Effects of low sodium diet versus high sodium diet on blood pressure, renin, aldosterone, catecholamines, cholesterols, and triglyceride (Unknown)

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ABSTRACT

Background
One of the controversies in preventive medicine is, whether a general reduction in sodium intake can decrease the blood pressure of a population and thereby reduce cardiovascular mortality and morbidity. In recent years the debate has been extended by studies indicating that reducing sodium intake has effects on the hormone and lipid profile.

Objectives
To estimate the effects of low sodium versus high sodium intake on systolic and diastolic blood pressure (SBP and DBP), plasma or serum levels of renin, aldosterone, catecholamines, cholesterol and triglycerides.

Search strategy
"MEDLINE" and reference lists of relevant articles were searched from 1966 through December 2001.

Selection criteria
Studies randomising persons to low sodium and high sodium diets were included if they evaluated at least one of the above outcome parameters.

Data collection and analysis
Two authors independently extracted the data, which were analysed by means of Review Manager 4.1.

Main results
In 57 trials of mainly Caucasians with normal blood pressure, low sodium intake reduced SBP by -1.27 mm Hg (CI: -1.76; -0.77)(p<0.0001) and DBP by -0.54 mm Hg (CI: -0.94; -0.14) (p = 0.009) as compared to high sodium intake. In 58 trials of mainly Caucasians with elevated blood pressure, low sodium intake reduced SBP by -4.18 mm Hg (CI: -5.08; - 3.27) (p < 0.0001) and DBP by -1.98 mm Hg (CI: -2.46; -1.32) (p < 0.0001) as compared to high sodium intake. The median duration of the intervention was 8 days in the normal blood pressure trials (range 4-1100) and 28 days in the elevated blood pressure trials (range 4-365). Multiple regression analyses showed no independent effect of duration on the effect size. In 8 trials of blacks with normal or elevated blood pressure, low sodium intake reduced SBP by -6.44 mm Hg (CI: -9.13; -3.74) (p < 0.0001) and DBP by -1.98 mm Hg (CI: -4.75; 0.78) (p = 0.16) as compared to high sodium intake. The magnitude of blood pressure reduction was also greater in a single trial in Japanese patients. There was also a significant increase in plasma or serum renin, 304% (p < 0.0001), aldosterone, 322%, (p < 0.0001), noradrenaline, 30% (p < 0.0001), cholesterol, 5.4% (p < 0.0001) and LDL cholesterol, 4.6% (p < 0.004), and a borderline increase in adrenaline, 12% (p = 0.04) and triglyceride, 5.9% (p = 0.03) with low sodium intake as compared with high sodium intake.

Reviewer's conclusions
The magnitude of the effect in Caucasians with normal blood pressure does not warrant a general recommendation to reduce sodium intake. Reduced sodium intake in Caucasians with elevated blood pressure has a useful effect to reduce blood pressure in the short-term.

The results suggest that the effect of low versus high sodium intake on blood pressure was greater in Black and Asian patients than in Caucasians. However, the number of studies in black (8) and Asian patients (1) was insufficient for different recommendations. Additional long-term trials of the effect of reduced dietary sodium intake on blood pressure, metabolic variables, morbidity and mortality are required to establish whether this is a useful prophylactic or treatment strategy.

SYNOPSIS

This review of short-term studies shows that in people with elevated blood pressure low salt diets lead to useful drops in blood pressure, but overall harms or benefits are not known.

We are commonly advised to cut down on salt. However, a pair of Cochrane reviews has found that there is little evidence for long-term benefit from reducing salt intake. This review looked at mostly short-term strategies to reduce salt intake. The other review (Hooper 2003) looked at long-term strategies to reduce the amount of salt in foods and drinks.

Advice about reducing salt intake did lower blood pressure but only by a small amount. It was not enough to expect an important health benefit. It is also very hard to keep to a low salt diet. However, the reduction was larger for people with high blood pressure. The studies were not designed to measure long-term health effects so, we don't know if low salt diets improve health outcomes.

The studies in which some people were given low salt diets and compared with others on a normal diet, found that the blood pressure did fall while the people were in the trial. But, it's not known if it stayed down after the trials. This means that the available evidence does not suggest that people with normal blood pressure should reduce the amount of salt they eat or drink. However, for people with high blood pressure low salt diet caused a larger reduction in blood pressure, and would be useful as part of a program to reduce blood pressure.

Most of the people who took part in the studies were Caucasians, but in the small number of non-Caucasians (mostly African) the blood pressure reduction was, if anything, greater. More research on salt intake is required, particularly in non-Caucasian populations. See also the long-term salt review: Hooper 2003.

BACKGROUND

The recommendation to reduce sodium intake is based on the effect on a surrogate marker (blood pressure (BP)) and on the hypothetical benefits in terms of reduction in cardiovascular morbidity and mortality (Collins 1990). There is evidence from other published reviews (Law 1991; Midgley 1996; Cutler 1997; Ebrahim 1998; Graudal 1998; Hooper 2002) and another Cochrane review (Hooper 2003) of the effects of reduced sodium intake on BP. In recent years other surrogate markers, such as the renin-angiotensin- aldosterone system, catecholamines and serum lipid, have been shown to be affected by sodium intake. Before advising the public to lower sodium intake, long-term studies on morbidity and mortality should be conducted. In the absence of such studies in addition to measuring blood pressure, effects on as many surrogate markers as possible should be investigated. Since some of these effects are expected to be mutually dependent, the investigation of more than one effect makes it possible to detect the consistency of the results between the studies. The present review represents an update of the first cumulative meta-analysis that includes an analysis of hormones and lipids in addition to blood pressure (Graudal 1998).

OBJECTIVES

The purpose of the present study was to estimate the influence of low versus high dietary sodium intake on systolic blood pressure (SBP), diastolic blood pressure (DBP), and blood concentrations of renin, aldosterone, catecholamines and lipids.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Controlled clinical trials randomly allocating patients (randomised controlled trials (RCTs)) to either a low or a high sodium diet and in which the sodium intake was estimated by the 24-h urinary sodium excretion (either measured on the basis of a 24-h urine collection, or estimated from a collection over at least 8 hours)

Types of participants

Persons with normal or elevated blood pressure irrespective of race who are above 15 years of age. Studies on pregnant women and children were not included. Studies systematically investigating unhealthy patients with other diseases than elevated blood pressure, for instance diabetes, were excluded.

In our previous meta-analysis (Graudal 1998) different races were mixed. Due to the recent finding in the DASH study (DASH 1, 2001) that blacks may have a greater response to sodium reduction than Caucasians, studies in which more than 50% of persons were black were included in a separate meta-analysis. Because only a few such studies existed (5 references, 8 populations) subjects with normal and elevated blood pressure were combined in one analysis. One study of 70 Japanese patients (Uzu 1999) was reported separately.

Types of intervention

The intervention was changed sodium intake, randomly dividing the investigated population into a group eating a low sodium diet and a group eating high sodium diet. Confounding was not allowed, i.e. studies treating persons with a concomitant intervention such as an antihypertensive medication, potassium supplementation or weight reduction were only included if the concomitant intervention was identical during the low and the high sodium diet.

Types of outcome measures

Outcome measures were effects on SBP, DBP, renin, aldosterone, adrenaline, noradrenaline, triglyceride, cholesterol, low-density lipoprotein (LDL) and high-density lipoprotein (HDL). In our previous meta-analysis (Graudal 1998) the MBP effect of studies only reporting MBP was accepted as both an SBP and a DBP effect. This could underestimate the SBP effect and overestimate the DBP effect. To avoid this in the present review, SBP (effect) was estimated from MBP effect + 1/3 of MBP(effect) and DBP (effect) was estimated from MBP effect - 1/3 of MBP (effect). Separate meta-analyses were performed for each outcome measure.

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

See: search strategy

Trial search: The first RCT of the effect of sodium reduction on BP was published by Parijs et al. in 1973 (Parijs 1973). In our first meta-analysis (Graudal 1998), a literature search in "MEDLINE" (1966-through December 1997) was performed using the following combinations of search terms: 1) salt or sodium, 2) restriction or dietary, 3) blood pressure or hypertension, 4) randomised or randomised or random. We combined 1, 2, 3 and 4 and found 291 references. Of these, 76 randomised trials from 60 references fulfilled the inclusion criteria. From the reference lists of these articles and from 4 previous meta-analyses (Grobbee 1986, Cutler 1991, Law 1991,Midgley 1996) additional 23 references including 39 trials were identified in our previous review (Graudal 1998). Of these 83 references three dealing exclusively with diabetes patients were excluded in the present review. A repeated search was performed in January 2002 through December 2001, revealing additional 11 references, of which one was excluded because it only included patients with diabetes. SBP and DBP from hypertensive study samples and SBP and DBP from normotensive study samples were integrated in 4 separate meta-analyses. Similar searches were made for hormones and lipids changing the third search term (blood pressure or hypertension) with the hormone or lipid term. Additional 5 references including data on hormones and lipids but not blood pressure were revealed during the first search (1998) and one during the second search (2002). Thus a total of 96 references were included in the present review, of which 6 dealt only with hormones and lipids. An additional search in CCTR and EMBASE did not reveal further studies. The search was not limited to English language studies but no non-English language studies were identified.

METHODS OF THE REVIEW

Effect size: This was defined as the difference between the changes from baseline to end of treatment during a low and a high sodium diet.

