

## RESEARCH

# Effect of longer term modest salt reduction on blood pressure: Cochrane systematic review and meta-analysis of randomised trials

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## Abstract

**Objective** To determine the effects of longer term modest salt reduction on blood pressure, hormones, and lipids.

**Design** Systematic review and meta-analysis.

**Data sources** Medline, Embase, Cochrane Hypertension Group Specialised Register, Cochrane Central Register of Controlled Trials, and reference list of relevant articles.

**Inclusion criteria** Randomised trials with a modest reduction in salt intake and duration of at least four weeks.

**Data extraction and analysis** Data were extracted independently by two reviewers. Random effects meta-analyses, subgroup analyses, and meta-regression were performed.

**Results** Thirty four trials (3230 participants) were included. Meta-analysis showed that the mean change in urinary sodium (reduced salt v usual salt) was  $-75$  mmol/24 h (equivalent to a reduction of 4.4 g/day salt), and with this reduction in salt intake, the mean change in blood pressure was  $-4.18$  mm Hg (95% confidence interval  $-5.18$  to  $-3.18$ ,  $I^2=75%$ ) for systolic blood pressure and  $-2.06$  mm Hg ( $-2.67$  to  $-1.45$ ,  $I^2=68%$ ) for diastolic blood pressure. Meta-regression showed that age, ethnic group, blood pressure status (hypertensive or normotensive), and the change in 24 hour urinary sodium were all significantly associated with the fall in systolic blood pressure, explaining 68% of the variance between studies. A 100 mmol reduction in 24 hour urinary sodium (6 g/day salt) was associated with a fall in systolic blood pressure of 5.8 mm Hg (2.5 to 9.2,  $P=0.001$ ) after adjustment for age, ethnic group, and blood pressure status. For diastolic blood pressure, age, ethnic group, blood pressure status, and the change in 24 hour urinary sodium explained 41% of the variance between studies. Meta-analysis by subgroup showed that in people with hypertension the mean effect was  $-5.39$  mm Hg ( $-6.62$  to  $-4.15$ ,  $I^2=61%$ ) for systolic blood pressure and  $-2.82$  mm Hg

( $-3.54$  to  $-2.11$ ,  $I^2=52%$ ) for diastolic blood pressure. In normotensive people, the figures were  $-2.42$  mm Hg ( $-3.56$  to  $-1.29$ ,  $I^2=66%$ ) and  $-1.00$  mm Hg ( $-1.85$  to  $-0.15$ ,  $I^2=66%$ ), respectively. Further subgroup analysis showed that the decrease in systolic blood pressure was significant in both white and black people and in men and women. Meta-analysis of data on hormones and lipids showed that the mean change was 0.26 ng/mL/h (0.17 to 0.36,  $I^2=70%$ ) for plasma renin activity, 73.20 pmol/L (44.92 to 101.48,  $I^2=62%$ ) for aldosterone, 187 pmol/L (39 to 336,  $I^2=5%$ ) for noradrenaline (norepinephrine), 37 pmol/L ( $-1$  to 74,  $I^2=12%$ ) for adrenaline (epinephrine), 0.05 mmol/L ( $-0.02$  to 0.11,  $I^2=0%$ ) for total cholesterol, 0.05 mmol/L ( $-0.01$  to 0.12,  $I^2=0%$ ) for low density lipoprotein cholesterol,  $-0.02$  mmol/L ( $-0.06$  to 0.01,  $I^2=16%$ ) for high density lipoprotein cholesterol, and 0.04 mmol/L ( $-0.02$  to 0.09,  $I^2=0%$ ) for triglycerides.

**Conclusions** A modest reduction in salt intake for four or more weeks causes significant and, from a population viewpoint, important falls in blood pressure in both hypertensive and normotensive individuals, irrespective of sex and ethnic group. Salt reduction is associated with a small physiological increase in plasma renin activity, aldosterone, and noradrenaline and no significant change in lipid concentrations. These results support a reduction in population salt intake, which will lower population blood pressure and thereby reduce cardiovascular disease. The observed significant association between the reduction in 24 hour urinary sodium and the fall in systolic blood pressure, indicates that larger reductions in salt intake will lead to larger falls in systolic blood pressure. The current recommendations to reduce salt intake from 9-12 to 5-6 g/day will have a major effect on blood pressure, but a further reduction to 3 g/day will have a greater effect and should become the long term target for population salt intake.

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**Appendix 1:** Search strategy to identify randomised salt reduction trials

**Appendix 2:** Changes in plasma hormones and lipids from usual to reduced salt intake in individual trials included in meta-analysis

## Introduction

The current public health recommendations in most countries are to reduce salt intake from about 9–12 g/day to 5–6 g/day.<sup>1 2</sup> Much evidence shows that such a reduction in salt intake lowers blood pressure.<sup>3</sup> The evidence comes from different types of studies including epidemiological,<sup>4</sup> migration,<sup>5</sup> population based intervention,<sup>6</sup> genetic,<sup>7</sup> and animal studies,<sup>8</sup> as well as treatment trials.<sup>9</sup> As raised blood pressure throughout its range is a major cause of cardiovascular disease,<sup>10</sup> a reduction in salt intake, if it lowered blood pressure, would reduce cardiovascular risk. Indeed, both prospective cohort studies and outcome trials have shown that a lower salt intake is related to a reduced risk of cardiovascular disease.<sup>11 12</sup>

A recent meta-analysis by Graudal and colleagues,<sup>13 14</sup> however, claimed that salt reduction can have adverse effects on hormones and lipids, which might mitigate any benefit that occurs with the reduction in blood pressure. They also implied that the fall in blood pressure in normotensive people was doubtful of public health benefit. The meta-analysis, however, was flawed from a public health perspective, as they included a large number of short term trials with a large change in salt intake—for example, from 20 g/day to less than 1 g/day for only four to five days—and such metabolic studies are irrelevant to the current public health recommendations for a modest reduction in salt intake for a long period of time.

We carried out a meta-analysis to determine the effects of a longer term modest reduction in salt intake on blood pressure, plasma renin activity, aldosterone, noradrenaline (norepinephrine), adrenaline (epinephrine), total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol, and triglycerides, as well as further subgroup analyses by ethnic group and sex.

## Methods

### Literature search

We developed a search strategy (see appendix 1) to search electronic databases for randomised salt reduction trials: Medline from 1950 to November 2012; Embase from 1980 to November 2012; Hypertension Group Specialised Register; and Cochrane Central Register of Controlled Trials. Additionally, we reviewed reference lists of relevant original and review articles to search for more trials. There were no language restrictions.

### Inclusion criteria

For inclusion, trials needed to satisfy the following criteria:

- Random allocation either to a modestly reduced salt intake or usual salt intake (control)
- No concomitant interventions (such as non-pharmacological interventions, antihypertensive or other drugs) in either group
- The reduction in 24 hour urinary sodium had to be within the range of 40–120 mmol (equivalent to a reduction of 2.3–7.0 g/day salt). The reduction in 24 hour urinary sodium (UNa) was calculated as  $UNa(Post) - UNa(Pre)$  for crossover trials, where UNa(Post) designated to the average 24 hour urinary sodium at the end of the reduced salt intake period and UNa(Pre) designated to the average 24 hour urinary sodium at the end of the usual salt intake period (that is, the control period). In parallel trials the 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 hour

urinary sodium at the end of follow-up and UNa(Pre) designated to the average 24 hour urinary sodium at baseline.

- Duration of salt reduction had to be four weeks or more
- Study participants were not children (that is, not aged <18) or pregnant women or individuals with other diseases other than hypertension, such as diabetes or heart failure.

### Study quality

Criteria for the assessment of study quality were as follows.

*Allocation concealment*—The allocation sequences were defined as adequately concealed if participants and investigators could not foresee assignment—for example, a previously numbered or coded drug container of identical appearance prepared by an independent pharmacy or central randomisation—and as inadequately concealed if participants and investigators could foresee assignment—for example, open list of random numbers.

*Blinding*—We distinguished trials by the methods of blinding—that is, double blind, observer blind to blood pressure, or open study.

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

### Data extraction and outcome measures

Two authors (FJH and JL) independently extracted data using a standard form and resolved differences by discussion with the third author. Recorded data included characteristics of the study, design (parallel or crossover), type of the study (open, single blind, or double blind), method of randomisation, method of blinding (use of placebo, random zero or automated sphygmomanometers, or observer blind to blood pressure), study duration, and results before and after intervention. From each trial we extracted the changes in systolic and diastolic blood pressure, 24 hour urinary sodium excretion, plasma renin activity, and aldosterone, noradrenaline, adrenaline, total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol, and triglyceride concentrations. For the purpose of pooled analyses, we also recorded statistics that could be used to estimate the variance of the outcome measures.

### Statistical analyses

For each trial, we calculated the treatment effect for outcomes. In crossover trials, the treatment effect was the difference in outcomes between the end of the reduced salt period and the end of the usual salt (control) period. In parallel trials, the treatment effect was the difference between the two treatment groups in the change in outcomes from baseline to the end of follow-up.

