Randomized trials of sodium reduction: an overview\textsuperscript{1,2}

Jeffrey A Cutler, Dean Follmann, and P Scott Allender

ABSTRACT We updated a previously published overview of randomized clinical trials testing the effects of reducing sodium intake. We excluded trials that had confounded designs, enrolled preadolescent study populations, tested intakes outside the usual range for the US population, or reported neither systolic nor diastolic blood pressure. Thirty-two trials with outcome data for 2635 subjects were included. Two reviewers abstracted information independently and differences were reconciled. Pooled blood pressure differences between treated and control groups were highly significant for all trials combined and for trials in hypertensive and normotensive subjects pooled separately. The effects on blood pressure of lowering sodium in hypertensive and normotensive subjects, respectively (each trial weighted according to sample size), were $-4.8/-2.5$ and $-1.9/-1.1$ mm Hg (systolic/diastolic). Median differences in sodium excretion between sodium-reduction and control groups in these subgroups were $-77$ and $-76$ mmol/24 h, respectively. Weighted linear-regression analyses across the trials showed dose responses, which were more consistent for trials in normotensive subjects. These associations were, per 100 mmol Na/24 h, $-5.8/-2.5$ and $-2.3/-1.4$ mm Hg in hypertensive and normotensive subjects, respectively. There is no evidence that sodium reduction as achieved in these trials presents any safety hazards. The blood pressure reduction that would result from a substantial lowering of dietary sodium in the US population could reduce cardiovascular morbidity and mortality. Am J Clin Nutr 1997;65(suppl):643S-51S.

KEY WORDS Sodium reduction, blood pressure, clinical trials, meta-analysis

INTRODUCTION

Sound policy in clinical medicine and public health rests on a scientific base drawing from many areas of research, but randomized trials are critical in the hierarchy of evidence (1). Such studies can provide the least biased answers to two general questions: Can intake of dietary sodium be reduced? Should dietary sodium be reduced, to lower the risk of cardiovascular disease (CVD)? Clinical trials also generate quantitative estimates of the effect of intervention to reduce sodium intake on CVD risk, which are at least as important for decision making as qualitative conclusions.

Although providing some insights on the first question—the feasibility of sodium reduction—the focus of this overview is on the second, specifically the relation of change in sodium intake to change in systolic and diastolic blood pressure. Toward that end, we have updated through 1994 a previously published overview, which included both a descriptive summary and pooled analyses of unconfounded randomized trials of sodium reduction in adults (2).

METHODS

The method of quantitative overviews of trials, also called meta-analysis, has become reasonably standardized in recent years (3, 4). The primary steps are identification and selection of studies according to predetermined criteria, data abstraction and description, and statistical analysis and interpretation.

Selection of studies

We chose to limit our review to published trials to provide the basic quality standard afforded by peer review and to make the search task manageable. Our study covered publications through August 1994. Our methods included a MEDLINE (National Library of Medicine, Bethesda, MD) search supplemented by review of bibliographies of previous review articles (2, 5, 6). The complete text of each newly identified paper was evaluated by at least one of the authors (JAC or PSA) for satisfaction of the selection criteria, and all randomized trials were evaluated by both of these authors. For inclusion, trials needed to satisfy the following criteria:

1) random allocation to experimental conditions;
2) design free of confounding, ie, no planned use of blood pressure-lowering interventions differentially in sodium intervention and control groups;
3) reporting of an objective (laboratory-based) measure of change in sodium intake (in all but one case, 24-h or 8-h urinary sodium excretion);
4) reporting of change in systolic blood pressure, diastolic blood pressure, or both (not mean arterial pressure);
5) study subjects were not prepubertal children, whose lower blood pressures are less interpretable on a clinically and epidemiologically relevant scale; and
6) sodium intake goals for respective experimental conditions within usual levels for free-living adults in countries similar to the United States, taken as 2 SDs above and below the baseline mean 24-h excretion in the Trials of

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Hypertension Prevention, phase 1, or 28–273 mmol/24 h (7).