Data extraction: Two authors independently recorded the following data from each trial: 1) the sample size (N); 2) the mean age of participants; 3) the fraction of females, males; Caucasians and blacks or orientals 4) the duration of the intervention; 5) the sodium reduction measured as the difference between 24-h urinary sodium excretion during low -sodium and high - sodium diets and standard deviation (SD); 6) SBP (SD) and DBP (SD) before and after intervention; 7) difference between changes in SBP and DBP obtained during low-sodium and high sodium diets and the SD of these differences. In 24 studies SD of the change was either given or could be deduced from a given SE of the change (see "notes" in table "Characteristics of included studies"). In 7 studies SD of the change was deduced from a given 95%confidence interval (see "notes" in table "Characteristics of included studies"). In all other studies SD of the change was imputed from the formula SD (change) = sq root (SD1sq + SD2sq), SD1 is SD on blood pressure before intervention and SD2 is SD on blood pressure after intervention; 8) levels of hormones and lipids in the blood and their standard deviations during low-sodium and high-sodium diets. The number of urinary sodium excretions analysed per person per treatment period and data on the completeness of urine collections were also recorded. If there were discrepancies between reviewers they looked at the data together and came to an agreement.

Statistical methods: Data were analysed by means of Review Manager 4.1. Concerning lipids, cholesterol units of mmol/l were transformed to mg/dl by means of the factor 38.6 and triglyceride units of mmol/l were transformed to mg/dl by means of the factor 88.4. The weighted mean difference was calculated for outcome measures with identical units in the included studies (blood pressure, adrenaline, and lipids

(after transformation)). The standardized mean differences were calculated for outcome measures with different units (renin, aldosterone, and noradrenaline). With this method, the difference in effect between two treatments is divided by the standard deviation of the measurements. By that transformation the effect measures become dimensionless and the outcomes from trials which have used different units can consequently be combined. Finally, the standardized mean effect was transformed to the most commonly used unit.
If p was less than 0.05 in the test for heterogeneity, a random effect analysis was carried out (blood pressure in blacks, renin, aldosterone, and noradrenaline). In the homogenous meta-analyses the fixed effect model was used.

Level of significance: In case of multiple independent comparisons it is important to avoid coincidental significance. Fourteen meta-analyses were performed. In our previous analysis (Graudal 1998), we corrected the significance level for the number of meta-analyses. However, in the present review we now suggest that the blood pressure comparisons are not independent of each other and that the blood pressure depends on renin and aldosterone as well as catecholamines. Concerning lipids we suggest that these are mutually dependent, whereas the dependency on blood pressure and hormones is not obvious. Consequently the 14 meta-analyses could be subclassified into a group of meta-analyses of mutually dependent blood pressures and hormones and an independent group of meta-analyses of mutually dependent lipid fractions. Consequently, the level of significance was reduced by means of the formula 1-0.951/N = 1-0.951/2 = 0.025, (N = number of independent investigations).

DESCRIPTION OF STUDIES

See: Table "Characteristics of included studies".

Ninety-six references, including 137 randomised study populations, were included in the review. When results were reported by subgroup, the subgroup results were used.
In the 58 studies of Caucasians with elevated BP the mean age was 49 years (range 23-73); the median duration was 28 days (4-365). Concomitant anti-hypertensive treatment was given to both interventions groups for 13 trials. In the 57 studies of Caucasians with normal BP, the mean age was 27 years (range 15-67); the median duration was 8 days (4-1100).

METHODOLOGICAL QUALITY

See: Table "Characteristics of included studies".

The obligatory trial quality criterion was randomisation. Double blind, single blind or open studies with a parallel or a crossover design were accepted. A study was defined as single blind if BP was measured by an investigator without knowledge of the diet or by a computerized manometer and as open if precautions to decrease observer bias were not mentioned. Only five studies (Watt 1985, Egan 1991, Steegers 1991, TOHP I 1992, TOHP II 1997) sufficiently explained the allocation concealment and only two studies use the intention to treat principle (TOHP I 1992; TOHP II 1997).

RESULTS

See Meta-view graphs and lists of comparisons

Two univariate regression analyses of mean age (independent variable) versus 1) SBP effect (dependent variable) and 2) DBP effect (dependent variable) showed highly significant associations (SBP effect: t = 3.7, p = 0.0001; DBP effect: t = 2.8, p = 0.006). Because there is an association between age and blood pressure, the analyses were also performed as multiple regression analyses with initial SBP and initial DBP as the second independent variable. In these analyses there were no longer independent associations between age and blood pressure effect (SBP effect: t = 0.8, p = 0.40; DBP effect: t = 1.2, p = 0.25). This was confirmed by the lack of association between age and blood pressure effect in subgroups with equal initial blood pressure. However, there was still a significant association between initial BP and BP effect.
There was no association between magnitude and duration of sodium reduction and the effect on blood pressure. There was also no association seen in multiple regression analyses in which initial blood pressure, age of study population and size of study population were accounted for. In the multiple regression analysis, age and initial blood pressure were independently associated with blood pressure effect, but only when included one by one because of covariation. Furthermore, we found no differences between double blind, single blind and open studies, no difference between studies using diets and studies using sodium/placebo tablets, and no differences between studies that had blood pressure as primary outcome measure and studies that had blood pressure as secondary outcome measure.
In 8 studies (5 references) 55-100 % of the patients were black and in one study all patients were Japanese. In the Japanese study of 70 patients the effect of Na reduction was -14.5/-5.5 mm Hg (Uzu 1999). The 8 studies of blacks were heterogeneous and therefore analysed by means of the random effect model. Although the studies of blacks included a mixture of subjects with normal and elevated BP, the systolic blood pressure effect was numerically larger and the diastolic BP effect was the same (SBP: decrease -6.44 (-9.13;-3.74) mm Hg. DBP decrease -1.98 (-4.75;0.78) mm Hg) as in the studies of Caucasians with elevated BP .
In the meta-analyses of 57 studies of Caucasians with normal BP, the mean weighted effect of sodium reduction was a decrease in SBP of -1.27 (95%CI: -1.76; -0.28) and in DBP of -0.54(95%CI:-0.94; -0.14) mm Hg (p = 0.009). In the 58 trials of Caucasians

with elevated BP the mean weighted effect of sodium reduction on SBP was -4.18 (-5.08; - 3.27) and on DBP was -1.89(-2.46; -1.32) mm Hg (p < 0.0001).

Renin and aldosterone

In the trials of measurement of renin (n = 55), the standardized mean effect of a mean sodium reduction of 182 mmol was 1.27 (Z= 12.15, p<0.00001) corresponding to an increase from 2.1 to 6.9 ng/ml/h during sodium reduction. In the trials of measurement of aldosterone (n =39), the standardized mean effect of a mean sodium reduction of 186 mmol was 1.52 (Z= 11.39, p<0.00001) corresponding to an increase from 205 to 605 pmol/l during sodium reduction.

There was a highly significant correlation between magnitude sodium difference and renin (r = 0.66, p < 0.0001) and magnitude of sodium difference and aldosterone (r = 0.64, p < 0.0001).

The studies of persons with normal and elevated BP did not differ in their renin and aldosterone response to sodium reduction

Catecholamines

In the trials of measurement of noradrenaline (n = 28), the standardized mean effect of a mean sodium reduction of 196 mmol was 0.57 (Z= 5.6, p<0.00001) corresponding to an increase from 1.64 to 2.14 nmol/l during sodium reduction (random effect model). In the trials of measurement of adrenaline (n =11), the weighted mean increase of a mean sodium reduction of 126 mmol was 10 pmol/l (Z= 2.10, p<0.04) (fixed effect model). The correlation between magnitude of sodium reduction and increase in adrenalin was not significant. The noradrenaline response was stronger in the persons with elevated BP (r = 0.76, p = 0.002, n = 12) than in persons with normal BP (r = 0.12, p = 0.64, n = 16).

Lipids

The meta-analyses of the trials of lipids are homogenous after transformation of units to mg/dl in all studies.

Cholesterol (n = 19), a mean sodium reduction of 179 mmol caused a mean increase of 10.1 mg/dl (CI: 6.7-13.6); HDL (n = 15), a mean sodium reduction of 186 mmol caused no change (Z= 0.48, p=0.6); and LDL (n = 15) a mean sodium reduction of 203 mmol caused an increase of 6.4 mg/dl (CI: 2.1-10.6). Triglyceride (n = 15) a mean sodium reduction of 199 mmol caused an increases of 5.5 mg/dl (CI: 0.6-10.4).

DISCUSSION

The intake of sodium in the low sodium group was above 150 mmol in only three studies of the present meta-analysis, and it was below 120 mmol in all other studies. Consequently, this meta-analysis in general compares the effects of a dietary sodium intake which is lower than normal with a sodium intake which is either normal or above normal.

In our previous analysis there was considerable heterogeneity in BP effect between studies, but the exclusion of black and Japanese populations and studies in diabetic patients eliminated this heterogeneity except for the meta-analysis of SBP in persons with normal BP. However, the heterogeneity in this group was reduced markedly and could be ascribed to a few studies which subdivided the investigated population into a salt sensitive, a salt resistant and a counter regulatory groups. If the mean value of the subgroups was included in the meta-analysis instead of the subgroup results, the heterogeneity in the meta-analysis disappeared. We therefore consider the meta-analysis of SBP in normotensives to be also homogenous. The heterogeneity of the black populations could be ascribed to the mixture of normal and elevated BP studies.