For each trial, we also calculated the variance of the treatment effect for outcomes. 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<sup>15</sup> or between the two treatment periods in a crossover trial or, if these statistics were not given, from confidence intervals and exact *t* or *P* values. If we could not derive the exact variance of paired difference, we imputed it by inverting a boundary *P* value (for example,  $P < 0.05$  became  $P = 0.05$ ) or assuming a correlation coefficient of 0.5 between the initial and final measurement.<sup>16</sup>

To assess the mean effect sizes, we pooled the data by the inverse variance method in random effects meta-analysis. We used the  $I^2$  test to examine heterogeneity, with  $I^2 > 50\%$  considered to be important.<sup>17</sup> To explore the source of heterogeneity, we performed meta-regression analyses (multiple regression models) weighted by the inverse variance of the change in systolic or diastolic blood pressure. The meta-regression analysis was also used to examine whether there was a dose-response relation between the change in 24 hour urinary sodium and the change in blood pressure. We used funnel plot asymmetry to detect whether there was publication bias and Egger's regression test to measure funnel plot asymmetry.<sup>18 19</sup>

Prespecified subgroupings included blood pressure status (that is, hypertensive or normotensive) and further subgroupings by ethnic group and sex. The purpose of the subgroup analysis was to determine whether there was a significant effect of salt reduction on blood pressure in each group itself rather than identifying difference in the effect between groups. For the analysis stratified by ethnic group, we included trials in the group of "white" if  $\geq 85\%$  of participants were white. If the information on ethnic group was not available, we excluded the trial from this subgroup analysis. For hormone and lipid data, subgroup analyses were not performed because of the small number of trials that reported such outcomes.

Statistical analyses were performed with Cochrane Collaboration RevMan 5.1 software and SPSS.

## Results

Figure 1 shows the number of studies assessed and excluded through the stages of the meta-analysis. A total of 30 papers met our inclusion criteria and were included in our meta-analysis.<sup>20-49</sup> Among these 30 papers, four included both hypertensive and normotensive individuals.<sup>24 35 37 40</sup> In our meta-analysis, the main outcome data (blood pressure) were recorded for hypertensive and normotensive people separately. To avoid confusion in counting the number of trials, each of these four papers was counted as two trials. Therefore, our meta-analysis included a total of 34 trials, of which 22 were in hypertensive individuals and 12 in normotensive individuals. For two papers in which three levels of salt intake were studied,<sup>32 37</sup> we included the high and intermediate levels (that is, urinary sodium reduced from 190 to 108 mmol/24 h in one trial<sup>32</sup> and in the other<sup>37</sup> we included the high and low levels (that is, urinary sodium reduced from 145 to 65 mmol/24 h in hypertensive individuals and from 139 to 64 mmol/24 h in normotensive individuals on the normal American diet.<sup>37</sup> In three studies in which only subgroup data were reported,<sup>21 42 47</sup> they were entered for subgroups separately.

## Effect on blood pressure

### *Trials in all individuals*

We included 34 trials with 3230 participants. Table 1 summarises the characteristics of the trials included in the meta-analysis. The median age was 50 (range 22-73). Of the 34 trials, 23 used crossover design and 11 used parallel comparisons. Twenty two of the 34 trials were double blind, in 11 the observer was blind to blood pressure, and one did not report any blinding procedure. The study duration varied from four weeks to three years (median four weeks). With the usual salt intake the median 24 hour urinary sodium was 160 mmol (range 125-200 mmol), equivalent to a salt intake of 9.4 g/day (range 7.3-11.7 g/day) and the median blood pressure was 141/86 mm Hg. The pooled estimate of the change in 24 hour

urinary sodium from the usual to the reduced salt intake was  $-75$  mmol (range  $-40$ – $118$  mmol), equivalent to a reduction in salt intake of 4.4 g/day (range 2.3 to 6.9 g/day). This average reduction in salt intake is similar to that of the current public health recommendations.

Figure 2 shows the change in systolic blood pressure with salt reduction in individual trials included in the meta-analysis and the mean effect size. The pooled estimates of changes in blood pressure were  $-4.18$  mm Hg (95% confidence interval  $-5.18$  to  $-3.18$ ,  $P < 0.001$ ,  $I^2 = 75\%$ ) for systolic blood pressure and  $-2.06$  mm Hg ( $-2.67$  to  $-1.45$ ,  $P < 0.001$ ,  $I^2 = 68\%$ ) for diastolic blood pressure.

To explore the source of heterogeneity, we performed meta-regression analysis with the change of blood pressure (systolic or diastolic) as the dependent variable; the independent variables included age (mean age of the participants in individual trials), blood pressure status (hypertensive=1; normotensive=0), ethnic group (proportion of white people as a continuous variable), and the change in 24 hour urinary sodium. The results showed that the change in 24 hour urinary sodium, age, blood pressure status, and ethnic group were all significantly associated with the change in systolic blood pressure. The regression coefficients indicated that a 100 mmol reduction in 24 hour urinary sodium (6 g/day salt) was associated with a decrease of 5.8 mm Hg (95% confidence interval 2.5 to 9.2,  $P = 0.001$ ) in systolic blood pressure; a one year increase in age was associated with a 0.06 mm Hg (0.006 to 0.116,  $P = 0.030$ ) greater decrease in systolic blood pressure with salt reduction; being hypertensive was associated with a greater fall in systolic blood pressure ( $P = 0.042$ ) compared with having normal blood pressure; and a larger proportion of white people (or a smaller proportion of black people) was associated with a smaller fall in systolic blood pressure ( $P = 0.001$ ). These four variables together explained 68% of the variance between studies. In a separate regression model, sex (proportion of men as a continuous variable) was added to the list of independent variables, and there was little change to the adjusted  $R^2$  ( $R^2 = 0.68$  without sex and  $R^2 = 0.70$  with sex). Sex was not significantly associated with the change in systolic blood pressure. For diastolic blood pressure, age, ethnic group, blood pressure status, and 24 hour urinary sodium together explained 41% of the variance between studies. Among these four variables, only ethnic group was significant ( $P = 0.021$ ) and the three other variables were not significantly associated with the change in diastolic blood pressure. When sex was added to the regression model, there was little change in the adjusted  $R^2$  ( $R^2 = 0.41$  and 0.44 for the regression model with and without sex, respectively). Sex was not significantly associated with the change in diastolic blood pressure.

### *Trials in hypertensive individuals*

Nine hundred and ninety people with hypertension were studied in 22 trials. The median age was 50 (range 24-73). The study duration varied from four weeks to one year (median five weeks). With usual salt intake the median 24 hour urinary sodium was 162 mmol (range 125-191 mmol), equivalent to a salt intake of 9.5 g/day (range 7.3-11.2 g/day) and the median blood pressure was 148/93 mm Hg. The pooled estimate of the change in 24 hour urinary sodium from the usual to the reduced salt intake was  $-75$  mmol (range  $-53$ – $117$  mmol), equivalent to a reduction in salt intake of 4.4 g/day (range 3.1-6.8 g/day). The pooled estimates of changes in blood pressure were  $-5.39$  mm Hg (95% confidence interval  $-6.62$  to  $-4.15$ ,  $P < 0.001$ ,  $I^2 = 61\%$ ) for systolic and  $-2.82$  mm Hg ( $-3.54$  to  $-2.11$ ,  $P < 0.001$ ,  $I^2 = 52\%$ ) for diastolic blood pressure. Meta-regression

with the change in blood pressure as the dependent variable and age, ethnic group, and the change in 24 hour urinary sodium as independent variables, showed that the change in 24 hour urinary sodium and ethnic group were significantly associated with the fall in systolic blood pressure, whereas age was not significantly associated with the fall in systolic blood pressure. A 100 mmol reduction in 24 hour urinary sodium (6 g/day salt) was associated with a fall in systolic blood pressure of 10.8 mm Hg (3.5 to 18.2,  $P<0.01$ ) after adjustment for age and ethnic group. All three variables together explained 46% of the variance between studies. For diastolic blood pressure, the three variables together explained 11% of the variance between studies and none of the three variables was significantly associated with the fall in diastolic blood pressure.

### *Trials in normotensive individuals*

Two thousand two hundred and forty individuals with normal blood pressure were studied in 12 trials. The median age was 50 (range 22-67). The study duration varied from four weeks to three years (median four weeks). With usual salt intake the median 24 hour urinary sodium was 153 mmol (range 128-200 mmol), equivalent to a salt intake of 8.9 g/day (range 7.5-11.7 g/day) and the median blood pressure was 127/77 mm Hg. The pooled estimate of the change in 24 hour urinary sodium from the usual to the reduced salt intake was -75 mmol (range -40--118 mmol), equivalent to a reduction in salt intake of 4.4 g/day (range 2.3 to 6.9 g/day).