Data abstraction
The reports selected were abstracted onto a standard form by two reviewers independently, and differences were then reconciled by consensus. Information abstracted included the following: design (parallel or crossover study), nature and duration of intervention and follow-up under each randomized condition, methods of blinding to intervention assignment (use of placebo, random-zero or automated sphygmomanometers, and blinded blood pressure observers), sample size (at end of follow-up), characteristics of the study population (hypertensive or normotensive subjects and demographics), and outcome data. The outcome measures abstracted were the differences between the sodium-reduction and control groups for mean change from baseline (parallel design) or mean end-of-treatment values (crossover design) for systolic and diastolic blood pressure, 24-h sodium excretion, and potential confounding variables, whenever available. The potential confounding variables included body weight; excretion or intake of potassium, calcium, and magnesium; and intake of alcohol, total fat, and types of fatty acids (including n-3 fatty acids). Because of recent interest in the literature about possible side effects of sodium reduction, any data on plasma lipids or renin were also noted. For purposes of pooled analyses, statistics that could be used to estimate the variances of the blood pressure outcome measures were also abstracted.

Statistical analyses
We calculated two weighted estimates of the mean treatment effect on the basis of inverse variance and sample size, respectively (see Appendix A). Because sample sizes were uniformly available, we chose to emphasize these estimates in this manuscript. We report weighted means along with 95% CIs. We explored the relation between the estimated treatment effects and characteristics of each trial by using graphs, weighted linear regression, and rank correlation. Examined characteristics included baseline blood pressure group (hypertensive or normotensive), amount of sodium reduction, study design (parallel or crossover, double-blind or other), and study duration. P values < 0.05 were deemed significant.

To examine whether there was evidence of publication bias, we graphed treatment effects against the inverse sample size (see Appendix A). Such a graph can help detect whether small negative studies are not being reported in the literature. If publication bias is a substantial problem, a regression line through such data tends to have a nonzero slope.

RESULTS
Thirty-two trials met the selection criteria (8–40). Seven of these were reported only as two strata or two phases; thus, there are 39 entries in the descriptive tables. [Note that the two parts of one study are reported in two separate publications (15, 27).]

Trials in hypertensive subjects
Of the 22 trials that included hypertensive subjects, 9 were crossover trials (8–16), including the terminal phases of two parallel trials described below (14, 15) (Table 1). There were 241 subjects studied for treatment periods of 1–2 mo (median: 1 mo). Seven of the crossover trials used a double-blind design with sodium chloride tablets or placebo superimposed on a sodium-reduction diet (9, 10, 12–16); the others did not report any blinding procedure. The net reductions in sodium excretion ranged from −56 to −105 mmol (median: −76 mmol). [We did not include data from the lowest dose period of MacGregor et al’s study (13) to avoid double-counting of the control period data.] All nine trials found lower systolic blood pressure with sodium reduction, significantly so in five (9, 13–16), and eight showed lower diastolic blood pressure, significantly so in four (9, 13, 15, 16). Eight trials provided data on body weight, and eight provided data on potassium. Of these, only MacGregor et al’s first trial (9) found significant weight loss (0.54 kg), and only Richard et al (11) found a significant change in potassium excretion (increase of 10 mmol/24 h). Benetos et al (16) reported the only calcium data; they found no treatment-related differences in urinary excretion.

Fourteen trials with parallel designs reported results for 802 hypertensive subjects (17–29), including subjects who entered the terminal crossover phases in two trials described above (14, 15) and the two sex strata of the study by Morgan and Myers (18) (Table 1). The treatment phases of these studies lasted from 1 to 24 mo (median: 3 mo). Only three were double-blind, placebo-controlled (27–29), but all except four (19, 22, 23, 25) reported that blood pressure observers were blinded to treatment group. Net sodium changes ranged from −27 to −171 mmol, with a median of −71 mmol. In one trial (19) no excretion data were reported, but intracellular sodium concentrations were 23% lower in the active treatment group at the end of follow-up. Fourteen of 16 comparisons of systolic blood pressure change favored the sodium-reduction group; the differences were significant in 7 (14, 17, 19, 22, 25, 27, 28). Diastolic blood pressure decreased more with intervention in 11 trials, significantly so in 7 (17–19, 22, 24, 25, 27). Three trials provided no data on confounders (17, 19, 24); 8 reported data on weight, 10 on potassium, 4 on alcohol, and 1 on fat intake. There were small but significant between-group differences for changes in weight in three trials (21, 22, 26), potassium in three (14, 18, 21), and alcohol in one (21).