The heterogeneity of the hormone meta-analyses could be ascribed to the use of different units. No heterogeneity could be detected in the adrenaline meta-analysis and the lipid meta-analyses in which identical units were used in the included studies.

Does sustained dietary salt restriction result in a reduction in the number of deaths and severe cardiovascular events? This important question cannot be answered from this meta-analysis because most trials were not long enough and the relevant outcomes were not reported. What can be concluded based on the basis of the available clinical and paraclinical surrogate measures. Blood pressure is a relevant surrogate measure, because the relation between blood pressure and cardiovascular events has been well documented (Collins 1990). However, interest in other surrogate variables included in this review is new. The inclusion of other surrogates such as left ventricular hypertrophy or left ventricular ejection fraction could be relevant, but as far as we know no studies measuring these outcomes have been published.

The present meta-analysis only includes RCTs. Unrandomised studies and meta-analyses including unrandomised studies will not be debated in the present context, because the quality of such studies is considered to be inferior to RCTs.

The public health relevance of some of the included RCTs, for instance short-term and high dose studies, may be questioned. However, it is interesting to note that dose and duration appeared to have no influence on the final effect size. This finding could not have been assessed, if studies using extreme doses and duration had been excluded. Previous meta-analyses of RCTs with other selection criteria have shown similar results. In 1986, Grobbee and Hofman combined 13 studies of persons with normal and elevated BP in a meta-analysis and found a significant hypotensive effect of reduced sodium intake on SBP of -3.6 mm Hg and a non-significant effect on DBP of -2.0 mm Hg (Grobbee 1986). In 1991, a second meta-analysis of 24 RCTs showed an effect of -4.0/-2.5 mm Hg for persons with elevated BP and -1.0/-0.2 for persons with normal BP (Cutler 1991). This was verified in an update from 1997 (Cutler 1997). In 1996, a meta-analysis of 53 RCTs showed an effect of -3.7/-0.9 mm Hg in persons with elevated BP and -1.0/-0.1 in persons with normal BP (Midgley 1996). In a meta-analysis including only 26 RCTs with a sodium reduction of at least 40 mmol lasting for more than 4 weeks, the

effect was -4.2/-2.4 mm Hg in persons with elevated BP and the effect -1.6/-0.6 mm Hg in persons with normal BP (He 2000).
In an analysis of 8 RCTs lasting for at least 6 months the effect was -2.9/-2.1 mm Hg for persons with elevated BP and -1.3/-0.8 mm Hg for persons with normal BP (Ebrahim 1998). These results have recently been confirmed in an update (Hooper 2002) and Cochrane Review (Hooper 2003). All these results are very similar to the results of the present meta-analysis. Consequently, they confirm that selection of RCTs based on magnitude of Na difference or duration of the intervention does not significantly change the overall effect size estimate.

The recent DASH study (DASH 1, 2001) found a significantly higher effect of sodium reduction on blood pressure than the present and previous meta-analyses. However, the majority of persons in this study were non-Caucasians and/or had elevated BP. It was not possible to separate the effect on diastolic blood pressure in normotensive Caucasians, but sufficient data is given in a later publication (DASH 2, 2001) to estimate this effect to be 1.4 mm Hg (Jürgens 2002). Considering that the DASH study only included persons from the upper 50 percentile of normal BP, this somewhat larger effect than the present meta-analysis is not unexpected.
The DASH finding of a larger effect in blacks prompted us to separate out the trials in blacks and it confirmed that the effect in blacks seems to be higher than in Caucasians. Our cumulative meta-analysis (Graudal 1998) showed that up to 11 studies needed to be included before the result of the meta-analysis was stable; the early effect was higher than the final effect. Consequently, it is probably too early to draw final conclusions about the effect of a low versus high sodium diet in blacks.

Oliver et al. demonstrated that the Yanomamo Indians, who ingest extremely small amounts of sodium, had a 3 times higher level of renin in the blood and a 10 times higher excretion of aldosterone in the urine, than did normal controls (Oliver 1975). In the present meta-analysis the increase in aldosterone and renin was 5-6 times in those whose sodium excretion was reduced to less than 20 mmol/24-hours, i.e. to a level almost as low as the Yanomamo Indians (range 0.3-6.8 mmol). In 20 populations with a reduced sodium excretion between 40 and 100 mmol/24h, renin and aldosterone increased about 2 times indicating that the renin-angiotensin-aldosterone system is also activated when sodium intake is reduced to a moderate level. Combined with our findings of a significant increase in renin and aldosterone in long-term studies (> 4 weeks) with a low reduction (< 100 mmol) in sodium intake, this suggests that the acute increase in renin and aldosterone may be maintained, if the reduced sodium intake is maintained. Thus, the present meta-analysis provides a possible explanation for the relatively small effect of reduced sodium intake on blood pressure: compensatory activation of the renin-aldosterone system is proportional to the degree of sodium reduction. Furthermore, an increase in noradrenaline may contribute to this counter-regulation (Warren 1980).

The results of the present and previous meta-analyses of RCTs indicating an effect of sodium reduction on BP of 1-4/0-2 mm Hg are in accordance with large population studies. One study (the Intersalt study of 10079 persons) showed a moderate, but significant correlation between sodium intake and SBP, but not DBP (Intersalt 1988), whereas another (the Scottish Heart Health Study including 7354 persons) found no correlation between sodium intake and blood pressure (Smith 1988).
Another position indicates an effect of sodium reduction of 6-10/3-5 mm Hg. This position is summarized in a meta-analysis including unrandomised studies as well as RCTs (Law 1991), and is supported in a recent reanalysis of Intersalt (Elliot 1996). Among those who accept that the effect of sodium reduction on BP is relatively small, there is disagreement regarding the relevance of the effect size. As pointed out by Stammler, even a small reduction in BP may be relevant if it could be applied to the whole population (Stammler 1991), since a small average reduction in BP could decrease the number of strokes and cardiovascular events substantially. Cutler et al. share that point of view (Cutler 1997), whereas Midgley et al. do not and emphasize the potential adverse effects of reduced sodium intake (Midgley 1996). This disagreement exists in spite of similar effect size estimates in the two meta-analyses (Midgley 1996; Cutler 1997). In their regression analysis of sodium reduction versus BP effect, Cutler et al. assumed that there was no confounding and consequently they forced their regression line through 0.0. This resulted in a significant dose-response relationship between sodium reduction and BP effect (SBP in persons with elevated BP. The regression line declined 5.8 mm Hg per 100 mmol/24 h of reduced sodium intake) corresponding to an estimated effect size (SBP in hypertensives 4.8 mm Hg per 76 mmol/24 h of reduced sodium intake). Midgley et al. did not force their regression line through 0.0 and found a dose-response relationship in which SBP in persons with elevated BP declined 3.7 mm Hg per 100 mmol/24 h of reduced sodium intake, which was considerably smaller than the mean estimated effect size (SBP decreased 5.9 mm Hg for a 95 mmol/24 h of reduced sodium intake). They suggested that a part of the estimated effect size might be attributed to an unidentified confounder.

Concerning the absence of a dose-response relationship between magnitude of sodium reduction and blood pressure effect as seen in this review, it has been argued that the reason is that many short term studies investigate large sodium reductions, whereas the long term studies investigate low to moderate reductions. However, it was possible to detect highly significant correlations between magnitude of sodium reduction and change in renin, aldosterone and noradrenaline. Furthermore, adjustment for duration was not sufficient to produce a significant relationship between dose of sodium reduction and blood pressure effect in a multiple regression analysis.
The blood pressure effect of reduced sodium intake has also been related to age. Freedman and Petitti analysed data from Intersalt and found the paradox that along with the significant association

between increase in blood pressure with age and the salt excretion in urine, there was an inverse relationship between estimated blood pressure and salt excretion in urine at age 20. Freedman stated that unless you preferred to conclude that salt should be eaten in high doses by youngsters and in reduced amounts by the elderly, the findings were probably due to uncontrolled confounding, not to variation in salt intake (Freedman 2001). Furthermore, it is not clear whether the blood pressure of different age cohorts in a cross-sectional study like Intersalt is representative, and therefore the age/blood pressure relationship may not be verified in a longitudinal study (Graudal 2000). This position is confirmed by a recent study showing that recent birth cohorts attained lower blood pressure than did earlier birth cohorts in the period 1887-1994 (Goff 2001).

The present results indicate that the effect on the normotensive population is small in spite of a considerable reduction in sodium intake. Furthermore extreme sodium reduction could lead to unfavourable increases in lipids. Concerning cholesterol there was an increase of about 5% with mean sodium reduction of about 180 mmol. This increase was highly significant and correlated significantly with the magnitude of sodium reduction. This suggests that more relevant reductions of about 100 mmol would cause an increase of 2-3%. For comparison, the decrease in blood pressure was about 1% in patients with normal BP. However, it is too early to draw final conclusions because of lack of long-term studies (> 4 weeks) with moderate sodium reduction (about 100 mmol/24 h). Blood lipids were only investigated in 2-4 longer-term studies with a mean sodium reduction of 75 mmol (Grobee 1987, Sciarrone 1992, Schorr 1996 and McCarron 1997). The evidence from these was not statistically significant. The effect on the lipid profile may be secondary to a shift in fluid balance such as hemoconcentration. In the present study this premise is supported by a significant body weight reduction of about 1-kg in the sodium-reduced group (Graudal 1998), probably reflecting a decrease in total body water. However, if this was the only explanation, a similar percent change should have been expected for all lipids and this was not the case. There was a significant increase in LDL, but no increase in HDL. Thus, hemoconcentration is probably not the only explanation for the increase in LDL.