The pooled estimates of changes in blood pressure were -2.42 mm Hg (95% confidence interval -3.56 to -1.29,  $P<0.001$ ,  $I^2=66%$ ) for systolic blood pressure and -1.00 mm Hg (-1.85 to -0.15,  $P=0.02$ ,  $I^2=66%$ ) for diastolic blood pressure.

Meta-regression with the change in blood pressure as the dependent variable and age, ethnic group, and the change in 24 hour urinary sodium as independent variables, showed that the change in 24 hour urinary sodium was significantly associated with the fall in systolic blood pressure, whereas age and ethnic group were not significantly associated with the fall in systolic blood pressure. A 100 mmol reduction in 24 hour urinary sodium (6 g/day salt) was associated with a fall in systolic blood pressure of 4.3 mm Hg (95% confidence interval 0.1 to 8.5,  $P<0.05$ ) after adjustment for age and ethnic group. All three variables together explained 51% of the variance between studies. For diastolic blood pressure, the three variables together explained 43% of the variance between studies. Among these three variables, only ethnic group was significant ( $P=0.04$ ) and the two other variables were not significantly associated with the change in diastolic blood pressure.

### *Further subgroup analysis*

Table 2<sup>||</sup> shows the pooled results of 24 hour urinary sodium and blood pressure by ethnic group and sex for hypertensive and normotensive people separately. There was a significant fall in systolic blood pressure in white and black people and in men and women. The fall in diastolic blood pressure was significant in most of the subgroups (table 2). There was only one trial in Asian people with hypertension, which showed a significant fall in both systolic and diastolic blood pressure with salt reduction (table 2).

### **Effect on hormones and lipids**

Appendix 2 shows the hormone and lipid data reported in individual trials included in the meta-analysis and table 3 shows the mean effects<sup>||</sup>. As one study reported plasma renin concentration rather than activity,<sup>40</sup> we excluded it from the

analysis. One trial<sup>33</sup> was excluded from the aldosterone analysis as the plasma aldosterone was extremely high after the unit conversion (235 278 pmol/L with usual salt intake and 269 167 pmol/L with reduced salt intake). One other trial reported that "no changes were observed in plasma catecholamines" but did not provide the data.<sup>48</sup> We therefore excluded this trial from the pooled analysis for noradrenaline and adrenaline. Two trials reported no significant change in cholesterol concentration,<sup>26 28</sup> though no data were provided for the pooled analysis. One trial reported no significant change in plasma high density lipoprotein concentration but did not provide data<sup>26</sup> so we excluded this trial from the pooled analysis.

### **Study quality**

Among the 34 trials included in our meta-analysis, 26 were judged to have adequate concealment of allocation of treatment. In eight trials, the information on concealment of allocation was not available. Despite the fact that only seven out of 34 trials performed intention to treat analysis, the percentage of participants lost to follow-up after randomisation was small (6.7% on average).

We included double blind, blood pressure observer blind, and open studies because some trials, such as the DASH (Dietary Approaches to Stop Hypertension)-Sodium,<sup>37</sup> although non-double blinded, were well conducted with good compliance to different diets and it is difficult to make any dietary intervention study double blind. In relation to salt, this can be done only by the use of salt tablets (such as Slow Sodium and placebo). Among the 34 trials included in our meta-analysis, 22 were double blind, 11 were blood pressure observer blind, and only one small trial in people with hypertension was non-blind. Re-analysis of the data after exclusion of the non-blind study<sup>20</sup> did not change the results. The pooled estimate of the change in blood pressure for hypertensive people was -5.35 mm Hg (95% confidence interval -6.62 to -4.09,  $P<0.001$ ) for systolic blood pressure and -2.88 mm Hg (-3.58 to -2.18,  $P<0.001$ ) for diastolic blood pressure after we excluded the non-blinded study.

### **Publication bias**

We created funnel plots by plotting the treatment effect against the reciprocal of the standard error of the treatment effect. For diastolic blood pressure the funnel plot was symmetrical around the mean effect size line (asymmetry test  $P=0.416$ ).<sup>18</sup> For systolic blood pressure, the graphic plot was suggestive of bias (asymmetry test  $P=0.025$ ) (fig 3<sup>||</sup>). 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 caused by the smaller effects of two larger and longer term trials.<sup>44 49</sup> The smaller effects in these two trials are attributable to the smaller reduction of salt intake achieved in the longer term trials. When we removed these two trials from the analysis, the asymmetry test was not significant ( $P=0.247$ ).

### **Discussion**

Our meta-analysis shows that a longer term modest reduction in salt intake of 4.4 g/day on average, causes significant and, from a population viewpoint, important falls in blood pressure in people with both raised and normal blood pressure. The blood pressure falls, on average, by 5/3 mm Hg in hypertensive people and 2/1 mm Hg in normotensive people. Further subgroup analyses show that a modest reduction in salt intake leads to a significant fall in systolic blood pressure in white and black

people and in men and women. These results provide further strong support for a reduction in population salt intake, which will result in a lower population blood pressure and, thereby, a reduction in strokes, heart attacks, and heart failure.

The effect of a chronic high salt intake is a gradual increase in blood pressure throughout life. The INTERSALT study (International Study of Salt and Blood Pressure) suggested a strong relation between salt intake and a progressive increase in blood pressure with age—that is, 0.4 mm Hg per year for a 6 g/day salt intake.<sup>4</sup> A reduction in salt intake is therefore likely to attenuate the rise of blood pressure with ageing, in addition to the immediate blood pressure lowering effect.

### Dose-response to salt reduction

Our meta-regression analysis shows a significant dose-response relation between the reduction in salt intake and the fall in systolic blood pressure—that is, the greater the reduction in salt intake, the greater the fall in systolic blood pressure. A reduction of 6 g/day in salt intake predicts a decrease of 5.8 mm Hg in systolic blood pressure after adjustment for age, ethnic group, and blood pressure status.

It is acknowledged that the dose-response relation from meta-regression (that is, between study investigation) should be viewed as exploratory and could be prone to confounding. Meta-analysis with individual participant data would have an advantage both statistically and clinically<sup>50 51</sup> and, if available, should be used in the future to explore the dose-response relation further. Nevertheless, the dose-response relation found in our study is consistent with that observed from rigorously controlled trials with multiple levels of salt intake, which provided the most persuasive evidence. There have been two trials that studied three levels of salt intake. The first one was the randomised double blind cross-over study in 20 individuals with untreated essential hypertension, where salt intake was reduced from 11.2 to 6.4 and to 2.9 g/day, each for one month.<sup>32</sup> Blood pressure decreased from 163/100 to 155/95 and to 147/91 mm Hg with the reductions in salt intake. After the trial was completed, individuals continued the lowest salt intake. After one year, blood pressure remained controlled without any antihypertensive drugs in 16 individuals, and the average blood pressure was 142/87 mm Hg with a salt intake of 3.2 g/day.<sup>32</sup> The other trial that studied the dose-response relation is the DASH-Sodium study. Over 400 individuals with normal or mildly raised blood pressure were randomised to receive either the normal American diet (control group) or the DASH diet, which is rich in fruits, vegetables, and low fat dairy products. Within each group, participants were given three levels of salt intake (8 to 6 and to 4 g/day) in a randomised crossover manner, each for four weeks. The results showed a clear dose-response relation both on the normal American diet and on the DASH diet. The fall in blood pressure was greater at a lower level of salt intake—that is, from 6 to 4 g/day compared with that from 8 to 6 g/day.<sup>37</sup>

From the evidence above, it is clear that the recommendations to reduce salt from the current levels of about 9-12 g/day to 5-6 g/day will have a significant effect on blood pressure but are not ideal. A further reduction to 3 g/day will have a much greater effect on blood pressure, and we consider that this should become the long term target for population salt intake. Indeed, the UK government's health advisory agency, the National Institute for Health and Clinical Excellence (NICE) has recommended a reduction in the population's salt consumption to 3 g/day by 2025.<sup>52</sup> In the United States, it is recommended that sodium intake should be reduced to less than 2.3 g/day

(equivalent to about 6 g/day salt) for most adults, with a further reduction to 1.5 g/day (4 g/d salt) for about half the population, including African Americans, all adults aged 51 and older, and individuals with hypertension, diabetes, or chronic kidney disease.<sup>53</sup>

### Study duration

Despite inclusion of trials with duration of one month or longer, the median duration of salt reduction in our meta-analysis was only five weeks in the hypertensive people and four weeks in the normotensive people. Whether salt reduction has exerted its maximum effect by four to five weeks is not known, but evidence would suggest that this is unlikely. Among the 34 trials included in our meta-analysis, two had duration of over one year<sup>44 49</sup> and both trials were in normotensive individuals. These two trials did not show a greater fall in blood pressure compared with other trials in normotensive individuals. The reduction in salt intake achieved in these two trials, however, was half that achieved in other trials. On average, salt intake was reduced by 2.4 g/day in these two longer term trials, whereas in the other trials in normotensive people, salt intake was reduced by 4.8 g/day. These studies clearly highlight the difficulty in keeping individuals on a lower salt intake for a long period of time because of the widespread presence of salt in nearly all processed, canteen, restaurant, and fast food.