For purposes of pooling results, only the initial (parallel) portions of the trials by Dodson et al (14) and Chalmers et al (25) were included to avoid double-counting. The pooled estimates of blood pressure effects (± 95% CIs) among hypertensive subjects from the 22 trials were as follows: when sample size weights were used, −4.83 (± 1.04)/−2.45 (± 0.68) mm Hg for systolic/diastolic blood pressure (Figure 1). When inverse variance weights were used, the estimates were slightly smaller: −3.83 (± 1.03)/−2.14 (± 0.64) mm Hg. As is evident from the CIs, all of these effects were highly significant.

We also examined relations between mean sodium reduction in each trial and mean blood pressure change by using weighted linear regression and assuming a zero intercept. (The latter assumption is consistent with accepting the absence of other important blood pressure influences that differ between randomized treatments, ie, lack of confounding by other factors of the effect of sodium reduction.) These analyses yielded dose-response estimates (with 95% CIs) of −5.75 (± 1.88)/ −2.54 (± 1.39) per 100-mmol Na decrease for systolic/diastolic blood pressure (Figure 2 and Figure 3). When we performed weighted linear regressions without fixing the ori-
TABLE 1
Descriptive summary of sodium-reduction trials in hypertensive subjects

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Duration</th>
<th>Blinding</th>
<th>Urinary Na change</th>
<th>(No) Changes in confounders</th>
<th>Blood pressure change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mo</td>
<td>mmol/24 h</td>
<td></td>
<td></td>
<td>mm Hg</td>
</tr>
<tr>
<td>Crossover trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parijs et al 1973 (8), (n = 15)</td>
<td>1</td>
<td>NR</td>
<td>-98 (Wt)</td>
<td></td>
<td>-6.7 (Wt) 3.2</td>
</tr>
<tr>
<td>MacGregor et al 1982 (9), (n = 19)</td>
<td>1</td>
<td>DB</td>
<td>-76 (Wt, K)</td>
<td></td>
<td>-10.0 5.0</td>
</tr>
<tr>
<td>Watt et al 1983 (10), (n = 18)</td>
<td>1</td>
<td>DB</td>
<td>-56 (Wt, K)</td>
<td></td>
<td>-0.5 (Wt) 0.3</td>
</tr>
<tr>
<td>Richards et al 1984 (11), (n = 12)</td>
<td>1-1.5</td>
<td>NR</td>
<td>-105 (Wt, K)</td>
<td></td>
<td>-5.2 1.8</td>
</tr>
<tr>
<td>Grobbee et al 1987 (12), (n = 40)</td>
<td>1.5</td>
<td>DB</td>
<td>-72 (Wt, K)</td>
<td></td>
<td>-0.8 (Wt) 0.8</td>
</tr>
<tr>
<td>MacGregor et al 1989 (13), (n = 20)</td>
<td>1</td>
<td>DB</td>
<td>-82 (Wt, K)</td>
<td></td>
<td>-8.0 5.0</td>
</tr>
<tr>
<td>Dodson et al 1989 (14), (n = 9)</td>
<td>1</td>
<td>DB</td>
<td>-76 (Wt, K)</td>
<td></td>
<td>-9.7 5.1</td>
</tr>
<tr>
<td>ANHMRC 1989 (15), (n = 88)</td>
<td>2</td>
<td>DB</td>
<td>-67 (K)</td>
<td></td>
<td>-2.6 2.7</td>
</tr>
<tr>
<td>Benetos et al 1992 (16), (n = 20)</td>
<td>1</td>
<td>DB</td>
<td>-78 (Wt, K, Ca)</td>
<td></td>
<td>-6.5 3.7</td>
</tr>
<tr>
<td>Parallel trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morgan et al 1978 (17), (n = 31, 31)</td>
<td>24</td>
<td>BP obs</td>
<td>-27 NR</td>
<td></td>
<td>-1.5 6.9</td>
</tr>
<tr>
<td>Morgan and Myers 1981 (18), (n = 6, 6)</td>
<td>2</td>
<td>BP obs</td>
<td>-98 K</td>
<td></td>
<td>NR 6.0</td>
</tr>
<tr>
<td>Morgan and Myers 1981 (18), (n = 6, 6)</td>
<td>2</td>
<td>BP obs</td>
<td>-78 K</td>
<td></td>
<td>NR 4.0</td>
</tr>
<tr>
<td>Costa et al 1981 (19), (n = 20, 21)</td>
<td>12</td>
<td>NR</td>
<td>NR</td>
<td></td>
<td>-18.3 5.9</td>
</tr>
<tr>
<td>Simian et al 1983 (20), (n = 10, 15)</td>
<td>12</td>
<td>BP obs</td>
<td>-53 (Wt, K)</td>
<td></td>
<td>-8.7 6.3</td>
</tr>
<tr>
<td>Pusk et al 1983 (21), (n = 15, 19)</td>
<td>1.5</td>
<td>BP obs</td>
<td>-117 (Wt, K, Ca)</td>
<td></td>
<td>1.8 0.5</td>
</tr>
<tr>
<td>Fagerberg et al 1984 (22), (n = 15, 15)</td>
<td>2.3</td>
<td>NR</td>
<td>-89 (Wt, K, Ca)</td>
<td></td>
<td>-13.3 6.7</td>
</tr>
<tr>
<td>Maxwell et al 1984 (23), (n = 18, 12)</td>
<td>3</td>
<td>NR</td>
<td>-171 Wt</td>
<td></td>
<td>-2.0 2.0</td>
</tr>
<tr>
<td>Erwetsum et al 1984 (24), (n = 44, 50)</td>
<td>6</td>
<td>BP obs</td>
<td>-58 NR</td>
<td></td>
<td>-2.7 3.4</td>
</tr>
<tr>
<td>Chalmers et al 1986 (25), (n = 48, 52)</td>
<td>3</td>
<td>NR</td>
<td>-54 (K)</td>
<td></td>
<td>-5.1 4.2</td>
</tr>
<tr>
<td>Logan et al 1986 (26), (n = 37, 38)</td>
<td>6</td>
<td>BP obs</td>
<td>-32 Wt, K</td>
<td></td>
<td>-1.1 0.2</td>
</tr>
<tr>
<td>Dodson et al 1989 (14), (n = 17, 17)</td>
<td>3</td>
<td>BP obs</td>
<td>-59 (Wt, K)</td>
<td></td>
<td>-13.0 1.8</td>
</tr>
<tr>
<td>ANHMRC 1989 (27), (n = 50, 53)</td>
<td>2</td>
<td>DB</td>
<td>-71 (Alc)</td>
<td></td>
<td>-5.5 2.8</td>
</tr>
<tr>
<td>Sciarrone et al 1992 (28), (n = 46, 45)</td>
<td>2</td>
<td>DB</td>
<td>-84 (Wt, K)</td>
<td></td>
<td>-6.0 1.0</td>
</tr>
<tr>
<td>Parker et al (29) (low Alc), (n = 16, 15)</td>
<td>1</td>
<td>DB</td>
<td>-80 (Wt, Alc, Ca)</td>
<td></td>
<td>2.2 0.5</td>
</tr>
<tr>
<td>Parker et al (29) (norm Alc), (n = 15, 13)</td>
<td>1</td>
<td>DB</td>
<td>-52 (Wt, Alc, Ca)</td>
<td></td>
<td>-0.1 0.8</td>
</tr>
</tbody>
</table>