REVIEWER'S CONCLUSIONS

Implications for practice

The present meta-analysis shows that short-term low versus high sodium diet in Caucasians with normal blood decreases BP by only about 1%. The blood pressure reduction may be limited by a large concomitant increase in plasma renin, plasma aldosterone and plasma noradrenaline. At extreme sodium reductions of about 200 mmol there was a significant increase in plasma cholesterol (5%), LDL cholesterol (5%) and plasma triglyceride (5%). These effect sizes do not justify a general recommendation for sodium reduction in societies dominated by Caucasians.

In Caucasians with elevated BP short-term sodium reduction decreases BP by about 2-2.5%, indicating that sodium reduction be recommended as a supplementary treatment for elevated blood pressure.

In Asians and Blacks the effect of sodium reduction was greater, but at present too few studies have been carried out to make a recommendation different from that above.

Implications for research

Trials are needed to determine the effects on BP and other parameters of long-term reductions in sodium intake of about 100 mmol/24 hours. The data suggesting that Blacks and Asians are more sensitive to sodium reduction than Caucasians requires further studies. In future studies of mixed populations it is important that the effects on Caucasians, Blacks, and Asians are reported separately.

Long-term RCTs with mortality and morbidity outcomes are needed to determine whether the benefits of sodium reduction outweigh the harms.

POTENTIAL CONFLICT OF INTEREST

None.

All authors are employed at public institutions. None of the authors has any connection with or receives funds from the food and salt industries or has commercial interests that might bear on this article.

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* *Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	**ANHMRCDS 1986**
Methods	SB
	P
Participants	N100
	Hyp
	Age53
Interventions	SR70
	Dur 84
Outcomes	SBP -4.8
	DBP-4.2

Notes	Included 108 LoFo:8 IT: No SD of the change calculated from SEM of the change
Allocation concealment	B

Study	**ANHMRCDS 1989**
Methods	Op P
Participants	N103 Hyp Age58
Interventions	SR63 Dur 48
Outcomes	SBP -5.5 DBP-2.9
Notes	Included 111 LoFo:8 IT: No SD of the change calculated from SEM of the change
Allocation concealment	B

Study	**Ambrosioni 1982**
Methods	SB CO
Participants	N25 Hyp Age23
Interventions	SR60 Dur 42
Outcomes	SBP -2.2 DBP -0.4
Notes	LoFo:1 IT: No
Allocation concealment	B

Study	**Ames 2001**
Methods	SB CO
Participants	13 Hyp Age 60
Interventions	SR 133 Dur 28
Outcomes	SBP -7 DBP -2 NA -114 A -3

	TG: 6 Chol: 6 HDL: 3 LDL: 2
Notes	21 patients included 8 diabetes patients excluded LoFo: 0
Allocation concealment	B

Study	**Beard 1982**
Methods	Op P
Participants	N90 Hyp Age48
Interventions	SR124 Dur 84
Outcomes	SBP -5.2 DBP-3.4
Notes	Included 113 LoFo:23 IT: No
Allocation concealment	B

Study	**Benetos 1992**
Methods	DB CO
Participants	N20 Hyp Age42
Interventions	SR78 Dur 28
Outcomes	SBP -6.5 DBP-3.7 Aldo 12.2 ng/ml Renin 1.6 ng/ml NA 52 pg/ml A 19.4 pg /ml (CI31.8)
Notes	Included 22 LoFO: 2 IT: No
Allocation concealment	B

Study	**Bruun 1990**
Methods	Op CO
Participants	N10 Norm

Characteristics of included studies (*Continued*)

	Age46
Interventions	SR341 Dur4
Outcomes	SBP -5 DBP -1 Aldo 240pmol/l Renin 27.1 mIU/l
Notes	LoFo: 0
Allocation concealment	B

Study	**Bruun 1990 b**
Methods	Op CO
Participants	N12 Hyp Age47
Interventions	SR331 Dur4
Outcomes	SBP -8 DBP -4 Aldo 250pmol/l Renin 50 mIU/l
Notes	LoFo: 0
Allocation concealment	B

Study	**Buckley 1994**
Methods	SB CO
Participants	N12 (3 blacks) Hyp Age49
Interventions	SR 296 Dur 5
Outcomes	SBP -8.7 DBP -8.7
Notes	LoFo: 0
Allocation concealment	B

Study	**Burnier 1993**
Methods	Op CO
Participants	N16 Norm Age29
Interventions	SR186 Dur6
Outcomes	SBP -1 DBP 0.5

	Aldo 29 pg/ml Renin 0.54 ng/ml/h
Notes	LoFo:0
Allocation concealment	B

Study	**Burnier 1993 b**
Methods	Op CO
Participants	N7 Norm Age29
Interventions	SR218 Dur 6
Outcomes	SBP -1 DBP 1.2 Aldo 31.8 pg /ml Renin 0.31 ng/ml/h
Notes	LoFo:1 IT: No
Allocation concealment	B

Study	**Capuccio 1997**
Methods	DB CO
Participants	N47 Hyp Age67
Interventions	SR83 Dur 30
Outcomes	SBP -7.3 DBP -3.2
Notes	Included 52 randomised 48 LoFo: 1 IT: No SD of the change calculated from 95% CI
Allocation concealment	B

Study	**Carney 1991**
Methods	DB CO
Participants	N11 Hyp Age54
Interventions	SR102 Dur 42
Outcomes	SBP -1 DBP 1

	Renin 2.3 ng/ml/h
Notes	LoFo: 0
Allocation concealment	B

Study	**Cobiac 1992**
Methods	DB P
Participants	N52 Norm Age66
Interventions	SR75 Dur28
Outcomes	SBP -3.1 DBP -2.8
Notes	Included 114(1992+1992b) LoFo: 8 IT: No
Allocation concealment	B

Study	**Cobiac 1992 b**
Methods	DB P
Participants	N54 Norm Age67
Interventions	SR73 Dur28
Outcomes	SBP -2.7 DBP 0.6
Notes	Included 114(1992+1992b) LoFo: 8 IT: No
Allocation concealment	B

Study	**Cooper 1984**
Methods	SB CO
Participants	N59 Norm Age16
Interventions	SR55 Dur 24
Outcomes	SBP -1.4 DBP -3.4
Notes	Included 124(1984+1984b) LoFo: 11 IT: No
Allocation concealment	B

Characteristics of included studies (*Continued*)

Study	**Cooper 1984 b**
Methods	SB CO
Participants	N54 Norm Age16
Interventions	SR72 Dur 24
Outcomes	SBP 0.3 DBP 0.7
Notes	Included 124(1984+1984b) LoFo: 11 IT: No
Allocation concealment	B

Study	**Cuzzola 2001**
Methods	DB CO
Participants	N 19 Hyp Age 47
Interventions	SR 161 Dur: 14
Outcomes	SBP -5.1 DBP 0.1 Aldo 52.4 ng/ml Renin 0.88 ng/ml/h
Notes	Data available in patients in upper tertile of sodium excretion (19 of 55 patients)
Allocation concealment	B

Study	**DASH 1, 2001**
Methods	DB CO
Participants	N54 Norm Non-black Age 48
Interventions	SR55 Dur30
Outcomes	SBP -4 DBP not mentioned, see DASH 2
Notes	LoFo: 5% IT: No SD of the change calculated from 95% CI
Allocation concealment	B

Study	**DASH 1b, 2001**
Methods	DB

	CO
Participants	N37 Hyp Non-black Age 48
Interventions	SR 55 Dur 30
Outcomes	SBP -7 DBP not mentioned, see DASH 2b
Notes	LoFo: 5% IT: No SD of the change calculated from 95% CI
Allocation concealment	B

Study	**DASH 1c, 2001**
Methods	DB CO
Participants	N68 Norm Black Age 48
Interventions	SR55 Dur30
Outcomes	SBP -7 DBP not mentioned, see DASH 2c
Notes	LoFo: 5% IT: No SD of the change calculated from 95% CI
Allocation concealment	B

Study	**DASH 1d, 2001**
Methods	DB CO
Participants	N46 Hyp Black Age 48
Interventions	SR 55 Dur 30
Outcomes	SBP -9 DBP not mentioned, see DASH 2d
Notes	LoFo: 5% IT: No SD of the change calculated from 95% CI
Allocation concealment	B

Study	**DASH 2, 2001**
Methods	DB

Characteristics of included studies (*Continued*)

	CO
Participants	N54 Norm Non-black Age 48
Interventions	SR 55 Dur 30
Outcomes	DBP: Table 4: referent+ 50% of female+50% of age = -1.3+0.3+(-0.4) = -1.4
Notes	LoFo: 5% IT: No SD of the change calculated from SEM of the change
Allocation concealment	B

Study	**DASH 2b, 2001**
Methods	DB CO
Participants	N37 Hyp Non-black Age 48
Interventions	SR 55 Dur 30
Outcomes	DBP: -1.2 + hypertensive = -1.4 + (-1.3) = -2.7
Notes	LoFo: 5% IT: No SD of the change calculated from SEM of the change
Allocation concealment	B

Study	**DASH 2c, 2001**
Methods	DB CO
Participants	N68 Norm Black Age 48
Interventions	SR 55 Dur 30
Outcomes	DBP: -1.4 + African American = -1.4 + (-2.5) = -3.9
Notes	LoFo: 5% IT: No SD of the change calculated from SEM of the change
Allocation concealment	B