### Variations of blood pressure response to salt reduction

Previous studies have shown that for a given reduction in salt intake the fall in blood pressure was larger in individuals of African origin, in older people, and in those with raised blood pressure compared with white people, young people, and individuals with normal blood pressure, respectively.<sup>54 55</sup> The results from our meta-regression analyses are consistent with these observations.

The term "salt sensitivity" has been commonly used to describe the variations of blood pressure response to salt reduction. Almost all of the studies on "salt sensitivity," however, have used a protocol of large and sudden changes in salt intake. Such studies are irrelevant to the public health recommendations of more modest reduction in salt intake for a prolonged period of time. Our meta-analysis shows that a longer term modest reduction in salt intake has a significant effect on blood pressure in both hypertensive and normotensive individuals, men and women, and white and black people, although there is a variation in the extent of the fall in blood pressure. These results in conjunction with other evidence,<sup>3</sup> particularly that a reduction in salt intake also lowers blood pressure in children,<sup>56</sup> provide strong support that salt reduction should be carried out in the whole population. A reduction in population salt intake lowers population blood pressure. Even a small reduction of blood pressure across the entire population would have a large impact on reducing the burden of cardiovascular disease.

### Effect on hormones and lipids

A recent meta-analysis by Graudal and colleagues<sup>13</sup> implied that salt reduction can have adverse effects on plasma hormones and lipids, which might mitigate any benefit that occurs with a long term fall in blood pressure. That meta-analysis, however, included a large number of short term trials with a large change in salt intake—for example, from 20 g/day to less than 1 g/day for only four to five days—and such metabolic studies are irrelevant to the current public health recommendations for a modest reduction in salt intake for a long period of time. Our

meta-analysis shows that with such a reduction there is no significant change in plasma concentrations of total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol, or triglycerides. Indeed, in the meta-analysis by Graudal and colleagues the changes in lipids occurred only with short term trials, and a subgroup analysis including trials with a duration of four or more weeks showed no significant change in lipid concentrations.<sup>13</sup>

When salt intake is reduced, there is a fall in extracellular volume and physiological stimulation of the renin-angiotensin-aldosterone system, as well as the sympathetic nervous system. These compensatory responses are bigger with sudden and large decreases in salt intake and much smaller or minimal with a longer term modest salt reduction. Our meta-analysis shows that with a longer term modest reduction in salt intake there was only a small physiological increase in plasma renin activity, aldosterone, and noradrenaline. It is worth noting that all of the studies included in our meta-analysis in which these hormones were measured had a duration of only four to six weeks (median duration four weeks). It is likely that such effects might attenuate over time. Indeed, a study by Beckmann and colleagues showed that a modest reduction in salt intake, along with a reduction in body weight and saturated fat for one year, significantly reduced arterial plasma noradrenaline and adrenaline in people with hypertension.<sup>57</sup>

Salt reduction lowers blood pressure by a similar mechanism to that of thiazide diuretics. Both stimulate the renin-angiotensin system and, in the short term, the sympathetic nervous system. Outcome trials have shown that long term treatment with thiazide diuretics significantly reduces cardiovascular morbidity and mortality in hypertensive individuals.<sup>58</sup>

## Effect of salt reduction on cardiovascular risk

There is much evidence that raised blood pressure throughout its range starting at 115/75 mm Hg is a major cause of cardiovascular disease.<sup>10</sup> A modest reduction in salt intake lowers blood pressure and, therefore, should reduce cardiovascular risk. It was estimated that a reduction of 6 g/day in salt intake could reduce stroke by 24% and coronary heart disease by 18%.<sup>9</sup> This could prevent about 35 000 stroke and coronary heart disease deaths a year in the UK<sup>9</sup> and about 2.5 million deaths worldwide.

Both prospective cohort studies and outcome trials have shown that a lower salt intake is related to a reduced risk of cardiovascular disease.<sup>11-59</sup> Two recent papers in *JAMA (Journal of the American Medical Association)*, however, claimed that, firstly, a lower salt intake was associated with higher cardiovascular mortality<sup>60</sup> and, secondly, there was a J shaped association between salt intake and cardiovascular risk.<sup>61</sup> These two papers have many methodological flaws, such as measurement error in assessing daily salt intake, confounding factors not controlled for, and reverse causality (that is, the low salt intake is the result rather than the cause of participants' illness).<sup>62-63</sup> Therefore, the results from these studies should be interpreted with great caution. A meta-analysis of 12 cohort studies showed that an increase of 5 g/day in salt intake was associated with a 23% increase in the risk of stroke and a 17% increase in the risk of cardiovascular disease.<sup>11</sup>

Evidence from outcome trials of long term salt reduction is limited because of the innate difficulty in conducting such trials. A recent meta-analysis of seven randomised trials by Taylor and colleagues, published simultaneously in the *Cochrane Library*<sup>64</sup> and the *American Journal of Hypertension*,<sup>65</sup> claimed that "Cutting down on the amount of salt has no clear benefits

in terms of likelihood of dying or experiencing cardiovascular disease"<sup>64</sup> and the *Cochrane Library's* press release headline stated "Cutting down on salt does not reduce your chance of dying."<sup>66</sup> Both of these statements were incorrect and yet received misleading worldwide media publicity.

Among the seven trials included in the meta-analysis by Taylor and colleagues, one in heart failure<sup>67</sup> should not have been included as the participants were already severely salt and water depleted from aggressive treatment with diuretics.<sup>67</sup> Indeed, salt restriction without a reduction in the dose of diuretics is already known to be dangerous. Additionally, the findings in patients with severe heart failure who were receiving multiple drug treatments are not generalisable to the general population. In the six remaining trials in hypertensive and normotensive people, there was a reduction in all clinical outcomes (that is, all cause mortality, cardiovascular mortality, and events), although none of these were significant. The non-significant findings are most likely because of a lack of statistical power, particularly as Taylor and colleagues analysed the trials for hypertensive and normotensive people separately. A re-analysis of the data by combining these people, indeed, shows that there is a significant reduction in cardiovascular events by 20% (P<0.05) and a non-significant reduction in all cause mortality (5-7%), despite the small reduction in salt intake of 2.0-2.3 g/day. These results show that salt reduction has a major impact on reducing strokes, heart attacks, and heart failure.<sup>12</sup>

Several cost effectiveness analyses have shown that a reduction in salt intake is one of the most cost effective interventions to reduce cardiovascular disease in both developed and developing countries.<sup>68-74</sup> For example, a paper in the *Lancet* showed that in 23 low and middle income countries that account for 80% of chronic disease burden in the developing world a 15% (about 1.5-2.3 g/day) reduction in mean population salt intake could avert 8.5 million cardiovascular deaths and a 20% reduction in smoking prevalence could avert 3.1 million cardiovascular deaths over 10 years.<sup>70</sup> The costs for implementing a salt reduction strategy were estimated to be \$0.09 (£0.06, €0.07) per person per year and the cost for tobacco control, including both price and non-price measures, was \$0.26 per person per year.<sup>70</sup> These figures clearly suggest that a reduction in salt intake is more or at the least just as cost effective as tobacco control in terms of reducing cardiovascular disease on its own, the leading cause of death and disability worldwide.

The UK salt reduction campaigns, which started in 2003-04 have been successful and the average salt intake, as measured by 24 hour urinary sodium, had fallen gradually from 9.5 to 8.1 g/day by 2011 (that is, a 15% reduction, P<0.05 for the downward trend).<sup>75</sup> A cost effective analysis by NICE showed that the UK salt reduction campaigns cost £15m (\$23m, €17m) and a 0.9 g/day reduction in salt intake that was achieved by 2008, led to about 6000 fewer deaths from cardiovascular disease a year, saving the UK economy about £1.5bn a year.<sup>52-76</sup> Based on NICE's estimation, the further reduction of 0.5 g/day from 2008 to 2011, would prevent about 3000 additional deaths from cardiovascular disease a year and result in even greater cost savings to the UK economy.

## Conclusions

Our meta-analysis shows that a modest reduction in salt intake, as currently recommended, has a significant effect on blood pressure both in individuals with raised blood pressure and in those with normal blood pressure. The fall in blood pressure is seen in white and black people and in men and women. These findings provide further support for a reduction in population

salt intake. This will lower population blood pressure and thereby reduce strokes, heart attacks, and heart failure. Furthermore, our analysis shows a dose-response relation—that is, the greater the reduction in salt intake, the greater the fall in blood pressure. The current recommendations to reduce salt intake to 5–6 g/day will have a major effect on blood pressure, but are not ideal. A further reduction to 3 g/day will have a greater effect. Therefore, 3 g/day should become the long term target for population salt intake. Indeed, NICE has recommended a reduction in salt intake to 3 g/day by 2025 for the UK adult population.<sup>52</sup>

Many developed countries are now adopting a policy of reducing salt intake, firstly by persuading the food industry to reformulate food with less salt, as is occurring successfully in the UK<sup>75</sup> and Finland,<sup>77</sup> and also encouraging people to use less salt in their own cooking and at the table. The major challenge now is to spread this out to all other countries, particularly the low and middle income countries, where often salt intake is high and about 80% of the global burden of disease related to blood pressure occurs. All countries should adopt a coherent and workable strategy to reduce salt intake. A reduction in population salt intake will have major beneficial effects on health along with major cost savings in all countries around the world.

