published	2004/3
Date of most recent amendment	24 May 2006
Date of most recent SUBSTANTIVE amendment	09 May 2005
What's New	Compared with the first version published in the Journal of Human Hypertension in 2002, the following changes have been made: A repeated search using the same search strategy was carried out in April 2005. Fourteen new references have been found. Among these 14 references, 3 met the inclusion criteria (Meland 1997, Gates 2004 and Swift 2005) and have been included in the meta-analysis. The other 11 did not meet the inclusion criteria and have, therefore, been excluded.

	We have also added the following to the discussion: A recent randomised double-blind trial in hypertensive blacks demonstrates that a modest reduction in salt intake not only lowers blood pressure, but also reduces urinary protein excretion which is an independent risk factor for the progression of renal disease and cardiovascular disease. Another randomised double-blind trial in individuals with stage 1 isolated systolic hypertension shows that modest salt reduction lowers blood pressure, and also improves the directly measured large elastic artery compliance. The results from these recent studies provide further support to the accumulating evidence that a modest reduction in salt intake not only lowers blood pressure, but also has other beneficial effects on the cardiovascular system.
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	01 April 2005
Date authors' conclusions section amended	Information not supplied by author
Contact address	Dr Graham MacGregor Professor of Cardiovascular Medicine Blood Pressure Unit St. George's Hospital Medical School Cranmer Terrace London SW17 0RE UK E-mail: g.macgregor@sghms.ac.uk Tel: +44 20 8725 2848 Fax: +44 20 8725 2959
DOI	10.1002/14651858.CD004937
Cochrane Library number	CD004937
Editorial group	Cochrane Hypertension Group
Editorial group code	HM-HTN

Figure 01. Relationship between the net change in urinary sodium excretion and systolic blood pressure. The open circles represent normotensives and the solid circles represent hypertensives. The slope is weighted by the inverse of the variance of the net change in systolic blood pressure. The size of the circle is in proportion to the weight of the trial.

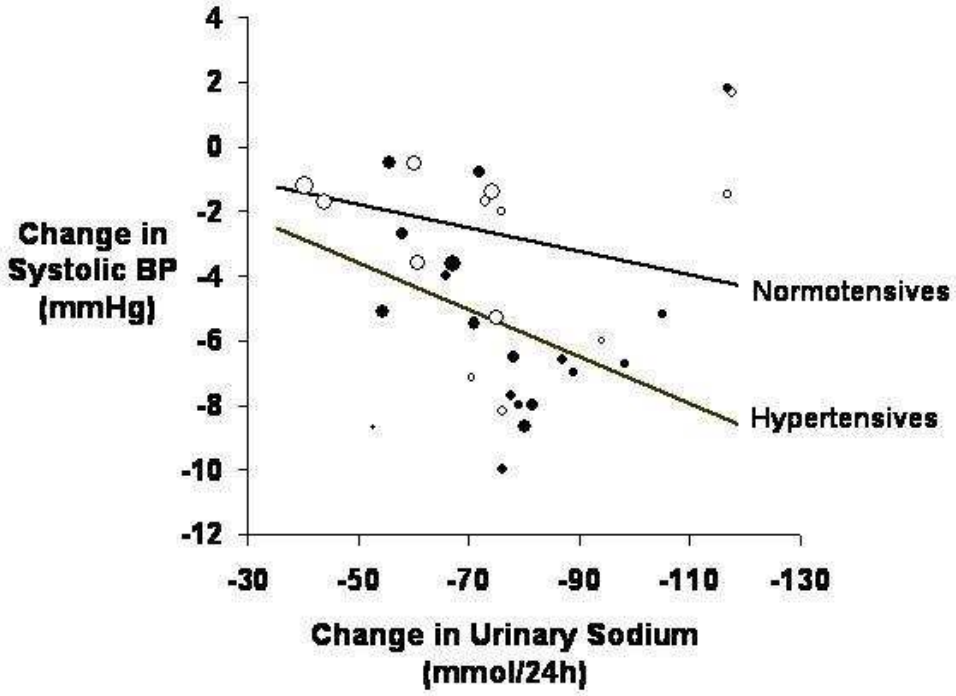


Figure 02. Relationship between the net change in urinary sodium excretion and diastolic blood pressure. The open circles represent normotensives and the solid circles represent hypertensives. The slope is weighted by the inverse of the variance of the net change in diastolic blood pressure. The size of the circle is in proportion to the weight of the trial.