1 NR, not reported; Wt, body weight; DB, double blind; K, potassium intake/excretion; ANHMRC, Australian National Health and Medical Research Council; Ca, calcium intake/excretion; BP obs, observers blinded; RZ, random zero manometer; Alc, alcohol intake; P:S, ratio of polyunsaturated to saturated fatty acid; Mg, magnesium excretion.
2 P < 0.05.
3 n values given for each study are the number of subjects in the sodium-reduction treatment and control groups, respectively.
4 23% intracellular Na.

gin, slopes were not significantly different from zero for either systolic or diastolic blood pressure; for systolic blood pressure, the slope had a positive sign, in agreement with findings for regression through the origin, whereas for diastolic blood pressure, the sign was negative. The regression results for diastolic blood pressure were surprising in that they showed a significantly negative intercept (−4.85; P = 0.008). This reflects small clusters of points with large sodium reductions and little blood pressure effect and with modest sodium lowering and large mean blood pressure changes (Figure 3).

Trials in normotensive subjects

Of the 12 trials involving normotensive subjects (Table 2), 2 presented findings separately for strata defined by parental blood pressure (32) and by sex (40), leading to 14 entries in the table. [Also included are results for normotensive subjects from a study stratified by blood pressure; the results for hypertensive subjects were included above (21).]