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- 1 Joint WHO/FAO expert consultation on diet, nutrition and the prevention of chronic diseases. WHO, 2003. [http://whqlibdoc.who.int/trs/who\\_trs\\_916.pdf](http://whqlibdoc.who.int/trs/who_trs_916.pdf).
- 2 Scientific Advisory Committee on Nutrition. Salt and health. Stationery Office, 2003. [www.sacn.gov.uk/pdfs/sacn\\_salt\\_final.pdf](http://www.sacn.gov.uk/pdfs/sacn_salt_final.pdf).
- 3 He FJ, MacGregor GA. Reducing population salt intake worldwide: from evidence to implementation. *Prog Cardiovasc Dis* 2010;52:363–82.
- 4 Elliott P, Stamler J, Nichols R, Dyer AR, Stamler R, Kesteloot H, et al. Intersalt revisited: further analyses of 24 hour sodium excretion and blood pressure within and across populations. *BMJ* 1996;312:1249–53.
- 5 Poulter NR, Khaw KT, Hopwood BE, Mugambi M, Peart WS, Rose G, et al. The Kenyan Luo migration study: observations on the initiation of a rise in blood pressure. *BMJ* 1990;300:967–72.
- 6 Forte JG, Miguel JM, Miguel MJ, de Padua F, Rose G. Salt and blood pressure: a community trial. *J Hum Hypertens* 1989;3:179–84.
- 7 Lifton RP. Molecular genetics of human blood pressure variation. *Science* 1996;272:676–80.
- 8 Denton D, Weisinger R, Mundy NI, Wickings EJ, Dixon A, Moisson P, et al. The effect of increased salt intake on blood pressure of chimpanzees. *Nat Med* 1995;1:1009–16.

- 9 He FJ, MacGregor GA. How far should salt intake be reduced? *Hypertension* 2003;42:1093–9.
- 10 Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. 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;360:1903–3.
- 11 Strazzullo P, D'Elia L, Kandala NB, Cappuccio FP. Salt intake, stroke, and cardiovascular disease: meta-analysis of prospective studies. *BMJ* 2009;339:b4567.
- 12 He FJ, MacGregor GA. Salt reduction lowers cardiovascular risk: meta-analysis of outcome trials. *Lancet* 2011;378:380–2.
- 13 Graudal NA, Hubeck-Graudal T, Jurgens G. Effects of low sodium diet versus high sodium diet on blood pressure, renin, aldosterone, catecholamines, cholesterol, and triglyceride. *Cochrane Database Syst Rev* 2011;11:CD004022.
- 14 Graudal NA, Hubeck-Graudal T, Jurgens G. Effects of low-sodium diet vs. high-sodium diet on blood pressure, renin, aldosterone, catecholamines, cholesterol, and triglyceride (Cochrane Review). *Am J Hypertens* 2012;25:1–15.
- 15 Cappuccio FP, MacGregor GA. Does potassium supplementation lower blood pressure? A meta-analysis of published trials. *J Hypertens* 1991;9:465–73.
- 16 Follmann D, Elliott P, Suh I, Cutler J. Variance imputation for overviews of clinical trials with continuous response. *J Clin Epidemiol* 1992;45:769–73.
- 17 Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–60.
- 18 Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.
- 19 Sterne JA, Egger M, Smith GD. Systematic reviews in health care: Investigating and dealing with publication and other biases in meta-analysis. *BMJ* 2001;323:101–5.
- 20 Parijs J, Joossens JV, Van der Linden L, Verstreken G, Amery AK. Moderate sodium restriction and diuretics in the treatment of hypertension. *Am Heart J* 1973;85:22–34.
- 21 Morgan TO, Myers JB. Hypertension treated by sodium restriction. *Med J Aust* 1981;2:396–7.
- 22 MacGregor GA, Markandu ND, Best FE, Elder DM, Cam JM, Sagnella GA, et al. Double-blind randomised crossover trial of moderate sodium restriction in essential hypertension. *Lancet* 1982;319:351–5.
- 23 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;1:179–82.
- 24 Puska P, Iacono JM, Nissinen A, Korhonen HJ, Vartiainen E, Pietinen P, et al. Controlled, randomised trial of the effect of dietary fat on blood pressure. *Lancet* 1983;1:1–5.
- 25 Watt GC, Edwards C, Hart JT, Hart M, Walton P, Foy CJ. Dietary sodium restriction for mild hypertension in general practice. *BMJ* 1983;286:432–6.
- 26 Erwtaman 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. *BMJ* 1984;289:406–9.
- 27 Richards AM, Nicholls MG, Espiner EA, Ikram H, Maslowski AH, Hamilton EJ, et al. Blood-pressure response to moderate sodium restriction and to potassium supplementation in mild essential hypertension. *Lancet* 1984;1:757–61.
- 28 Chalmers J, Morgan T, Doyle A, Dickson B, Hopper J, Mathews J, et al. Australian National Health and Medical Research Council dietary salt study in mild hypertension. *J Hypertens* 1986;4:S629–37.
- 29 Grobbee DE, Hofman A, Roelandt JT, Boomsma F, Schalekamp MA, Valkenburg HA. Sodium restriction and potassium supplementation in young people with mildly elevated blood pressure. *J Hypertens* 1987;5:115–9.
- 30 Australian National Health and Medical Research Council Dietary Salt Study Management Committee. Fall in blood pressure with modest reduction in dietary salt intake in mild hypertension. *Lancet* 1989;1:399–402.
- 31 Australian National Health and Medical Research Council Dietary Salt Study Management Committee. Effects of replacing sodium intake in subjects on a low sodium diet: a crossover study. *Clin Exp Hypertens* 1989;A11:1011–24.
- 32 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;334:1244–7.
- 33 Benetos A, Xiao YY, Cuhe JL, Hannaert P, Safar M. Arterial effects of salt restriction in hypertensive patients. A 9-week, randomized, double-blind, crossover study. *J Hypertens* 1992;10:355–60.
- 34 Fotherby MD, Potter JF. Effects of moderate sodium restriction on clinic and twenty-four-hour ambulatory blood pressure in elderly hypertensive subjects. *J Hypertens* 1993;11:657–63.
- 35 Cappuccio FP, Markandu ND, Carney C, Sagnella GA, MacGregor GA. Double-blind randomised trial of modest salt restriction in older people. *Lancet* 1997;350:850–4.
- 36 Meland E, Laerum E, Aakvaag A, Ulvik RJ, Hostmark AT. Salt restriction: effects on lipids and insulin production in hypertensive patients. *Scand J Clin Lab Invest* 1997;57:501–5.
- 37 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. DASH-Sodium Collaborative Research Group. *N Engl J Med* 2001;344:3–10.
- 38 Gates PE, Tanaka H, Hiatt WR, Seals DR. Dietary sodium restriction rapidly improves large elastic artery compliance in older adults with systolic hypertension. *Hypertension* 2004;44:35–41.
- 39 Swift PA, Markandu ND, Sagnella GA, He FJ, MacGregor GA. Modest salt reduction reduces blood pressure and urine protein excretion in black hypertensives. A randomised control trial. *Hypertension* 2005;46:308–12.
- 40 Melander O, von Wornen F, Frandsen E, Burri P, Willstean G, Aurell M, et al. Moderate salt restriction effectively lowers blood pressure and degree of salt sensitivity is related to baseline concentration of renin and N-terminal atrial natriuretic peptide in plasma. *J Hypertens* 2007;25:619–27.
- 41 He FJ, Marciniak M, Visagie E, Markandu ND, Anand V, Dalton RN, et al. Effect of modest salt reduction on blood pressure, urinary albumin, and pulse wave velocity in white, black, and Asian mild hypertensives. *Hypertension* 2009;54:482–8.
- 42 Watt GCM, Foy CJW, Hart JT, Bingham G, Edwards C, Hart M, et al. Dietary sodium and arterial blood pressure: evidence against genetic susceptibility. *BMJ* 1985;291:1525–8.
- 43 Mascioli S, Grimm R Jr, Launer C, Svendsen K, Flack J, Gonzalez N, et al. Sodium chloride raises blood pressure in normotensive subjects. The study of sodium and blood pressure. *Hypertension* 1991;17:121–6.
- 44 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;267:1213–20.
- 45 Cobiac L, Nestel PJ, Wing LMH, Howe PRC. A low-sodium diet supplemented with fish oil lowers blood pressure in the elderly. *J Hypertens* 1992;10:87–92.