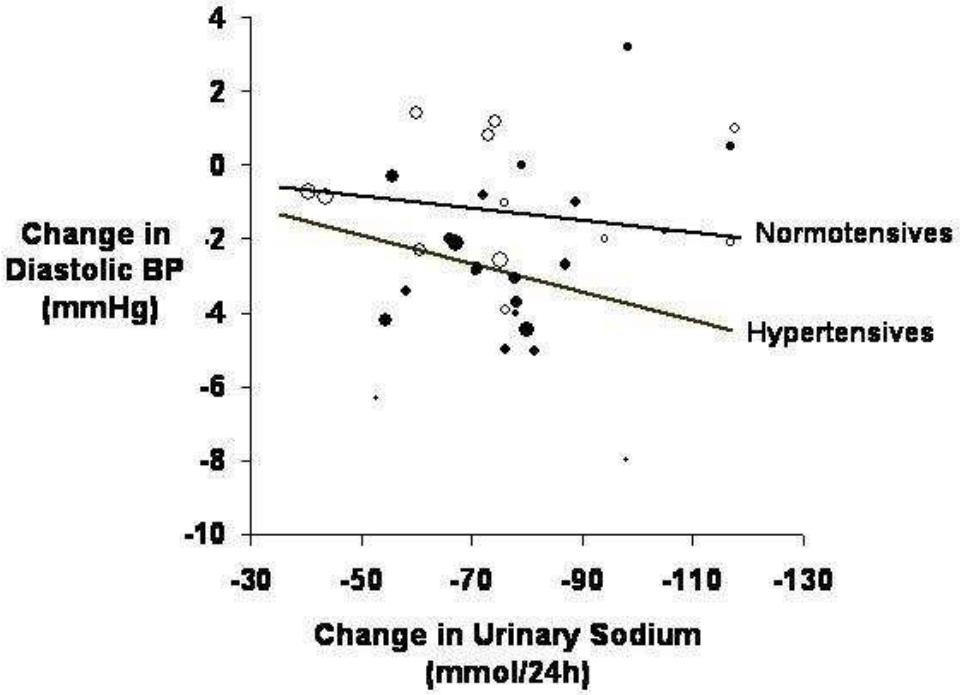


Figure 03. Funnel plot to explore publication bias (systolic). The vertical line is at the mean effect size. Precision is the reciprocal of the standard error of the net change in systolic blood pressure.