Eight of the 14 were crossover trials and included a total of 436 subjects. Each treatment phase lasted from 2 wk to 2 mo (median: 1 mo). One-half of the eight trials used placebo-controlled designs; three of the other four reported blinding the blood pressure observers. For seven trials net changes in sodium excretion ranged from −60 to −210 mmol/24 h (median: −106 mmol); one trial used overnight collections and reported a difference of −20 mmol/8 h (36). Systolic blood pressure was lower with reduced sodium for all trials, significantly so in three (34–36). Diastolic blood pressure was lower with reduced sodium in six trials, with a significant difference in the same three as for systolic blood pressure. All trials, except one placebo-controlled study (36), also reported data on body weight and potassium excretion. There were small, significant differences in weight in two studies (30, 31) and in potassium in three studies (32, 33); none of these differences occurred in trials with significant blood pressure effects (34–36).

The six parallel trials and trial strata included a total of 1253 subjects, with treatment phases lasting from 2 wk to 36 mo (median: 6 mo). In three samples a placebo-controlled design was used; these were also two by two factorial trials (i.e., another intervention—a polyunsaturated oil in each case—also was tested) (38, 40). In the other trials, blood pressure observers were blinded, and in two of them a random-zero manometer was also used (37, 39). Net sodium change ranged from −16 to −117 mmol/24 h (median: −71 mmol). Systolic blood pres-
FIGURE 2. Dose-response analysis: weighted linear regression of systolic blood pressure (SBP) as a function of mean net change in sodium excretion. Lines are forced through the origin. Trials involving hypertensive and normotensive subjects are analyzed separately. T, treatment group; C, control group.

FIGURE 1. Mean net changes, with 95% CIs, pooled for all sodium-reduction trials and for various subsets. SBP, systolic blood pressure; DBP, diastolic blood pressure. *Mean change compared with control, with upper 95% CI.

potentially confounding factors were seen only in the Finnish trial (21) (weight, intake of potassium, and alcohol intake) and for potassium excretion in the Hypertension Prevention Trial (37).

The pooled estimates of blood pressure effects (± 95% CIs) for normotensive subjects from these 12 trials with weighting by sample size were −1.90 (± 0.72)/−1.09 (± 0.48) mm Hg for systolic/diastolic blood pressure (Figure 1); and with inverse variance weights were −1.54 (± 0.58)/−0.77 (± 0.50).
FIGURE 3. Dose-response analysis: weighted linear regression of diastolic blood pressure (DBP) as a function of mean net change in sodium excretion in mmol/24 h. Lines are forced through the origin. Trials involving hypertensive and normotensive subjects are analyzed separately. T, treatment group; C, control group.

We also performed dose-response analyses, as for the trials in hypertensive subjects, yielding estimates (± 95% CIs) of \(-2.28 (± 1.09)\) to \(-1.39 (± 0.84)\) mm Hg per 100 mmol Na for systolic/diastolic blood pressure (Figures 2 and 3). As shown by the CIs, all of these foregoing effect estimates are highly significant. When we performed weighted linear-regression analyses without fixing the intercepts, the results were remarkably similar to those described above with a fixed origin:

**TABLE 2**

Descriptive summary of sodium-reduction trials in normotensive subjects

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Duration</th>
<th>Blinding</th>
<th>Urinary Na change</th>
<th>(No) Changes in confounders</th>
<th>Blood pressure change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mo</td>
<td>mmol/24 h</td>
<td></td>
<td></td>
<td>Systolic Diastolic</td>
</tr>
<tr>
<td>Crossover trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skrabal et al 1981 (30), (n = 20)</td>
<td>0.5</td>
<td>NR</td>
<td>-170</td>
<td>Wt (K)</td>
<td>-2.7 - 3.0</td>
</tr>
<tr>
<td>Cooper et al 1984 (31), (n = 113)</td>
<td>2</td>
<td>BP obs</td>
<td>-68</td>
<td>Wt, (K)</td>
<td>-0.6 - 1.4</td>
</tr>
<tr>
<td>Watt et al 1985 (H) (32), (n = 35)</td>
<td>1</td>
<td>DB</td>
<td>-74</td>
<td>(Wt), K</td>
<td>-1.4 1.2</td>
</tr>
<tr>
<td>Watt et al 1985 (L) (32), (n = 31)</td>
<td>1</td>
<td>DB</td>
<td>-60</td>
<td>(Wt), K</td>
<td>-0.5 1.4</td>
</tr>
<tr>
<td>Teow et al 1985 (33), (n = 9)</td>
<td>0.5</td>
<td>BP obs</td>
<td>-210</td>
<td>(Wt), K</td>
<td>-0.6 - 2.7</td>
</tr>
<tr>
<td>Myers 1989 (34), (n = 172)</td>
<td>1</td>
<td>BP obs</td>
<td>-130</td>
<td>(Wt), (K)</td>
<td>-3.52 - 1.92</td>
</tr>
<tr>
<td>Hargreaves et al 1989 (35), (n = 8)</td>
<td>0.5</td>
<td>DB</td>
<td>-106</td>
<td>(Wt), (K)</td>
<td>-6.02 - 3.02</td>
</tr>
<tr>
<td>Mascioli et al 1991 (36), (n = 48)</td>
<td>1</td>
<td>DB</td>
<td>-20.2/8h</td>
<td>NR</td>
<td>-3.62 - 2.32</td>
</tr>
<tr>
<td>Parallel trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Puska et al 1983 (21), (n = 19, 19)</td>
<td>0.5</td>
<td>BP obs</td>
<td>-117</td>
<td>Wt, K, Alc, (P:S)</td>
<td>-1.5 - 1.1</td>
</tr>
<tr>
<td>HPTRG 1990 (37), (n = 174, 177)</td>
<td>36</td>
<td>BP obs (RZ)</td>
<td>-16</td>
<td>(Wt), K</td>
<td>0.1 0.2</td>
</tr>
<tr>
<td>Cobiac et al 1992 (38), (n = 26, 28)</td>
<td>1</td>
<td>DB</td>
<td>-71</td>
<td>(Wt), (K)</td>
<td>-1.7 0.8</td>
</tr>
<tr>
<td>TOHPRG 1992 (39), (n = 327, 417)</td>
<td>18</td>
<td>BP obs (RZ)</td>
<td>-44</td>
<td>(Wt), (K), (Ca), (Mg), (Alc), (fat)</td>
<td>-1.72 - 0.92</td>
</tr>
<tr>
<td>Nestel et al 1993 (40), (F: n = 15, 15)</td>
<td>6</td>
<td>DB</td>
<td>-94</td>
<td>(Wt), (K)</td>
<td>-6.02 - 2.02</td>
</tr>
<tr>
<td>Nestel et al 1993 (40), (M: n = 17, 19)</td>
<td>6</td>
<td>DB</td>
<td>-76</td>
<td>(Wt), (K)</td>
<td>-2.02 - 1.02</td>
</tr>
</tbody>
</table>

1 NR, not reported; Wt, body weight; K, potassium excretion; BP obs, observers blinded; H, high blood pressure; L, low blood pressure; DB, double blind; Alc, alcohol intake; P:S, ratio of polyunsaturated to saturated fat; HPTRG, Hypertension Prevention Trial Research Group; RZ, random zero manometer; TOHPRG, Trials of Hypertension Prevention Collaborative Research Group; Ca, calcium intake; Mg, magnesium intake; fat, fat intake.

2 *P < 0.05.

3 *n values are the number of subjects in the sodium-reduction treatment and control groups, respectively.
essentially all nutrients suspected of lowering blood pressure and found no differences between the intervention and control groups. Furthermore, the similarity of blood pressure effects between placebo-controlled trials and those in which subjects were aware of their treatment assignments gives additional reassurance. Nearly all of the non-double-blind trials used procedures to ensure that blood pressure measurement would be free of observer bias. In the other comparison by study design, there was no evidence that crossover trials underestimated treatment effects relative to parallel trials.

With regard to the possibility of publication bias favoring positive trials, a common concern in meta-analysis, there was no indication for diastolic blood pressure from graphic and regression analyses that small negative trials were underrepresented; for systolic blood pressure, the graphic plot was more suggestive of bias, but the regression slope was not significant. It seems unlikely that either positive or negative trials remain selectively unpublished in this historically controversial area.