Study	**DASH 2d, 2001**
Methods	DB CO
Participants	N46

	Hyp Black Age 48
Interventions	SR 55 Dur 30
Outcomes	DBP: -1.4 + African American + hyperetnesive = -1.2 + (-2.5) + (-1.3) = -5.2
Notes	LoFo: 5% IT: No SD of the change calculated from SEM of the change
Allocation concealment	B

Study	**Davrath 1999**
Methods	SB CO
Participants	N8 Norm Age25
Interventions	SR95 Dur5
Outcomes	SBP 8 DBP 5 Renin 0.75 ng/ml/h NA 167pg/ml A 36pg/ml
Notes	LoFo: 0
Allocation concealment	B

Study	**Del Rio 1993**
Methods	DB CO
Participants	N30 Hyp Age49
Interventions	SR151 Dur 14
Outcomes	SBP -1.4 DBP -0.5 Renin 1.8 ng/ml/h Chol 9.6 mg/dl HDL -2.8 mg/dl TG 3.8 mg/dl
Notes	Included 47 LoFo. 17 IT: no
Allocation concealment	B

Study	**Dimsdale 1990**
Methods	Op

	CO
Participants	N19 (White) Norm Age34
Interventions	SR183 Dur5
Outcomes	SBP 1.4 DBP 4.1 Renin 8.4 ng/ml/h
Notes	LoFo: 0 SD of the change calculated from SEM of the change
Allocation concealment	B

Study	**Dimsdale 1990 b**
Methods	Op CO
Participants	N23 (Black) Norm Age34
Interventions	SR178 Dur5
Outcomes	SBP 1 DBP 4.4 Renin 8.1 ng/ml/h
Notes	LoFo: 0 SD of the change calculated from SEM of the change
Allocation concealment	B

Study	**Dimsdale 1990 c**
Methods	Op CO
Participants	N16 (Black) Hyp Age34
Interventions	SR178 Dur5
Outcomes	SBP -6.4 DBP 2 Renin 8.1 ng/ml/h
Notes	LoFo: 0 SD of the change calculated from SEM of the change
Allocation concealment	B

Study	**Dimsdale 1990 d**
Methods	Op CO
Participants	N17 (White)

	Hyp Age34
Interventions	SR 198 Dur 5
Outcomes	SBP -0.1 DBP 0.8 Renin 3.9 ng/ml/h
Notes	LoFo: 0 SD of the change calculated from SEM of the change
Allocation concealment	B

Study	**Donovan 1993**
Methods	SB CO
Participants	N8 Norm Age36
Interventions	SR152 Dur5
Outcomes	SBP -2 DBP 1 Aldo 31ng/dl Renin 4.5 ng/ml/h
Notes	LoFo. 0
Allocation concealment	B

Study	**Egan 1991**
Methods	DB CO
Participants	N27 Hyp Age39
Interventions	SR194 Dur7
Outcomes	SBP (MBP+1/3) -1.5 DBP (MBP-1/3) -0.7 Renin 2.0 ng/ml/h NA 90 pg/ml Chol 6.0 mg/dl LDL 4.8 mg/dl
Notes	Eandomisation schedule LoFo: 0 SD of the change calculated from SEM of the change
Allocation concealment	A

Study	**El Ashry 1987**
Methods	SB

	CO
Participants	N13 Norm Age24
Interventions	SR222 Dur14
Outcomes	SBP 0 DBP -4 Renin 5.1 ng/ml/h
Notes	LoFo: 0
Allocation concealment	B

Study	**El Ashry 1987 b**
Methods	SB CO
Participants	N13 Norm Age27
Interventions	SR232 Dur 14
Outcomes	SBP 0 DBP -1 Renin 4.5 ng/ml/h
Notes	LoFo: 0
Allocation concealment	B

Study	**Erwteman 1984**
Methods	S BP
Participants	N94 (22 blacks) Hyp Age46
Interventions	SR58 Dur28
Outcomes	SBP -2.7 DBP -2.5
Notes	Included 107 LoFo: 13 IT: No SD of the change calculated from SEM of the change
Allocation concealment	B

Study	**Fagerberg 1984**
Methods	Op P
Participants	N30 Hyp Age51

Characteristics of included studies (*Continued*)

Interventions	SR99 Dur63
Outcomes	SBP -3.7 DBP -3.1
Notes	Included 34 LoFo: 4 IT: No
Allocation concealment	B

Study	**Feldman 1996**
Methods	DB CO
Participants	N5 Norm Age27
Interventions	SR176 Dur7
Outcomes	SBP (MBP+1/3) 7.5 DBP (MBP-1/3) 2.5 NA 726 pmol/l A 19 pmol/l Chol 0.3 mmol/L
Notes	LoFo: 0
Allocation concealment	B

Study	**Feldman 1996 b**
Methods	DB CO
Participants	N8 Hyp Age27
Interventions	SR178 Dur7
Outcomes	SBP (MBP+1/3) 2.7 DBP (MBP-1/3) 1.3 NA 444 pmol/l A 3 pmol/l Chol 0.4 mmol/L
Notes	LoFo: 0
Allocation concealment	B

Study	**Ferri 1996**
Methods	DB CO
Participants	N61 Hyp Age47
Interventions	SR264 Dur14

Characteristics of included studies (*Continued*)

Outcomes	SBP -7.4 DBP -3.5 Aldo 120.5 pmol/l Renin 0.36 ng/l/s
Notes	79 were included. 65 were randomised. LoFo: 4 IT: No
Allocation concealment	B

Study	**Fliser 1993**
Methods	SB CO
Participants	N8 Norm Age25 +Doxazosin
Interventions	SR190 Dur8
Outcomes	SBP (MBP+1/3) -1.7 DBP (MBP-1/3) -0.9 NA 140 pg/ml Chol 9.0 mg/dl HDL -2mg/dl LDL 8 mg/dl TG 2 mg/dl HDL -2 mg/dl (CI 14.1) LDL 8 mg/dl (CI 17.2) TG 2 mg/dl (CI 20.5)
Notes	LoFo: 0
Allocation concealment	B

Study	**Fliser 1993 b**
Methods	SB CO
Participants	N8 Norm Age26 ●Doxazosin
Interventions	SR181 Dur8
Outcomes	SBP (MBP+1/3) -0.8 DBP (MBP-1/3) -0.4 NA 79 pg/ml Chol 2.0 mg/dl HDL 0mg/dl LDL 1 mg/dl TG 1 mg/dl

Notes	LoFo: 0
Allocation concealment	B

Study	**Fotherby 1993**
Methods	DB CO
Participants	N17 Hyp Age73
Interventions	SR79 Dur 35
Outcomes	SBP -8 DBP 0 Aldo 171 ng/L Renin 0.35 ng/ml/h
Notes	Included 18 LoFo. 1 IT: No SD of the change calculated from 95% C
Allocation concealment	B

Study	**Frieberg 1990**
Methods	Op CO
Participants	N10 Norm Age33
Interventions	SR117 Dur 13
Outcomes	SBP 0 DBP -1 Renin 0.28 ng/ml/h NA 29 pg/ml
Notes	LoFo:4 IT: No SD of the change was given as SE and reported to be 0 for SBP and 2 for DBP. As "0" is unacceptable for the software, SD of the change was calculated from the diastolic SE for both SBP and DBP. .
Allocation concealment	B

Study	**Fuchs 1987**
Methods	Op CO
Participants	N6 Norm Age20
Interventions	SR99 Dur9
Outcomes	SBP -5.8

	DBP 3
Notes	LoFo:0
Allocation concealment	B

Study	**Fuchs 1987 b**
Methods	Op CO
Participants	N11 Norm Age20
Interventions	SR93 Dur9
Outcomes	SBP -1.1 DBP 1
Notes	LoFo:0
Allocation concealment	B

Study	**Gow 1992**
Methods	Op CO
Participants	N9 Norm Age not given
Interventions	SR177 Dur7
Outcomes	SBP -8 DBP -3
Notes	LoFo: 0
Allocation concealment	B

Study	**Grey 1996**
Methods	DB CO
Participants	N34 Norm Age23
Interventions	SR133Dur7
Outcomes	SBP -1 DBP 1 Chol 0.06 mmol/l HDL 0.03 mmol/l LDL -0.04 mmol/L TG 0.01 mmol/L
Notes	LoFo: 0
Allocation concealment	B

Study	**Grobee 1987**
Methods	DB

	CO
Participants	N40 Hyp Age24
Interventions	SR72 Dur42
Outcomes	SBP -0.8 DBP -0.8 Renin 2.5 Ug/ml NA 19 pg/ml A 15 pg/ml Chol 0 mg/dl
Notes	Included 42 LoFo: 2 IT: No
Allocation concealment	B

Study	**HPTRG 1990**
Methods	S P
Participants	N228 (45 blacks) Norm Age40
Interventions	SR23 Dur 1100
Outcomes	SBP 0.3 DBP 0.1
Notes	Included 252 LoFo: 24 IT: No SD of the change calculated from SEM of the change
Allocation concealment	B

Study	**Hargreaves 1989**
Methods	DB CO
Participants	N8 Norm Age23
Interventions	SR106 Dur14
Outcomes	SBP -6 DBP -3 Aldo 503 pmol/l Renin 1.1 pmolAng1/ml/h
Notes	LoFo: 0
Allocation concealment	B

Characteristics of included studies (*Continued*)