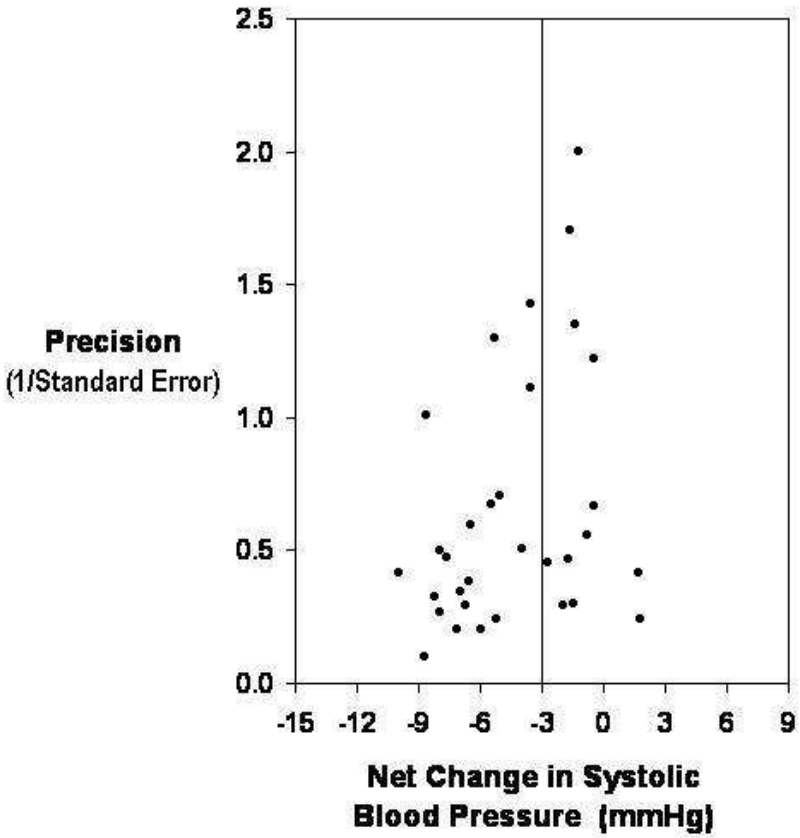
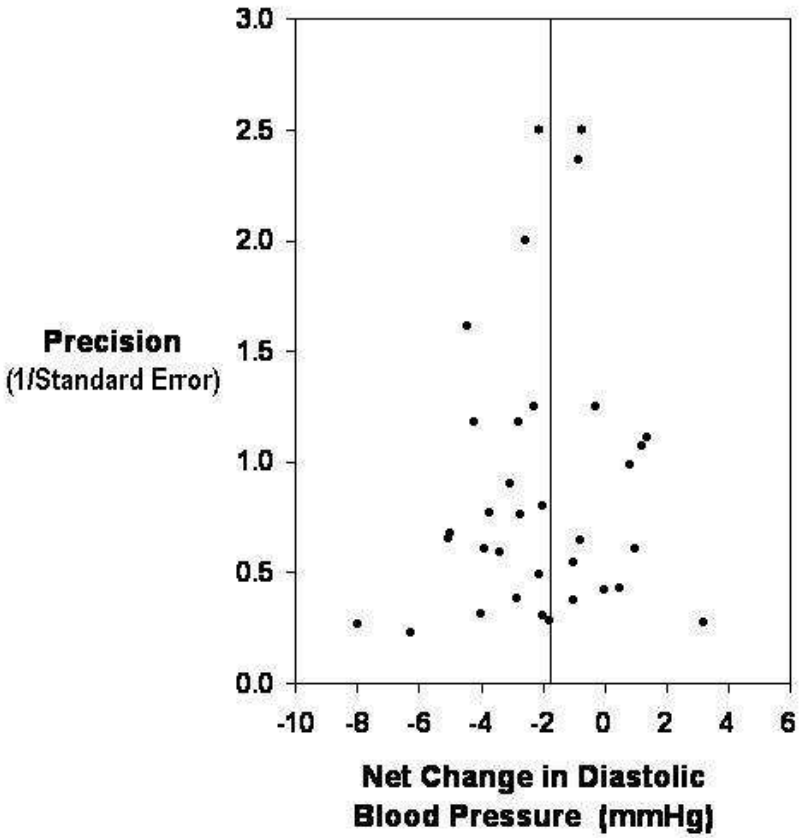


Figure 04. Funnel plot to explore publication bias (diastolic). The vertical line is at the mean effect size. Precision is the reciprocal of the standard error of the net change in diastolic blood pressure.