Our primary dose-response analyses were conducted assuming a zero intercept and produced results similar to those reported in 1991 (2). This approach was based on the reasonable notion that with no sodium reduction there would be no blood pressure effect in a properly designed and conducted trial. Further support for this assumption comes from the lack of important confounding observed in these trials as discussed above. (Some potential confounders, such as alcohol intake and physical activity, were seldom measured.) These analyses yielded estimates, per 100 mmol of sodium reduction, of $-5.8/−2.5$ mm Hg in hypertensive subjects and −2.3/−1.4 mm Hg in normotensive subjects. Further analyses seeking a better fit by allowing a non-zero intercept produced results similar to these for normotensive subjects, but for hypertensive subjects the slopes were not significantly different from zero. Inspection of the plots for hypertensive subjects identified several influential outlier data points meriting further evaluation. Perhaps one lesson from this exercise is that study of dose response is not ideally pursued through this approach: more trials directly addressing this issue, such as the three-dose-level trial of MacGregor et al (13), are still needed. That trial did indeed find a graded blood pressure response for intakes of 150, 100, and 50 mmol Na/24 h.

One of the limitations of the reports included in this overview may modify conclusions about the dose relation: few reported sample sizes for urine collections. In the Trials of Hypertension Prevention, phase 1, 24-h urine values were available for 71% of the active intervention group and 79% of the control group (38). If one makes the worst-case assumption that those who provided no urine sample made no changes in intake, the actual net reduction in sodium intake may be up to one-third less than reported (30 rather than 44 mmol) (41). Thus, a larger though plausible estimate of systolic blood pressure lowering per 100 mmol Na/24 h may be calculated by using the actual blood pressure change achieved with the estimated 30-mmol Na reduction (1.7 mm Hg) multiplied by 100/30 mmol, or 5.7 mm Hg. This effect size is similar to those estimated more recently in the INTERSALT Study through use of contemporary statistical approaches (42).

For reasons already stated or that are self-evident, this overview excluded trials in children, trials with an outcome mea-

*DISCUSSION*

Our overview of these 32 randomized trials involving 2635 subjects provides conclusive evidence that moderate sodium reduction lowers systolic and diastolic blood pressure over periods of several weeks to a few years. An effect is seen in both hypertensive and normotensive subjects: about $-5/-3$ mm Hg and $-2/-1$ mm Hg, respectively. These conclusions appear to be robust because the level of statistical significance effectively rules out chance as an explanation (pooled estimates all differ by 3–9 SEs from the null), both trial-by-trial review and pooling of subsets by design features provide little evidence of biases operating, there is no support for important publication bias, and there is evidence of dose response. Several of these points merit further comment.

Most trials provided data on body weight and potassium excretion and were not confounded by changes in these factors; where differences occurred they were small and not always in a direction to increase the blood pressure effect. Fewer trials furnished data on other nutrients, including alcohol, but the large Trials of Hypertension Prevention, phase 1, reported on

*All trials*

The pooled results for all 32 trials, using sample-size weighting, were $-2.81 (± 0.58)/-1.52 (± 0.38)$ mm Hg (± 95% CIs) (Figure 1). However, mean blood pressure effects were all substantially and significantly larger for hypertensive than for normotensive subjects, as would be expected from experience with any blood pressure–lowering intervention. Other than for baseline blood pressure values, these subsets of trials were not much different: median sodium reduction was almost identical ($-76$ compared with $-77$ mmol) and median duration of intervention was different only among parallel trials, for which duration was longer for trials in normotensive subjects. With regard to the influence of duration on outcome measures, the rank-correlation between duration and net sodium reduction was $-0.50 (P = 0.0002)$, indicating that the longer the trial, the smaller the intervention effect. In contrast, the correlation of duration with both systolic and diastolic blood pressure was nonsignificantly positive, indicating that the smaller sodium reduction over time is not translated into lesser blood pressure reduction.

Other design features did not appear to have important effects on blood pressure results (Figure 1). Crossover trials, despite being shorter and involving the theoretical risk of carryover effects, found effects similar to those of parallel trials. Finally, blood pressure effects in double-blind, placebo-controlled trials were not significantly different from those with less trials of blinding; in fact, the estimate for systolic blood pressure was 1 mm Hg larger in the double-blind trials. The median sodium reduction values were nearly identical in the two groups of trials. Thus, the greater potential for bias in non-double-blind trials appears not to be a serious concern. The regression analyses for publication bias failed to reject the null hypothesis that the effect estimates are independent of sample size ($P = 0.57$ for diastolic blood pressure, $P = 0.34$ for systolic blood pressure; data not shown).
sure other than blood pressure change, and those confounded by design with other lifestyle or drug treatments. In general, such trials provide additional support to the usefulness of sodium reduction as a clinical and public health strategy. For example, Hofman et al (43) found that reduction in the sodium content of infant formula led to a significant lowering of systolic blood pressure (2.1 mm Hg) at 6 mo of age. In the Dietary Intervention Study of Hypertension, which targeted secondary prevention of hypertension, Langford et al (44) showed that sodium reduction doubled the odds of remaining off antihypertensive medication for both obese and nonobese subjects. A subsequent trial by the same investigators with a more complex design, the Trial of Antihypertensive Interventions and Management, failed to show that sodium reduction (to a quite modest degree) combined with potassium increase lowered diastolic blood pressure in the short term or reduced the need for medication over several years (45). Subgroup analyses, however, suggested benefit in less obese individuals and in women.