Study	**Jula 1992**
Methods	SB P
Participants	N35 Hyp Age43
Interventions	SR146 Dur180
Outcomes	NA 40 pg/ml A 10 pg/ml
Notes	Included 91 Hormones available in a subgroup
Allocation concealment	B

Study	**Jula 1992(2)**
Methods	SB P
Participants	N36 Hyp Age45
Interventions	SR82 Dur180
Outcomes	Renin 0.24 ng/ml/h Aldosterone 84 micmol/l
Notes	Included 91 Hormones available in a subgroup
Allocation concealment	B

Study	**Jula 1994**
Methods	Op P
Participants	N76 Hyp Age44
Interventions	SR57 Dur365
Outcomes	SBP -6.7 DBP -3.8 Aldo 84 micmol/l Renin 0.24 ng/ml/h NA 40 pg/ml A 10 pg/ml
Notes	Included 91 LoFo: 15 IT: No
Allocation concealment	B

Characteristics of included studies (*Continued*)

Study	**Koolen 1984**
Methods	Op CO
Participants	N20 Hyp Age41
Interventions	SR213 Dur14
Outcomes	SBP -6.5 DBP -4.9 Aldo 93.5 pg/ml Renin 1.3 ng/ml/h NA 85 pg/ml
Notes	LoFo: 0
Allocation concealment	B

Study	**Koolen 1984(2)**
Methods	S CO
Participants	N25 Caucasians Hyp Age41
Interventions	SR 208 Dur 14
Outcomes	NA 85 (pg/ml)
Notes	LoFo:0
Allocation concealment	B

Study	**Kurtz 1987**
Methods	DB CO
Participants	N5 Hyp Age58
Interventions	SR217 Dur7
Outcomes	SBP -16 DBP -8.4
Notes	Included 7 LoFo: 2 IT: No SD of the change calculated from SEM of the change
Allocation concealment	B

Study	**Lawton 1988**
Methods	Op CO
Participants	N13

	Norm Age24
Interventions	SR313 Dur6
Outcomes	SBP -2 DBP 2 Renin 3.0 ng/ml/h NA 122 pg/ml
Notes	LoFo: 0
Allocation concealment	B

Study	**Lawton 1988 b**
Methods	Op CO
Participants	N9 Hyp Age25
Interventions	SR328 Dur6
Outcomes	SBP -1 DBP 4 Renin 2.9 ng/ml/h NA 103 pg/ml
Notes	LoFo: 0
Allocation concealment	B

Study	**Logan 1986**
Methods	Op P
Participants	N86 Hyp Age47
Interventions	SR43 Dur180
Outcomes	SBP -1.1 DBP -0.2
Notes	LoFo: ?
Allocation concealment	B

Study	**Manunta 2001**
Methods	SB CO
Participants	N20 Hyp Age 48
Interventions	SR 110 Dur 14
Outcomes	Renin 5.6 ng/ml

	Aldosteron
Notes	138 included in acute study. 20 with SR> 100 mmol included in 14 day study. LoFo: 0
Allocation concealment	B

Study	**Mark 1975**
Methods	Op CO
Participants	N6 Hyp Age28
Interventions	SR305 Dur10
Outcomes	SBP -13.1 DBP -7.7 Renin 5.6 ng/ml
Notes	LoFo: 0
Allocation concealment	B

Study	**Mascioli 1991**
Methods	DB CO
Participants	N48 Norm Age52
Interventions	SR70 Dur28
Outcomes	SBP -3.6 DBP -2.3
Notes	included 50 LoFo. 2 IT: No SD of the change calculated from SEM of the change
Allocation concealment	B

Study	**Maxwell 1984**
Methods	Op P
Participants	N30 Hyp Age 46
Interventions	SR161 Dur 84
Outcomes	SBP -2 DBP 2
Notes	LoFo: 0
Allocation concealment	B

Characteristics of included studies (*Continued*)

Study	**McCarron 1997**
Methods	DB CO
Participants	N99 (24 blacks) Hyp Age52
Interventions	SR56 Dur28
Outcomes	SBP -4.9 DBP -2.9 Chol 8.2 mg/dl HDL 0.1 mg/dl LDL 5.9 mg/dl TG 16.2 mg/dl
Notes	LoFo: 0
Allocation concealment	B

Study	**McGregor 1982**
Methods	DB CO
Participants	N19 Hyp Age49
Interventions	SR76 Dur28
Outcomes	SBP -10 DBP -5 Aldo 171 pmol/l Renin 0.69 ng/ml/h
Notes	LoFo:0
Allocation concealment	B

Study	**McGregor 1987**
Methods	DB CO
Participants	N15 Hyp Age52
Interventions	SR100 Dur30
Outcomes	SBP -13 DBP -9
Notes	LoFo:0
Allocation concealment	B

Study	**McGregor 1989**
Methods	DB CO
Participants	N20

	Hyp Age57
Interventions	SR150 Dur30
Outcomes	SBP -16 DBP -9 Aldo 243 pmol/l Renin 0.9 ng/ml/h NA - 10 pg/ml
Notes	LoFO: 0
Allocation concealment	B

Study	**Morgan 1978**
Methods	S BP
Participants	N62 Hyp Age60
Interventions	SR23 Dur90
Outcomes	SBP -1 DBP-2
Notes	LoFO: 3 IT: No
Allocation concealment	B

Study	**Morgan 1981**
Methods	S BP
Participants	N12 Hyp Age38
Interventions	SR67 Dur56
Outcomes	SBP not shown DBP -4
Notes	LoFo:0
Allocation concealment	B

Study	**Morgan 1981b**
Methods	S BP
Participants	N12 Hyp Age40
Interventions	SR92 Dur56
Outcomes	SBP not shown

	DBP -8
Notes	LoFo:0
Allocation concealment	B

Study	**Morgan 1987**
Methods	SBP
Participants	N20 Hyp Age58
Interventions	SR57 Dur60
Outcomes	SBP -6 DBP -4
Notes	LoFo: 0
Allocation concealment	B

Study	**Morgan 1988**
Methods	SB CO
Participants	N16 Hyp Age63
Interventions	SR50 Dur14
Outcomes	SBP -3 DBP -4 Renin 0.45 pmolAng1/ml/h SD of the change calculated from SEM of the change
Notes	LoFo: 0
Allocation concealment	B

Study	**Mtabaji 1990**
Methods	Op P
Participants	N30 (Black) Norm Age
Interventions	SR272 Dur7
Outcomes	SBP (MBP +1/3) -12 DBP (MBP-1/3) -6
Notes	LoFo: 0
Allocation concealment	B

Study	**Myers 1982**
Methods	Op CO

Characteristics of included studies (*Continued*)

Participants	N136 Norm Age39
Interventions	SR130 Dur14
Outcomes	SBP -3.3 DBP -2.7
Notes	Included 182 LoFo: 46 IT: yes (results not shown, but reported to be "similar") SD of the change calculated from SEM of the change
Allocation concealment	B

Study	**Nestel 1993**
Methods	DB P
Participants	N36 Norm Age66
Interventions	SR56 Dur42
Outcomes	SBP -2 DBP -1
Notes	Included 70 (1993+1993b) LoFo: 4 IT: No
Allocation concealment	B

Study	**Nestel 1993 b**
Methods	DB P
Participants	N30 Norm Age65
Interventions	SR73 Dur42
Outcomes	SBP -6 DBP -2
Notes	Included 70 (1993+1993b) LoFo: 4 IT: No
Allocation concealment	B

Study	**Overlack 1993**
Methods	SB CO
Participants	N30 saltsensitive

	Norm Age46
Interventions	SR270 Dur7
Outcomes	Aldo 195 pg/ml Renin 5.0 ng/ml/3h NA 128 pg/ml
Notes	LoFo: 0
Allocation concealment	B

Study	**Overlack 1993b**
Methods	SB CO
Participants	N108 saltresistant Norm Age36
Interventions	SR275 Dur7
Outcomes	Aldo 254 pg/ml Renin 6.7ng/ml/3h NA 166 pg/ml
Notes	LoFo: 0
Allocation concealment	B

Study	**Overlack 1993c**
Methods	SB CO
Participants	N25 counterregulatory Norm Age35
Interventions	SR279 Dur7
Outcomes	Aldo 299 pg/ml Renin 10.5ng/ml/3h NA 240 pg/ml
Notes	LoFo: 0
Allocation concealment	B

Study	**Overlack 1995**
Methods	DB CO
Participants	N11 Hyp Age61
Interventions	SR240

	Dur7
Outcomes	SBP (MBP+1/3) -13.2 DBP (MBP-1/3) -6.6 Aldo 216 pg/ml Renin 7.1 ng/ml/3h NA 263 pg/ml
Notes	LoFo: 0
Allocation concealment	B

Study	**Overlack 1995 b**
Methods	DB CO
Participants	N27 Hyp Age40
Interventions	SR249 Dur7
Outcomes	SBP (MBP+1/3) -1.1 DBP (MBP-1/3) -0.5 Aldo 211 pg/ml Renin 7.2 ng/ml/3h NA 112 pg/ml
Notes	LoFo: 0
Allocation concealment	B

Study	**Overlack 1995 c**
Methods	DB CO
Participants	N8 Hyp Age43
Interventions	SR234 Dur7
Outcomes	SBP (MBP+1/3) 8 DBP (MBP-1/3) 4 Aldo 114 pg/ml Renin 2.9 ng/ml/3h NA 324pg/ml
Notes	LoFo: 0
Allocation concealment	B