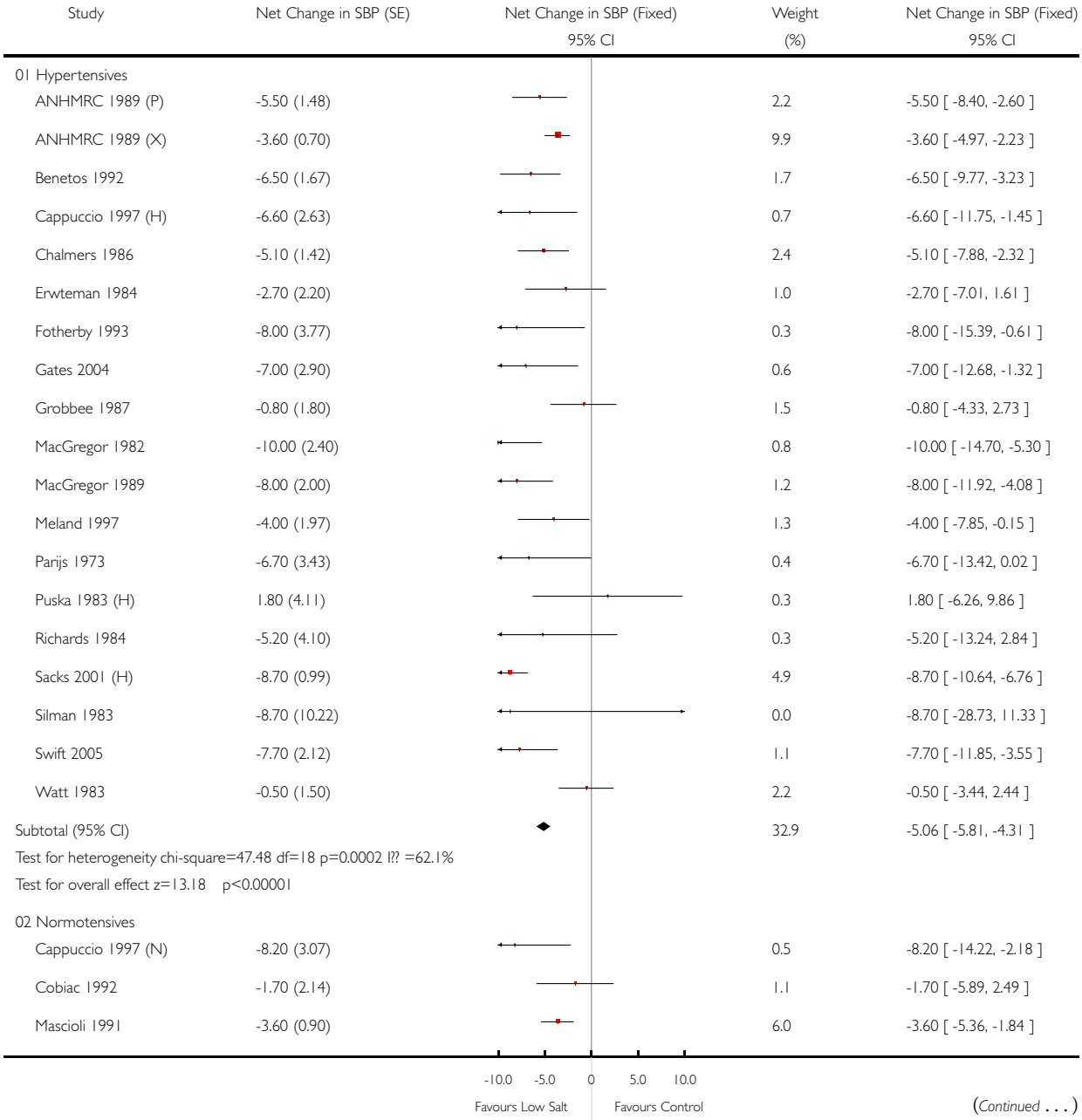


Analysis 01.01. Comparison 01 Mean Net Change in Blood Pressure with Salt Reduction (Fixed Effect Model), Outcome 01 Systolic Blood Pressure (Fixed Effect Model)

Review: Effect of longer-term modest salt reduction on blood pressure

Comparison: 01 Mean Net Change in Blood Pressure with Salt Reduction (Fixed Effect Model)

Outcome: 01 Systolic Blood Pressure (Fixed Effect Model)



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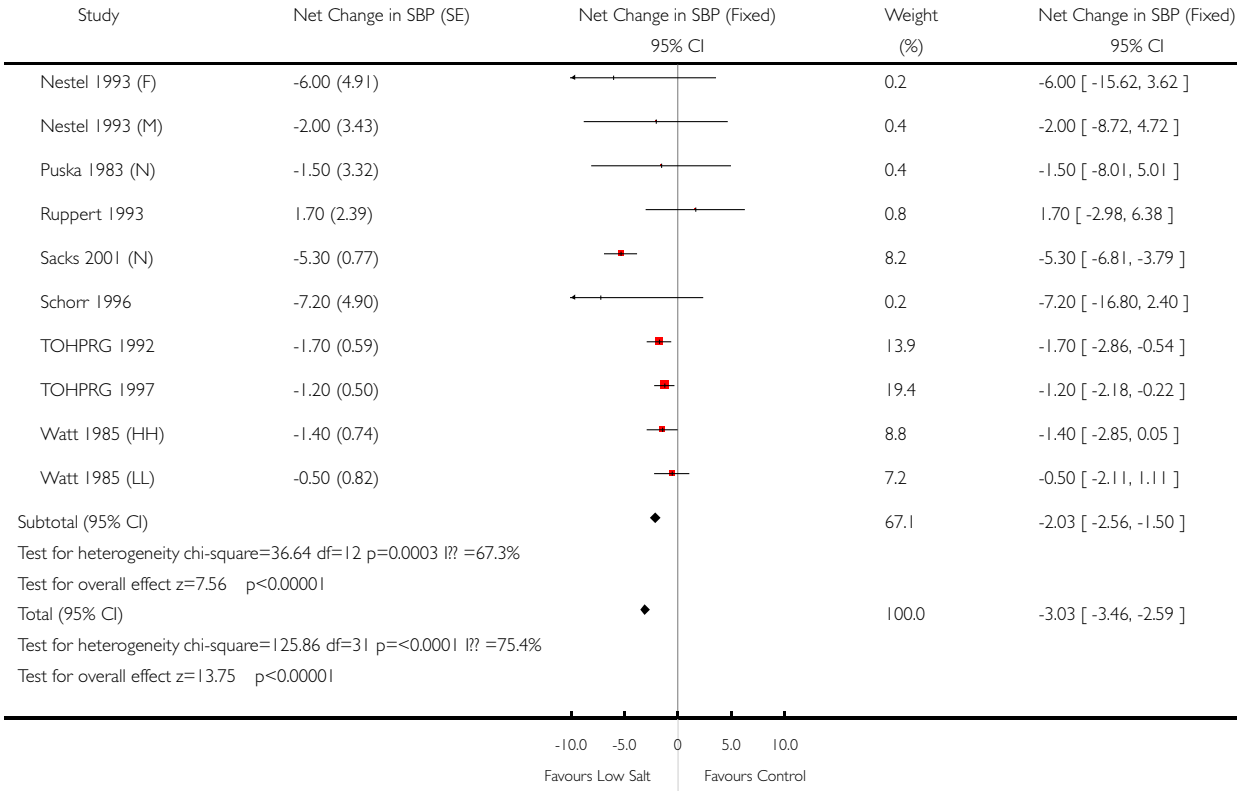