**What is already known on this topic**

A modest reduction in salt intake lowers blood pressure and thereby reduces cardiovascular risk

A recent meta-analysis of salt reduction trials implied that salt reduction had adverse effects on hormones and lipids, which might mitigate any benefit that occurs with the reduction in blood pressure. This meta-analysis, however, included a large number of trials with a large change in salt intake for only a few days, which are irrelevant to the current public health recommendations for a modest reduction in salt intake for a long period of time

**What this study adds**

A longer term modest reduction in salt intake leads to significant and, from a population viewpoint, important falls in blood pressure in both hypertensive and normotensive individuals, irrespective of sex and ethnic group

With salt reduction, there is a small physiological increase in plasma renin activity, aldosterone, and noradrenaline and no significant change in lipid concentrations

There is a dose-response relation between the reduction in salt intake and the fall in systolic blood pressure. The current recommendations to reduce salt intake from 9-12 to 5-6 g/day will have a major effect but a further reduction to 3 g/day will have a greater effect

- 46 Ruppert M, Overlack A, Kolloch R, Kraft K, Göbel B, Stumpe KO. Neurohormonal and metabolic effects of severe and moderate salt restriction in non-obese normotensive adults. *Hypertension* 1993;11:743-9.
- 47 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. *J Hypertens* 1993;11:1387-94.
- 48 Schorr U, Distler A, Sharma AM. Effect of sodium chloride- and sodium bicarbonate-rich mineral water on blood pressure and metabolic parameters in elderly normotensive individuals: a randomized double-blind crossover trial. *J Hypertens* 1996;14:131-5.
- 49 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;157:657-67.
- 50 Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. *BMJ* 2010;340:c221.
- 51 Berlin JA, Santanna J, Schmid CH, Szczec LA, Feldman HI. Individual patient- versus group-level data meta-regressions for the investigation of treatment effect modifiers: ecological bias rears its ugly head. *Stat Med* 2002;21:371-87.
- 52 National Institute for Health and Clinical Excellence (NICE). Guidance on the prevention of cardiovascular disease at the population level. NICE, 2010. <http://guidance.nice.org.uk/PH25>.
- 53 Institute of Medicine. Strategies to reduce sodium intake in the United States. April 2010. [www.iom.edu/Reports/2010/Strategies-to-Reduce-Sodium-Intake-in-the-United-States.aspx](http://www.iom.edu/Reports/2010/Strategies-to-Reduce-Sodium-Intake-in-the-United-States.aspx).
- 54 Bray GA, Vollmer WM, Sacks FM, Obarzanek E, Svetkey LP, Appel LJ. A further subgroup analysis of the effects of the DASH diet and three dietary sodium levels on blood pressure: results of the DASH-Sodium Trial. *Am J Cardiol* 2004;94:222-7.
- 55 He FJ, Markandu ND, Sagnella GA, MacGregor GA. Importance of the renin system in determining blood pressure fall with salt restriction in black and white hypertensives. *Hypertension* 1998;32:820-4.
- 56 He FJ, MacGregor GA. Importance of salt in determining blood pressure in children: meta-analysis of controlled trials. *Hypertension* 2006;48:861-9.
- 57 Beckmann SL, Os I, Kjeldsen SE, Eide IK, Westheim AS, Hjermann I. Effect of dietary counselling on blood pressure and arterial plasma catecholamines in primary hypertension. *Am J Hypertens* 1995;8:704-11.
- 58 ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002;288:2981-97.
- 59 Cook NR, Cutler JA, Obarzanek E, Buring JE, Rexrode KM, Kumanyika SK, et al. Long term effects of dietary sodium reduction on cardiovascular disease outcomes: observational follow-up of the trials of hypertension prevention (TOHP). *BMJ* 2007;334:885.
- 60 Stolarz-Skrzypek K, Kuznetsova T, Thijs L, Tikhanoff V, Seidlerova J, Richard T, et al. Fatal and nonfatal outcomes, incidence of hypertension, and blood pressure changes in relation to urinary sodium excretion. *JAMA* 2011;305:1777-85.
- 61 O'Donnell MJ, Yusuf S, Mente A, Gao P, Mann JF, Teo K, et al. Urinary sodium and potassium excretion and risk of cardiovascular events. *JAMA* 2011;306:2229-38.
- 62 He FJ, Appel LJ, Cappuccio FP, de Wardener HE, Macgregor GA. Does reducing salt intake increase cardiovascular mortality? *Kidney Int* 2011;80:696-8.
- 63 He FJ, Macgregor GA. Cardiovascular disease: salt and cardiovascular risk. *Nat Rev Nephrol* 2012;8:134-6.
- 64 Taylor RS, Ashton KE, Moxham T, Hooper L, Ebrahim S. Reduced dietary salt for the prevention of cardiovascular disease. *Cochrane Database Syst Reviews* 2011;7:CD009217.
- 65 Taylor RS, Ashton KE, Moxham T, Hooper L, Ebrahim S. Reduced dietary salt for the prevention of cardiovascular disease: a meta-analysis of randomized controlled trials (Cochrane Review). *Am J Hypertens* 2011;24:843-53.
- 66 Cutting down on salt doesn't reduce your chance of dying. <http://eu.wiley.com/WileyCDA/PressRelease/pressReleaseId-99517.html>.
- 67 Paterna S, Gaspare P, Fasullo S, Sarullo FM, Di Pasquale P. Normal-sodium diet compared with low-sodium diet in compensated congestive heart failure: is sodium an old enemy or a new friend? *Clin Sci (Lond)* 2008;114:221-30.
- 68 Selmer RM, Kristiansen IS, Haglerod A, Graff-Iversen S, Larsen HK, Meyer HE, et al. Cost and health consequences of reducing the population intake of salt. *J Epidemiol Community Health* 2000;54:697-702.
- 69 Joffres MR, Campbell NR, Manns B, Tu K. Estimate of the benefits of a population-based reduction in dietary sodium additives on hypertension and its related health care costs in Canada. *Can J Cardiol* 2007;23:437-43.
- 70 Asaria P, Chisholm D, Mathers C, Ezzati M, Beaglehole R. Chronic disease prevention: health effects and financial costs of strategies to reduce salt intake and control tobacco use. *Lancet* 2007;370:2044-53.
- 71 Murray CJ, Lauer JA, Hutubessy RC, Niessen L, Tomijima N, Rodgers A, et al. 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.
- 72 Bibbins-Domingo K, Chertow GM, Coxson PG, Moran A, Lightwood JM, Pletcher MJ, et al. Projected effect of dietary salt reductions on future cardiovascular disease. *N Engl J Med* 2010;362:590-9.
- 73 Palar K, Sturm R. Potential societal savings from reduced sodium consumption in the US adult population. *Am J Health Promot* 2009;24:49-57.
- 74 Smith-Spangler CM, Juusola JL, Enns EA, Owens DK, Garber AM. Population strategies to decrease sodium intake and the burden of cardiovascular disease: a cost-effectiveness analysis. *Ann Intern Med* 2010;152:481-7, W170-483.
- 75 Department of Health. Assessment of dietary sodium levels among adults (aged 19-64) in England, 2011. <http://transparency.dh.gov.uk/2012/06/21/sodium-levels-among-adults/>.
- 76 Ofcom (Office of Communications). Impact assessment. [http://stakeholders.ofcom.org.uk/binaries/consultations/foodads\\_new/ia.pdf](http://stakeholders.ofcom.org.uk/binaries/consultations/foodads_new/ia.pdf).
- 77 Karppanen H, Mervaala E. Sodium intake and hypertension. *Prog Cardiovasc Dis* 2006;49:59-75.
- 78 Harsha DW, Sacks FM, Obarzanek E, Svetkey LP, Lin PH, Bray GA, et al. Effect of dietary sodium intake on blood lipids: results from the DASH-sodium trial. *Hypertension* 2004;43:393-8.