These results from the Trial of Antihypertensive Interventions and Management highlight the issue of heterogeneity of response to sodium reduction (so-called sodium sensitivity). Variation in response undoubtedly exists—as it does to most environmental exposures—but effects on average systolic and diastolic blood pressure shown in this overview provide strong evidence that most of the population, both hypertensive and normotensive, is sodium sensitive. A mean blood pressure reduction may mask divergent responses in qualitatively different subgroups, but intervention studies of various designs have in general not identified such a bimodal distribution of response.

The trials reviewed have not focused on putative adverse effects of sodium reduction, a literature that has largely come from the studies excluded from this overview that exposed subjects to very low sodium intakes, usually 20 mmol/d, for short periods (46). One trial in our series reported no effect on total or low-density-lipoprotein cholesterol of a reduction in sodium excretion from 134 to 52 mmol/24 h over an 8-wk period (28). Two trials reported contrasting effects on plasma renin activity and aldosterone: levels of both were raised by sodium reduction to 50 mmol/d for 2 wk (35) whereas neither was different from values in control subjects after 9 wk with sodium lowering to 85 mmol/d (16). These results suggest that moderate, longer-term sodium reduction is free of biochemical side effects.

The body of trial evidence has been criticized for not providing demonstrated benefits for mortality or major morbidity. The fallacy of this reasoning is discussed elsewhere (42). Completed trials do suggest that sodium reduction aids in the primary prevention of hypertension (37, 39), and other studies suggest that lowering dietary sodium reduces left ventricular mass, a powerful cardiovascular risk factor (47, 48).

The reduction of average blood pressure values by lowered sodium intake has great potential, especially along with other public health measures, for shifting the whole blood pressure distribution in populations such as that in the United States. Changes in intake seen in clinical trials have been achieved despite the widespread presence of excess sodium in the food supply. For these and other reasons detailed above, the aggregate results of these trials probably understate the potential benefit for the currently above-optimal blood pressure distribution. However, even the effects shown have great public health importance, as illustrated by calculations based on associations of a 3-mm Hg difference in mean systolic blood pressure with various CVD outcomes: 11% fewer strokes, 7% fewer coronary artery disease events, and 5% fewer total deaths (49).

A few years ago, addressing the issue of dietary recommendations regarding salt, the late Lot Page stated most eloquently a guiding philosophy that is still relevant: "... we can never wait for final proof when making recommendations in the public interest. In science, no proof is ever final. ... Inevitably, public health recommendations are made over the protests of special interest groups and honest dissenters. Nevertheless, they must be made in the interest of promoting good health for the public" (50).

REFERENCES


control change in blood pressure for the ith trial. The variance of this weighted mean is given by

$$\frac{1}{\sum(1/v_i)}$$  \hspace{2cm} (A2)

We replace $v_i$ with the reported or imputed sample variance for the ith trial.

To define the sample-size-weighted mean, let $n$ be the number of patients in a crossover trial and $n_t$ ($n_c$) the number of patients in the treatment (control) arms in a parallel trial. Now define the weight for the ith trial as $w_i = n$ for crossover trials and $w_i = n_t n_c/(n_t + n_c)$ for parallel trials. If we assume that the variance of the change, say $\sigma^2$, is the same over all studies, then $v_i = \sigma^2/w_i$. By replacing $v_i$ with $\sigma^2/w_i$ in (Eq A1) and (Eq A2), we obtain a sample-size-weighted mean and its variance. The change variance $\sigma^2$ is estimated by a weighted average of the reported change variances. For the analysis of publication bias we define inverse sample size by $1/w_i$.

**REFERENCE**