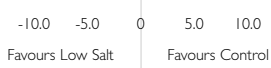
Analysis 01.02. Comparison 01 Mean Net Change in Blood Pressure with Salt Reduction (Fixed Effect Model), Outcome 02 Diastolic Blood Pressure (Fixed Effect Model)

Review: Effect of longer-term modest salt reduction on blood pressure

Comparison: 01 Mean Net Change in Blood Pressure with Salt Reduction (Fixed Effect Model)

Outcome: 02 Diastolic Blood Pressure (Fixed Effect Model)

Study	Net Change in DBP (SE)	Net Change in DBP (Fixed) 95% CI	Weight (%)	Net Change in DBP (Fixed) 95% CI
01 Hypertensives				
ANHMRC 1989 (P)	-2.80 (0.85)		3.4	-2.80 [-4.47, -1.13]
ANHMRC 1989 (X)	-2.10 (0.40)		15.4	-2.10 [-2.88, -1.32]
Benetos 1992	-3.70 (1.29)		1.5	-3.70 [-6.23, -1.17]
Cappuccio 1997 (H)	-2.70 (1.32)		1.4	-2.70 [-5.29, -0.11]
Chalmers 1986	-4.20 (0.85)		3.4	-4.20 [-5.87, -2.53]
Erwteman 1984	-3.40 (1.70)		0.9	-3.40 [-6.73, -0.07]
Fotherby 1993	0.00 (2.39)		0.4	0.00 [-4.68, 4.68]
Gates 2004	-1.00 (1.83)		0.7	-1.00 [-4.59, 2.59]
Grobbee 1987	-0.80 (1.55)		1.0	-0.80 [-3.84, 2.24]
MacGregor 1982	-5.00 (1.47)		1.1	-5.00 [-7.88, -2.12]
MacGregor 1989	-5.10 (1.53)		1.0	-5.10 [-8.10, -2.10]
Meland 1997	-2.00 (1.25)		1.6	-2.00 [-4.45, 0.45]
Morgan 1981 (F)	-4.00 (3.22)		0.2	-4.00 [-10.31, 2.31]
Morgan 1981 (M)	-8.00 (3.78)		0.2	-8.00 [-15.41, -0.59]
Parijs 1973	3.20 (3.62)		0.2	3.20 [-3.90, 10.30]
Puska 1983 (H)	0.50 (2.34)		0.4	0.50 [-4.09, 5.09]
Richards 1984	-1.80 (3.55)		0.2	-1.80 [-8.76, 5.16]
Sacks 2001 (H)	-4.50 (0.62)		6.4	-4.50 [-5.72, -3.28]
Silman 1983	-6.30 (4.42)		0.1	-6.30 [-14.96, 2.36]
Swift 2005	-3.10 (1.11)		2.0	-3.10 [-5.28, -0.92]
Watt 1983	-0.30 (0.80)		3.8	-0.30 [-1.87, 1.27]
Subtotal (95% CI)			45.4	-2.70 [-3.16, -2.24]
Test for heterogeneity chi-square=39.95 df=20 p=0.005 I?? =49.9%				
Test for overall effect z=11.61 p<0.00001				
02 Normotensives				
Cappuccio 1997 (N)	-3.90 (1.65)		0.9	-3.90 [-7.13, -0.67]



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