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## Tables

**Table 1 | Characteristics of trials included in meta-analysis of studies on effect of salt reduction on blood pressure**

	No of participants	Mean (range) age (years)	Male (%)	White (%)	Design	Blinding	Study duration	Change in UNa (mmol/24h)	Change in BP (mm Hg)	
									Systolic (SE)	Diastolic (SE)
<b>Hypertensive people</b>										
Parijs 1973 <sup>20</sup>	15	41 (NR)	43	—	X	NR	4 wk	-98	-6.7 (3.43)	3.2 (3.62)
Morgan 1981 (M) <sup>21</sup>	6+6	40 (NR)	100	100	P	BP obs	8 wk	-98	—	-8.0 (3.78)
Morgan 1981 (F) <sup>21</sup>	6+6	38 (NR)	0	100	P	BP obs	8 wk	-78	—	-4.0 (3.22)
MacGregor 1982 <sup>22</sup>	19	49 (30-66)	59	63	X	DB	4 wk	-76	-10.0 (2.40)	-5.0 (1.47)
Silman 1983 <sup>23</sup>	10+15	NR (50-64)	—	—	P	BP obs(RZ)	12 mo	-53	-8.7 (10.22)	-6.3 (4.42)
Puska 1983 (H) <sup>24</sup>	15+19	NR (30-50)	—	100	P	BP obs	6 wk	-117	1.8 (4.11)	0.5 (2.34)
Watt 1983 <sup>25</sup>	18	52 (31-64)	33	100	X	DB	4 wk	-56	-0.5 (1.50)	-0.3 (0.80)
Erwtaman 1984 <sup>26</sup>	44+50	46 (20-70)	62	76	P	BP obs(RZ)	6 mo	-58	-2.7 (2.20)	-3.4 (1.70)
Richards 1984 <sup>27</sup>	12	NR (19-52)	67	100	X	BP obs (A)	4-6 wk	-105	-5.2 (4.10)	-1.8 (3.55)
Chalmers 1986 <sup>28</sup>	48+52	52 (NR)	85	100	P	BP obs (A)	12 wk	-54	-5.1 (1.42)	-4.2 (0.85)
Grobbbee 1987 <sup>29</sup>	40	24 (18-28)	85	—	X	DB	6 wk	-72	-0.8 (1.80)	-0.8 (1.55)
ANHMRC 1989 (P) <sup>30</sup>	50+53	58 (NR)	83	100	P	DB	8 wk	-71	-5.5 (1.48)	-2.8 (0.85)
ANHMRC 1989 (X) <sup>31</sup>	88	59 (NR)	83	100	X	DB	8 wk	-67	-3.6 (0.70)	-2.1 (0.40)
MacGregor 1989 <sup>32</sup>	20	56 (43-73)	55	75	X	DB	4 wk	-82	-8.0 (2.00)	-5.1 (1.53)
Benetos 1992 <sup>33</sup>	20	42 (22-55)	45	100	X	DB	4 wk	-78	-6.5 (1.67)	-3.7 (1.29)
Fotherby 1993 <sup>34</sup>	17	73 (66-79)	24	100	X	DB	5 wk	-79	-8.0 (3.77)	0.0 (2.39)
Cappuccio 1997 (H) <sup>35</sup>	29	67 (60-78)	51	89	X	DB	4 wk	-87	-6.6 (2.63)	-2.7 (1.32)
Meland 1997 <sup>36</sup>	16	50 (NR)	81	100	X	DB	8 wk	-66	-4 (1.97)	-2 (1.25)
Sacks 2001 (H) <sup>37</sup>	76	52 (NR)	39	40	X	BP obs(RZ)	4 wk	-80	-8.7 (0.99)	-4.5 (0.62)
Gates 2004 <sup>38</sup>	12	64 (NR)	50	100	X	DB	4 wk	-89	-7 (2.90)	-1 (1.83)
Swift 2005 <sup>39</sup>	40	50 (40-60)	43	0	X	DB	4 wk	-78	-7.7 (2.11)	-3.1 (1.11)
Meland 2007 (H) <sup>40</sup>	19	53 (42-64)	53	100	X	DB	4 wk	-93	-8.3 (1.83)	-5.9 (1.55)
He 2009 <sup>41</sup>	169	50 (30-75)	67	42	X	DB	6 wk	-55	-4.8 (0.82)	-2.2 (0.44)
<b>Normotensive people</b>										
Puska 1983 (N) <sup>24</sup>	19+19	NR (30-50)	—	100	P	BP obs	6 wk	-117	-1.5 (3.32)	-2.1 (2.03)
Watt 1985 HH <sup>42</sup>	35	22 (25-69)	37	100	X	DB	4 wk	-74	-1.4 (0.74)	1.2 (0.93)
Watt 1985 LL <sup>42</sup>	31	23 (25-69)	45	100	X	DB	4 wk	-60	-0.5 (0.82)	1.4 (0.90)
Mascioli 1991 <sup>43</sup>	48	52 (NR)	79	98	X	DB	4 wk	-20/8h	-3.6 (0.90)	-2.3 (0.80)
TOHP I 1992 <sup>44</sup>	327+417	43 (30-54)	71	77	P	BP obs(RZ)	18 mo	-44	-1.7 (0.59)	-0.9 (0.42)
Cobiac 1992 <sup>45</sup>	26+28	67 (60-80)	67	100	P	DB	4 wk	-73	-1.7 (2.14)	0.8 (1.01)
Ruppert 1993 <sup>46</sup>	25	47 (27-75)	40	100	X	DB	4 wk	-118	1.7 (2.39)	1.0 (1.64)
Nestel 1993 (F) <sup>47</sup>	15+15	65 (60-79)	0	100	P	DB	6 wk	-94	-6.0 (4.91)	-2.0 (3.31)
Nestel 1993 (M) <sup>47</sup>	17+19	66 (60-79)	100	100	P	DB	6 wk	-76	-2.0 (3.43)	-1.0 (2.65)
Schorr 1996 <sup>48</sup>	16	64 (60-72)	48	100	X	DB	4 wk	-71	-7.2 (4.90)	-2.9 (2.61)
Cappuccio 1997 (N) <sup>35</sup>	18	67 (60-78)	51	89	X	DB	4 wk	-76	-8.2 (3.07)	-3.9 (1.65)
TOHP II 1997 <sup>49</sup>	515+514	44 (30-54)	67	82	P	BP obs(RZ)	36 mo	-40	-1.2 (0.50)	-0.7 (0.40)
Sacks 2001 (N) <sup>37</sup>	116	47 (NR)	50	46	X	BP obs(RZ)	4 wk	-75	-5.3 (0.77)	-2.6 (0.50)
Meland 2007 (N) <sup>40</sup>	20	53 (42-64)	50	100	X	DB	4 wk	-85	-4.6 (2.1)	-2.8 (1.03)

**Table 1 (continued)**

	No of participants	Mean (range) age (years)	Male (%)	White (%)	Design	Blinding	Study duration	Change in UNa (mmol/24h)	Change in BP (mm Hg)	
									Systolic (SE)	Diastolic (SE)
<p>UNa=urinary sodium; BP=blood pressure; SE=stand error; X=crossover; P=parallel; NR=not reported; DB=double blind; BP obs=blood pressure observer blinded; RZ=random zero manometer; A=automated sphygmomanometer; HH=offspring of two parents with high blood pressure; LL=offspring of two parents with low blood pressure; N=normotensive; H=hypertensive.</p>										

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**Table 2** Change in 24 hour urinary sodium (UNa) and systolic and diastolic blood pressure (SBP, DBP) in hypertensive and normotensive individuals in salt reduction studies by ethnic group and sex

	Trials	Participants	Mean effect* (95% CI)	P value
<b>Ethnic group</b>				
Hypertensive-white <sup>21 22 24 25 27 28 30-38 40 41</sup> :				
SBP (mm Hg)	16	599	-5.12 (-6.27 to -3.96)	<0.001
DBP (mm Hg)	17	623	-2.66 (-3.37 to -1.95)	<0.001
24h UNa (mmol)	17	623	-77.44 (-85.22 to -69.66)	<0.001
Hypertensive-black <sup>22 32 37 39 41</sup> :				
SBP (mm Hg)	5	171	-7.83 (-10.96 to -4.71)	<0.001
DBP (mm Hg)	5	171	-4.08 (-5.90 to -2.26)	<0.001
24h UNa (mmol)	5	171	-66.87 (-82.79 to -50.95)	<0.001
Hypertensive-Asian <sup>41</sup> :				
SBP (mm Hg)	1	29	-5.41 (-9.27 to -1.56)	0.008
DBP (mm Hg)	1	29	-2.17 (-4.31 to -0.03)	0.047
24h UNa (mmol)	1	29	-68.42 (-89.19 to -47.64)	<0.001
Normotensive-white <sup>24 35 37 40 42-49</sup> :				
SBP (mm Hg)	12	1901	-2.11 (-3.03 to -1.19)	<0.001
DBP (mm Hg)	12	1901	-0.88 (-1.68 to -0.08)	0.03
24h UNa (mmol)	12	1901	-76.45 (-89.52 to -63.38)	<0.001
Normotensive-black <sup>37 44 49</sup> :				
SBP (mm Hg)	3	412	-4.02 (-7.44 to -0.61)	0.02
DBP (mm Hg)	3	412	-1.98 (-4.45 to 0.49)	0.12
24h UNa (mmol)	3	412	-40.31 (-97.16 to 16.55)	0.16
<b>Sex</b>				
Hypertensive-men <sup>21 22 32 35-41</sup> :				
SBP (mm Hg)	9	227	-6.40 (-8.00 to -4.80)	<0.001
DBP (mm Hg)	10	239	-3.96 (-5.47 to -2.46)	<0.001
24h UNa (mmol)	10	239	-86.07 (-100.17 to -71.97)	<0.001
Hypertensive-women <sup>21 22 32 35-41</sup> :				
SBP (mm Hg)	9	181	-7.11 (-8.81 to -5.41)	<0.001
DBP (mm Hg)	10	193	-3.41 (-4.29 to -2.53)	<0.001
24h UNa	10	193	-69.56 (-77.56 to -61.55)	<0.001
Normotensive-men <sup>35 37 40 44 47 49</sup> :				
SBP (mm Hg)	6	1391	-3.39 (-5.63 to -1.16)	0.003
DBP (mm Hg)	6	1391	-1.78 (-3.01 to -0.55)	0.005
24h UNa (mmol)	6	1391	-67.26 (-81.90 to -52.62)	<0.001
Normotensive-women <sup>35 37 40 44 47 49</sup> :				
SBP (mm Hg)	6	691	-4.26 (-6.20 to -2.31)	<0.001
DBP (mm Hg)	6	691	-2.18 (-2.95 to -1.41)	<0.001
24h UNa (mmol)	6	691	-62.98 (-88.59 to -37.37)	<0.001