Study	**Parijs 1973**
Methods	Op CO
Participants	N15 Hyp Age41
Interventions	SR98

	Dur28
Outcomes	SBP -6.7 DBP 3.2
Notes	LoFo: 5 IT: No
Allocation concealment	C

Study	**Parker 1990**
Methods	DB P
Participants	N31 Hyp Age50
Interventions	SR73 Dur28
Outcomes	SBP 1.9 DBP -0.1
Notes	1990 + 1990 b Included 63 LoFo: 4 IT: No
Allocation concealment	B

Study	**Parker 1990 b**
Methods	DB P
Participants	N28 Hyp Age54
Interventions	SR49 Dur28
Outcomes	SBP 1.9 DBP 1.8
Notes	1990 + 1990 b Included 63 LoFo: 4 IT: No
Allocation concealment	B

Study	**Puska 1983**
Methods	SB P
Participants	N38 Norm Age40
Interventions	SR90 Dur72
Outcomes	SBP -1.5 DBP -2.1
Notes	LoFo: 4

	IT: No
Allocation concealment	B

Study	**Puska 1983 b**
Methods	SB P
Participants	N34 Hyp Age40
Interventions	SR90 Dur72
Outcomes	SBP 1.8 DBP 0.5
Notes	LoFo: 4 IT: No
Allocation concealment	B

Study	**Redon-Mas 1993**
Methods	Op P
Participants	N418 Hyp Age55
Interventions	SR104 Dur28
Outcomes	SBP 1 DBP 1.9
Notes	574 included LoFo: 156 IT: 0
Allocation concealment	B

Study	**Resnick 1985**
Methods	Op CO
Participants	N12 Hyp Age
Interventions	SR190 Dur5
Outcomes	SBP -3 DBP -1 Renin 4.2 ng/ml/h
Notes	LoFo: 0
Allocation concealment	B

Study	**Richards 1984**
Methods	SB

	CO
Participants	N12 Hyp Age36
Interventions	SR100 Dur28
Outcomes	SBP -4 DBP -3 Aldo 112 pmol/l Renin 0.31 mmol/l/h NA 24 pg/ml NA 1 pg/ml
Notes	Included 16 LoFo: 4 IT: No
Allocation concealment	B

Study	**Richards 1986**
Methods	SB CO
Participants	N8 Norm Age36
Interventions	SR181 Dur4
Outcomes	SBP -2 DBP 7 Aldo 22.9 ng/100ml Renin 112 micU/ml
Notes	LoFo:0
Allocation concealment	B

Study	**Ruilope 1993**
Methods	DB P
Participants	N19 Hyp Age
Interventions	SR69 Dur21
Outcomes	SBP -4 DBP -4
Notes	LoFo. 0
Allocation concealment	B

Study	**Ruppert 1991**
Methods	SB CO

Characteristics of included studies (*Continued*)

Participants	N98 Norm Age35 Sodium resistant
Interventions	SR275 Dur7
Outcomes	SBP (MBP+1/3) -0.45 DBP (MBP-1/3) -0.15 Aldo 28.5 ng/dl Renin 2.96 ng/ml/h NA 104 pg/ml Chol 19 mg/dl HDL -2 mg/dl LDL 18 mg/dl TG 7 mg/dl
Notes	LoFo: 0
Allocation concealment	B

Study	**Ruppert 1991 b**
Methods	SB CO
Participants	N24 Norm Age36 Sodium counterregulatory
Interventions	SR275 Dur7
Outcomes	SBP (MBP+1/3) 8 DBP (MBP-1/3) 4 Aldo 21.8 ng/dl Renin 2.14 ng/ml/h NA 70 pg/ml Chol 10 mg/dl HDL 1mg/dl LDL 8 mg/dl TG -1 mg/dl
Notes	LoFo: 0
Allocation concealment	B

Study	**Ruppert 1991 c**
Methods	SB CO
Participants	N25 Norm Age46 Sodium sensitive
Interventions	SR262 Dur7
Outcomes	SBP (MBP+1/3) -10

	DBP (MBP-1/3) -5 Aldo 19.4 ng/dl Renin 1.49 ng/ml/h NA 31 pg/ml Chol 14 mg/dl HDL 5 mg/dl LDL 9 mg/dl TG 17 mg/dl
Notes	LoFo: 0
Allocation concealment	B

Study	**Ruppert 1993**
Methods	SB CO
Participants	N30 Norm Age46 saltsensitive
Interventions	SR270 Dur7
Outcomes	SBP -12.6 DBP -5.6 Aldo 195.2 pg/ml Renin 5.1 ng/ml/3h NA 128 pg/ml
Notes	LoFo: 0
Allocation concealment	B

Study	**Ruppert 1993 b**
Methods	SB CO
Participants	N108 Norm Age36 saltresistant
Interventions	SR275 Dur7
Outcomes	SBP -1.4 DBP 1.2 Aldo 254 pg/ml Renin 6.7 ng/ml/3h NA 127 pg/ml
Notes	LoFo: 0
Allocation concealment	B

Study	**Ruppert 1993 c**
Methods	SB CO
Participants	N25

	Norm Age35 counteresulatory
Interventions	SR280 Dur7
Outcomes	SBP 5.9 DBP 8 Aldo 298.6 pg/ml Renin 10.5 ng/ml/3h NA 107 pg/ml
Notes	LoFo: 0
Allocation concealment	B

Study	**Ruppert 1994**
Methods	SB CO
Participants	N30 Norm Age46 saltsensitive
Interventions	SR270 Dur7
Outcomes	Chol 1 mg/dl HDL 2 mg/dl LDL -2 mg/dl TG 12 mg/dl
Notes	LoFo: 0
Allocation concealment	B

Study	**Ruppert 1994b**
Methods	SB CO
Participants	N108 Norm Age36 saltresistant
Interventions	SR275 Dur7
Outcomes	Chol 5 mg/dl HDL 0 mg/dl LDL 5 mg/dl TG 1 mg/dl
Notes	LoFo: 0
Allocation concealment	B

Study	**Ruppert 1994c**
Methods	SB CO
Participants	N25

	Norm Age35 counteresulatory
Interventions	SR280 Dur7
Outcomes	Chol 17 mg/dl HDL -1 mg/dl LDL 14 mg/dl TG 15 mg/dl
Notes	LoFo: 0
Allocation concealment	B

Study	**Schmid 1990**
Methods	SB CO
Participants	N9 Norm Age32
Interventions	SR190 Dur7
Outcomes	SBP -3 DBP 0
Notes	Allocation: random numbers LoFo: 0
Allocation concealment	B

Study	**Schmid 1990 b**
Methods	SB CO
Participants	N9 Hyp Age36
Interventions	SR181 Dur7
Outcomes	SBP -6 DBP -1.9
Notes	Allocation: random numbers LoFo: 0
Allocation concealment	B

Study	**Schorr 1996**
Methods	DB CO
Participants	N16 Norm Age 64
Interventions	SR61 Dur28

Outcomes	SBP -1 DBP 0 Aldo 0.01 nmol/L Renin 0.23 micg/L/min Chol 5.0 mg/dl HDL 3 mg/dl LDL 7 mg/dl TG 17 mg/dl
Notes	Included 21 LoFo: 5 IT: 0
Allocation concealment	B

Study	**Schorr 1997**
Methods	SB CO
Participants	N27 Norm Age25 sodium sensitive
Interventions	SR208 Dur7
Outcomes	SBP (MBP+1/3) - 7.5 DBP (MBP-1/3) - 3.7
Notes	LoFo: 0 SD of the change given
Allocation concealment	B

Study	**Schorr 1997 b**
Methods	SB CO
Participants	N76 Norm Age25 sodium resistent
Interventions	SR208 Dur7
Outcomes	SBP (MBP+1/3) 3.7 DBP (MBP-1/3) 1.9
Notes	LoFo: 0 SD of the change given
Allocation concealment	B

Study	**Sciarrone 1992**
Methods	DB P
Participants	N91 Hyp

	Age54
Interventions	SR82 Dur 56
Outcomes	SBP -5.8 DBP -0.4 Chol -0.124 mmol/l HDL -0.13 mmol/l LDL-0.16 mmol/l TG 0.198 mmol/l
Notes	95 included LoFO: 4 IT: No Lipid values were estimated on the basis of initial values(table 2) and changes (figure 4)
Allocation concealment	B

Study	**Sharma 1990**
Methods	SB CO
Participants	N15 Norm Age24
Interventions	SR192 Dur 7
Outcomes	SBP -0.9 DBP -3.7 Chol 0.26 mmol/l HDL -0.04 mmol/l LDL 0.27 mmol/l TG 0.08 mmol/l
Notes	LoFo: 0
Allocation concealment	B

Study	**Sharma 1991**
Methods	SB CO
Participants	N13 Norm Age25
Interventions	SR 246 Dur6
Outcomes	SBP -3 DBP 0.5 Aldo 800 pmol/l
Notes	1991 + 1991b included 25 LoFo. 2 IT: No
Allocation concealment	B

Characteristics of included studies (*Continued*)

Study	**Sharma 1991 b**
Methods	SB CO
Participants	N10 Norm Age24
Interventions	SR247 Dur6
Outcomes	SBP -6.4 DBP -5.9 Aldo 700 pmol/l
Notes	1991 + 1991b included 25 LoFo. 2 IT: No
Allocation concealment	B