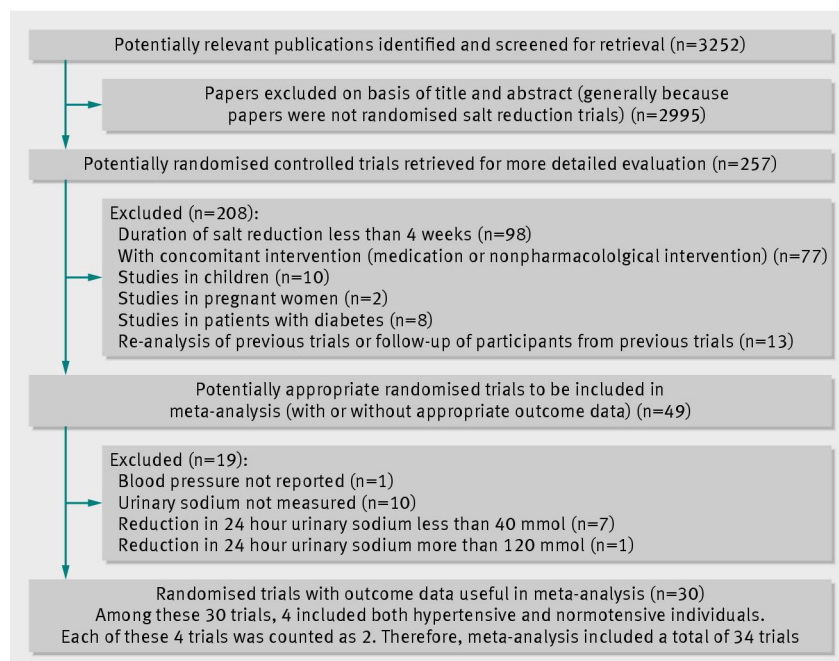
SBP=systolic blood pressure; DBP=diastolic blood pressure; UNa=urinary sodium.

\*Mean effect refers to comparisons of reduced salt with usual salt intake, and negative value indicates that effect favours reduced salt.

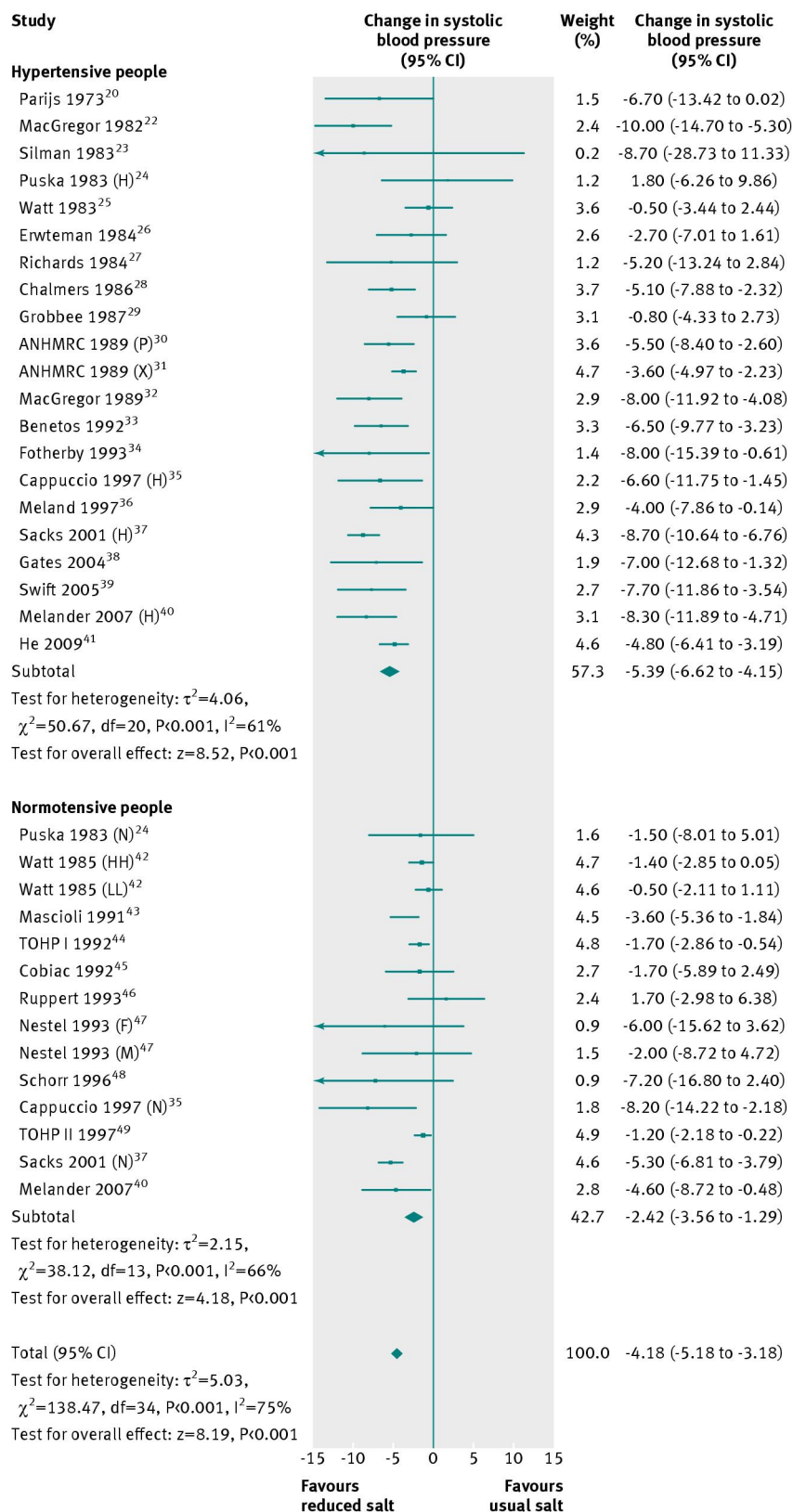
Table 3| Effect of salt reduction on hormones and lipids in studies included in meta-analysis

	No of trials	No of participants	Median measurement with usual salt intake	Change (95% CI) with salt reduction
Plasma renin activity (ng/mL/h)	14	455	1.07	0.26 (0.17 to 0.36), P<0.001, I <sup>2</sup> =70%
Aldosterone (pmol/L)	9	340	299	73.20 (44.92 to 101.48), P<0.001, I <sup>2</sup> =62%
Noradrenaline (pmol/L)	6	129	2075	187 (39 to 336), P=0.01, I <sup>2</sup> =5%
Adrenaline (pmol/L)	4	84	349	37 (-1 to 74), P=0.06, I <sup>2</sup> =12%
Total cholesterol (mmol/L)	8	365	5.3	0.05 (-0.02 to 0.11), P=0.18, I <sup>2</sup> =0%
Low density lipoprotein cholesterol (mmol/L)	5	262	3.2	0.05 (-0.01 to 0.12), P=0.11, I <sup>2</sup> =0%
High density lipoprotein cholesterol (mmol/L)	6	278	1.3	-0.02 (-0.06 to 0.01), P=0.19, I <sup>2</sup> =16%
Triglycerides (mmol/L)	6	309	1.3	0.04 (-0.02 to 0.09), P=0.22, I <sup>2</sup> =0%

## Figures

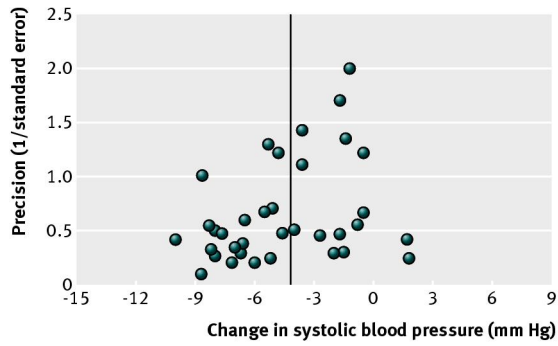


**Fig 1** PRISMA flow diagram of studies included in review of salt reduction on blood pressure



**Fig 2** Change in systolic blood pressure and corresponding 95% confidence interval in individual trials included in meta-analysis and mean effect size

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**Fig 3** Funnel plot to explore publication bias. Vertical line is at mean effect size. Precision is reciprocal of standard error of change in systolic blood pressure