Study	**Sharma 1993**
Methods	SB CO
Participants	N16 Norm Age24
Interventions	SR 224 Dur7
Outcomes	SBP -0.8 DBP -0.5
Notes	LoFo: 0
Allocation concealment	B

Study	**Shore 1988**
Methods	SB CO
Participants	N6 Hyp Age
Interventions	SR 97 Dur5
Outcomes	SBP -9 DBP -5.6 Aldo 136.1 pmol/l Renin 0.6 ng/ml/h
Notes	LoFo: 0
Allocation concealment	B

Study	**Silman 1983**
Methods	Op P

Participants	N28 Hyp Age55
Interventions	SR 63 Dur 90
Outcomes	SBP 3.5 DBP 0.5
Notes	LoFo: 5 IT: No Weighted average of BP effects obtained ar 1,2,3,6 and 12 months.
Allocation concealment	B

Study	**Singer 1991**
Methods	DB CO
Participants	N21(6 blacks) Hyp Age54
Interventions	SR91 Dur30
Outcomes	SBP -9 DBP -3 Aldo 123 pmol/l Renin 1.04 pmolAng1/ml/h
Notes	LoFo: 0 SD of the change calculated from SEM of the change
Allocation concealment	B

Study	**Skrabal 1981**
Methods	Op CO
Participants	N20 Norm Age23
Interventions	SR150 Dur14
Outcomes	SBP -2.7 DBP -3 Aldo 10.6 ng/dl Renin 0.27 ng/ml/h NA 252 pg/ml A 9 pg/ml
Notes	LoFo:0
Allocation concealment	B

Study	**Skrabal 1984**
Methods	Op CO

Characteristics of included studies (*Continued*)

Participants	N30 Norm Age23
Interventions	SR137 Dur14
Outcomes	SBP 1.4 DBP 0.8 Aldo 14.4ng/dl Renin 0.24 ng/ml/h NA -46 pg/ml A -2 pg/ml
Notes	LoFo: 0
Allocation concealment	B

Study	**Skrabal 1984 b**
Methods	Op CO
Participants	N22 Norm Age23
Interventions	SR167 Dur14
Outcomes	SBP -7.7 DBP -4.6 Aldo 27ng/dl Renin 0.69 ng/ml/h NA 28 pg/ml A 23 pg/ml
Notes	LoFo: 0
Allocation concealment	B

Study	**Skrabal 1985**
Methods	SB CO
Participants	N34 Norm Age23
Interventions	SR144 Dur14
Outcomes	SBP -0.1 (CI 1.22) DBP -0.6(CI 1.4)
Notes	LoFo: 0 SD of the change calculated from SEM of the change
Allocation concealment	B

Study	**Skrabal 1985 b**
Methods	SB CO

Characteristics of included studies (*Continued*)

Participants	N28 Norm Age23
Interventions	SR163 Dur14
Outcomes	SBP -5.8 DBP -3.3
Notes	LoFo: 0
Allocation concealment	B

Study	**Steegers 1991**
Methods	S BP
Participants	N36 Norm Age27
Interventions	SR63 Dur140
Outcomes	SBP 2 DBP 2
Notes	allocation: closed envelope system Included 42 LoFo. 6 IT: No
Allocation concealment	A

Study	**Sullivan 1980**
Methods	Op CO
Participants	N27 Norm Age29
Interventions	SR146 Dur4
Outcomes	SBP 7.1 DBP 1.1 Aldo 10.9 ng/dl Renin 2.3 ng/ml/h
Notes	LoFo: 0
Allocation concealment	C

Study	**Sullivan 1980 b**
Methods	Op CO
Participants	N19 Hyp Age27
Interventions	SR153

	Dur4
Outcomes	SBP 1.2 DBP 1.2 Aldo 11.0 ng/dl Renin 2.6 ng/ml/h
Notes	LoFo: 0
Allocation concealment	C

Study	**TOHP I 1992**
Methods	SB P
Participants	N744 (131 blacks) Norm Age43
Interventions	SR 47 Dur 550
Outcomes	SBP -1 DBP -0.9 SD of the change calculated from SEM of the change
Notes	LoFo: 50 IT: yes
Allocation concealment	A

Study	**TOHP II 1997**
Methods	SB P
Participants	N1190 (203 blacks) High norm Age 42
Interventions	SR40 Dur 1100
Outcomes	SBP -1.2 DBP -0.7
Notes	LoFo: 99 IT: yes
Allocation concealment	A

Study	**TONE 2001**
Methods	SB P
Participants	N 471 (non-blacks) Hyp Age 66
Interventions	SR 40 DUR: 105
Outcomes	SBP -4

	DBP -1.7
Notes	2001 + 2001b included 681 LoFo. 68 IT: No SD of the change given
Allocation concealment	B

Study	**TONE 2001 b**
Methods	SB P
Participants	N 142 (blacks) Hyp Age 66
Interventions	SR 40 DUR: 105
Outcomes	SBP -5 DBP -3
Notes	2001 + 2001b included 681 LoFo. 68 IT: No SD of the change given
Allocation concealment	B

Study	**Teow 1986**
Methods	Op CO
Participants	N9 Norm Age25
Interventions	SR200 Dur14
Outcomes	SBP -0.6 DBP -2.7
Notes	LoFo: 0
Allocation concealment	B

Study	**Uzu 1999**
Methods	CO SB
Participants	N70 (Japanese) Hyp Age50
Interventions	SR173 Dur7
Outcomes	SBP -14.6 DBP -5.5

Notes	LoFo: 0
Allocation concealment	B

Study	**Watt 1983**
Methods	DB CO
Participants	N18 Hyp Age52
Interventions	SR 56 Dur 28
Outcomes	SBP -0.5 DBP -0.3 Renin 1.63 ng/ml/h
Notes	Included 20 LoFo:2 IT: No SD of the change calculated from SEM of the change
Allocation concealment	B

Study	**Watt 1985**
Methods	DB CO
Participants	N31 Norm Age23
Interventions	SR60 Dur28
Outcomes	SBP -0.5 DBP 1.4
Notes	Included 75 (1985+1985b) LoFo: 9 IT: No SD of the change calculated from SEM of the change
Allocation concealment	A

Study	**Watt 1985 b**
Methods	DB CO
Participants	N35 Norm Age22
Interventions	SR75 Dur28
Outcomes	SBP -1.4 DBP 1.2
Notes	Included 75 (1985+1985b) LoFo: 9

	IT: No SD of the change calculated from SEM of the change SD of the change calculated from SEM of the change
Allocation concealment	A

Study	**Weir 1995**
Methods	SB CO
Participants	N11 (8 black) Hyp Age60 sodium sensitive
Interventions	SR146 Dur14
Outcomes	SBP -9 DBP -7
Notes	LoFo: 0
Allocation concealment	B

Study	**Weir 1995 b**
Methods	SB CO
Participants	N11 (6 black) Hyp Age60 sodium resistent
Interventions	SR127 Dur14
Outcomes	SBP 4 DBP 5
Notes	LoFo: 0
Allocation concealment	B

Study	**Wing 1998**
Methods	DB CO
Participants	N17 Hyp Age61
Interventions	SR59 Dur42
Outcomes	SBP -7 DBP -4
Notes	39 included 19 randomised LoFo: 2 IT: No
Allocation concealment	B

Study	Zoccali 1994
Methods	SB CO
Participants	N 15 Hyp Age 45
Interventions	SR 163 Dur 7
Outcomes	SBP -14 DBP -8 Aldo 170 pg/ml Renin 2.8 ng/ml/h
Notes	LoFo: 0
Allocation concealment	B

Op: open; SB: single blind; DB: double blind; P: parallel; CO: cross-over; N: number of persons in trial; Hyp:Hypertensive; Norm: Normotensive; Age: mean age of persons in trial; SR: Sodium Reduktion, mmol/24-h; Dur.: duration of intervention, days; SBP: netchange of systolic bloodpressure, mmHg; DBP: netchange of diastolic bloodpressure, mmHg; NA: Noradrenaline; A: Adrenaline; Chol: Cholesterole; HDL: High Density Lipoproteine; LDL: Low Density Lipoproteine.
TG: triglyceride
LoFo: Number lost to follow up
IT: "intention to treat" of those lost to follow-up

Characteristics of excluded studies

Study	Reason for exclusion
Dodson 1989	Includes only patients with diabetes mellitus
Imanishi M 2001	Includes only patients with diabetes mellitus
Miller JA 1997	Includes only patients with diabetes mellitus
Mühlhauser I 1996	Includes only patients with diabetes mellitus

GRAPHS

Comparison 01. Low salt diet vs high salt diet (Blood Pressure)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
Caucasians, normal diastolic BP	57	5030	Weighted Mean Difference (Fixed) 95% CI	-0.54 [-0.94, -0.14]
Caucasians, normal systolic BP	57	5096	Weighted Mean Difference (Fixed) 95% CI	-1.27 [-1.76, -0.77]
Caucasians, elevated diastolic BP	58	3391	Weighted Mean Difference (Fixed) 95% CI	-1.89 [-2.46, -1.32]
Caucasians, elevated systolic BP	56	3367	Weighted Mean Difference (Fixed) 95% CI	-4.18 [-5.08, -3.27]
Blacks, normal and elevated diastolic BP	8	522	Weighted Mean Difference (Random) 95% CI	-1.98 [-4.75, 0.78]
Blacks, normal and elevated systolic BP	8	522	Weighted Mean Difference (Random) 95% CI	-6.44 [-9.13, -3.74]